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U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA)  
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FEDERAL INSECTICIDE, FUNGICIDE AND  
RODENTICIDE ACT SCIENTIFIC ADVISORY PANEL  
(FIFRA SAP)

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REEVALUATION OF THE HUMAN HEALTH EFFECTS OF  
ATRAZINE: REVIEW OF EXPERIMENTAL ANIMAL  
AND IN VITRO STUDIES AND DRINKING WATER  
MONITORING FREQUENCY

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TUESDAY,  
APRIL 27, 2010

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The Panel convened at 8:30 a.m. in the  
  
Hamilton Ballroom of the Hamilton Crowne Plaza  
Hotel, located at 1001 14th Street, N.W.,  
Washington, D.C., Steven G. Heeringa, Ph.D.,  
Chair, and Kenneth M. Portier, Ph.D., Session  
Chair, presiding.

FIFRA SAP MEMBERS PRESENT:

- STEVEN G. HEERINGA, Ph.D., Chair
- KENNETH M. PORTIER, Ph.D., Session Chair
- JOHN R. BUCHER, Ph.D., DABT
- JANICE E. CHAMBERS, Ph.D., DABT, ATS
- GERALD A. LeBLANC, Ph.D.
- DANIEL SCHLENK, Ph.D.

FQPA SCIENCE REVIEW BOARD MEMBERS PRESENT:

SUSAN F. AKANA, Ph.D.

RICHARD H. COUPE, Ph.D.

KENNETH BARRY DELCLOS, Ph.D.

PENELOPE A. FENNER-CRISP, Ph.D., DABT

ROBERT J. GILLIOM, Ph.D.

RICHARD GREENWOOD, Ph.D.

WILLIAM L. HAYTON, Ph.D.

STEVEN D. HOLLADY, Ph.D.

TERESA H. HORTON, Ph.D.

KANNAN KRISHNAN, Ph.D.

HERBERT K.H. LEE, Ph.D.

KEVIN T. O'BYRNE, Ph.D.

NU-MAY RUBY REED, Ph.D., DABT

JEAN F.L. REGAL, Ph.D.

DANIEL J. SELVAGE, Ph.D.

CARMEN J. WILLIAMS, M.D., Ph.D.

LINDA J. YOUNG, Ph.D.

ALSO PRESENT:

JOSEPH E. BAILEY, Designated Federal Official

C-O-N-T-E-N-T-S

Opening Remarks and Introductions . . . . .4

EPA Presentation: Use of Bootstrapping

    Methods . . . . . 11

    Mary Frankenberry

EPA Presentation: Artificial Neural

    Networks. . . . . 35

    Mike Messner

EPA Summary - Nelson Thurman. . . . . 69

Public Comments . . . . . 96

Charge Questions . . . . .340

1 P-R-O-C-E-E-D-I-N-G-S

2 8:31 a.m.

3 MR. BAILEY: Let's get started  
4 here this morning. My name is Joe Bailey  
5 again. I'm serving as the designated federal  
6 official for the meeting. This is the  
7 Reevaluation of the Human Health Effects of  
8 Atrazine.

9 I just want to make a couple of  
10 quick comments. EPA's presentations from  
11 yesterday are in the docket, so if anybody  
12 wants to see them, they're there.

13 We will have a public comment  
14 session this morning. And I would ask anybody  
15 who has electronic copy of their comments to  
16 e-mail them to me. I will get them -- I'll  
17 give you the e-mail at break or sometime if  
18 you do need that.

19 And the final reminder is just to  
20 please state your name when you're making  
21 comments so that we can get the name recorded  
22 into the audio and written transcript.

1                   And I think that's all I have to  
2                   announce this morning. And I'll turn the  
3                   meeting over to Ken Portier. Thank you.

4                   SESSION CHAIR PORTIER: Good  
5                   morning. Welcome to day two of this EPA SAP  
6                   meeting on Reevaluation of Human Health  
7                   Effects of Atrazine: Review of Experimental  
8                   Animal and In Vitro Studies and Drinking Water  
9                   Monitoring Frequency.

10                  We're continuing the presentation  
11                  from day one. But as we normally do with the  
12                  panel on the second day we're going to go  
13                  around and introduce everyone from the panel.  
14                  I'm Ken Portier, the director of statistics at  
15                  the American Cancer Society national home  
16                  office in Atlanta. I'm a bio-statistician, a  
17                  member of the permanent panel. And we'll  
18                  start with John.

19                  DR. BUCHER: John Bucher. I'm the  
20                  associate director of the National Toxicology  
21                  Program. I'm a toxicologist and a member of  
22                  the permanent panel.

1 DR. SCHLENK: Dan Schlenk,  
2 professor of aquatic ecotoxicology, Department  
3 of Environmental Sciences, University of  
4 California, Riverside, and a member of the  
5 permanent panel.

6 DR. CHAMBERS: I'm Jan Chambers, a  
7 professor in the College of Veterinary  
8 Medicine at Mississippi State University. I'm  
9 a pesticide toxicologist and a member of the  
10 permanent panel.

11 DR. LEBLANC: I'm Gerry LeBlanc.  
12 I'm head of the Department of Environmental  
13 and Molecular Toxicology, North Carolina State  
14 University. And I'm a permanent panel member.

15 DR. HOLLADAY: I'm Steve Holladay.  
16 I'm a professor at University of Georgia  
17 College of Veterinary Medicine. I'm head of  
18 Anatomy and Radiology Department. I'm an  
19 immunotoxicologist, first time on the panel.

20 DR. REGAL: Jean Regal, University  
21 of Minnesota Medical School, Duluth --  
22 immunotoxicology.

1 DR. WILLIAMS: Carmen Williams,  
2 National Institute of Environmental Health  
3 Sciences, and I'm a reproductive endocrine and  
4 fertility specialist and reproductive tract  
5 biologist.

6 DR. DELCLOS: Barry Delclos from  
7 the FDA, National Center for Toxicological  
8 Research, toxicologist.

9 DR. HORTON: Teresa Horton,  
10 Department of Neurobiology and Physiology,  
11 Northwestern University, Evanston, Illinois,  
12 reproductive neuroendocrinology, maternal  
13 fetal interactions and development of the  
14 reproductive system and neuroendocrine system.

15 DR. AKANA: Susan Akana from the  
16 University of California, San Francisco. I'm  
17 a research physiologist with a specialty in  
18 the stress axis and its interaction with  
19 energy balance.

20 DR. O'BYRNE: I'm Kevin O'Byrne  
21 from King's College London, the Department of  
22 Anatomy and Human Sciences. And I'm a

1 reproductive physiologist.

2 DR. SELVAGE: Dan Selvage, Idaho  
3 State University. I study stress and gonadal  
4 hormones. I'm banished to the corner over  
5 here.

6 SESSION CHAIR PORTIER: Dr.  
7 Gilliom?

8 DR. GILLIOM: Bob Gilliom, U.S.  
9 Geological Survey. And I am director of  
10 pesticide studies for the National Water  
11 Quality Assessment Program.

12 DR. COUPE: Richard Coupe, U.S.  
13 Geological Survey.

14 DR. YOUNG: Linda Young,  
15 Department of Statistics, University of  
16 Florida.

17 DR. LEE: Herbert Lee, University  
18 of California, Santa Cruz, Department of  
19 Applied Mathematics and Statistics.

20 DR. REED: Nu-may Ruby Reed,  
21 California Environmental Protection Agency.  
22 I do pesticide risk assessment and risk

1 assessment issues.

2 DR. FENNER-CRISP: Penny Fenner-  
3 Crisp, private consultant, Charlottesville,  
4 Virginia. My area of interest is toxicology  
5 and risk assessment.

6 DR. GREENWOOD: Richard Greenwood  
7 from University of Portsmouth in the U.K. I'm  
8 a toxicologist, pesticides and environment.

9 DR. KRISHNAN: Kannan Krishnan,  
10 professor and director of the Toxicology  
11 Research Center of the University of Montreal,  
12 Canada. My expertise is in pharmacokinetics  
13 and risk assessment methods.

14 DR. HAYTON: William Hayton from  
15 the College of Pharmacy at The Ohio State  
16 University., professor of pharmacy. And my  
17 area is pharmacokinetics.

18 CHAIR HEERINGA: Steve Heeringa,  
19 the University of Michigan. I'm a  
20 statistician for the Institute for Social  
21 Research and I'm currently the Chair of the  
22 FIFRA Science Advisory Panel.

1                   SESSION CHAIR PORTIER: Thank you.  
2           Dr. Selvage, I think after we do the public  
3           comments we're going to move you around and  
4           kind of give you a little room. We added two  
5           more members since yesterday so -- as if it  
6           wasn't tight enough.

7                   Just to give you a little idea of  
8           how we readjusted the agenda, we're going to  
9           spend the first period this morning before the  
10          break on the remaining EPA presentation.

11                   Following the break we have six  
12          groups of public commenters that have asked to  
13          spend time. You have some documents added to  
14          what was already in the docket. We'll take a  
15          look at those during the break. I doubt if  
16          we'll get through all the public commenters.

17                   We have about three hours of  
18          public comment, so we'll do two hours of that  
19          before lunch. We'll take an hour, hour-and-  
20          fifteen-minute lunch, and then we'll come back  
21          for public comments. And then we'll start on  
22          the questions.

1                   And even though we -- our agenda  
2                   says we'll stop at 5:00 we'll probably push it  
3                   a little bit to 5:30 -- maybe a quarter to  
4                   6:00 today to kind of capture a little bit of  
5                   the time we've lost.

6                   And, with that, I'm going to turn  
7                   it over to Mr. Thurman to continue the --  
8                   introducing the speakers for the water part.

9                   MR. THURMAN:   Okay.  Where we're  
10                  going to go next is we presented two examples  
11                  in the white paper for you.  And Mary  
12                  Frankenberry is going to give a presentation  
13                  on the use of bootstrapping methods to  
14                  evaluate how well different sampling frequency  
15                  estimate time average concentrations over  
16                  time.  And then Mike Messner is going to talk  
17                  about how an application of artificial neural  
18                  networks to simulate pesticide concentration  
19                  patterns and how that might be applied.  So  
20                  I'm going to turn this over to Mary.

21                  MS. FRANKENBERRY:  Thank you,  
22                  Nelson.  As Nelson said, we'll be looking --

1 I'll be looking this morning at evaluating  
2 sampling strategies for estimating maximum  
3 concentrations of different durations.

4 And as we also said yesterday, we  
5 talked about recent work by Crawford and  
6 others that have evaluated the performance of  
7 different sampling strategies for estimating  
8 the upper percentiles of true values -- so-  
9 called true chemograph profiles -- and we'll  
10 get into that a little more.

11 In the white paper that OPP did we  
12 carried out two methods that were variations  
13 on the Crawford bootstrapping approach, and  
14 one of which I'll be presenting today.

15 Crawford's work created synthetic  
16 true chemographs using linear interpolation to  
17 augment less than daily sampling up to 365-day  
18 profiles. OPP, however, chose three -- I'm  
19 sorry -- 30 community water system where  
20 Crawford looked at Heidelberg data. We chose  
21 these CWS data. They were normally sampled  
22 weekly or biweekly and augmented again to 365

1 days linearly.

2 The systems that we chose were  
3 taken to be representative of most of the  
4 systems -- AMP systems over the five years.  
5 So they included some low, medium, and high  
6 concentration systems.

7 While earlier work looked at the  
8 upper percentiles of a single day  
9 concentration, OPP is concerned with the  
10 maximum value of several different durations  
11 ranging from probably single day values all  
12 the way up 90-day averages at the current  
13 time. Similar to earlier methods, OPP looked  
14 at the performance of different sampling  
15 strategies for computing estimates of true  
16 values for these maximum running averages.

17 Sampling was carried out using the  
18 interpolated systems according to schedules  
19 which ranged from quarterly sampling to  
20 sampling every four days. We actually did put  
21 in also a seasonal daily strategy where we  
22 sampled every day during the season of April

1 through August. I think it was biweekly  
2 beginning and ends of the year.

3 Each sampling strategy was  
4 implemented with replacement over 4,500 times  
5 following a random start. Each resample was  
6 interpolated to 365 days, and then the maximum  
7 single day, maximum three-day, and so on  
8 average of each run was compiled with the  
9 range and percentiles of these maximum values  
10 reported. And we took this range of maximum  
11 values and presented it against the true value  
12 for each chemograph and the tables that will  
13 follow.

14 This is just a matrix of our  
15 sampling strategies versus the concentration  
16 durations that we looked at. On the left  
17 you'll see the sampling intervals going from  
18 daily down to quarterly. I put in single days  
19 up to 90-day averages here. But we also  
20 looked at 14-day averages, I think 28- or 30-  
21 day averages, 60-day averages as well.

22 Okay. Chemograph number 21 is

1 something -- well, I'll present some numbers  
2 on that. But just to show you what it looks  
3 like, it's an example of our middle group of  
4 systems. It rises to its peak and then  
5 declines somewhat slowly over the course of  
6 several weeks. If you look at the notches on  
7 the graph in the peak there those represent  
8 weekly samples. So you'll see that the --  
9 from beginning to end of this peak that's  
10 somewhere along the order of five to six  
11 weeks.

12           These are tables of the numbers  
13 that we ran for them. You can see the true  
14 value for single daily -- a single day value  
15 sampled at either four-day intervals, seven-  
16 day intervals, or 14-day intervals. The true  
17 single day value for this chemograph was  
18 31.25.

19           On the right-hand column here we  
20 show how many times we actually captured that  
21 mean in all of these 4- to 5,000 samples. And  
22 actually it's kind of what you'd expect for

1 sampling every four days. We might catch it  
2 once in four days or 25 percent of the time,  
3 sampling every seven days about 14 percent of  
4 the time, sampling every two weeks about 7  
5 percent of the time.

6 If we look at the mean returns or  
7 the mean runs on these resamples we see that  
8 we were 4 to 5 percent lower than the true  
9 value for sampling every four days. If we  
10 sampled every seven days we were 7 to 8  
11 percent lower on average, every two weeks 14  
12 to 15 percent lower on average. We also show  
13 the lowest runs, and they run from 11 up to 27  
14 percent underestimating. But, clearly, the  
15 performance is best if the sampling is more  
16 frequent than less frequent.

17 That was the first graph -- or  
18 table represented single day values. These  
19 are seven-day average concentrations --  
20 maximum seven-day average concentrations for  
21 the same chemograph. You can see that the  
22 performance is a little better when we go from

1 looking at a single-day peak to a seven-day  
2 average. On average we get between 2 and 3  
3 percent below, between 5 and 6 percent below,  
4 or between 13 and 14 percent below.

5 And up at the top we have  
6 captured -- the top runs capture the maximum  
7 fairly well. We're also starting to  
8 overestimate it just a little bit as this  
9 average gets a little longer than the single-  
10 day or the three-day average.

11 Just to summarize the results for  
12 this, which really are consistent with the  
13 results for all of the other systems, it  
14 appears that accuracy, as you might expect, is  
15 best for strategies which employ the most  
16 frequent sampling. Accuracy generally seems  
17 to improve for longer-term averages, that is,  
18 seven days, 30 days, 90 days, over the shorter  
19 term averages of single days or three days for  
20 instance.

21 Here I'm going to show two other  
22 peaks that are representative of two other

1 types of chemographs that we saw among those  
2 that we looked at. Number 4 represents a  
3 single narrow peak that is created and then  
4 declined again in the course of two weeks.  
5 And the values here go from a little bit over  
6 zero up to 73 parts per billion. And this is  
7 down close to 10.7 -- I think 11 parts per  
8 billion one week later. And that -- those  
9 differences are important when we look at how  
10 well we do with sampling.

11 Next graph is simply typical of a  
12 series of broad -- one broader series of  
13 extended peaks -- and we have a number of  
14 those. So we looked at examples of all of  
15 these in the exercise that we ran.

16 Okay. This is a busy table -- and  
17 I apologize. I took some things out of it  
18 actually that you may find yourselves asking  
19 about later. But these are the results for  
20 the three-day average concentrations sampled  
21 at four-day intervals. That's -- everything  
22 was done in that manner.

1                   This group at the top is the group  
2 of thin, skinny peaks and the performance for  
3 them. That's the average performance for four  
4 of them if you look at the mean returns.

5 Middle group is the -- some middle medium  
6 broad peaks. Bottom are the broad peaks. And  
7 if you look at our mean returns we go from a  
8 most underestimating by 9 percent, 4 percent,  
9 and then down to less than 2 percent. We do  
10 much better with the broad peaks. If you look  
11 at the right-hand -- these two columns at the  
12 90 -- 99.9 -- we've estimated the maximum with  
13 virtually no error there.

14                   Okay. Next slide. That was the  
15 three-day averages sampled every four days.  
16 This is three-day averages sampled daily  
17 during the season, 14 days during the rest of  
18 the year. And you can see the performance has  
19 gotten even better as you might expect for  
20 this kind of sampling. We're looking at, you  
21 know, 2 to 3 percent underestimating in the  
22 least performing group, 1 percent in the

1 middle group, and less than 1 percent  
2 recaptured on mean returns here. The lowest  
3 returns are -- have a little more  
4 underestimation, but they're not too bad.

5 Up at the top again at least 50  
6 percent of the time in 50 percent of the runs  
7 we capture the maximum with no error, and  
8 sometimes even higher -- 60 percent or more.

9 The final graph here is the --  
10 looks at 90-days averages for sampling every  
11 seven days during the season, 14 days during  
12 the remainder of the year. This is pretty  
13 much the way the current AMP program is run  
14 now.

15 And if we look at the mean  
16 returns, again -- and in all of these the mean  
17 and the median were very similar. So you can  
18 call it either way if you want to look at  
19 middle values and say half the time we're  
20 higher than these, half the time we do less  
21 well, all of these are less than 1 percent of  
22 the true value here and we still capture the

1 maximum a large percentage of the time.

2 In terms of what we think these  
3 indicate, well, as expected an end point with  
4 a shorter duration will require more frequent  
5 sampling than one with a longer duration to  
6 capture corresponding monitoring values with  
7 similar accuracy.

8 We think it also shows that the  
9 current sampling scheme of weekly and biweekly  
10 monitoring appears to perform adequately for  
11 estimating 90-day averages with reasonable to  
12 good accuracy.

13 Seasonally targeted sampling  
14 strategies generally seem to perform better  
15 than allocating samples equally throughout the  
16 year. Sampling strategies appear to perform  
17 differently according to the shape of the  
18 chemograph, and because of this it might be  
19 useful -- may not be practical. We're  
20 considering it might be useful to examine the  
21 shape properties of annual profiles and the  
22 subset of systems with the highest peaks over

1 the years -- across the years.

2 And here we're looking at -- I  
3 think Nelson might have shown this yesterday.  
4 This table looks at these individual peaks,  
5 not averages, above arbitrary cutoffs of 12  
6 parts per billion, 20, 30 parts per billion.  
7 To the right are the CWSes where these peaks  
8 were found -- 12, 20, 30. And, of course,  
9 these 30 and 20 are nested in the systems that  
10 are over 12. And as -- of course, as we go  
11 from lower to higher concentration we see  
12 fewer systems involved.

13 We also have seen that across the  
14 years many of these systems are the same; they  
15 repeat. There are some different ones each  
16 year, but there are some that are consistently  
17 among the higher ones each -- from year to  
18 year.

19 The other thing to point out is  
20 that sample sizes here on the left -- they're  
21 in the thousands year by year. Across year  
22 they're in the tens of thousands. But when we

1 get to the individual system where we need to  
2 do our risk assessments, it's system by system  
3 year by year. What we're dealing with terms  
4 of sample sizes here are 30 to 35 samples.  
5 And that's I think something to keep in mind.

6 So, as a result, what we're asking  
7 the Agency for certainly is feedback on  
8 looking at the population of systems from year  
9 to year. Can we do something with this  
10 exercise we've just done? Is there anything  
11 practical to do, and especially logistically?

12 But, frankly, our biggest concern  
13 in terms of doing our assessments is on the  
14 individual system level where we need to look  
15 at missing values that result from less than  
16 daily sampling.

17 So, by way of summary, results of  
18 this preliminary exercise agree with Crawford  
19 and others in pointing to smart sampling  
20 strategies that can target both spatial and  
21 temporal patterns among the CWSes. We think  
22 that more intense seasonal sampling among

1 perhaps some of the higher concentration  
2 systems in vulnerable areas might be a good  
3 allocation of sampling resources and we'll be  
4 seeking your feedback on that.

5 And Mike now will be talking about  
6 a modeling approach to all of this if you  
7 have -- after your questions.

8 SESSION CHAIR PORTIER: Questions?  
9 Dr. Young?

10 DR. YOUNG: We saw each other up  
11 in the hall, so I'll start kind of where I  
12 left off. You know the probability of hitting  
13 a peak is almost zero so -- as you go through  
14 here. So you -- as you say, everything is as  
15 you'd expect it. You're always  
16 underestimating that maximum value. But there  
17 are a whole host of literature on like extreme  
18 value theory. Have you -- is there a reason  
19 why you guys don't want to go that way?

20 MS. FRANKENBERRY: No. I think we  
21 just haven't gotten to it. But I think that  
22 what we did see -- and this is that -- while

1 we did not underestimate it on all of them the  
2 highest runs did catch it. And they caught it  
3 in percentages that you might expect. But  
4 that's the next step. And that's a good  
5 suggestion we're waiting to hear about.

6 MR. THURMAN: And, Dr. Young,  
7 if -- in the report and such, if you could  
8 provide us -- recommend some of those  
9 literature we'd be happy to look at them.

10 DR. YOUNG: I just was -- you  
11 know, just for information, I was wondering if  
12 you guys had already looked at it and there  
13 was a reason you were throwing it aside.

14 MS. FRANKENBERRY: No. This is  
15 very preliminary --

16 DR. YOUNG: Okay.

17 MS. FRANKENBERRY: -- and it's  
18 mostly descriptive statistics as you see.

19 DR. YOUNG: Okay. Thanks.

20 SESSION CHAIR PORTIER: Dr. Lee?

21 DR. LEE: One minor concern on  
22 what you did is, in developing your, quote,

1 true data sets you took the actual  
2 observations and then interpolated them. If  
3 you have a seven-day average -- you only have  
4 observations every seven days on the water  
5 sources that have very sharp peaks, like  
6 number 4 that you presented and number 22 on  
7 the white paper, you may be missing the actual  
8 peak. And then the analysis you're doing --

9 MS. FRANKENBERRY: To begin  
10 with --

11 DR. LEE: To begin with your  
12 actual data may be missing the peak and  
13 then -- so then this sort of analysis may be  
14 further underestimating the actual truth --

15 MS. FRANKENBERRY: No. We  
16 realized --

17 DR. LEE: -- and that might be a  
18 concern.

19 MS. FRANKENBERRY: -- that and this  
20 was the best we could do in this kind of  
21 thing.

22 SESSION CHAIR PORTIER: Yes, Dr.

1 Gilliom?

2 DR. GILLIOM: Well, I concur with  
3 that last point, which it sounds like you guys  
4 are already realizing that. But it could  
5 have -- it's kind of the known/unknown problem  
6 that -- was it Rumsfeld brought up. But  
7 it's -- it's one -- it can really bias what  
8 you end up with.

9 The other -- I guess a part of --  
10 kind of a question more than anything is the  
11 implication of the range of time frames you  
12 guys are investigating is that on your  
13 radar -- and I think the implication of what  
14 you want to have us on the radar for giving  
15 you comment is that it's possible their very  
16 short-term estimates should be within what  
17 we're looking at.

18 So this may be a simple point, but  
19 the implication is is it's possible that the  
20 biological arguments are going to say short  
21 term closure is important and we may need to  
22 include in our design a way to pick up a daily

1 or one-week maximum type of thing. So that's  
2 important for us to know.

3 MR. THURMAN: And that's exactly  
4 why we're here.

5 DR. GILLIOM: Yes. Okay. And  
6 then I guess related to that -- actually, you  
7 know, I think -- I've got a couple of  
8 questions related that I think are better to  
9 come after we hear the stochastic. So I'll  
10 defer and pass it on.

11 DR. COUPE: Richard Coupe. I just  
12 wondered if the way the data are presented  
13 here with the sharp peaks, medium peaks kind  
14 of organizes itself along basin size or  
15 intensity of agriculture within the basin.

16 MS. FRANKENBERRY: Along what?  
17 I'm sorry.

18 DR COUPE: Along the lines of --  
19 so are these organized -- do they fall into  
20 basin size, so sharper peaks, smaller basins,  
21 or more intense --

22 MS. FRANKENBERRY: Yes. I think

1 Crawford found that and we didn't go on to  
2 look at that. But I'm sure that probably is  
3 the case.

4 DR. COUPE: Yes. And his data you  
5 looked at you saw that you could get better  
6 statistics on the larger basins because they  
7 had slower changing.

8 MS. FRANKENBERRY: Right.

9 MR. THURMAN: This is Nelson  
10 Thurman. I just want to add, you know, as  
11 we've done that analysis and found the trends  
12 based on that I think there are some  
13 general -- not just basin size but reservoir  
14 versus stream intake. So I think those are  
15 things we're looking at as ways of grouping  
16 them.

17 DR. COUPE: Sure. I mean, there's  
18 an awful lot to become interested in that.  
19 And also in Crawford's day, you know, although  
20 he went from different sizes they all had the  
21 same percentage agriculture. In general  
22 that's not true the larger the basin the less

1 agriculture you have. So you won't have the  
2 same kind of distribution as you might have  
3 with a smaller basin. Thank you.

4 SESSION CHAIR PORTIER: This is  
5 Ken Portier. It's clear -- I just wanted to  
6 clarify that it's clear that you feel like you  
7 have enough information to be able to actually  
8 stratify these -- the CWSES based on expected  
9 profile or the variability of the profile  
10 which you didn't take into account in the  
11 simulation yet. Right?

12 But there is that feeling that you  
13 might be able to say these are very variable,  
14 these are ones that have one peak a year and  
15 it's very consistent. We don't know when that  
16 peak's going to occur. That's going to depend  
17 on climate and agricultural practice. But we  
18 usually expect one versus this one that could  
19 have two or three or some years it's -- right?  
20 So there's the opportunity for differential  
21 sampling -- clearly differential sampling  
22 there.

1 Any additional questions? Dr.  
2 Krishnan?

3 DR. KRISHNAN: I just wonder if  
4 you had calculated the areas under the curve.  
5 Or like, you know, I see the rolling averages  
6 doing a particular period, but have you done  
7 area-under-the-curve calculations even -- the  
8 same one applies to the presentation of  
9 yesterday; you know, taking the points,  
10 calculating the area under the curve as well  
11 as the interpolated or the modeled ones,  
12 because the error on the basis of the area  
13 under the curve may not be the same as what we  
14 were talking about here.

15 And eventually AUC could also be  
16 the more relevant one depending on the -- you  
17 know, how we're going to proceed further.

18 MR. THURMAN: This is Nelson  
19 Thurman. I just wanted to add on that, I  
20 think that's something we've considered, but  
21 I think this is also going to be where the  
22 toxicologists have to come into play with the

1 exposure folks to answer the questions, and an  
2 area under the curve type exposure equivalent.  
3 I mean, can we do it in that regard? And I  
4 think that's one of the reasons why we've got  
5 a diverse group here.

6 SESSION CHAIR PORTIER: Dr.  
7 Heeringa?

8 CHAIR HEERINGA: I'd like just to  
9 second that point. I think that's something  
10 that I struggled with a little bit yesterday  
11 afternoon, and I think it's going to be an  
12 issue. Clearly, if we're down to daily  
13 averages or even three-day averages, it may  
14 not make that much of a difference. But if  
15 you go out to longer periods that profile --  
16 that profile, which again, area under the  
17 curve may not even capture the profile because  
18 you could have several profiles that generate  
19 the same integral.

20 But I think that's something for  
21 us to keep in mind. And is it really acute  
22 exposures? Is it sort of medium-term semi-

1 acute exposures? Or is it longer term -- 90  
2 day -- maybe even 90 days isn't chronic, but  
3 it's more exemplary of a long-term exposure  
4 through the water system. So I think that's  
5 important for us to keep in mind over the next  
6 two days.

7 SESSION CHAIR PORTIER: Any  
8 additional questions?

9 (No response.)

10 SESSION CHAIR PORTIER: Doesn't  
11 look like it. We can move on to the next  
12 presentation.

13 Okay. Dr. Akana?

14 DR. AKANA: I just have a minor  
15 question. In my mind what I imagine visually  
16 is you have a map of the United States. And  
17 on it we saw the blue map with the blue dots.  
18 Okay.

19 If you take that map -- okay --  
20 and overlay it on the map with rainfall and on  
21 top of that another map with basin, reservoir  
22 size, and running water, can you factor an

1 algorithm through 3D -- through the 3D map?

2 MR. THURMAN: Actually, the blue  
3 you saw took into account use, rainfall,  
4 watershed size -- it took into account a  
5 number of those factors which is how we got to  
6 that map in the first place. So, yes, it can  
7 be done.

8 DR. AKANA: So you have a massive  
9 algorithm that just percolates everything  
10 through.

11 MR. THURMAN: It was a regression-  
12 based analysis, but it did take into account  
13 the factors that on a national scale were  
14 driving exposures. What we've learned in the  
15 separate monitoring study I mentioned, the  
16 ecological exposure monitoring study, is that  
17 there are also localized factors that start  
18 helping to explain the differences we're  
19 seeing in exposures even within that most  
20 vulnerable area. So those are things that  
21 we're looking at and exploring.

22 Separately from this but will tie

1 into this in terms of how can we zoom in maybe  
2 in a corn belt scale and take into account  
3 those additional local factors.

4 SESSION CHAIR PORTIER: Susan, the  
5 panel looked at that. Was it October or  
6 December last year? We went through a lot of  
7 that on the ecological one. If you can look  
8 at the SAP minutes on that you'll see that  
9 it -- actually it's another level above what  
10 you were talking about that they've actually  
11 done.

12 MR. THURMAN: It was actually May  
13 of last year.

14 SESSION CHAIR PORTIER: Was it  
15 May?

16 MR. THURMAN: So it's been almost  
17 a year.

18 SESSION CHAIR PORTIER: Time  
19 flies. It seems like I was here yesterday.

20 MR. MESSNER: My name's Michael  
21 Messner. I'm a statistician in the Office of  
22 Groundwater and Drinking Water. And I'm going

1 to speak about one use of a -- of artificial  
2 neural network modeling. I'm going to  
3 describe the mathematical formula of this  
4 particular kind of artificial neural network  
5 model. Then I'm going to show how it can be  
6 fit to some atrazine occurrence data.

7 Then I'm going to show how this  
8 model can be used to simulate different -- not  
9 just different patterns but different levels  
10 of atrazine occurrence to assess the  
11 performance of some strategies -- in other  
12 words, combinations of monitoring plans and  
13 decisions based on the monitoring data.

14 Finally, I'll provide a table with some pros  
15 and cons of the artificial neural network  
16 modeling.

17 My presentation's going to differ  
18 from Mary's in two ways. One is the kind of  
19 model that I'm using -- the neural network  
20 model. The other way though is the way the  
21 model's used to assess performance. And I'm  
22 kind of wishing I had a pros and cons table on

1 this. I think it's maybe something you're  
2 going to be struggling with.

3 And that is where Mary described  
4 how the use of statistics and the probability  
5 that a statistic would capture a true  
6 parameter value -- a true percentile -- my  
7 focus is going to be on the decision making  
8 using the data to decide that we have a  
9 positive or a negative -- sort of like do we  
10 put a star on one of those bar charts you  
11 looked at yesterday. So my focus is the  
12 assessing the probabilities of false positives  
13 and false negative. So that's a different way  
14 of looking at performance.

15 This is one flavor of artificial  
16 neural network model. The ugly looking  
17 equation here at the top describes a moving  
18 average of log concentration values. The  
19 first term here on the right,  $b_0$ , is an  
20 intercept that sets the baseline occurrence --  
21 that is, before any of the other fractions  
22 here begin to take effect.

1           Each fraction is called a node.  
2           And a node can describe either an increase or  
3           a decrease in the atrazine concentration. So  
4           if you take the first fraction here and let it  
5           describe an increase and then later on a  
6           second fraction describes a decrease, together  
7           they describe a peak in occurrence. So this  
8           particular formula with four of these  
9           fractions or nodes can very easily describe a  
10          double peak during a source water's year of  
11          atrazine occurrence.

12                 So with -- if one can understand  
13          what these different parameter values mean,  
14          one can construct a formula here that will  
15          mimic atrazine occurrence. And then with  
16          particular values for these 12 parameters here  
17          and also with the precision parameter that  
18          describes how the measured values can depart  
19          from the moving average. We can calculate the  
20          log likelihood. I guess you could think of it  
21          either as the likelihood of the data given the  
22          parameters or the likelihood of the parameters

1 given the data.

2 But with that in hand, there are  
3 number of programs -- a number of algorithms  
4 one could use then to optimize that -- to  
5 maximize the log likelihood and find the best  
6 fitting parameter values.

7 All of these routines requires  
8 though that you first have a decent initial  
9 value. So this just shows how I went about  
10 finding initial values for atrazine data from  
11 the Maumee River in 1998. I think this -- was  
12 this an ecological data set that you provided?  
13 Heidelberg? Ambient water. Okay.

14 There are a lot of daily  
15 measurement values here in the middle part of  
16 the year. These out here I think are every  
17 two weeks or so.

18 So the way I went about fitting  
19 this was first to say, okay, I'm going to let  
20 the intercept -- the  $b_0$  term -- be this value  
21 here. And then I wanted to have an increase  
22 occur at this time of the year. I wanted the

1 increase to be just so big and so fast that it  
2 sort of fit the data. I'm just doing this  
3 using my eyeball. Okay? And to my eye that  
4 looks like an awfully good fit.

5 Next I attacked the parameters in  
6 the second node and adjusted those until they  
7 kind of fit this downturn here. Then I added  
8 the parameters for the third node so that I  
9 had this increase occurring at that time of  
10 the year. And finally the fourth node  
11 described this decrease bringing the atrazine  
12 level back down. Now, that's not perfect.  
13 That's just an eyeball kind of fit to the data  
14 which gave me some initial values for those  
15 algorithms to do their thing.

16 This is the result. This is a  
17 maximum likelihood model. It's actually a  
18 three-node model rather than a four-node  
19 model. And you can see that it does a very,  
20 very nice job of following the data.

21 The way the three-node model  
22 works -- it's a little harder to understand

1 the parameters in the three-node model. The  
2 first node causes this increase here. The  
3 third node causes this increase here. And the  
4 second node actually causes the decrease that  
5 you see spanning the time from here to about  
6 here. So there's just one node that's sort of  
7 describing both of those drops in atrazine  
8 concentration.

9 I like this model because it  
10 provided -- in terms of log likelihood it  
11 provided this sort of the same quality of fit  
12 as the four-node model with fewer parameters.  
13 And the appearance is a little nicer. There  
14 was something funny going on in here with the  
15 four-node model. So this was a nice maximum  
16 likelihood model.

17 How do I go backwards? Okay. One  
18 thing a little bit odd here is there are  
19 couple of periods of time where there's a  
20 string of four or five values -- maybe more  
21 than four or five -- in a row that appear  
22 either above or below the curve. And I was

1 concerned that maybe that's a little more than  
2 would occur by chance if each day's value was  
3 sort of a -- had random error about the curve.

4           So I looked at the residuals and I  
5 also looked at something called an  
6 autocorrelation function. This figure here  
7 plots the autocorrelation function. This is  
8 called a correlogram, and you can there's a  
9 sort of a cosine -- dampened cosine shape to  
10 this that is characteristic of what's known as  
11 an AR2 model. So I wanted to build in this  
12 kind of autocorrelation.

13           This isn't the way one day's  
14 concentration is dependent on the previous  
15 day's so much as it is the way one day's  
16 departure from expected is related to the  
17 previous day's departure from expected.

18           So if you think of that artificial  
19 neural network, the smooth curve, as  
20 describing the expected log concentrations on  
21 different days, what I'm talking about here  
22 are the departures from that curve -- that

1       there's still some autocorrelation going on  
2       from day to day that you can't explain with --  
3       you know, as ugly as that model is it still  
4       doesn't quite account for everything that we  
5       might want to account for.

6                So I found that of all the AR  
7       models, AR2 did turn out to be the best  
8       fitting. These two parameters here tell how  
9       a day's departure from the expected value --  
10      that is, from this equation -- are related to  
11      the previous day and two days previous. So  
12      today's departure would be -- 38 percent of it  
13      would be -- or .38 times yesterday's departure  
14      plus about .2 times two days' ago departure  
15      would be added to some random error for today  
16      to produce today's departure from expected.  
17      So with those two additional parameters we can  
18      explain this additional autocorrelation  
19      feature of the data.

20               Okay. So given those model  
21      parameters we can drive some summary  
22      statistics. We can calculate the mean, the

1 median, we can calculate other percentiles of  
2 interest if those are things that you care  
3 about.

4 But what if we're concerned about  
5 making decision errors when the occurrence is  
6 either much higher or much lower than is given  
7 by that particular model? Now, this is -- I'm  
8 just going to pause right here. One thing we  
9 could do with the parameter values is we could  
10 estimate the concentrations on days where we  
11 don't have data -- we could do things like  
12 that. We could provide credible intervals,  
13 say, for those concentrations. We could  
14 provide credible intervals for these things,  
15 the mean concentration, the median  
16 concentration.

17 But the interest here -- I'm not  
18 going to go down that path. Rather, I'm going  
19 to be talking about how to use this particular  
20 model to study how different monitoring  
21 strategies behave. So if we just accept that  
22 this model is true and that we care about

1 occurrence when it behaves this way, we're  
2 going -- I'm going to use this model to  
3 evaluate how different monitoring strategies  
4 behave. Okay?

5 I sense the statisticians in the  
6 group might want to see uncertainty intervals  
7 about the parameter estimates -- Markov chain  
8 Monte Carlo samples. But, I'm sorry, but  
9 you're not going to see those things.

10 If we take the model with those  
11 parameter values and simply add a constant to  
12 that intercept term we preserve the shape of  
13 the occurrence pattern and we just -- we  
14 simply are changing the scale of it.

15 If the constant that we add is  
16 negative then the result is a lower overall  
17 level of occurrence. If  $K$  is positive then  
18 adding it will increase all of the  
19 concentration values. The mean, the median,  
20 and other percentiles of interest are all  
21 going to change by the same factor.

22 The error structure remains the

1 same. The shape of the occurrence  
2 distribution also remains the same. The only  
3 thing that we're doing is changing the overall  
4 occurrence level.

5 This next figure shows two  
6 simulations, both with the same random number  
7 seed but with different intercept values. And  
8 you can see they're identical except for the  
9 scaling of the vertical axis. I've drawn a  
10 red line here at the 99th percentile given  
11 this model. And in one case here on the right  
12 the 99th percentile is 10, and on the left  
13 it's 25. So there's a factor of two and a  
14 half difference. Each point here on the left  
15 is two and a half times as high as each point  
16 on the right.

17 So if decision makers were  
18 concerned about making a negative decision,  
19 say, failing to take action given this kind of  
20 occurrence pattern, we could simulate with  
21 this model -- simulate many years of  
22 occurrence to estimate the false negative

1 rate. Similarly, if the decision makers  
2 consider this to be a low occurrence pattern  
3 and level we could simulate a year of  
4 occurrence like this many, many times to  
5 estimate the probability of the false  
6 positive.

7 We could do this, say, 10,000  
8 times if we wanted to get good estimates of  
9 those error rates. And we could repeat this  
10 using different levels of our trigger or our  
11 critical value to see how the probabilities of  
12 those decision errors depend on the decision  
13 rule.

14 This figure shows how the  
15 probabilities of false positives and false  
16 negatives play against each other as the  
17 critical value for determining a positive is  
18 increased from zero here to some high value.  
19 If we set the critical value very high this  
20 could be like a -- this value could be a limit  
21 for, say, the maximum measured value or the  
22 sample mean or the second highest -- whatever

1 your test statistic is.

2 If it's high -- if your critical  
3 value is high you'll be controlling the false  
4 positive rate fairly well, but the price  
5 you'll pay is a higher false negative error  
6 rate. If you lower the critical value you'll  
7 find that you increase the false positive rate  
8 while decreasing the false negative rate.

9 Now, this curve sort of shows  
10 there's a sweet spot in the middle around  
11 about 10 percent. If you could tolerate 10  
12 percent false positive and false negative  
13 errors you might like a critical value here in  
14 the middle. I don't want to suggest that  
15 that's where the answer should be. It may be  
16 that when you think about consequences of  
17 decision errors you may be much more concerned  
18 with one kind of an error than another, and  
19 that -- what appears to be a sweet spot in the  
20 middle might not be acceptable.

21 But my message here is that we can  
22 use these kinds of models and these kinds of

1 simulations to get an understanding of how a  
2 strategy in a decision rule can perform so  
3 that a strategy can be selected with open  
4 eyes -- with an understanding of what these  
5 error probabilities are.

6           So what often happens is that we  
7 can't find a spot where we can craft a  
8 decision rule that satisfies both constraints  
9 for false positives and false negatives. This  
10 almost always happens in my experience. We  
11 find that decision makers can't tolerate the  
12 idea of errors of any sort and they'll  
13 initially want very small probabilities of  
14 false positives and false negatives. And we  
15 find that we can't achieve that without, say,  
16 millions and millions of samples.

17           And so some back and forth is  
18 required asking decision makers, well, what  
19 can you really live with and what can really  
20 be afforded in terms of sampling. Maybe we  
21 can afford hundreds of samples or maybe we can  
22 afford to challenge thousands of rats in a

1 dose response study. But it's normal to have  
2 this back and forth to arrive at a design that  
3 one can live with.

4 So, in summary, artificial neural  
5 network models are one kind of artificial  
6 neural network model, but it's showing you it  
7 can be used -- I'm sure there are others.  
8 There are also other time series models that  
9 can be used to characterize these occurrence  
10 patterns and simulate occurrence patterns that  
11 are of concern to decision makers -- simulate  
12 low occurrence patterns, low levels for which  
13 there's concern for the false positive, also  
14 simulate high levels where there's concern for  
15 the false negative.

16 We can simulate high variability  
17 patterns and low variability patterns --  
18 simulate levels and patterns that are of  
19 concern to the decision makers and use this to  
20 assess candidate monitoring strategies for  
21 their ability to satisfy the requirements for  
22 false positive and false negative error rates.

1                   Here I've listed some of the  
2                   advantages and disadvantages of the artificial  
3                   neural network models. At the top on  
4                   disadvantage I listed the complexities. It  
5                   can be difficult to understand the parameters.  
6                   A key advantage is that they can be very  
7                   flexible and they seem to do a nice job of  
8                   representing realistic occurrence patterns for  
9                   atrazine.

10                   I've left some blanks here. You  
11                   all can read these yourselves. I'm sure you  
12                   have -- you can think of additional pros and  
13                   cons for this type of modeling. And I'll just  
14                   stop there and leave those blanks and  
15                   encourage you to add to those lists.

16                   SESSION CHAIR PORTIER: So, Dr.  
17                   Lee, first question.

18                   DR. LEE: I think this was a very  
19                   nice use of neural networks. Let me start  
20                   with a technical question. Did you look at  
21                   the autocorrelation plot for the four-node  
22                   network that you fit?

1 DR. MESSNER: I don't think I did.

2 DR. LEE: Because I suspect there  
3 will be much less autocorrelation there --  
4 possibly none or close enough to none. The  
5 four-node one -- I think this is the first  
6 time I've had to try to convince someone to  
7 use more nodes. Usually it's going the other  
8 direction, trying to convince someone they're  
9 using way too many nodes and it's not going to  
10 predict well.

11 Particularly in this case where  
12 you're trying to look for potentially a peak  
13 or a very short-term average. The three-node  
14 model is smoothing a lot more than the four-  
15 node model. And I suspect you'll get better  
16 results if you look at the four-node model in  
17 this case rather than the three-node model.  
18 It's going to fit much more tightly.

19 And one of the things is that sort  
20 of the shape of a peak that you can  
21 estimate -- the more nodes you use the more  
22 variability you can get in different types of

1 shape of peaks you can fit. And so by  
2 restricting yourself to three nodes you're  
3 forcing a more particular shape of peak that  
4 doesn't quite fit the data as much. And for  
5 sort of a longer term average that's fine, but  
6 if you're looking at a very short-term average  
7 or a peak that's going to make a bigger  
8 difference. And so I suspect you can get even  
9 better results here with a four-node network.  
10 And I can put some additional comments in the  
11 minutes about model selection there.

12 DR. MESSNER: In the paper I  
13 describe another data set that I modeled using  
14 a two-node model. And interestingly I found  
15 that an AR1 model fit quite well for that even  
16 though it has fewer nodes than this.

17 SESSION CHAIR PORTIER: Dr.  
18 Heeringa?

19 CHAIR HEERINGA: Thank you for  
20 that presentation. One question for you and  
21 then one for Nelson. In these models is there  
22 any way to incorporate prior -- I know it's in

1 your notes -- prior year information? In  
2 other words, if we assume that these community  
3 water systems had a response profile that was  
4 dependent on intake and volume of water and  
5 sources of water I would expect if peaks occur  
6 they would subside with some type of profile  
7 that may be unique to that water system. If  
8 you had data like that how would you factor  
9 that into this model?

10 DR. MESSNER: What I'd really like  
11 to have first is an expert that I could sort  
12 of interview. I would wonder is it -- do you  
13 really expect only one peak? Would you expect  
14 two peaks? How many peaks would you expect in  
15 a year? I imagine that would depend on things  
16 like rainfall, and I think it would be very  
17 difficult to interview an expert and extract  
18 from that expert prior knowledge about these  
19 things.

20 But I suppose you could do it.  
21 And if you had many years of data also for  
22 that particular source water you could perhaps

1 roll all that together. This sort of speaks  
2 to my third disadvantage here, year-to-year  
3 variability. That's a lot of parameters, and  
4 the hierarchal structure -- it would be really  
5 fun to try, but I think it would be very  
6 difficult. What's your feeling on that, Dr.  
7 Lee?

8 DR. LEE: Neural networks are  
9 really not the best model to try to  
10 incorporate the year-to-year variability. It  
11 probably could be done, but it would be really  
12 difficult. I think you'd probably find better  
13 success with like the kriging-type approach  
14 that's also discussed in there or some other  
15 sorts of models.

16 CHAIR HEERINGA: Second question  
17 was for Nelson. I -- what data do we have  
18 available? We know for a select set of  
19 community water systems that we have the  
20 registrant's data that's been provided as  
21 being provided for the 90-day average. And  
22 are there other sources in terms of the

1 national water quality programs that produce  
2 periodic or annualized estimates of atrazine  
3 concentration for community water systems,  
4 say, in atrazine use areas? What data could  
5 we expect to have across the various sources?

6 MR. THURMAN: Well, NAWQA hasn't  
7 really focused on community water systems.  
8 They focus on ambient waters, some of which  
9 are similar to what you would see in community  
10 water systems. They focused on flowing water.  
11 So for streams they have places where they  
12 have monitored years to year-to-year that you  
13 can start to get that.

14 This particular data set that we  
15 have now on the community water systems, which  
16 is a range from 130 to 150--some systems --  
17 several of those we've got probably at least  
18 five years of data that we can start looking  
19 at.

20 Now, some of those systems have  
21 been monitored historically back years longer  
22 before that that we could also take a look at.

1 Some of it would be going back to -- you know,  
2 part of the challenge is -- we've also in some  
3 of these areas we now have the ability to  
4 getting at land use patterns that change year  
5 to year over the watersheds, probably more in  
6 some of the more recent years than in previous  
7 years. So we can start taking a look at that.

8 The one data set that comes to  
9 mind that has a whole lot of years of history  
10 is the Heidelberg University data set. That  
11 is something that we're also going to take a  
12 look at.

13 SESSION CHAIR PORTIER: I've got  
14 the next question -- Ken Portier. Can you  
15 slide back to your best-fitting ANN model  
16 picture? I just had a couple of questions on  
17 the best fit. So if we're interested in the  
18 maximum annual concentration -- right? -- your  
19 model underestimates that. And that was one  
20 of the reasons you do a -- what is it? --  
21 k0 -- or b0 shift. If you shift it up you  
22 could do a better job -- that one -- do a

1 better job of estimating that overall maximum.  
2 Right?

3 DR. MESSNER: I don't think I'd  
4 put it that way. The reason I was adjusting  
5 that intercept was to be able to simulate  
6 occurrence levels that are of concern to the  
7 decision makers, not to provide a better  
8 estimate of the maximum.

9 With -- so if we think of a year  
10 as being -- say, this data set is being -- if  
11 we could measure every day of the year we  
12 would have 365 measurements -- some of them  
13 may be missing here -- we could use this model  
14 to estimate some missing values -- some  
15 concentrations on days that weren't measured.  
16 So that's something that could be done  
17 pretty -- it would be pretty straightforward  
18 using this model, but it wasn't what I was  
19 interested in.

20 SESSION CHAIR PORTIER: I guess I  
21 see a lot of uses for the model. If you're  
22 moving b0 up and down what does that do to the

1 lowest level? Does that shift the whole  
2 profile down?

3 DR. MESSNER: Yes. Everything is  
4 increased by the same factor.

5 SESSION CHAIR PORTIER: Because  
6 your model fits well where there's stuff  
7 happening. But if you look on both tails at  
8 the BDL levels you're not fitting very well at  
9 all -- right? -- because you don't put very  
10 much weight on the winter -- I guess it would  
11 be the winter time periods -- right? --  
12 where -- I mean, if you look at this point  
13 over here you've got a whole bunch of -- you  
14 know, three or four levels of zero --  
15 right? -- close to -- below detection limit or  
16 near detection limit data that the model  
17 doesn't fit very well.

18 DR. MESSNER: Right. Of course,  
19 we're not terribly concerned about how --

20 SESSION CHAIR PORTIER: Concerned  
21 about those.

22 DR. MESSNER: -- high those values

1 might be. But the likelihoods actually are  
2 fairly decent for those sensitized --

3 SESSION CHAIR PORTIER: And it's on  
4 a low scale and they're very small. The other  
5 thing is your 99th percentile line -- does  
6 that take into account these BDL values here?

7 DR. MESSNER: Yes. When I use  
8 this model to estimate a 99th percentile or a  
9 95th percentile I'm --

10 SESSION CHAIR PORTIER:  
11 Integrating?

12 DR. MESSNER: -- integrating and  
13 summing over the 365 days of the year. And so  
14 it's not the percentile for this particular  
15 year, it's actually a percentile for the  
16 model. So if I could simulate 10,000 years  
17 the percentile for that simulation, let's say,  
18 would be very, very, very, very close to what  
19 I get by integrating and summing across the  
20 days of the year for the model.

21 SESSION CHAIR PORTIER: You talked  
22 about credible intervals. Is it possible with

1 this model to establish a credible interval of  
2 time above a certain threshold? So if I were  
3 to pick this curve and say I want to know the  
4 time above zero -- log -- whatever -- on this  
5 scale --

6 DR. MESSNER: Right. So --

7 SESSION CHAIR PORTIER: -- can you  
8 estimate that time period -- how many weeks,  
9 how many days --

10 DR. MESSNER: So, if like you were  
11 to tell me that we want to know what fraction  
12 of the time the levels above ten parts per  
13 billion?

14 SESSION CHAIR PORTIER: Right.

15 DR. MESSNER: Yes. I could tell  
16 you what percent of the time with this model  
17 I'd expect the concentration to be above that  
18 level. And, again, we're talking about  
19 percent of the days.

20 SESSION CHAIR PORTIER: Yes.

21 Because -- I mean, one of the things we heard  
22 yesterday is they may not be the maximum

1 concentration. They may be how many days a  
2 person is exposed above a certain threshold.  
3 So if I'm drinking the water and I'm drinking  
4 it for four weeks at above 10 parts per  
5 mission that may cause the health effect. And  
6 so I'd want to know for this site what's the  
7 probability it's going to be more than ten  
8 weeks or more than five weeks. That's turning  
9 the model backwards. It's the inverse --

10 DR. MESSNER: Yes. Estimating the  
11 percent of days above a level is very easy to  
12 do. What's difficult to do and requires  
13 simulation is estimating how many years --  
14 during how many years one would have, say,  
15 consecutive days above a level. That's --

16 SESSION CHAIR PORTIER: But it can  
17 be done.

18 DR. MESSNER: -- something that can  
19 be done --

20 SESSION CHAIR PORTIER: It may be  
21 difficult --

22 DR. MESSNER: -- but --

1                   SESSION CHAIR PORTIER: Yes.

2                   DR. MESSNER: -- you know, I sort  
3 of cringe at the thought of programming that.

4                   SESSION CHAIR PORTIER: Dr.  
5 Gilliom.

6                   DR. GILLIOM: As you've applied it  
7 for evaluating sample strategies the value of  
8 any of these interpolation models basically  
9 producing an estimate of the true population  
10 is -- it depends on how well it estimates  
11 truth basically.

12                   And when you have a really dense  
13 data set, like almost every day like the  
14 Heidelberg data, you're probably -- I mean,  
15 frankly, you're probably better off just  
16 connecting the dots because you've actually  
17 then included these maximums that we're  
18 worried about. You don't have to worry about  
19 smoothing distorting things or anything.

20                   And then, on the other hand, if  
21 you apply the same method to sparser data then  
22 you've got a severe problem with whether you

1 can replicate truth because you're missing so  
2 many true events. So you're kind of in a fix  
3 there.

4 So I think ironically for dense  
5 data sets you can use the method to get a  
6 pretty good quantitative tool for producing  
7 test data sets for evaluating sample  
8 strategies. And then, on the other hand, when  
9 you get to all the more normal circumstances  
10 we have it's got the problem of not being able  
11 to fill things in because it's not related to  
12 predictor variables that have connection to  
13 what's really going on in the field, like used  
14 patterns and precipitation events and all that  
15 which are what's really creating the extreme  
16 events.

17 So I guess what I'd like to see in  
18 the direction of thinking when we're looking  
19 at how to simulate reality for the purpose of  
20 these sampling experiments is to get an  
21 approach that takes into account the maximum  
22 we can about cause and effect variables that

1 actually simulate the type of distributions we  
2 expect in reality.

3 And I think that direction would  
4 give us a better foundation for defending how  
5 it is and give you more reality in what the  
6 concentrations are and incorporate error  
7 better and yield a better sampling design.

8 SESSION CHAIR PORTIER: This is Ken  
9 Portier. Kind of like filling in the blanks  
10 with knowledge rather than just kind of  
11 interpolating or smoothing is really what  
12 you're talking about. Linda -- Dr. Young?

13 DR. YOUNG: Yes. Just kind of a  
14 follow up on the whole discussion I think  
15 because this what's bothering -- this is --  
16 what's been bothering me is kind of in the  
17 same realm. How many -- you're heavily  
18 relying on getting a very dense data set to do  
19 this -- right? -- to really get a good fit for  
20 your ANN model. Right?

21 DR. MESSNER: I'll say yes. There  
22 are many parameters here and it takes a lot of

1 data to get good estimates when you have so  
2 many parameters. But, on the other hand,  
3 personally what I'm concerned with is trying  
4 to model something that causes concern for the  
5 decision maker -- something realistic such  
6 that if this were the true case -- if you  
7 really had a system that behaved like this  
8 you'd be concerned about either false  
9 positives or false negatives.

10 So I like it to be realistic, but  
11 I'm finding I don't care so terribly much  
12 about explaining a particular data set and  
13 making predictions for a particular stream.

14 DR. YOUNG: So the key seems to be  
15 to be able to get -- if that's the philosophy  
16 then to get a series of what seems to be a  
17 range of profiles that you might want to do.  
18 And then -- and if you do that then you  
19 have -- then I'm not sure the value of the  
20 model. I mean, once I begin to do that the  
21 connect the dots does seem to be a reasonable  
22 thing.

1                   So I -- so at one point I thought  
2                   you were going to try to do this for each  
3                   community water system. But you're not.  
4                   You're just going to look at a range of these  
5                   types of things. Right?

6                   DR. MESSNER: Perhaps.

7                   DR. YOUNG: Okay. I'm just trying  
8                   to get where you're coming from.

9                   SESSION CHAIR PORTIER: This is Ken  
10                  Portier. I was thinking the same thing as Dr.  
11                  Young was and realizing you have 13 plus three  
12                  parameters -- what is that? -- 16 parameters  
13                  and the average data set has 36 data points,  
14                  many of which are in the no-detect winter  
15                  range. Right? So you're down to almost a  
16                  data point per parameter.

17                  And you're trying to fit a two-  
18                  point autocorrelation structure, and you start  
19                  getting missing values and you just can't --  
20                  so the model, while nice mathematically -- we  
21                  love it, and it's pretty. When you've got a  
22                  lot of data, it's nice. When you have -- you

1 start getting missing data and low counts,  
2 you're starting to have faith rather than  
3 data.

4 Yes, Dr. Lee.

5 DR. LEE: If I could actually just  
6 respond to that briefly. Known networks have  
7 a particular structure such that the effective  
8 number of parameters tend to be smaller than  
9 the actual number of parameters. So you don't  
10 necessarily need quite the same multiplier of  
11 data points to parameters as you would in,  
12 say, a standard regression model.

13 And you can get fairly -- I mean,  
14 you wouldn't need, say, this dense a data set  
15 to get a fit like this. Just sort of  
16 eyeballing it, guessing -- certainly I think  
17 if you had a quarter as many data points, you  
18 could still get it pretty much the same fit.  
19 I don't know how the fit would change beyond  
20 that.

21 DR. YOUNG: But the point would be  
22 that you'd probably miss some of those peaks,

1 which is really what you want. So as soon as  
2 you start doing that, yes, the fit's good to  
3 what you saw, but you didn't see what you  
4 wanted to see.

5 SESSION CHAIR PORTIER: Well, I  
6 think the statisticians have had their fun  
7 here.

8 Mr. Thurman, we'll send it back to  
9 you for a summary.

10 MR. THURMAN: Okay. Actually, I  
11 was having fun too. All right. What I'm  
12 going to try to do is bring this back to --  
13 all right -- what are we going to do with this  
14 stuff. As Anna Lowit said yesterday, when the  
15 rubber hits the road how are we going to use  
16 this, so that when you folks are commenting on  
17 our questions you kind of know where we're  
18 coming from and where we're hoping to go on  
19 that.

20 Let's start with what we know and,  
21 hopefully, I can even fill in some of the  
22 holes or questions that maybe didn't answer as

1 well. Earlier -- we know pesticide  
2 concentrations in water varies both spatially  
3 and temporally. We're operating under the  
4 feeling that the variability you're going to  
5 see spatially and temporally outweigh the  
6 other variability you'll see in sampling and  
7 analytical.

8 And there may be -- I mean, I  
9 think in general we believe that's true. If  
10 there are more exceptions to that then,  
11 General, I'm sure the USGS folks who have a  
12 lot more experience in that are going to tell  
13 us that and we can take that into account.  
14 But that's where we're operating right now.

15 We have -- and particularly for  
16 those of you who have been on the SAP a year  
17 ago and then those two years before that,  
18 we've been doing a lot with the ecological  
19 exposure monitoring wrapping our minds around  
20 the spatial variability and how do we capture  
21 that and how do we use that to particularly  
22 focus on the areas where we think there's

1 going to be more exposure concerns.

2 For this particular drinking water  
3 assessment with atrazine we're zooming in on  
4 community water systems that happen to be in  
5 those areas that spatially are having a high  
6 exposure history. And so we're looking at the  
7 temporal pattern -- how do we get at the  
8 temporal pattern.

9 And, now, we know when you start  
10 looking at timing and frequency of sampling it  
11 has to take into account that temporal  
12 pattern. But it also needs to keep in mind  
13 what is our exposure duration of concern. We  
14 have a monitoring data set that for these  
15 community water systems that took weekly  
16 samples during the use season to characterize  
17 a 90-day exposure. And that's -- and we think  
18 that's been working pretty well for what we're  
19 doing.

20 If we end up with a shorter  
21 duration of exposure how well does that data  
22 work for us? How well can we use it? What --

1       how can we characterize the uncertainty we  
2       have in that -- and if we do it to the point  
3       where we don't have to have additional more  
4       frequent monitoring, or do we need to go to  
5       that approach. That's a question we're  
6       wrestling with in that regard.

7                    You heard in Mary Frankenberry's  
8       presentation that obviously shape of the  
9       exposure chemograph influences that. And we  
10      are looking at ways that can we bend the  
11      community water system based on whether it's  
12      a flowing water body or a reservoir, and even  
13      within that it's a -- you know, how big is the  
14      basin size, how big is the use -- how great is  
15      the use within that basin size. So we're  
16      going to be taking a look at that in ways  
17      that -- once again, it's helping us be smarter  
18      in where -- in how we're going to do.

19                   And the complexity of the approach  
20      is going to depend on the quality of the  
21      monitoring data. When I first started doing  
22      this work we were really criticized as you

1 guys are using deterministic models that  
2 aren't real that generate exposures that don't  
3 really happen. We did it for screening  
4 purposes.

5 I would argue that when you've got  
6 monitoring data that -- of any sample  
7 frequency and when you're trying to interpret  
8 that you're applying a model to interpret that  
9 monitoring data. And some of the models can  
10 be fairly simplistic; some of them are going  
11 to be more complex.

12 All of them are going to have some  
13 degree of wrongness in terms of estimating  
14 your exposure. To the extent that we can  
15 characterize the uncertainty in that that  
16 helps us when we're making our decisions on  
17 the assessment.

18 So you're going to see a question  
19 I have later is how simple is -- when it  
20 simple good enough. That's what we're taking  
21 a look at -- you know, when can we live with  
22 that and when do we need to go more complex.

1                   So here's what we plan to do. And  
2                   I think I want to emphasize a few things. And  
3                   Dr. Lee and others pointed this out.

4                   Whenever -- and particularly in the paper we  
5                   started looking at the community water systems  
6                   to start taking a look at how we might apply  
7                   this. And, once again, this wasn't the  
8                   drinking water exposure assessment itself.

9                   It's let's look at methods that we can use to  
10                  apply to interpret that exposure assessment.

11                  And so, you know, we're already  
12                  starting out with a data set that's weekly  
13                  sampling. And when I gave you my presentation  
14                  and I started saying, well, let's try -- I  
15                  want to try to illustrate what this means.  
16                  The first thing I did is I looked at that  
17                  weekly -- that data -- interpolated weekly  
18                  data set and said, All right, now if I show  
19                  you an example of weekly sampling then I've  
20                  got the same data set you have there.

21                  So I went back to use what we had  
22                  the monitoring on the ecological exposure data

1 set which is much more robust in sampling  
2 frequency to illustrate that point. We know  
3 that for the most part those are going to  
4 occur farther up in the watershed. We tend to  
5 expect higher concentrations from those  
6 particular sites than we're going to find in  
7 community water systems further downstream.  
8 But it still gives us an idea of how can we  
9 put together an approach that we can then  
10 apply to the community water systems.

11 So we're going to take a look at  
12 robust monitoring data sets. The Heidelberg  
13 University has a lot of intensive sampling in  
14 a number of streams in varying -- with varying  
15 basins that we'll be able to look at. We're  
16 going to be looking at several of the  
17 ecological exposure monitoring sites that had  
18 more intensive sampling. And the idea is to  
19 evaluate the approach that we will then apply  
20 to how well is the community water system data  
21 working.

22 We're going to take a look at

1 sampling these data sets at different  
2 intervals. We'll use anywhere from three,  
3 seven, 14, 30-day sampling. So some of the  
4 discussions you've had before is how well do  
5 some of these models perform when you have  
6 less frequent monitoring, when your chemograph  
7 shape from the monitoring data isn't as well  
8 defined. So we're going to be taking a look  
9 at that.

10 We're going to use -- then use as  
11 the approaches that we described in Section  
12 5.4 of our white paper we presented here any  
13 other things that you folks think maybe we  
14 need to take a look at in doing that  
15 evaluation. And we're going to see to use  
16 that to evaluate how well these different  
17 approaches estimate exposures between sampling  
18 points and generate exposures for varying  
19 rolling average periods.

20 Right now for atrazine we're  
21 working with a 90-day exposure period -- is  
22 our exposure period of concern. We may end up

1 looking at a shorter duration of exposure.  
2 Now we don't know yet -- this is part of what  
3 we'll be hearing in this SAP and probably  
4 continuing into September. If we have a much  
5 shorter duration how well can we use the  
6 existing weekly monitoring data. That's one  
7 of the things we're trying to evaluate out of  
8 that.

9 So when ultimately we come up with  
10 an exposure duration of concern we can say,  
11 all right, this is what we need to do to  
12 provide your exposure estimates on that with  
13 whatever confidence bounds we need to place on  
14 that.

15 And so our ultimate focus is on  
16 taking into account the spatial, temporal,  
17 and, in particular in this case, the temporal  
18 nature of the pesticide concentrations to  
19 answer those two questions you see at the  
20 bottom -- how frequently does sampling need to  
21 be in order to adequately characterize various  
22 exposure durations with a specified confidence

1 interval and how much can we derive from  
2 existing less frequent sampling.

3 We're applying this to the  
4 atrazine in community water system data. We  
5 think this type of question we wrestle with  
6 with other pesticides as well. And, to be  
7 honest with you, we wrestle with it not just  
8 for drinking water exposures but for  
9 ecological exposures. And so these are things  
10 that -- we're focusing on atrazine but have  
11 applications beyond atrazine. And so we're  
12 aware of that and we see the value of this not  
13 just for atrazine but going beyond.

14 We have four questions that you  
15 will be getting to later in the week. I tried  
16 to simplify these into two main issues for you  
17 to look at. Given the nature of the temporal  
18 patterns, in this case atrazine in surface  
19 water, but pesticide currents in general --  
20 how do we best develop the confidence bounds  
21 and exposure estimates for monitoring data of  
22 different sampling frequencies.

1                   Now, a converse of this would be  
2                   if you're designing a monitoring study to  
3                   provide exposure estimates with -- for certain  
4                   duration how frequently do you have to sample  
5                   to give a level of confidence. So that's  
6                   where a couple of our questions are coming  
7                   from on that.

8                   We presented approaches to you  
9                   that are common in literature. We've already  
10                  heard a couple of suggestions that we haven't  
11                  looked at yet and we may want to look at. And  
12                  so the questions we want you to -- as you look  
13                  at those approaches or any others what are the  
14                  advantages and disadvantages in -- for  
15                  estimating pesticide concentrations for either  
16                  short or moderate or long duration of  
17                  exposure.

18                  And it comes down to that  
19                  question. When is simple good enough and when  
20                  do we need to look at more complex methods?  
21                  And I think -- yes, you've heard enough of me.

22                  SESSION CHAIR PORTIER: Dr. Young?

1 DR. YOUNG: So you know in  
2 designing a study there's often this tradeoff  
3 in what we'd like and what we can actually do.  
4 Okay? So how much -- is there room for  
5 tradeoff in one day would be good but we can't  
6 really do that as well as what we would need  
7 to to actually talk about one-day maximum. So  
8 seven day -- is that part of this discussion  
9 or not? You understand my question?

10 MR. THURMAN: I think I do, but  
11 I'm going to respond to you. And if I'm wrong  
12 you can say, No, that's not what I meant. I  
13 think -- you know, for a lot of it we know  
14 we're not going to get sampling, for the most  
15 part, if it's intense enough to give you daily  
16 peak. And we know that you're going to need  
17 less frequent sampling.

18 And so I think there are tradeoffs  
19 there. And this is where to the extent that  
20 through an uncertainty analysis or through  
21 supplemental modeling can we at least get an  
22 idea of what that peak is given what we have?

1 I'm not sure if that's what you're talking  
2 about and I may be off --

3 DR. YOUNG: Yes. And so what if  
4 the answer's no? I mean, just what if. I'm  
5 not saying it will be, but what if it's no?  
6 Does -- is there room for discussion of  
7 broadening that to get -- so that at least  
8 you're getting what you say you're getting?

9 MR. THURMAN: And that becomes a  
10 conversation not just with us on the exposure  
11 end but the folks in the tox end and our risk  
12 managers as well. I mean, so I think  
13 that's --

14 DR. LOWIT: That's basically what  
15 I was going to add to this. I said from the  
16 beginning yesterday this is really a rubber  
17 meets the road analysis, and you're asking a  
18 rubber meets the road question of a reality.  
19 What is the real situation of daily sampling  
20 throughout the Midwest in every water system  
21 is not going to happen.

22 So the first question is: is what

1 Syngenta is doing right now enough if it --  
2 and what is the relevant confidence in that  
3 and uncertainty in that. If the degree of  
4 uncertainty is very high is there a way to get  
5 a handle on that and how will more frequent  
6 sampling improve that? The balance comes in  
7 with the hazard assessment piece, the risk  
8 managers, the cost -- all of that goes into  
9 the decision process.

10 So the degree to which it's  
11 possible to fully understand all those  
12 components you can make a more full discussion  
13 of the pros and the cons of a lot of  
14 monitoring, smaller amounts of monitoring --  
15 and then when you blend that with the hazard  
16 assessment to come to the closest to ideal  
17 that we possibly can. So the degree to  
18 which -- I guess I don't really have anything  
19 else.

20 MR. THURMAN: No, but this is --  
21 honestly this is why we're here. And this is  
22 what -- we want -- scientifically how far can

1 we go -- how far can we take this. And your  
2 feedback will then lead us to whatever  
3 discussion we need to do in terms of -- Okay,  
4 we can only go this far -- how do we deal with  
5 that. And we want your honest feedback on  
6 that so when we have that discussion we know  
7 where we can go.

8 SESSION CHAIR PORTIER: Dr.  
9 Heeringa?

10 CHAIR HEERINGA: I asked about data  
11 earlier, Nelson. The other part in designing  
12 any statistical process costs and technologies  
13 come into play here. And I'm not sure I  
14 understand -- and maybe it would be helpful  
15 for the panel to understand -- where the costs  
16 enter in these water samples. Are they in the  
17 labor to physically visit the site each day or  
18 each sampling point, pick the water sample and  
19 transport it? Is it in the assay?

20 The reason I ask is that, you  
21 know, one strategy which is hinted at here is  
22 for more intensive sampling during periods of

1 sort of high runoff and after application.

2 And that's just intuitive from a lot of  
3 statistical arguments.

4 But the cost of doing that -- I  
5 mean, is it the assay? Is it the physical  
6 labor -- you know, the assistance to do this  
7 collection? Do you have a sense of where that  
8 cost structure -- how that breaks down?

9 MR. THURMAN: I'm sure the USGS  
10 and Syngenta as well can give you a much  
11 better -- but I know there is a substantial  
12 cost in physically going out, visiting the  
13 site, taking the sample, transporting it back.  
14 So there is a substantial cost involved in  
15 doing that in that regard.

16 CHAIR HEERINGA: Hopefully we can  
17 hear from them. And the other thing I think  
18 when we looked at the ecological side, in  
19 addition to the point sampling -- the time  
20 specific sampling -- there are integrated  
21 samplers too, are there not?

22 MR. THURMAN: That's correct.

1 CHAIR HEERINGA: And from a  
2 statistical standpoint the ability to sort of  
3 integrate concentration over a period of time,  
4 while it doesn't give you the profile it at  
5 least gives you the mass. And that might be  
6 actually useful in estimation. And I don't  
7 think Dr. Lee and Dr. Young have been thinking  
8 about this, but I think it would be useful if  
9 we can have a little description of what those  
10 measurement technologies and what those costs  
11 look like as we think about this process.

12 MR. THURMAN: Yes, that's correct.  
13 And I know that the technology is improving in  
14 water sampling in general and that there are  
15 auto-samplers that will take sips over time,  
16 and so you can get an integrated sample over  
17 a time period.

18 Some of them will do this for a  
19 number of periods. The samples will be stored  
20 so that it reduces the number of trips you  
21 have to make. So I -- and I think as Syngenta  
22 has continued with the ecological monitoring

1 they've gone more toward these because it  
2 does -- there is a savings involved in that.

3 SESSION CHAIR PORTIER: Dr.  
4 Gilliom?

5 DR. GILLIOM: I have a few  
6 thoughts on those other things I can bring out  
7 later, but not now I don't think. On the --  
8 an issue we haven't talked about that I think  
9 I'm interested in in having the biological  
10 side of the panel understand, but also  
11 understand from EPA how we might need to  
12 factor this into sampling design evaluation,  
13 is the whole area of co-occurrence with other  
14 contaminants and mixtures.

15 It's kind of unrealistic in these  
16 agricultural systems to isolate out one  
17 chemical like atrazine and its degradants in  
18 terms of exposure. And so if we're looking at  
19 the sampling design problems and there's going  
20 to be a need to even take the simplest case of  
21 combining it with simazine which is part of  
22 the total chlorinated triazine group it has

1 different seasonal patterns than atrazine.  
2 And those are changing, in fact, as cropping  
3 patterns change and GMO crops come in and  
4 herbicide use patterns change.

5 So one of the things I was  
6 thinking about as we look at our charge, which  
7 is really to help give you guys a roadmap to  
8 a decision making process for coming up with  
9 monitoring we're not given a specific target  
10 like we need the five-day moving average or  
11 the one day. Ours is -- our charge is more --  
12 given these circumstances what process should  
13 we follow as an agency to come up with an  
14 approach.

15 Well, you have more to deal with  
16 than just atrazine, of course. And some of  
17 the specific toxicological related studies  
18 maybe we're talking about this week are  
19 specific to atrazine. But then in the next  
20 panel, which is also relevant to the  
21 monitoring design problem, you're going to be  
22 talking about the epidemiological studies more

1 in there.

2 And there's going to be a lot more  
3 issues come up about how to separate out the  
4 potential co-occurrence effects -- just simple  
5 ones like there's nitrate in atrazine -- does  
6 that interact to have a different concern than  
7 just atrazine alone or does atrazine with  
8 fungicides or whatever.

9 And the point being is that when  
10 we look at the sampling design needs for that  
11 it may totally change how we look at what  
12 knobs are really -- need to be turned to get  
13 the right frequency and the right moving  
14 average values through the year. So we may  
15 look at atrazine and say, Well, if we know we  
16 need a seven-day moving average for atrazine  
17 we can dial that right into a three-month  
18 period and come up with a really efficient  
19 design.

20 We could even go into the sampling  
21 tricks. We could do some -- since we're  
22 moving average sampling composite sampling and

1 use amino assays that are cheap and screen and  
2 then analyze. But if the problem goes beyond  
3 atrazine and it has to be captured in the same  
4 monitoring thing then it changes how we  
5 approach it.

6 So I guess it's a concern I have  
7 to the process of how we give guidance on  
8 monitoring design, but it's also kind of a  
9 question of the rest of you looking at the  
10 biology as we go through this how comfortable  
11 are we with limiting the scope to atrazine  
12 with making these kinds of decision.

13 MR. THURMAN: I just -- I want to  
14 add one thing to what you were saying, Bob.  
15 When we're looking at community water system  
16 monitoring they actually measure for total  
17 chlorotriazines. And some of the figures  
18 we've seen labeled atrazine -- and we do have  
19 the atrazine measurements as well as simazine  
20 measurements, but we also have total  
21 chlorotriazines, and that's ultimately what  
22 the drinking water assessment will be based

1 on.

2 But you made some other points  
3 that -- but as long as everyone knows we do  
4 have -- for the drinking water exposure we are  
5 considering total chlorotriazines.

6 DR. GILLIOM: I guess just one  
7 follow up that I lose track of once in a while  
8 too is that this monitoring design and purpose  
9 is in supplement to the regular Safe Drinking  
10 Water Act monitoring. So it's -- people may  
11 not always realize that, that you have every  
12 system being done quarterly just for the  
13 regulated compound atrazine, and then you have  
14 this special program layered onto it that's  
15 required by FIFRA that Steve explained  
16 yesterday what the trigger points are and  
17 everything.

18 So I'm assuming that that is still  
19 the conceptual model you're moving ahead with.  
20 There's kind of a double monitoring plan.

21 MR. THURMAN: That is correct.

22 SESSION CHAIR PORTIER: Very good.

1 Dr. Coupe?

2 DR. COUPE: Yes. Thank you. Hey,  
3 I was just curious. I heard two of you  
4 mention already that daily sampling is off the  
5 table or whatever, but why would that be if  
6 you can't answer the question as to what's the  
7 cost of the collection or what-not? What if  
8 human health says, you know, you need to  
9 collect daily and that's what has to be. No  
10 offense to the statisticians, but it's a  
11 model, and all models are wrong -- some are  
12 useful maybe.

13 DR. BRADBURY: Sometimes. Always  
14 useful but how you interpret them. This is  
15 Steve Bradbury speaking. I would suggest you  
16 don't constrain yourself in terms of sampling  
17 design frequency, different scenarios of how  
18 you may have embedded sampling within a  
19 different sampling design. Do what you think  
20 is right in terms of the scientific  
21 perspectives that we should consider.

22 At some point we'll have to decide

1       how to implement the scientific perspectives  
2       that you raise or you offer to us. I wouldn't  
3       constrain yourself. I think Dr. Lowit though  
4       made a good point yesterday when we were  
5       talking about some of the toxicology, and it  
6       would apply to the sampling design too.

7               As you describe different  
8       approaches that we should consider we would  
9       respectfully request you also be very clear on  
10      what it is -- what's the question that you  
11      think we should have and that we should come  
12      up with an answer for and perspectives on how  
13      good an answer can be with different  
14      approaches.

15              Because we also want to ensure  
16      that we're focusing on issues that we need to  
17      get resolved -- a resolution to. And with all  
18      due respect to my previous history, as well as  
19      my colleagues in the room, we're talking about  
20      issues here that aren't in a research mode.  
21      We will learn things and will contribute to  
22      research, but we'd also like a focus on what

1 are the issues that we can take on tomorrow,  
2 six months from now, 12 months from now which  
3 will certainly contribute to the broad  
4 scientific knowledge, but ought to focus on  
5 real decisions that we have to be making in  
6 real time.

7 And we'll never know everything.  
8 And so it's how to make informed decisions  
9 with what we do know. And some of Nelson's  
10 comments and Anna's comments on helping us  
11 think about uncertainty and variability  
12 interpretation will be critical.

13 But the bottom line is don't  
14 constrain yourself in terms of where you need  
15 to go, but offer some insights into the  
16 perspectives in terms of the range of options  
17 that you may consider.

18 SESSION CHAIR PORTIER: Okay. I  
19 think we're ready for the overall summary and  
20 conclusion. Dr. Lowit.

21 DR. LOWIT: I don't have a slide  
22 and I won't say much. I thought it just would

1 make sense to go back to where we started.

2 Last fall a group of us sat in  
3 front of the permanent panel and announced we  
4 were doing this reevaluation and we would come  
5 to the SAP several times in 2010. And we told  
6 you yesterday we're going to add another one  
7 in 2011 -- that our initial hope had been in  
8 September of this year to have a harmonized  
9 weight of the evidence across cancer/non-  
10 cancer. But our colleagues at NCI are not  
11 going to have their agricultural health study  
12 reconsideration done in time, so we're going  
13 to separate the cancer.

14 So we still have the exact same  
15 two goals today that we did back last fall --  
16 that we have two pretty practical questions.  
17 And the first one has to do with drinking  
18 water monitoring frequency required of  
19 Syngenta. And the second one is a basic  
20 question -- do we need to reopen the human  
21 health risk assessment.

22 And we're doing a lot on two major

1 fronts that you've heard a lot about. The  
2 hazard assessment component -- we're in the  
3 sort of mid -- a snapshot on time on the  
4 update of the literature review of the hazard  
5 assessment. And the new data since the last  
6 risk assessment suggests that the HPA axis  
7 happens on a -- maybe on a shorter temporal  
8 scale than does the data that supported the  
9 2003 risk assessment.

10 And so as we think about that HPA  
11 data and its temporality and how you would  
12 take that and think about linking key events  
13 across that pathway of toxicity -- how to link  
14 those together to -- across time and across  
15 dose to think about the relationship of one to  
16 the other and how to translate that -- the  
17 temporal component of that into the drinking  
18 water frequency, which we've talked a lot  
19 about this morning and I won't reiterate.

20 And part of that hazard assessment  
21 is to rethink things like the points of  
22 departure, the uncertainty factors, the --

1 whether it's a rolling average or some other  
2 dose metric. So we're really looking forward  
3 to the discussion over the next few days. I  
4 guess that's -- do you have anything else? I  
5 think that's it.

6 SESSION CHAIR PORTIER: Very well.  
7 I think at this point we'll take a 15-minute  
8 break. I have 10:08. We'll return at 10:25.

9 MR. BAILEY: If I could ask all  
10 the people who are making public comments to  
11 please come up here and check with us so we  
12 can get your files loaded into the laptop  
13 ready to go. Thanks.

14 (Whereupon, the above-entitled  
15 matter went off the record at 10:09 a.m. and  
16 resumed at 10:27 a.m.)

17 SESSION CHAIR PORTIER: Okay.  
18 Let's begin. Before lunch we're going to have  
19 presentations first by the Triazine Network  
20 with a Mr. White, Laura Knoth, and Richard  
21 Fawcett. And following that we're going to  
22 have beginnings of the presentation from

1 Syngenta of crop protection. So we'll start  
2 with Mr. White.

3 MR. WHITE: Thank you, Mr.  
4 Chairman, members of the Committee. My name  
5 is Jere White. I live in east central Kansas.  
6 I'm the executive director of the Kansas Corn  
7 Growers Association and also Kansas Grain  
8 Sorghum Producers. And if you're not from the  
9 Midwest you probably have no idea what grain  
10 sorghum is. But it's a grain crop actually  
11 similar to corn in some ways and, yet, very  
12 different. I'm here on behalf of Kansas  
13 farmers.

14 I also serve as chairman of the  
15 Triazine Network. The network was formed in  
16 1995 as a response by the grower community to  
17 the EPA announcement of a special review and  
18 the reregistration efforts.

19 We represent over 30 commodities  
20 in over 40 states. Most of our members are  
21 organizations like my own, but also includes  
22 many individuals farmers. Network membership

1 encompasses farm groups literally from border  
2 to border and sea to sea -- in fact, some  
3 across some seas. We have an executive  
4 committee that's formed from states like  
5 Kansas, Missouri, Florida, California, and  
6 Hawaii.

7 We certainly are a very diverse  
8 group focused on a single outcome. And our  
9 objective has always been to ensure that EPA  
10 understands the value and the utility of  
11 atrazine. We also have assumed that role with  
12 the registrants because, as you can imagine a  
13 long process like this, it's not only  
14 important that the people regulating the  
15 product understand its value it's important  
16 that the people that are producing the  
17 product -- and I might add an off-patent  
18 product -- understand the value to farmers.  
19 And so we've engaged on all points on that.

20 But the fact is that atrazine has  
21 been the foundation of our weed control  
22 programs for 50 years now. We know the

1 product well. We know how to steward atrazine  
2 in a way that provides safety for ourselves in  
3 the environment. And that's the environment  
4 that we live and farm in.

5 I'm going to turn over comments  
6 now to Laura Knoth. Laura is the executive  
7 director of Kentucky Corn Growers, and then  
8 she'll pass the baton to Dr. Fawcett, and then  
9 I'll wrap up. Laura?

10 MS. KNOTH: Thank you. Thanks,  
11 Jere. Mr. Chairman and members of the panel,  
12 as Jere said, my name is Laura Knoth. I'm the  
13 executive director for the Kentucky Corn  
14 Growers and Kentucky Small Grain Growers in  
15 Kentucky.

16 I grew up on a Kentucky farm that  
17 I still own and operate there today.  
18 Graduated the University of Kentucky with an  
19 agriculture degree, natural resources major.  
20 I started my career as an environmental  
21 consultant and then came home to agriculture.

22 I wanted to just talk today about

1 stewardship and conservation as it relates to  
2 atrazine. And please pardon nervousness.

3 This is obviously my first advisory panel.

4 It's because American agriculture  
5 and American farmers are dependent upon the  
6 integrity of their soil and other natural  
7 resources for their livelihood that they work  
8 to protect and improve the land. As a result  
9 significant benefits to society have been  
10 achieved and improvements and efficiencies  
11 will continue to lessen the environmental  
12 impacts of food production.

13 Crops cannot be produced without  
14 disturbing the soil in some way. Tillage is  
15 the farmer's way of preparing the ground for  
16 planting, for breaking it up and smoothing it  
17 out. Tillage also helps control weeds and  
18 aerates the soil. Yet there are consequences  
19 to tillage: Rain and wind carry loosened soil  
20 off of the fields, adding silt to the  
21 waterways and particulate matter in the air.  
22 Old school cultivating with a moldboard plow

1 had even greater impacts on soil and water.

2 In today's agriculture when  
3 tillage is necessary farmers have adapted from  
4 the historical tillage practices of intensive  
5 soil disruptive for weed control to simpler  
6 practices, such as conservation tillage, which  
7 minimizes soil disturbance.

8 By leaving the crop residue on the  
9 field for cover and eliminating additional  
10 trips across the field for tilling farmers are  
11 better able to protect the soil from water and  
12 wind erosion. It conserves moisture, reduces  
13 runoff, and improves the wildlife habitat, and  
14 it limits our output as farmers of labor,  
15 fuel, and machinery to produce a crop.

16 Several crop production systems  
17 fall under the heading of conservation  
18 tillage, including no till, ridge till, low  
19 till, and minimum till. But common to all of  
20 these is a crop mulch covering left on the  
21 ground to provide a protective cover to the  
22 soil between the seasons. And it improves the

1 soil fertility by maintaining that nutrient  
2 rich organic matter on the field.

3 Conservation tillage allows  
4 organic matter to build up in the soil,  
5 absorbing carbon dioxide, and reducing a  
6 significant amount of greenhouse gas. Just  
7 like our lawns and gardens, compost and mulch  
8 are good things in agriculture.

9 As a result of increasing adoption  
10 of conservation tillage and other soil  
11 conservation practices soil erosion from U.S.  
12 crop land has steadily declined. A natural  
13 resources inventory report from 2007 published  
14 by the Natural Resources Conservation Service  
15 states that soil erosion resulting from  
16 rainfall and runoff declined 42 percent  
17 between 1982 and 2003. And, likewise, soil  
18 erosion from high winds declined 44 percent  
19 during that same time frame.

20 In 2008 atrazine was applied to  
21 over 650 percent of the conservation and no  
22 till corn acres. As America's original

1       stewards of the environment growers value  
2       atrazine for its capability with conservation  
3       tillage.

4               The ability of atrazine to move  
5       off the surface crop residue of the top soil  
6       to where the weeds germinate -- it moves down  
7       into the soil as well as the length of that  
8       weed control that makes atrazine the tool of  
9       choice for no till farmers and adopters of  
10      other conservation tillage practices.

11             Effective weed control -- it's not  
12      a luxury. It's a necessity in conservation  
13      tillage systems. So without herbicide use no  
14      till agriculture becomes impossible. And  
15      that -- you know, that causes additional  
16      increased erosion estimated to be over 300  
17      billion pounds of soil annually.

18             Much of this soil erosion would  
19      enter waterways. Sediment is the largest  
20      contaminate of surface water by weight and  
21      volume. And it's identified by the states as  
22      the leading pollution problem in rivers and

1 streams and the fourth leading problem in  
2 lakes. Sediment in surface water is largely  
3 a result of soil erosion, which is influenced  
4 by soil properties, and for agriculture the  
5 production practices that farmers choose.

6 Farmers and industries have  
7 heavily invested in research on BMPs for  
8 pesticides, including atrazine. Stewardship  
9 requirements on the label for atrazine are  
10 unique. And they are not typical with other  
11 pesticides. BMPs effective in reducing runoff  
12 of atrazine into surface water, including  
13 those conservation tillage practices, buffer  
14 strips, vegetative filter strips, terraces,  
15 contour planning, post-emergence application,  
16 and mechanical incorporation.

17 It should be noted that atrazine  
18 BMPs and stewardship provide benefits, not  
19 just for atrazine but for a variety of other  
20 concerns, including nutrients and other  
21 pesticides. BMPs and other stewardship  
22 efforts used by farmers often depend on site

1 specific conditions. And on our farms  
2 stewardship is -- occurs every day. It's an  
3 important part of continuing to be able to  
4 farm.

5 I want to thank the panel for its  
6 deliberations this week. As I said, this is  
7 my first SAP and I have to say the volume of  
8 science put in front of you all seems  
9 staggering. So good luck on your  
10 deliberations. I wish you well. At this time  
11 I'll turn it over to Dr. Fawcett.

12 DR. FAWCETT: Thank you, Laura.  
13 My name is Richard Fawcett, and I'm here  
14 appearing on behalf of the Triazine Network.

15 My background is as a weed  
16 scientist and also working in water quality.  
17 I've done a lot of work in developing best  
18 management practices and being involved in  
19 educational efforts to try to get those on the  
20 land.

21 I appreciate the opportunity to  
22 share some information about atrazine use with

1 this SAP panel that has a very important task.  
2 And it's very important to weigh carefully,  
3 because atrazine remains a very important tool  
4 to American agriculture.

5 It may seem surprising a product  
6 that's been around for 50 years is so widely  
7 used. But the reason it's so widely used is  
8 that it works so well. It works better than  
9 alternatives or, maybe better said, it makes  
10 alternatives work better.

11 It's interesting when a new  
12 herbicide active ingredient for corn is  
13 registered and hits the market the first thing  
14 that usually happens is it is marketed with a  
15 combination of atrazine as a prepackaged  
16 product or labeled as a tank mix in  
17 combination with atrazine because usually a  
18 relatively low rate of atrazine improves that  
19 product; controls weeds maybe missed by the  
20 alternative herbicide.

21 We've heard about the  
22 environmental benefits that atrazine's

1 important and with conservation tillage.  
2 Atrazine is also an essential tool in  
3 herbicide resistance management that has  
4 become so important as herbicide tolerant  
5 crops have been planted over such a large  
6 acreage.

7 We scientists routinely recommend  
8 to farmers that they do not use the same  
9 herbicide mode of action alone year after year  
10 after year because that brings on weed --  
11 herbicide resistant weeds. And atrazine is  
12 very often in corn. That alternative mode of  
13 action is used to manage weed resistance.

14 I've been involved in several  
15 analyses of very large databases to exam the  
16 hypothesis that there is a yield benefit from  
17 using atrazine. I'd like to briefly share a  
18 little bit of that with you. There are  
19 actually two ten-year analyses over a 20-year  
20 period where we used the research report of  
21 the North Central Weed Science Society as a  
22 source of studies.

1                   The North Central Weed Science  
2                   Society published the research report as an  
3                   outlet for universities for their annual  
4                   progress report. And it's by far the largest  
5                   published source of the herbicide efficacy  
6                   trials.

7                   In comparing treatments that  
8                   either had atrazine or atrazine alternatives  
9                   we haven't -- be very careful that they were  
10                  logical comparisons or fair comparisons. The  
11                  treatments had to have -- they had to control  
12                  both broadleaves and grass and so usually had  
13                  to have at least two active ingredients. They  
14                  had to be registered for use at the time of  
15                  the analysis -- they have been experimental  
16                  when the study was done. They had to be used  
17                  as registered rates. So there's a lot of  
18                  criteria that the studies and treatments had  
19                  to meet.

20                  But over the period of 1986 to  
21                  `95, the first analysis that was done in  
22                  response to the special review for atrazine --

1 over that time period atrazine -- treatments  
2 containing atrazine yielded 6.3 bushels or 5.9  
3 percent higher than alternatives -- treatments  
4 without atrazine.

5 After ten years had passed to see  
6 whether that benefit still remained we went  
7 back to that research report, used the same  
8 methods, and analyzed another ten years of  
9 data from -- see you get the years -- I guess  
10 it would be '96 to 2005. During that time  
11 period the atrazine treatments yielded 5.4  
12 bushels or 4.6 percent higher -- very similar  
13 benefit despite the introduction of many new  
14 herbicide active ingredients, new technologies  
15 like herbicide tolerant crops -- that benefit  
16 was really rather surprisingly constant. And  
17 there were 236 studies and 5,811 treatments in  
18 those analyses -- very, very large database.

19 Well, after 62 years of  
20 publication the North Central Weed Science  
21 Society terminated their publication of the  
22 research report in 2006 for budgetary reasons.

1 And so in order to look at the most recent  
2 years and do a similar analysis we had to come  
3 up with a different way of getting studies.

4 We started by contacting all the  
5 states that traditionally submitted studies to  
6 the research report. And this is, again,  
7 north center -- primarily corn belt. And we  
8 got studies directly from them, often from  
9 websites, sometimes directly from the  
10 universities.

11 But to try to go on a broader  
12 scale to get more data and actually to look at  
13 regions outside the corn belt we also utilized  
14 an electronic database, so it's Syngenta crop  
15 protection have that contain mainly university  
16 studies but also some company-sponsored  
17 studies.

18 We actually analyzed those  
19 separately -- took out the Syngenta studies  
20 and we was -- actually there was less benefit  
21 in the Syngenta studies than the university  
22 studies. So we used the entire database. We

1 wanted to make sure there wasn't any bias  
2 there. We used the entire database.

3 For the three years 2006 to 2008  
4 there were 310 qualifying studies of 4,293  
5 treatments -- a huge stack data -- very large  
6 analysis. There were 24 U.S. universities in  
7 22 states that represent all the major corn  
8 growing regions that did over 80 percent of  
9 the studies. So for that three-year time  
10 period corn yielded an average 5.3 bushels or  
11 3.5 percent higher -- again, a very similar  
12 benefit that remains despite all the new  
13 technologies. And these -- all these were  
14 statistics that we analyzed. They were  
15 significant by t-test and Wilcoxon signed-  
16 rank test.

17 Thus, despite the introduction of  
18 many new herbicide active ingredients, new  
19 technologies like herbicide tolerant crops,  
20 the benefit of atrazine remains. It's the  
21 most -- it's also cost effective. When you  
22 consider both the lower cost and the yield

1 increase the benefit from atrazine remains  
2 over \$30 per acre.

3 But besides just an economic  
4 benefit we've heard about the environmental  
5 benefits from the conservation tillage. And  
6 one thing I am concerned about is when you  
7 survey farmers and ask them if they're  
8 considering to go to conservation tillage what  
9 their biggest worry is, is always weed  
10 control. They're worried that if they give up  
11 that tried and true tillage method that they  
12 won't be able to control weeds.

13 If atrazine were not available I'm  
14 afraid we would backslide. Some of the  
15 farmers that are in conservation tillage would  
16 start doing more tillage. Some of the farmers  
17 considering that shift would not make that  
18 shift.

19 Atrazine remains a valuable tool  
20 in agriculture, producing both economic and  
21 environmental benefits. With that I'd like to  
22 shift it back to Jere White and have him make

1 some closing comments.

2 MR. WHITE: Thanks, Dick. As of  
3 now we've participated in every SAP concerning  
4 atrazine since the beginning of this special  
5 review in 1994. We missed the 1988 --  
6 obviously special review was not in place, but  
7 I must say my total of SAPs regarding atrazine  
8 was somewhat higher than what was reported to  
9 the panel yesterday. And I hope my wife  
10 doesn't read the report because I've told her  
11 I've been going to these SAPs in 2007, and I  
12 don't think any of those were on the list.

13 But, regardless, we do want the  
14 panel to know that although we see the value  
15 and we understand the benefits and we've  
16 shared them with EPA and actually EPA I think  
17 has incorporated a lot of our work into their  
18 analysis of benefits of the product.

19 We also understand that there are  
20 other issues. And we certainly do not  
21 casually dismiss activists' claims of harm  
22 from the use of atrazine, but we do insist

1 that sound scientific weight of evidence  
2 prevail on regard to regulatory action further  
3 lending its use.

4 In the course of time in my career  
5 that I've been involved with atrazine we've  
6 seen significant changes in labeled use rate.  
7 There is stewardship incorporated into the  
8 labels, and, quite frankly, agriculture has  
9 adapted and the product has maintained its  
10 value.

11 Obviously there are issues we need  
12 to be concerned. We're the primary handlers  
13 of the product. Our kids and our grandkids  
14 are a part of our farms, they're a part of our  
15 land, they're a part of our lives. And we  
16 need safe tools in our toolbox. And we  
17 believe atrazine because of our experience and  
18 simply -- you know, to put it -- simply put,  
19 because of our participation in now 16 years  
20 of scientific review we believe atrazine to be  
21 one of the safest tools that we have in our  
22 toolbox. That's important to us.

1                   Personally, I do understand the  
2                   implications of cancer. I buried my father a  
3                   few years ago after he lost his fight with  
4                   prostate cancer. Don't take it lightly.  
5                   Cancer strikes unique fear in all of us, and  
6                   certainly I'm not exception.

7                   I've also had experience with  
8                   birth defects. My first grandchild was born  
9                   still because he suffered severe developmental  
10                  birth defects. And so, you know, even though  
11                  there was no implications of pesticide  
12                  exposure or anything like that in that case  
13                  it's -- we understand what these tragedies in  
14                  life are. And if they were going to affect  
15                  anyone we would expect them to affect  
16                  ourselves and our families. And we do not  
17                  take it lightly at all.

18                  If we believed that these were  
19                  scientifically weight of evidence issues that  
20                  we should be considering or that we believed  
21                  we wouldn't be here today. We don't believe  
22                  that.

1                   And, quite frankly, the EPA did  
2                   not believe it until the New York Times and  
3                   Huffington Post supplied their version of the  
4                   peer review to an NRDC report last summer.  
5                   And that report was taken on by certain  
6                   political appointees at EPA.

7                   And you can simply go back to what  
8                   EPA was posting on its own website in July of  
9                   last year. Upon reregistration in 2006 EPA  
10                  determined that triazine herbicides post no  
11                  harm that would result in the general U.S.  
12                  population, infants, children, or other,  
13                  including consumers.

14                  I know this process did not begin  
15                  a year ago, as was inferred yesterday, to take  
16                  a look at the new reports and the new science  
17                  that's out there. We're not opposed to that  
18                  obviously. If there's legitimate concerns  
19                  that surface they could surface at any time.  
20                  You could finish a review one day. The next  
21                  day you could have issues. But there is a  
22                  certain amount of process that certainly comes

1 under question at this point.

2 From the growers' standpoints our  
3 growers often ask when is enough enough. You  
4 know, take the case of water. Atrazine  
5 certainly has the most comprehensive database  
6 of any pesticide. Is it enough? I mean, the  
7 discussions this morning -- at some point  
8 people involved in science and policy have to  
9 make determinations. But, certainly, when you  
10 look at the substantial data on atrazine  
11 compared to anything else that you look at out  
12 there -- and I would argue any contaminant the  
13 water system looks at -- the database is  
14 certainly more robust.

15 When you further consider that the  
16 levels of concern have multiple safety  
17 factors -- tremendous safety factors backed by  
18 decades of scientific review there seems to be  
19 little doubt that the robust data -- and since  
20 conservative safety factors provide confidence  
21 for farmers, for regulators, and for  
22 consumers.

1                   Mark Twain wrote in Life on the  
2                   Mississippi that there is something  
3                   fascinating about science. One gets such  
4                   wholesale returns of conjecture of such  
5                   trifling investment of fact. EPA, in fact,  
6                   has a process designed to avoid absence of  
7                   fact, and that's what this process is.

8                   This week, however, you have 123  
9                   studies in front of you for your deliberations  
10                  and have less than a month to review them.  
11                  For stakeholders the charge questions were  
12                  only released on the evening of the 8th,  
13                  allowing a mere eleven working days to develop  
14                  a response.

15                  To have a re-review of atrazine  
16                  and stated two-thirds of the way through the  
17                  normal pesticide registration process when it  
18                  was scheduled for a 2013 registration review  
19                  is contrary to the process established under  
20                  FIFRA and not based on sound science.

21                  I must give each of you special  
22                  thanks. You are being asked to review two

1 completely separate disciplines in this SAP:  
2 toxicology on many fronts and drinking water  
3 monitoring; requiring unusually wide span of  
4 research expertise. And though the average  
5 number of studies submitted for SAP review --  
6 the average per session numbers around 15 --  
7 the EPA has generously provided you with 123.  
8 Actually I think the number is slightly higher  
9 than that.

10 And while that might just be a  
11 sign of EPA's confidence in the scientific  
12 capabilities of the panel -- and I'm sure it  
13 is -- given the short time frame involved, it  
14 does not -- it certainly does bring into  
15 question the agency's definition of open and  
16 transparent and inviting stakeholder  
17 participation.

18 Regulators, government bodies, and  
19 organizations around the world, including the  
20 U.K. in 2000, Canada in 2004, WHO and FAO in  
21 2007, Australia in 2008, and most recently the  
22 state of Minnesota have recently given

1 atrazine favorable reviews.

2           And despite activists' lies to the  
3 contrary, no country has ever banned atrazine  
4 for health concerns, none, including the  
5 European Union. EU regulations do restrict  
6 the use of any pesticide that has a potential  
7 to occur in groundwater at amounts greater  
8 than one part per billion -- or .1 part per  
9 billion, but that is a political not a  
10 scientific standard.

11           While EU farmers do not currently  
12 use atrazine, they use a similar triazine  
13 herbicide with nearly the same safety profile:  
14 terbuthylazine. But you don't hear that when  
15 you read the reports or look at the news  
16 articles; not because the reporters don't  
17 know -- because I've told them -- but because  
18 it doesn't fit into their story.

19           The continuous restatement of this  
20 activist propaganda has taken on its own life  
21 and has been declared as fact; probably be  
22 declared as fact again before the day's over

1 with, yet it is a falsehood.

2           Extensive monitoring show the  
3 levels of atrazine in raw and finished water  
4 is steadily decreasing due to a number of  
5 factors, including label changes that occurred  
6 in the early nineties and stewardship  
7 activities on the farm which you've just heard  
8 about.

9           But atrazine is one of many  
10 regulated chemicals that are present in safe  
11 water -- in safe amounts in our drinking  
12 water. We know that it's safe because of the  
13 extensive scientific body of research  
14 available to us. Other chemicals like  
15 fluoride added to drinking water to protect  
16 our teeth and the byproducts of chlorination  
17 trihalomethanes are also in our drinking  
18 water, but they're there to do important jobs  
19 like kill dangerous pathogens such as E. Coli.  
20 They're present in water and they're present  
21 in safe amounts. However, most of these other  
22 contaminants do not have the same massive body

1 of science supporting their safe presence in  
2 water as atrazine does.

3 On December 20, 2008, the  
4 President-elect Obama said in his weekly  
5 address, it's about ensuring facts and  
6 evidence are never twisted or obscured by  
7 politics or ideology. For more than 50 years  
8 atrazine use has been conservatively regulated  
9 and approved for use in agriculture by EPA and  
10 its predecessor agencies through both  
11 Democratic and Republican administrations.

12 For instance, one of the most  
13 significant determinations made in the past  
14 two decades regarding atrazine that atrazine  
15 was not likely to be a carcinogen actually  
16 occurred during the Clinton administration.  
17 The current politically driven, second  
18 guessing of previous EPA and SAP decisions  
19 suggest twisting and obscuring at levels that  
20 should make a politician blush.

21 We would argue that those  
22 decisions were not made in some black box. We

1 are confident that the past -- that when the  
2 dust settles the scientists who have been  
3 working diligently for years -- many of you in  
4 this room have been a part of many SAPs -- and  
5 in this room today both have the agency and  
6 the SAPs will be vindicated for their past  
7 regulatory decisions.

8 And make no mistake about it. We  
9 believe that the reviews that have been  
10 done -- while we might not have agreed with  
11 every turn or twist that EPA, the agency, and  
12 their SAPs have made in the past collectively  
13 we think it has been a very solid, very deep  
14 process. It's not something that the agency  
15 under any administration has taken lightly.

16 It's not something that the  
17 SAPs -- the previous SAPs have taken lightly.  
18 And, again, many of you have been involved in  
19 those. And to suggest that somehow a SAP  
20 process under a different administration was  
21 somehow lacking I think is a disservice to  
22 people that have dedicated a lot of their time

1 and effort to this project.

2 But, having said that, we  
3 certainly will roll up our sleeves. We'll be  
4 back in September and we certainly look  
5 forward to working with all parties as the  
6 process continues. Thank you.

7 SESSION CHAIR PORTIER: Thank you.  
8 Any questions from the panel? Yes, Dr. Regal.

9 DR. REGAL: Just is there any  
10 number out there in terms of corn yields with  
11 no herbicide versus corn yields with  
12 herbicide?

13 DR. FAWCETT: I can't give you a  
14 firm number. But just from looking at -- it  
15 depends on how many weeds you have in a field.  
16 Some fields have a lot of weeds; some have  
17 less. Typically in our research plots we  
18 always have controls without any herbicide.  
19 They may not yield anything. They may be 20  
20 bushels compared to 200 bushels for a  
21 herbicide. But if you have a field that's  
22 relatively clean it might yield 100 bushels.

1 It just depends on how many weeds are there.

2 SESSION CHAIR PORTIER: Dr.  
3 Gilliom?

4 DR. GILLIOM: So is it reasonable  
5 to assume given the continued need for  
6 atrazine that the use should still remain  
7 pretty constant in the corn belt total?

8 MR. WHITE: You know, we would  
9 argue that the use has -- you know, certainly  
10 it's changed in the 15, 16 years since the  
11 special review was initiated. The use today  
12 is really tied -- you know, if you go back 30  
13 years ago atrazine might have been the main  
14 component of weed control, and label grades  
15 would have reflected it. They would have been  
16 very high.

17 Today it's more of a component in  
18 a mixture of new chemistries. But as Dr.  
19 Fawcett said the really issue is even some of  
20 the most popular new chemistries like  
21 glyphosate quickly found problems with weed  
22 resistance. And so you have to have some

1 alternative. And the reality is, is that, you  
2 know, it's surprising to us. But the utility  
3 and the need for atrazine today, although it's  
4 in a different fashion, is probably just as  
5 profound as it was 20 years ago or 30 years  
6 ago. But it's different.

7 DR. FAWCETT: I'll just quickly  
8 give an example from Iowa. Today in Iowa I  
9 think atrazine's actually used on more acres  
10 today than it was 20, 30 years ago. It's used  
11 at lower rates, different ways, some post-  
12 emergence and combinations. So the  
13 environmental load is actually less, but it's  
14 just as important, if maybe not more  
15 important, than it was 20 or 30 years ago.

16 MR. WHITE: And I guess the other  
17 point I'd add, in conservation tillage it is  
18 absolutely critical.

19 SESSION CHAIR PORTIER: Dr.  
20 Horton?

21 DR. HORTON: Yes. I have a  
22 question. One of the things we're going to be

1       considering on the biology panel is that the  
2       health effects may occur at many different  
3       levels and different stages of development.  
4       We may be looking at fetal periods, perinatal,  
5       pubertal, adult, cancer, neurotoxicity.

6                       And so in your statement you  
7       commented that the European Union safety  
8       review said atrazine would not harm humans.  
9       Could you comment on what specific human  
10      health effects the European Union evaluated --  
11      what stages of development, which health  
12      effects they were evaluating?

13                      MR. WHITE: In fairness I probably  
14      would need to go back and take a look at all  
15      that. You know, I'm sure that those reviews  
16      did not include some of the newer stuff that  
17      this panel and future panels will be taking a  
18      look at.

19                      But I do believe that it certainly  
20      included some of the things that we are  
21      looking at and probably the Syngenta folks  
22      might be better equipped. But I'd be happy to

1 go back and specifically give a list of those  
2 things that were reviewed. I don't know it  
3 off the top of my head.

4 SESSION CHAIR PORTIER: Dr.  
5 O'Byrne?

6 DR. O'BYRNE: Kevin O'Byrne. I  
7 don't think any sane person would say that  
8 there is not a requirement for herbicides, and  
9 I get a sense that as the commitment to reduce  
10 the amount of usage globally -- perhaps  
11 globally.

12 But I have a simple question. The  
13 application of these herbicides, are they  
14 coordinated with weather forecasts and things  
15 like that by the farmers?

16 MR. WHITE: Well, certainly one of  
17 the BMPs that we encourage farmers to utilize  
18 is if it looks like a significant rainfall  
19 event's on the horizon, you don't go out and  
20 spray the field. But having said that, you  
21 know, Mother Nature is somewhat fickle  
22 sometimes, and so you don't always know when

1 those will occur.

2           And having been involved in other  
3 water issues in my state, I can tell you that  
4 in spite of your best modeling, in spite of  
5 your best efforts, there will be, you know,  
6 acts of nature that will fall out of your  
7 parameters. You know, I think farmers do a  
8 much more precise job today. I mean, you  
9 know, a lot of herbicide goes down using  
10 satellites to drive the sprayer, not farmers.  
11 You know, the issues like over-applying  
12 because of overlaps that were very common  
13 were -- you know, a couple of decades ago are  
14 somewhat unheard of on the most modern farms.

15           One of the challenges, though, is  
16 that as a society we like the notion of small,  
17 what we call family farms in this country.  
18 It's not -- you know, it's kind of a romantic  
19 notion. But the bottom line is is that most  
20 of the very smallest of farmers are the ones  
21 doing the poorest job of applying herbicides  
22 and things like that because they're using the

1 economies of scale. They're not using GPS to  
2 help them put the product where it needs to  
3 be. They're probably using a sprayer that  
4 they bought at a sale that had been used by  
5 another farmer that might represent technology  
6 that's 20 or 30 years old.

7           So there's -- it's like new cars.  
8 It takes a long time for the transportation  
9 system to cycle through. It does the same on  
10 farms. But everyone's about efficiency. And  
11 the most efficient use of a herbicide is to  
12 use the least amount that you need. But if  
13 you use less than the least amount that you  
14 need you've done a disservice because you  
15 improve the chances for resistance, you've  
16 spent money and you get no benefit.

17           And there are levels -- you know,  
18 you could go back -- with atrazine you can go  
19 back as the labeled rate was reduced in the  
20 nineties, you saw weed control come off the  
21 label for different weeds just simply because  
22 it wasn't efficacious anymore.

1                   SESSION CHAIR PORTIER:  Dr.  
2                   LeBlanc?

3                   MR. WHITE:  I don't know if I  
4                   rambled too much on that.

5                   DR. LEBLANC:  You mentioned that  
6                   atrazine was banned in the U.K. not for health  
7                   concerns but because levels in drinking water  
8                   exceeded a somewhat arbitrary limit.

9                   MR. WHITE:  No.  Actually I said  
10                  it was not banned in the U.K.  It's use was  
11                  discontinued.

12                  DR. LEBLANC:  Okay.

13                  MR. WHITE:  And not because the  
14                  levels in drinking water -- because of  
15                  detections in groundwater.

16                  DR. LEBLANC:  Detection in  
17                  groundwater.  And the -- and you also  
18                  mentioned that an alternative, or a  
19                  substitute, triazine is used in place of  
20                  atrazine.

21                  MR. WHITE:  Yes, terbuthylazine.

22                  DR. LEBLANC:  So I assume that

1 levels of that herbicide are not found in  
2 excess of that limit in groundwater?

3 MR. WHITE: I would assume that  
4 they've not detected it in groundwater at that  
5 level. So that it's a concern but, you know,  
6 again, it's a very similar product. You know,  
7 I'm not familiar with terbuthylazine because,  
8 in fact, we don't have it registered in the  
9 United States.

10 DR. LEBLANC: I'm not familiar  
11 with it either.

12 MR. WHITE: Yes.

13 DR. LEBLANC: And perhaps I'm  
14 going above your level of understanding and  
15 expertise.

16 MR. WHITE: Well, other than my --  
17 my understanding is that the tox and actually  
18 the compound is very similar, as are the other  
19 triazines.

20 DR. LEBLANC: I just wonder if  
21 its -- presumably its levels are lower than  
22 the limit I think you said was 0.1 parts per

1 billion.

2 MR. WHITE: 0.1 parts, yes.

3 DR. LEBLANC: Is it because it  
4 degrades more rapidly or that is -- is it used  
5 effectively as a lesser concentration?

6 MR. WHITE: I don't think that  
7 would be the case, but there's probably people  
8 in the room that can answer that better than  
9 I can.

10 SESSION CHAIR PORTIER: I think we  
11 want to stop at this point. I really want to  
12 get on to some of the other commentators. And  
13 I appreciate the Triazine Network being  
14 represented. I've heard you many times, and  
15 it's always good to be reminded of where this  
16 product fits into agricultural practice and  
17 its key component. Thank you very much.

18 The next group that's up is the  
19 Syngenta. Syngenta has seven presenters. And  
20 they're going to begin their presentation and  
21 we'll stop at some good point for lunch and  
22 then they'll finish after lunch.

1 Joe, I don't even see seven chairs  
2 there so you're going to have to pick and  
3 choose who gets to sit at the table. And I  
4 guess first up is Dr. Simpkins. Is that  
5 first? Or who's your lead on this. You are.  
6 Syngenta has provided a large packet of  
7 material to the panel and to the online  
8 archive.

9 DR. BRECKENRIDGE: Mr. Chairman,  
10 I'm Charles Breckenridge. I'm a senior  
11 toxicology fellow with Syngenta. I've been  
12 responsible for the safety assessment of the  
13 product since about 1994.

14 Today we have invited our  
15 colleagues who assist us with the  
16 interpretation of the endocrine effects of  
17 atrazine. And we're going to be making multi-  
18 part presentation. The other two Syngenta  
19 presenters are, in fact, going to address the  
20 water questions and so they'll come up later.

21 To give you an orientation of the  
22 sequence of speakers today, and also, Mr.

1 Chairman, just to inquire how you wish to  
2 proceed, we have diverse topics that we are  
3 going to be talking about and we have  
4 approximately in this section 90 minutes of  
5 presentation. I trust that it's most  
6 convenient to ask questions after each  
7 subsection. So if you choose to do that that  
8 would be fine.

9 SESSION CHAIR PORTIER: With  
10 questions we may only be able to get two-  
11 thirds of that. So we'll --

12 DR. BRECKENRIDGE: Sure. It's as  
13 you choose. So the first topics -- two topics  
14 deal with one of the charge questions, the  
15 cancer mode of action, and whether or not it  
16 still pertains.

17 The first speaker will be Dr. Jim  
18 Swenberg from North Carolina in Chapel Hill.  
19 He will be dealing with the framework analysis  
20 as it was conducted and presented to the SAP  
21 in 2000 and refreshing our memories about the  
22 conclusions reached at that time and the

1 implications of any new research on that  
2 topic.

3 Dr. James Simpkins from the  
4 University of North Texas will then address  
5 the question of aromatase and whether or not  
6 atrazine is a -- first off, the evidence that  
7 it induces aromatase in vitro and the  
8 relevance of those observations to the whole  
9 animal. As you know, aromatase is a  
10 significant enzyme in the conversion of  
11 testosterone to estrogen.

12 And any time you would have  
13 another mode of action that would lead to the  
14 production of estrogen one would be concerned  
15 that perhaps that mechanism would be operative  
16 in humans. And so Syngenta initiated a  
17 program of research with Dr. Simpkins more  
18 than three years ago to investigate those  
19 studies and try to understand exactly the  
20 relevancy of those observations in vitro to  
21 the human. And we'll be summarizing about  
22 three years of research on that.

1                   You have in your packet three  
2 papers that were submitted by us at the  
3 beginning of the year. These are the papers  
4 by Yee et. al. These have not yet actually  
5 gone to publication. We've been adding new  
6 data to them and we will be publishing those  
7 shortly.

8                   Finally, I'm going to round up the  
9 section where we're making a transition from  
10 discussion of the cancer mode of actions and  
11 the potential mechanisms to a discussion of  
12 the endocrine effects of atrazine relative to  
13 non-cancer end points. So that's the bridge  
14 section there. It will be very short.

15                   We then turn to our Dr. Robert  
16 Handa. And when we ended the more animal  
17 descriptive toxicology around about the 2000  
18 SAP, we turned our attention to the question  
19 about the GnRH pulse generator and exactly  
20 what were the mechanisms whereby atrazine was  
21 affecting that system.

22                   Dr. Handa will be summarizing that

1 program of research which also is being  
2 carried out over about three years. There are  
3 several publications, and those by Foradori  
4 et. al. are the ones that are in your packet.  
5 But more importantly for us today, we're going  
6 to share some of the new research that we have  
7 conducted and for studies that are still  
8 ongoing.

9 Finally, when we come out of that  
10 particular section we're going to turn our  
11 attention to the question of the toxicologic  
12 consequences of effects on the endocrine  
13 system, especially as it pertains to the HPA  
14 axis.

15 We're fortunate that Dr. Steve  
16 Pruett has agreed to come and speak about his  
17 research -- and this is not Syngenta funded  
18 research -- that he began in 2003 looking at  
19 the relationship between the area under the  
20 curve exposure to corticosterone induced by  
21 atrazine and immune system responses.

22 In addition to that, Dr. Pruett is

1       advising us on studies that we have ongoing  
2       relative to the question of the  
3       immunotoxicologic potential of atrazine and  
4       we'll share preliminary results of those  
5       investigations -- or at least their study  
6       designs. We have committed to the agency we  
7       will submit those two studies to the agency by  
8       about end of July.

9                   And, incidentally, those studies  
10       were conceptualized and initiated in December  
11       of last year and in February I believe of this  
12       year. So we're working on a fairly fast track  
13       here to try to get data that is meaningful to  
14       the questions that are in front of this group.

15                   So, with that, I'll turn it over  
16       to Dr. Swenberg.

17                   DR. SWENBERG: Thank you very  
18       much, Charles. And it's a pleasure to be here  
19       with the SAP as a former member of this  
20       organization.

21                   And what I'd like to do today is  
22       talk to you about -- since many of the members

1 this is your first SAP on atrazine -- bring  
2 you up to date on kind of where we are in  
3 understanding the carcinogenic potential of  
4 this very important compound.

5 So this slide just gives you an  
6 overview of how comprehensive the  
7 carcinogenicity database is on atrazine.  
8 There have been three different mouse cancer  
9 bioassays in males and females. All of these  
10 are negative at all sites.

11 There has been a series of Sprague  
12 Dawley cancer bioassays. Four of these have  
13 been in female Sprague Dawleys and they are a  
14 single site, single sex, single tumor type  
15 positive. Ovariectomized females were also  
16 evaluated, and they are negative at all sites.  
17 Sprague Dawley males are negative at all  
18 sites. And the Fischer 344 rat, male and  
19 females, are negative at all sites.

20 Next please. So what I'd like to  
21 do is -- you may or may not be familiar with  
22 the international program for chemical safety

1 and the EPA framework for evaluating  
2 mechanistic data. This way of examining data  
3 came about -- it started at a meeting in  
4 Hanover, Germany in 1997, and one of your  
5 panel members, Dr. Fenner-Crisp, and myself  
6 were at that meeting.

7 It then evolved into more  
8 intensive study. A number of publications  
9 have come out on it, and, most importantly to  
10 you, it is part of the 2005 cancer risk  
11 assessment guidelines of the EPA. So we'll  
12 walk through these different bullets as they  
13 pertain to atrazine.

14 Next please. So the first  
15 thing -- go back please. The first thing one  
16 does in this framework approach -- and it was  
17 brought about to increase the transparency of  
18 how decisions are made -- is to postulate the  
19 mode of action after a thorough review of, you  
20 know, the literature and the findings.

21 And so the postulated mode of  
22 action for atrazine is that it causes an

1 increase in mammary tumors by a species,  
2 strain, and sex specific mode of action that  
3 is the result of prolonged exposure to  
4 endogenous estrogen.

5 Next please. So we want to then  
6 examine the key events that are driving this  
7 phenomenon. So as you heard yesterday from  
8 Dr. Cooper, and we'll expand upon today,  
9 atrazine inhibits the LH surge in female  
10 Sprague Dawley and, as he showed, Wistar rats.

11 The Sprague Dawley rat is well  
12 known that its reproductive senescence is  
13 characterized by constant estrus. And chronic  
14 exposure to atrazine promotes early  
15 reproductive senescence in female Sprague  
16 Dawley rats. This results in prolonged  
17 exposure to endogenous estrogen.

18 So we want to evaluate these key  
19 events. According to the framework we'll be  
20 looking at dose response relationships,  
21 temporal relationships evaluating the  
22 strength, the consistency, and the specificity

1 of this association, as well as the biological  
2 plausibility and coherence of the results.

3 Next please. So this is a  
4 slide -- I think Ralph also showed this  
5 yesterday. This is a very high dose cancer  
6 bioassay that was done. And one of the things  
7 you'll notice -- in the blue are the  
8 controls -- that the Sprague Dawley female  
9 rats has a very high background incidence of  
10 mammary tumors, but that with exposure to  
11 atrazine what we're doing is we are decreasing  
12 the latency time, i.e. the curve shifts to the  
13 left as we're looking at that screen, and we  
14 have an increase in incidence. These are the  
15 hallmarks of a dose response in  
16 carcinogenicity.

17 Next please. I think that Dr.  
18 Cooper also showed one of these slides. Now,  
19 this slide is very interesting. So he  
20 explained how he used vaginal smears to  
21 characterize the estrus cycle of the rat.  
22 What this slide represents is on the y-axis

1 there are 90 individual lines of animal data.  
2 These are the 90 animals that were in this  
3 study. This is the six-month period of time.

4 And what you see is this starting  
5 of these red lines, and the red lines  
6 represent persistent estrus. And what's  
7 unusual about the Sprague Dawley rat is that  
8 this is a control animal that this early  
9 senescence, i.e. persistent estrus, starts  
10 very early in their life. It's -- this is  
11 about a 90-day into the study where we start  
12 seeing this. That's markedly in contrast to  
13 most other strains.

14 Next please. Now, if you expose  
15 these rats to 400 parts per billion of  
16 atrazine for six months and you're doing the  
17 same thing -- this is actually the same study  
18 now -- these are the 400 PPM atrazine  
19 animals -- and you can readily appreciate that  
20 the increase in reproductive senescence and  
21 the persistent estrus has clearly increased.

22 Next please. This is shown more

1 easily with a -- over on the y-axis we have  
2 percent of days in estrus. And you can see  
3 the controls are running around between 40 and  
4 45 percent, and in a dose-related manner it's  
5 going up to 65 percent. So this is the  
6 evidence for chronic exposure to endogenous  
7 estrogen.

8 Next please. Now, the mechanism  
9 for this is this inhibition of the LH surge  
10 that Dr. Cooper spoke of yesterday. And what  
11 you can see -- it's probably most easily seen  
12 in this repeat sample group -- that you have  
13 a complete inhibition of the LH surge at high  
14 doses. These are the same high doses that  
15 result in the increase in mammary cancer. So  
16 this shows the dose response relationship for  
17 this key event.

18 Next please. Here is a comparison  
19 of two bioassays, a second Sprague Dawley  
20 bioassay and a Fischer 344 bioassay. These  
21 are the female animals. And you see the much  
22 higher incidence of the mammary cancer in the

1 Sprague Dawleys and that there is a dose-  
2 related increase. And now we're up to a 80  
3 percent incidence in the control animals --  
4 just showing you how susceptible these animals  
5 are. The Fischer rat on the other hand has a  
6 much lower background of mammary cancer and  
7 there is no dose response relationship.

8 Next please. If one looks then at  
9 the percent of days in estrus you also see a  
10 very striking difference. We have the  
11 increase and dose response relationship in the  
12 Sprague Dawleys in days in constant estrus  
13 compared to the Fischer rat where this effect  
14 just does not happen. In fact, the amount of  
15 estrogen days decreases with increasing age.

16 Next please. This is then  
17 compared across the board for the Sprague  
18 Dawley rat, the Fischer rat, and the human.  
19 So you can see I spoke about when senescence  
20 starts. You can see that the Sprague stands  
21 out here at 30 to 40 percent of the life span,  
22 whereas the Fischer rat and the human are more

1 in the 60 to 70 percent range.

2 The principal cause of senescence  
3 in the Fischer -- or the in Sprague Dawley rat  
4 is this lack of the LH surge and the lack  
5 of -- so it's a hypothalamic failure rather  
6 than an ovarian failure.

7 In the Fischer rat we also have  
8 hypothalamic failure, but now it's not for LH  
9 release, it's for controlling prolactin  
10 surges. And in the human it's depletion of  
11 ovarian follicles that drive reproductive  
12 senescence.

13 So if we look at the LH surge  
14 capacity the Sprague Dawley loses this, the  
15 Fischer rat maintains it, and the human  
16 maintains it. Estrogen and progesterone  
17 ratios are elevated and prolonged in the  
18 Sprague Dawley, they're reduced in the  
19 Fischer, and they're reduced in the human.

20 The predominant cyclic pattern is  
21 one of persistence estrus in the Sprague  
22 Dawley rat, pseudopregnancy episodes in the

1 Fischer rat, and menopause in the human.  
2 Prolactin secretion is persistency elevated.  
3 It's -- in the Sprague, it's episodically  
4 elevated in the Fischer, and it's reduced in  
5 women. And prolactin dependence is high in  
6 the Sprague Dawley, medium in the Fischer, and  
7 non-existent in the women.

8 Next please. So pulling this all  
9 together one can look at the human relevance  
10 of this. The LH surge suppression does not  
11 increase estrogen exposure in humans. The  
12 ovary, not the hypothalamus, drives  
13 reproductive senescence in humans, and  
14 reproductive aging in human results in  
15 estrogen deprivation, not increased exposure  
16 to estrogen.

17 Next please. So the next part of  
18 the framework mode of action analysis is to  
19 consider are there other potential modes of  
20 action that we need to be examining? And  
21 three of them that have continually been  
22 evaluated are shown here. Is the compound

1 genotoxic, is it estrogenic, and does it  
2 affect aromatase? Many of these issues on the  
3 hormonal milieu were covered also by Dr.  
4 Cooper yesterday.

5 Next please. So the next two  
6 slides will just give you the large number of  
7 in vitro studies that have been conducted on  
8 atrazine for genotoxic potential. And they  
9 cover virtually all of the types of assays  
10 that are normally done for hazard I.D. You'll  
11 notice that they're predominantly negative  
12 with very few positive studies.

13 Next slide. You also see it in  
14 this slide. This is the status of the data in  
15 the year 2000.

16 Next please. So the weight of  
17 evidence in the year 2000 strongly indicated  
18 that atrazine is not genotoxic. This is  
19 derived from two reviews by David Brusick in  
20 1994 and again in 2000. Again, in 2000 Dr.  
21 Andrew Kligerman from the Research Triangle  
22 Park EPA did sister chromatid exchange in

1 chromosome analysis studies. They were  
2 negative.

3 And there are a number of studies  
4 that have been done between 2000 and the  
5 present time that were in your package. And  
6 these also do not change the weight of  
7 evidence. So atrazine is not genotoxic and we  
8 can put away that mode of action.

9 Next please. The second was the  
10 estrogenic potential of atrazine, and, there  
11 again, have been a wide number of screening  
12 studies that have been -- that have evaluated  
13 this as well as some of the traditional  
14 reproductive toxicology studies. They are all  
15 negative. So estrogen is not -- or I should  
16 say atrazine is not estrogenic.

17 Next slide. But we still do have  
18 uncertainties. This is the last step in a  
19 framework mode of action. So the mode of  
20 action underlying the tumor response in the  
21 Sprague Dawley females is very well  
22 understood. However, the precise targets

1 still have more to be known.

2 Since the 2000 review Dr. Handa's  
3 laboratory has started to work on this, and he  
4 is primarily focused on the HPG and the HPA  
5 targets that Dr. Cooper also talked about  
6 yesterday. And he will speak later on on this  
7 new research so that you are brought right up  
8 to date on where we're at.

9 Furthermore, the significance of  
10 the in vitro induction of aromatase was  
11 unknown. There has been research now on  
12 amphibians and on fish that has been  
13 conducted, and it did not show any evidence  
14 for functional consequences in vivo.

15 Furthermore, Dr. Simpkins will  
16 bring you up to date on his laboratory's  
17 efforts to assess the mechanisms -- the in  
18 vitro mechanisms and to explore why we're not  
19 seeing these effects in vitro, again, to bring  
20 you up to the very latest point.

21 Next please. So one can use the  
22 cancer risk assessment guidelines, go through

1 the human evidence, the animal evidence, the  
2 mode of action, and the human relevance of  
3 that mode of action, and you see the checks in  
4 these boxes that is -- this was based back in  
5 the year 2000 -- it has not changed.

6 Next please. So, in conclusion,  
7 the mode of action underlying the increased  
8 risk and incidence of mammary tumors to a  
9 female Sprague Dawley rat is very well  
10 characterized. The key events that are  
11 leading to this carcinogenic response have  
12 been elucidated and are dose dependent and  
13 temporally consistent.

14 The mode of action has been  
15 determined to not be relevant to humans. And  
16 plausible alternative modes have been  
17 experimentally discounted.

18 The U.S. EPA concluded that  
19 atrazine is not likely to be carcinogenic in  
20 humans. And other international groups,  
21 including IARC, Australia, the EU, and the WHO  
22 have reached similar conclusions. New

1 research that has been conducted since 2000  
2 has strengthened the confidence in this  
3 conclusion.

4 Now, I'd like to end with one last  
5 thing that came up yesterday. Could we have  
6 the next slide? There was a question raised  
7 about polycystic ovary syndrome in women.  
8 This was a major focus in the 2000 SAP  
9 assessment of atrazine. And Dr. John Marshall  
10 from the University of Virginia, who is a  
11 recognized expert on PCOS, put together this  
12 slide and gave a presentation.

13 So you can see the comparison here  
14 of atrazine versus PCOS. Atrazine has reduced  
15 LH secretion. PCOS is associated with  
16 elevated LH secretion. Atrazine has decreased  
17 LH pulse amplitude. PCOS has increased LH  
18 pulse amplitude. There is no change in  
19 pituitary sensitivity to GNRH -- or H I should  
20 say -- whereas in PCOS there is increased  
21 pituitary sensitivity.

22 There is -- it is correlated with

1 weight loss -- atrazine exposure is -- in the  
2 rat, whereas PCOS is commonly correlated with  
3 both obesity and diabetes. Androgen levels  
4 are decreased or unchanged with atrazine.  
5 They are markedly increased in PCOS. They are  
6 not associated with endometrial cancer in  
7 atrazine. PCOS has an increased association  
8 with endometrial cancer.

9 Atrazine is associated, as you  
10 heard, with mammary tumors. PCOS does not  
11 have any association with breast cancer.  
12 Atrazine induces reproductive senescence.  
13 PCOS does not resemble menopause. And the  
14 neuroendocrinology of atrazine is well  
15 understood. It is not well understood for  
16 PCOS.

17 Last slide please. So this is  
18 just a quote out of the 2000 SAP on atrazine  
19 cancer classification meeting. Further, if  
20 this and this relied -- or was -- if you went  
21 back to the previous sentence was associated  
22 with LH -- flattening of the LH response --

1 occurred in humans. It could not result in  
2 PCOS since this condition is associated with  
3 elevated LH.

4 Therefore, the conclusion that  
5 there could be a potential for human cancer  
6 from elevated estrogen levels if atrazine had  
7 effects on conserved hypothalamic mechanisms  
8 in humans similar to those in Sprague Dawley  
9 rats is at odds with the arguments and other  
10 conclusions of the agency draft assessment.

11 So I hope this is helpful to the  
12 discussions on PCOS. Thank you very much.

13 SESSION CHAIR PORTIER: I think at  
14 this point we'll open it up to a couple of  
15 questions. Is there some? Dr. Holladay.

16 DR. HOLLADAY: Nice overview.  
17 Thank you. One of your slides indicated there  
18 were no functional differences found in fish  
19 exposed to atrazine. I think there was a  
20 review in EHP, or Environmental Health  
21 Perspectives, in '10 -- 2010. There's a meta-  
22 analysis of the literature available that

1 suggested something like 30 out of 40 immune  
2 end points were suppressed in freshwater fish  
3 with atrazine exposure. Are you aware of why  
4 that might be the case what these guys found  
5 as compared to what you were suggesting?

6 DR. BRECKENRIDGE: Yes, sir.

7 Charles Breckenridge from Syngenta. I'll  
8 respond first with respect to the statements  
9 on Cloath and Tanguay. Those comments were  
10 pertaining to reproductive effects on  
11 aromatase specifically as a mechanism whereby  
12 a sex reversal could be accounted for by  
13 atrazine exposure.

14 And, in fact, this panel in  
15 earlier times has reviewed the Cloath work,  
16 and the evidence suggests that there's no  
17 evidence of aromatase modification in those  
18 animals. In regard to immunotoxicity in  
19 native species, I think that would be more  
20 appropriate at another SAP rather than here  
21 because today we're going to be mainly  
22 focusing on the endocrine mechanism. So if I

1       could ask to defer any kind of a detailed  
2       discussion on that, sir, I'd appreciate it.

3                   SESSION CHAIR PORTIER:  Dr. Reed?

4                   DR. REED:  I have two questions.  
5       One is in your slide 14.  So you line up the  
6       Sprague Dawley and Fischer 344 and then women.  
7       Since the mice bioassay also indicated  
8       negative response for mammary gland tumors,  
9       could you line up mice -- adding another  
10      column for mice in this schematic of things,  
11      or is it not --

12                  DR. SWENBERG:  I don't believe  
13      those studies have been conducted because of  
14      the negative bioassay, but certainly it could  
15      be looked at.  But the mouse doesn't go into  
16      the same reproductive senescence that the  
17      Sprague Dawley female does.

18                  DR. REED:  Right.  That's what I  
19      was asking about -- if you could line them up  
20      together with that.

21                  DR. SWENBERG:  Yes.  I don't think  
22      that's been attempted --

1 DR. REED: Mode of action --

2 DR. SWENBERG: -- but it's a good  
3 suggestion.

4 DR. REED: Okay. My next question  
5 is that in the agency's issue paper there are  
6 two studies of Fukamachi 2004 and Ueda 2005  
7 that allude to the possibility of promotional  
8 potential. Would you care to comment on that?  
9 I mean, I understand that there's a lot of,  
10 you know, issues about the study design and  
11 also the interpretation of the data.

12 But given that it -- what the  
13 author is saying has merit, meaning that  
14 there's a possibility of promotional  
15 potential, how would that fit into the mode of  
16 action scheme?

17 DR. SWENBERG: Yes. This -- these  
18 two papers -- I've gone through them several  
19 times. They are very complex. So if the  
20 first paper, which is -- has the transgenic  
21 animals being used, I have not yet been able  
22 to find, you know, what are the numbers of

1 copies of the transgene in different animals  
2 and different cells. You'll remember this was  
3 an issue with the TGAC mouse -- transgenic  
4 mouse.

5 So I'm having a difficult time  
6 understanding it. The statistical analyses  
7 that were done are somewhat unusual. The  
8 model's quite unusual. If we go to the second  
9 paper where they use the fairly standard DMBA  
10 breast cancer induction model -- I am familiar  
11 with that model.

12 Again, the data are really  
13 difficult to interpret. There is some  
14 suggestion of a high dose effect there. But  
15 what the mechanism is I don't think we  
16 really -- I mean, those animals were  
17 ovariectomized. So it's not a mechanism  
18 that's similar to what we're seeing in these  
19 bioassays.

20 But they do deserve further  
21 consideration of all of the work that's been  
22 published related to genotoxicity and

1 promotion and that. Those are very  
2 interesting papers and provocative papers.  
3 But I've been working in carcinogenicity  
4 research for more years than I'd like to --  
5 going back to before 1970 -- let's put it that  
6 way -- including promotion and initiation  
7 promotion studies, and I can't fully interpret  
8 those studies.

9 SESSION CHAIR PORTIER: Dr.  
10 Williams.

11 DR. WILLIAMS: I just wanted to  
12 clarify. You said in on one of your --

13 SESSION CHAIR PORTIER: Pull the  
14 mike closer.

15 DR. WILLIAMS: Sorry -- LH  
16 suppression does not increase estrogen  
17 exposure in humans. What it looked like you  
18 were really saying was that PCOS is associated  
19 with elevated LH levels. But if you actually  
20 suppress LH is there any experimental evidence  
21 to say that in humans, or maybe in primates,  
22 that suppression of LH does not increase

1 estrogen exposure?

2 DR. SWENBERG: I'm going to turn  
3 that over to Dr. Simpkins. He's an expert in  
4 this area.

5 DR. HANDA: I'm not sure I  
6 understand the question completely. But since  
7 estrogen is driven by LH changes with age --  
8 and I'm assuming you mean changes with age in  
9 at menopause there's decrease --

10 DR. WILLIAMS: No. I'm actually  
11 not talking about menopause at all. So if you  
12 think about younger women who are  
13 anovulatory -- sometimes PCOS related but  
14 sometimes for reasons that we can't --

15 DR. HANDA: Hypothalamic  
16 amenorrhea or something like that.

17 DR. WILLIAMS: Or simply oligo-  
18 ovulatory for, you know, unexplained reasons.  
19 That type of women -- is there any evidence  
20 that their failure to ovulate potentially a  
21 slight dysregulation of LH, as opposed to  
22 complete ovarian failure where you don't --

1 you know, obviously estrogen has left.

2 DR. HANDA: Usually those are  
3 associated -- for example, hypothalamic  
4 amenorrhea will be associated with a decrease  
5 in LH, and, as a result, there's no  
6 corresponding increases in estrogen.

7 DR. WILLIAMS: But, again, so  
8 complete hypothalamic amenorrhea is -- you  
9 know, is again a complete failure. What about  
10 oligomenorrhea -- women who periodically don't  
11 ovulate? Where -- you know, here we're  
12 talking about this potentially intermittent  
13 suppression of LH release related to  
14 intermittent high levels of atrazine.

15 So if you see this happening how  
16 can you say that that would not necessarily  
17 increase estrogen exposure? Is there any  
18 evidence for that?

19 DR. HANDA: As far as I know, no.

20 SESSION CHAIR PORTIER: Okay. I  
21 think we'll move on to the next presentation.

22 DR. SIMPKINS: I'm Jim Simpkins

1 from the University of North Texas Health  
2 Science Center. And I think I can do this.

3 We will in the next few minutes  
4 try to sort out the observation that in  
5 certain transformed cell lines exposure to  
6 relatively high doses of atrazine induce  
7 expression of aromatase, enhanced aromatase  
8 activity. Whereas that observation is not  
9 made in vivo. The answer to that is we  
10 believe embedded in the metabolism of atrazine  
11 with exposure, certainly to mammals, and  
12 likely to every species.

13 Atrazine is a relatively short  
14 lived compound after dosing. It is converted  
15 to the chlorotriazines which are shown in the  
16 green area on that slide. Those  
17 chlorotriazines, as well as atrazine itself,  
18 are then conjugated as part of the process of  
19 their elimination. What is also shown on that  
20 slide is the percent of those metabolites that  
21 are present in the urine. This happens to be  
22 in humans, but the numbers are very similar in

1 primates as well as in rodents. Where the  
2 dominant form are the conjugated triazine and  
3 triazine metabolites. Ammeline and  
4 hydroxytriazine are plant metabolites shown  
5 here and here.

6 The point I will make is that we  
7 have an opportunity with cell lines to ask  
8 questions that simply cannot be asked in vivo  
9 because cell lines are not good at  
10 metabolizing atrazine so when we put atrazine  
11 in, we should, at the end of our studies have  
12 predominantly atrazine with very little  
13 metabolism occurring.

14 Now what I will show you are what  
15 I think are the most comprehensive studies  
16 done to date. For concentration and duration  
17 assessment of the effects of atrazine, and a  
18 variety of its metabolites, in an H295R cell,  
19 this is an adrenal cortical tumor cell line  
20 that was shown by Sanderson to be responsive  
21 to atrazine with increased expression in  
22 activity of aromatase. So we wanted to take

1 a careful look at that cell line. I will also  
2 point out to you that the data you see, will  
3 see, were presented in one of the manuscripts  
4 that Dr. Breckenridge refers to. The data you  
5 will see is essentially identical to data that  
6 we have in a placental tumor cell line which  
7 also responds to atrazine. So you will see  
8 part of the data but I think, as you will  
9 agree, it is an extensive data set.

10 What is shown here is aromatase  
11 messenger RNA levels in H295R cells that were  
12 treated from as short as a quarter of an hour  
13 to 72 hours at four doses, 0.100 nanomolar, 1  
14 micromolar, 10 micromolar. As you can see  
15 atrazine causes a consistent two- to three-  
16 fold increase in expression of aromatase  
17 messenger RNA that begins at about two hours  
18 and persists through 72 hours.

19 So with this high concentration of  
20 atrazine in a cell type that cannot metabolize  
21 you can induce, you can demonstrate a highly  
22 reliable consistent induction of aromatase.

1 If we look at two of the chlorinated  
2 metabolites, the desethyl and desisopropyl  
3 forms of atrazine, we see a modest response  
4 that is delayed relative to atrazine and is  
5 reduced in amplitude. You can notice, this is  
6 for both of those metabolites this is less  
7 than a two-fold induction of the message.

8 In contrast to that,  
9 hydroxyatrazine, ammeline, and  
10 diaminochlorotriazine are negative at all  
11 times and all doses, short of a sporadic hit  
12 here or there, but I will point out to you  
13 that for each of these metabolites there are  
14 essentially 44 samples, so we're not surprised  
15 that we get an occasional hit. Statistically  
16 we ought to see that happen occasionally. But  
17 we don't think these small occasional hits are  
18 significant. So these metabolites appear to  
19 be inactive.

20 We also then looked at two model  
21 conjugates of atrazine -- that is, the  
22 glutathione and the mercapturate form of

1 atrazine, keeping in mind that the atrazine is  
2 the active, and we wanted to know when they're  
3 conjugated does atrazine lose its activity.

4 Not only is atrazine negative when  
5 it's conjugated, there appears to be a  
6 reduction in aromatase message, at least at  
7 the 24-hour sampling point. So these  
8 metabolites, which are the predominant form  
9 soon after administration of atrazine, are not  
10 inducing aromatase in this cell line.

11 The doubling that we saw in  
12 message is very consistent with measurements  
13 of activity conducted by Dr. Sanderson, as  
14 well as with an increase in this case estrone  
15 concentrations in the media. And his  
16 metabolite response is very similar to that  
17 which we see. Two of the chlorometabolites  
18 show an increase in activity of aromatase,  
19 whereas the hydroxymetabolites are completely  
20 negative. So we think there's good  
21 concordance in the data sets to date.

22 So this message increase is

1 consistent with activity increase, and all of  
2 them are happening at or around ten micromolar  
3 atrazine in vitro. And we've identified those  
4 metabolites which are inactive in vitro, and  
5 those are the predominant metabolites that  
6 show up when atrazine exposure occurs in vivo.

7 An additional question we asked  
8 was the extent to which the induction of  
9 expression of aromatase could be secondary to  
10 cytotoxic effects of atrazine or its  
11 metabolites. And we undertook these series of  
12 studies because we had been studying nervous  
13 tissue, and it's very clear that chemical or  
14 physical insults to brain cells result in  
15 expression of aromatase, and that's probably  
16 part of a protective mechanism there.

17 So -- but before we do that I want  
18 to make a comment about all of these in vitro  
19 studies -- and it is for you the panel just a  
20 word of caution. Atrazine is very insoluble.  
21 What's shown here are photomicrograms of  
22 atrazine at 3 micromolar, 10, and 30

1 micromolar in culture. And in many of the  
2 documents that you've had to read folks are  
3 using in vitro exposures up in this range.

4 In PBS we see atrazine come out of  
5 solutions somewhere between 1 and 3  
6 micromolar. That's shown in these slides as  
7 the dark aggregates. Those aggregates are  
8 larger in number and in size at higher  
9 concentrations of atrazine. And at 30  
10 micromolars you can see they're completely  
11 covering the cells in this dish. If you  
12 solubilize in DMSO you can enhance the  
13 solubility of atrazine. But I'll point out to  
14 you, at 30 micromolar we start seeing atrazine  
15 come out of solution. So keep that in mind in  
16 interpreting data.

17 Despite those aggregates, when we  
18 look at solubility using any of three methods  
19 at times ranging from a few minutes all the  
20 way out to 72 hours -- and what's shown here  
21 is representative data at 24 hours -- even at  
22 extraordinarily high concentrations -- in this

1 case up to 300 micromolar -- in which cells  
2 are literally coated with atrazine we get no  
3 toxicity.

4 And we don't see toxicity for this  
5 which is a cell viability assay. We don't see  
6 it if we look at assays that require  
7 functioning mitochondria to report the health  
8 of cells. We don't see it if we look at  
9 production of reactive-oxygen species. We get  
10 a straight line over an extraordinarily wide  
11 range of atrazine concentrations.

12 We see no toxicity with any of the  
13 metabolites that I showed you in the previous  
14 slides at any of the times we assessed. And  
15 we see no interaction between atrazine and, in  
16 this case, three known cytotoxic agents,  
17 glutamate, succinate dehydrogenase inhibitor,  
18 NPA, and then exogenous administration of  
19 hydrogen peroxide.

20 So atrazine is neither protecting  
21 these cells nor enhancing the toxicity of  
22 known insults. So atrazine and its

1 metabolites are not cytotoxic in the cell  
2 lines, and they don't potentiate toxicity of  
3 other agents.

4 We then turn our attention to  
5 potential effects of triazines on  
6 phosphodiesterases. And we did that because  
7 in the literature there were a number of hints  
8 that atrazine may be interacting with the  
9 breakdown of cyclic AMP, which is one of the  
10 jobs of phosphodiesterases.

11 For example, dating way back to  
12 1997 there's a report that a high single dose  
13 of atrazine increase cyclic AMP levels in  
14 livers of rats. Leroux reported on a series  
15 of chemicals that he had synthesized using  
16 atrazine as a scaffold for the purpose of  
17 producing phosphodiesterase for inhibitors and  
18 showed very good evidence that he could  
19 improve the phosphodiesterase-4 inhibiting  
20 activity of atrazine.

21 Sanderson reported in 2002 that  
22 there was a strong correlation between

1 atrazine's effects on cyclic AMP  
2 concentrations and their ability to induce  
3 expression of aromatase. And then in 2004  
4 Roberge reported that atrazine inhibited  
5 phosphodiesterase using a bovine liver  
6 preparation. And there's a great deal of data  
7 from a variety of sources indicating that  
8 cyclic AMP is critical to aromatase gene  
9 expression.

10 So what we set about doing was  
11 asking the question, does atrazine or any of  
12 the metabolites that I showed you interfere  
13 with phosphodiesterase activity and thereby  
14 increase cyclic AMP and then signal to  
15 aromatase through this PKA CREB  
16 phosphorylation pathway.

17 And then I'll finish by showing  
18 you data that resulted from us identifying the  
19 phosphodiesterases in H295R cells as well as  
20 in the JEG3 cells and then designing and using  
21 small inhibitory RNAs to knock down message  
22 levels for those species and the effects that

1 that has on the atrazine signaling.

2 These are all results for atrazine  
3 inhibition of phosphodiesterase activity.

4 IBMX is a well-described phosphodiesterase  
5 inhibitor that has an IC50 value of about two  
6 micromolar. Atrazine does indeed repeatedly  
7 reduce phosphodiesterase activity. It's about  
8 20-fold less potent than IBMX.

9 And then the other metabolites  
10 that we assessed really had very little  
11 activity in this assay. Their IC50s, if we  
12 could calculate them, were in the millimolar  
13 or molar range, which means that they are very  
14 ineffective PDE inhibitors.

15 We then designed primer pairs to  
16 ask questions about what species of  
17 phosphodiesterase is made by the H295R cells,  
18 and we did the same with the JEG3 cells  
19 because both of those cell types essentially  
20 showed the same time course and magnitude of  
21 aromatase induction in response to atrazine.

22 We made the assumption that, that

1 being the case, the two cell lines should show  
2 comparable phosphodiesterases, and we could  
3 use those to identify the site of action of  
4 atrazine. And it turns out four  
5 phosphodiesterases were picked up by our  
6 primer pairs in both of those cell types.

7 But only two of those were present  
8 in the same relative concentration -- and that  
9 is the PDE4D and the PDE8. We then built  
10 siRNA constructs to knock down those species,  
11 and these are those data.

12 The siRNAs for PDE4 reduced PDE4D  
13 levels by about 50 percent. The siRNAs for  
14 PDE8 reduced levels by about 60 percent. In  
15 both cases reducing levels of these  
16 phosphodiesterases essentially blocked the  
17 ability of aromatase to induce -- excuse me --  
18 of atrazine to induce aromatase expression,  
19 suggesting that these PDE4s were indeed  
20 mediating the ability of atrazine to induce  
21 expression of aromatase.

22 What we haven't yet done, because

1 this is an ongoing set of studies, is  
2 transfected into these cells scrambled forms  
3 of the siRNA to make sure that we're not doing  
4 something else to the cells that's off target.  
5 Those things will be done and hopefully will  
6 be reported to you this summer.

7 So let me finish and conclude.

8 The in vitro-in vivo dichotomy and the effects  
9 of atrazine on aromatase we believe are  
10 because atrazine is very rapidly metabolized  
11 in vivo with the formation of essentially  
12 inactive or weakly active chlorotriazines as  
13 well as conjugates, and, therefore, atrazine  
14 doesn't stay around long enough to induce  
15 aromatase expression.

16 That's in contrast to what we  
17 believe is happening in cell types where the  
18 triazine that we put in is either not  
19 metabolized or only metabolized very slowly,  
20 is able to stay around and, likely through a  
21 PDE inhibition, able to increase expression of  
22 aromatase.

1                   And, finally, I would point out  
2                   that in the in vitro system these effects of  
3                   the triazines happen at very high  
4                   concentrations. Thank you.

5                   SESSION CHAIR PORTIER: Thank you.  
6                   We'll open it up for some questions. Dr.  
7                   Schlenk?

8                   DR. SCHLENK: I'm actually really  
9                   intrigued by your conjugate data because I  
10                  guess I wouldn't have expected the conjugates  
11                  to cross the cell membrane and get into the  
12                  cells. But, yet, the glutathione conjugate  
13                  does appear to actually impair transcription.  
14                  I'm just curious what your thoughts are in  
15                  particularly the glutathione conjugate and how  
16                  that may actually be impairing.

17                  DR. SIMPKINS: Yes. Keep in mind  
18                  in all of our study -- in vitro studies we do  
19                  these assessments with I think -- with 0.01  
20                  percent DMSO, which is probably affecting  
21                  solubility of membrane and maybe enhancing the  
22                  movement of the conjugates into the cells. I

1 don't know.

2 DR. GREENWOOD: Richard Greenwood.  
3 You in your figures say that I think it was 85  
4 percent was conjugated to glutathione and 15  
5 percent not. Which -- what's the source of  
6 the data? Because it's sort of flipped on  
7 that in quite a few of the rodents. That is  
8 where I think it's more or less exactly the  
9 converse.

10 DR. BRECKENRIDGE: Okay. There  
11 are several sources of the data. In fact,  
12 there are regulatory studies in radiolabeled  
13 compounds in regard to metabolism in rodents.  
14 And so when Dr. Simpkins mentioned there was  
15 a concordance between rodents and primates and  
16 humans, there is approximately -- and it's  
17 fairly well described, at least in our data  
18 and others -- that the chlorals represent only  
19 about a maximum 15 percent, and the rest are  
20 conjugates.

21 I'm sorry. I don't know the  
22 discrepancy between information you have and

1 what we understand. But that's roughly the  
2 situation. The rates of metabolism and the  
3 elimination kinetics are described in some  
4 rodent studies. We have done primate studies  
5 and we intend to do actually a much more  
6 thorough characterization of that on a shorter  
7 time scale given the concerns about short time  
8 frame events, especially as it relates to the  
9 HPA axis.

10 So to some extent we're going to  
11 come back with some pharmacokinetic data that  
12 gives a proper description of the early time  
13 events in the biotransformations using  
14 specific analyte techniques to get at all the  
15 metabolites that are pertinent I think to the  
16 toxicities we're discussing here. So perhaps  
17 if you'd give us a chance at the next  
18 occasion, we'll have a lot more data on that.

19 SESSION CHAIR PORTIER: Dr.  
20 Williams?

21 DR. WILLIAMS: I just have a short  
22 question about the different

1 phosphodiesterases. Is there any evidence that  
2 atrazine affects various PDEs differently? So  
3 you looked at 4 and 8, but what about PDE3 or  
4 others that are more prevalent function in  
5 other tissues?

6 DR. SIMPKINS: We have not  
7 assessed specific interaction of atrazine  
8 on -- to date on any of the specific  
9 phosphodiesterases, some of which, as you  
10 know, are cloned and the proteins are  
11 available. So those studies are doable -- we  
12 just don't have the data on them.

13 The data that I showed is a liver  
14 homogenate phosphodiesterase preparation. So  
15 atrazine could be affecting any of a number of  
16 phosphodiesterases. The other thing you would  
17 note is that the maximum suppression produced  
18 by atrazine, as well as IBMX, is only about a  
19 60, 65 percent reduction in phosphodiesterase  
20 activities. So there are other  
21 phosphodiesterases that appear to be resistant  
22 to both of those compounds.

1                   SESSION CHAIR PORTIER: Dr.  
2 Chambers?

3                   DR. CHAMBERS: Back to Dr.  
4 Schlenk's question, is it possible in your  
5 system that those conjugates were being  
6 hydrolyzed?

7                   DR. BRECKENRIDGE: Just as a  
8 further comment on the aspect of the uptake of  
9 chemicals into the cells, we are actually  
10 going to do a metabolite profiling in the  
11 media and intracellularly with these H295R  
12 cells just so we can ascertain whether any  
13 biotransformations are occurring.

14                   And, secondly, we want to know  
15 what the component of, lets say,  
16 bioconcentration due to the DMSO is.  
17 Obviously we're interested in biological  
18 processes under physiological conditions and  
19 not these kinds of model systems that are used  
20 for other purposes. So we have those  
21 investigations in plan as well.

22                   DR. SELVAGE: Dan Selvage. I just

1 had a question about the PDEs of 4B and 4D?  
2 Perhaps you can help me out here. Do you know  
3 their expression levels in the pituitary or  
4 hypothalamus? I thought 4B was in the  
5 pituitary but I'm not 100 percent sure on  
6 that.

7 DR. SIMPKINS: I don't know  
8 relative expression levels of the various  
9 subtypes in all the tissues. I don't know  
10 about the pituitary.

11 DR. DELCLOS: I'm not sure this is  
12 the appropriate place for the question. But  
13 since you mentioned pharmacokinetic studies  
14 and you mentioned -- you were discussing the  
15 solubility issue, I'm wondering if this is --  
16 are there pharmacokinetic studies being done  
17 closer to levels of human exposure?

18 There's some things that strike me  
19 as unusual about the pharmacokinetic data,  
20 either if there's double peak of absorption in  
21 the mouse and rat or with the flat level of  
22 atrazine appearing over time. And I'm

1 wondering if solubility in the gut has  
2 something to do with this, these higher dose  
3 levels.

4 DR. BRECKENRIDGE: Okay. Thank  
5 you very much. We are going to do really a  
6 study design prep work after this meeting, and  
7 we're going to kick those studies off so that  
8 we're welcoming any suggestions that would  
9 inform risk characterization as far as  
10 biotransformation over short time periods,  
11 including lower doses. And actually I think  
12 Dr. Swenberg is -- low doses are near and dear  
13 to his heart. And we tend to want to do  
14 studies in relative -- in meaningful dose  
15 ranges, both for animal modeling as well as  
16 human risk characterization. So we'll  
17 certainly take that into consideration, sir.

18 SESSION CHAIR PORTIER: For the  
19 record that was Dr. Delclos asked the  
20 question. Any additional comments?

21 This is probably a good point to  
22 break for lunch, but I -- but if you want to

1 have a closing remarks on this section,  
2 because I know your transition. I looked  
3 through your slides and it's more of the non-  
4 cancer stuff.

5 DR. BRECKENRIDGE: I don't think  
6 we need to make a closing statement. I'll  
7 make an introductory statement for the next  
8 two parts then when we return. Thank you very  
9 much, sir.

10 SESSION CHAIR PORTIER: So the  
11 panel's been sucking this all in. We need  
12 biological material to keep going. So we'll  
13 break until -- I have 12:02. We'll break till  
14 1:15. We'll reconvene at 1:15.

15 (Whereupon, the meeting adjourned,  
16 to reconvene this same day, April 27, 2010, at  
17 1:15 p.m.)

18  
19  
20  
21  
22

## A F T E R N O O N   S E S S I O N

1:15 p.m.

SESSION CHAIR PORTIER: So, Dr.

Breckenridge, I guess we'll continue with your -- what was it? -- transition from cancer to non-cancer.

DR. BRECKENRIDGE: Thank you very much, Mr. Chairman. So the next sections deal with the toxicologic consequences of the endocrine effects of atrazine, especially as it relates to non-cancer end points.

And the first thing we want to talk about is -- you will recall in November we postulated that there was a dose duration phenomenon relative to the responsiveness of the GnRH system to atrazine's effects. And this exhibit -- it appeared in handouts.

Short duration studies of Dr. Cooper referred to these the other day, and these are his data. Single day or three day leads to no effect levels on the LH surge suppression. In our own hands we have shown

1 that for five days we get effects as low as 50  
2 milligrams per KG. Longer duration studies of  
3 the no effect levels progressively get lower  
4 and lower.

5 The Stoker 2000 is an important  
6 study, and it didn't specifically measure LH  
7 in this particular study, but it measured the  
8 time to I believe vaginal opening, which is  
9 presumed to be attributed to some effect on  
10 pulsatile GnRH release.

11 And then the Morseth study is the  
12 six-month study that Dr. Swenberg was speaking  
13 of earlier where we measured LH in female  
14 Sprague Dawley rats after they had been  
15 treated for six months.

16 We recognize that there's an  
17 interaction between duration of treatment and  
18 sensitivity to the chemical. And so we wanted  
19 to postulate or try to separate those  
20 components.

21 This slide is a recapitulation of  
22 similar kind of characterization, so that the

1 shorter duration types of studies that usually  
2 set short duration toxicologic end points for  
3 the purpose of risk assessment tend to have  
4 higher no effect levels. Not all of the  
5 responses on this slide are relating to the LH  
6 effect, so that there's information here about  
7 pregnancy loss and so on.

8 But quite a number of them  
9 actually are relating presumably to effects on  
10 the LH pulsatile release. And so you go from  
11 shorter duration early in life time at no  
12 effect levels to older animals that are, in  
13 the case of the female Sprague Dawley rat,  
14 particularly sensitive.

15 Next slide. So we designed a  
16 study that would try -- would ask the question  
17 as to whether or not the young animal is more  
18 sensitive than the older animal relative to  
19 the effects on -- atrazine's effects on LH.  
20 And for this study we had two cohorts of  
21 animals. The first cohort called Cohort 1 the  
22 dams were treated from the point of conception

1 all the way through end of lactation. The  
2 pups were receiving atrazine in their milk  
3 through the mother at that time. And post-  
4 lactationally we started gavaging the pups  
5 with the appropriate dose.

6           These cohorts run for different  
7 durations of time. And the first time that we  
8 were interested in assessing them was five  
9 days after vaginal opening. And this was the  
10 earliest time that we thought we could  
11 challenge the system to find out if the LH  
12 surge would be suppressed.

13           So that subgroup is the group that  
14 we are looking at today. And this subgroup  
15 is -- they were treated identical except the  
16 dams were not exposed and the pups only were  
17 treated post-lactationally. So we can assess  
18 whether something's special about continuous  
19 treatment versus a short-term treatment. This  
20 study is still ongoing and you see we have  
21 sacrifices coming out in the middle to late  
22 June.

1                   And these animals who will then  
2                   have additional 90 days of treatment -- again,  
3                   we'll assess the LH surge. And at that point  
4                   we're going to have a recovery subgroup just  
5                   to see -- or test the hypothesis of  
6                   reversability, which you'll hear about later  
7                   from Dr. Handa.

8                   And, likewise, we get a window on  
9                   whether the vulnerability at this time is, in  
10                  fact, due to continuous treatment or due to,  
11                  in fact, the age of the animal. So the intent  
12                  is to try to separate out those factors that  
13                  are, let's say, a buildup of effect or a  
14                  deterioration of a function as a function of  
15                  dose duration versus a simple vulnerability  
16                  change as the animals age. Obviously we have  
17                  the hypothesis that it's a vulnerability  
18                  change that has actually occurred.

19                  Next slide. And today we are  
20                  providing you the information on this. And we  
21                  have committed to the agency to provide the  
22                  full report by the end of July.

1                   Next slide. This is more cut-down  
2 version of that particular schema focusing  
3 just on the animals that we're going to talk  
4 about today. So we're going to be discussing  
5 Cohort 1 animals, subgroup A. But, in fact,  
6 for certain metrics we're going to give data  
7 for group A, B, and C. At this point in age  
8 they're all identical. Some of those animals  
9 continue on and are dosed for additional  
10 duration of time.

11                   And in addition to that we were  
12 interested in putting in a control group that  
13 would show, in fact, that laboratory and this  
14 process of treatment and so on could detect LH  
15 surge suppression. So we took animals that  
16 were 12 weeks of age and dosed them for five  
17 days at 100 mgs per kg. We selected that does  
18 because we wanted to make sure we were going  
19 to get an LH effect. It would have been  
20 tidier if we'd have used 50 mgs per kg because  
21 that is the high dose in this study. But,  
22 nevertheless, we wanted to prove that, in

1 fact, in this lab and in this operation we  
2 could actually elaborate an effect of atrazine  
3 treatment on the LH surge.

4 Next slide. So the first results  
5 are from that first cohort of animals that are  
6 only treated when they're 12 -- approximately  
7 12 weeks of age, and they're given five days  
8 of atrazine treatment. They're  
9 ovariectomized, and LH surge is induced by the  
10 implantation of an estrogen pellet.

11 The light cycles are set such that  
12 we can sample them and get appropriate blood  
13 and measure LH. And what we see is, in fact,  
14 there is and has been described many times the  
15 LH suppression of atrazine at 100 mgs per kg  
16 as measured by both mean peak height and area  
17 under the curve.

18 Next slide. The animals that were  
19 treated either throughout entirely from  
20 conception to the point of LH effect at  
21 termination were unaffected by atrazine at any  
22 dose up to 50 mgs per kg. And, likewise, the

1 cohort that was only exposed from end of  
2 lactation to onset of sexual maturation were  
3 unaffected by atrazine treatment at that age.  
4 The statistics are shown below giving area  
5 under the curve and peak height.

6 Next slide. Now, because we took  
7 these animals to sexual maturity we were  
8 smearing -- or looking for vaginal opening --  
9 onset of sexual maturation. That was the  
10 entry into the cohort effectively -- they had  
11 to reach that end point. So effectively we  
12 knew what the vaginal opening dates were or  
13 duration to.

14 And these are the three subgroups  
15 in Cohort 1, and this is the combination of  
16 the subgroups. And we can see that while we  
17 have an LH surge suppression -- or we don't  
18 have an effect of atrazine on the LH surge  
19 suppression we do have an effect in these  
20 young animals on the presumed pulsatile LH  
21 release that's attributed to regulating sexual  
22 maturation -- or at least vaginal opening.

1                   So we observe that there's an  
2                   effective treatment, and the no-effect is 25  
3                   mgs per kg in this study. That's  
4                   approximately equivalent to what had been  
5                   reported previously by Laws et al., Ashby et  
6                   al. So there's several studies. And we  
7                   weren't terribly surprised by this result, but  
8                   it is confirmation of what had been given  
9                   before.

10                   Next slide. As one nuance around  
11                   this is this is the cohort that were actually  
12                   treated for the inception onward and that  
13                   difference was statistically significant.  
14                   This difference was not and we don't  
15                   understand why that is. It's trending up, but  
16                   it's not increased enough to be significant.

17                   So that's just a piece of  
18                   information that -- next slide. Okay. That  
19                   is addressing the question of age dependent  
20                   sensitivity to this particular system, perhaps  
21                   elaborated by both the LH surge mechanism and  
22                   the pulsatile LH mechanism. Dr. Handa will

1 have considerable more to say about those  
2 processes and the effects of atrazine on them.

3 So, with that, I would stop and  
4 maybe if there's any quick questions I could  
5 take them. But perhaps we could put them all  
6 together after the next piece if that's  
7 suitable.

8 SESSION CHAIR PORTIER: Dr.  
9 Chambers?

10 DR. CHAMBERS: This is real quick.  
11 Just on the dosing, the dams were given those  
12 doses and then the pups were given the very  
13 same doses?

14 DR. BRECKENRIDGE: That's correct.

15 DR. CHAMBERS: Okay.

16 SESSION CHAIR PORTIER: Okay. Dr.  
17 Handa.

18 DR. HANDA: Okay. Good afternoon.  
19 My name is Bob Handa. I'm a professor in the  
20 Department of Basic Medical Sciences at the  
21 University of Arizona, College of Medicine.

22 Today what I'd like to do is spend

1 a little time telling you about some of the  
2 studies that are ongoing in my lab regarding  
3 the examination of the mechanisms that might  
4 underlie atrazine suppression of LH secretory  
5 patterns. I think Dr. Breckenridge showed you  
6 a number of these questions that we'll try and  
7 answer today regarding the LH -- the  
8 hypothalamic-pituitary-gonadal axis and its  
9 regulation or its modification by atrazine  
10 exposure.

11 What I'd like to do today is spend  
12 a brief period of time addressing these first  
13 six questions. I want to thank Ralph Cooper  
14 for introducing the topic. This will allow me  
15 to go a little faster here.

16 And then bulk of my time today  
17 will be spent hopefully addressing these lower  
18 two questions, and that is whether atrazine  
19 alters the secretion of other hormones, most  
20 notably those involved in the hypothalamic-  
21 pituitary-adrenal axis, and whether these  
22 changes in the HPG axis that we see following

1 atrazine administration are secondary to the  
2 changes in the HPA axis.

3           So you've seen this type of data  
4 before showing that atrazine can reduce the  
5 hormonal induced LH surge in a female rat --  
6 rodent. This is data taken from Wistar  
7 females -- young adult Wistar females. And on  
8 the left side you can see that, in fact, under  
9 hormonal stimulation there's an increase in LH  
10 that occurs in the afternoon. And when  
11 atrazine is administered by gavage at three  
12 different doses, 5100 and 200 milligrams per  
13 kilogram, we can obliterate that LH surge.

14           We went one step forward. And,  
15 again, just to verify that this, in fact,  
16 might be due to effects generated at the GnRH  
17 neuron, or above the pituitary, we asked the  
18 question as to whether these effects are  
19 mediated by changes in pituitary sensitivity  
20 to GnRH.

21           But these data show that, in fact,  
22 if we take estrogen treated ovariectomized

1 female rats and we obliterate their endogenous  
2 GnRH by passive immunization that we can then  
3 have them respond to a synthetic GnRH agonist,  
4 D-ALA-6 GnRH, and, in fact, there's no  
5 difference in the response to following  
6 several different doses of atrazine.

7 So these results suggest that the  
8 pituitary sensitivity to GnRH has not changed  
9 and that the effects we see on the HPG axis  
10 are actually due to changes in hypothalamic  
11 function.

12 Now, to address this we used a  
13 GnRH EGFP transgenic rat model -- and in this  
14 rat model has been engineered such that GnRH  
15 neurons express enhanced green fluorescent  
16 protein which allows you to visualize these  
17 neurons in situ. We can couple this  
18 immunocytochemistry for a protein called cFos,  
19 and cFos is commonly used to demonstrate  
20 neuronal activity. When neurons are active  
21 cFos is expressed within the nucleus. And  
22 what we have known for several years now is

1 that during the LH surge that GnRH neurons  
2 express cFos during the LH surge but not  
3 before and not after the LH surge.

4 So we embarked on an experiment to  
5 determine if cFos was expressed in GnRH  
6 neurons and if atrazine modified that  
7 expression of cFos. What you can see is the  
8 panel on the right -- is that during the LH  
9 surge you get about 75 percent of GnRH neurons  
10 that express cFos indicating that their  
11 active, and that at high doses of atrazine,  
12 doses that inhibit the LH surge, you actually  
13 see a much reduced activation of GnRH neurons,  
14 suggesting that GnRH neurons -- changes in  
15 GnRH neuron activity may, in fact, underlie  
16 the deficits in LH secretion that we see in  
17 those animals treated with atrazine.

18 Now, based on these findings we  
19 also hypothesized that perhaps GnRH neurons  
20 might be altered in terms of their ability to  
21 produce GnRH. As a result, we examined GnRH  
22 mRNA as shown in this slide as well as other

1 primary transcript for GnRH. And as this  
2 slide shows we found no evidence that there  
3 are alterations in GnRH synthesis or  
4 expression.

5 Also, we counted the number of  
6 cells using in situ hybridization, as well as  
7 following immunocytochemistry, and found no  
8 changes in GnRH expression throughout the rat  
9 brain.

10 As a result of these studies we  
11 hypothesized that the GnRH neuronal system may  
12 be, in fact, not altered by GnRH and that --  
13 or may not be altered by atrazine and, as a  
14 result of the response of the GnRH system to  
15 estrogen, may, in fact, recovery following  
16 cessation of atrazine treatment.

17 So in this study we examined the  
18 ability to induce an LH surge in animals that  
19 were tested two days and four days after the  
20 cessation of atrazine treatment which occurred  
21 for four days prior. What you can see, again,  
22 is that when tested immediately at the end of

1 those four daily gavages with atrazine that  
2 you can see a decrease in the peak of the LH  
3 surge, and that's coupled with a decrease in  
4 the activity of GnRH neurons as measured by  
5 Fos expression -- that within two days after  
6 the termination of treatment that the peak of  
7 the LH surge begins to recover, and it's  
8 normal by four days following cessation of  
9 treatment, and that the same occurs in the  
10 activity of GnRH neurons.

11 These data suggest then that the  
12 inhibition of GnRH and the LH surge is  
13 transient and is very rapidly recovered  
14 following the loss of exposure to atrazine.

15 We also examined pulsatile hormone  
16 secretion -- and Dr. Cooper mentioned this  
17 briefly yesterday. In the absence of hormone  
18 administration LH and GnRH are released in a  
19 pulsatile fashion. And they are coupled in  
20 time such that each quanta of GnRH that's  
21 released from the hypothalamus initiates a  
22 small pulse of LH in response.

1                   This pulsatile pattern of LH and  
2 GnRH are of physiological importance. If GnRH  
3 is released in a constant fashion it very  
4 quickly loses the ability to drive LH  
5 secretion.

6                   So in these data you can see that,  
7 in fact, if we sample quickly enough we can  
8 identify discrete increases in LH secretion  
9 with a pulse period of about 30 minutes. And  
10 if we treat animals with atrazine ultimately  
11 what we see is something that looks like this  
12 where the number of pulses in a sampling  
13 session is dramatically reduced. And when we  
14 do see those pulses they're much larger. This  
15 suggests that there is a disruption of the  
16 GnRH pulse generator, and that's a very  
17 important component of the hypothalamic-  
18 pituitary-gonadal axis.

19                   Now, just to show you that this  
20 is -- my last slide showed you pulses of LH.  
21 Just to show you that the same changes occur  
22 in regard to GnRH secretion we began to

1 examine GnRH release in an ex vivo system  
2 where hypothalamic slices were peri-fused with  
3 media, and the results are shown here.

4 Animals were treated with 200 milligrams per  
5 kilogram atrazine for four days.

6 The hypothalami were removed.

7 They were put into the superfusion chamber and  
8 then we examined pulsatile GnRH release from  
9 these hypothalami. And what you can see is  
10 hypothalami taken from control animals have  
11 normal looking pulses of GnRH, which, again,  
12 occur about every 30 minutes. And hypothalami  
13 taken from animals that were treated with 200  
14 milligrams per kilogram atrazine you can see  
15 that the GnRH pulses are dramatically reduced  
16 in frequency, and when they do show up they're  
17 dramatically elevated in amplitude.

18 As a result we see no real change  
19 in mean GnRH levels or area under the curve.  
20 It's really just the dynamics of the system.  
21 Peak amplitude is increased and the number of  
22 peaks is reduced by atrazine.

1                   Okay. So I want to change gears  
2                   just a little bit. I think those data  
3                   indicate that there are dramatic effects of  
4                   atrazine on the hypothalamic-pituitary-gonadal  
5                   axis, both in terms of pulsatile hormone  
6                   secretion, as well as the generation of the  
7                   pre-ovulatory surge of LH.

8                   And we embarked on a series of  
9                   studies -- I'll tell you a little bit about  
10                  this one. Looking for change -- potential  
11                  changes in endocrine and immunological  
12                  function within male Sprague Dawley rats the  
13                  design of the experiment looks like this where  
14                  we have animals that were treated with three  
15                  different doses of atrazine -- 6.5, 25, and  
16                  100 milligrams per kilogram per day for either  
17                  1, 7, 14, or 28 days. The animals at 28 days  
18                  will be taken for an examination of  
19                  immunological function by Steve Pruett.

20                  We were able to take these animals  
21                  on 1, 7, and 14, and that's the data I'll  
22                  report to you today. We have not yet analyzed

1 these -- the blood from these animals at 28  
2 days.

3 So the design of the experiment  
4 then was to treat the animals with atrazine or  
5 a vehicle control and then to sacrifice them  
6 30 minutes after the end of gavage and examine  
7 the influence of that atrazine -- acute  
8 treatment of atrazine on a number of different  
9 hormones.

10 Now, I have to tell you a little  
11 bit about our approach to measuring these  
12 hormones. We use classical antibody based  
13 approaches to measure hormones such as  
14 corticosterone, prolactin, and progesterone,  
15 as well as ACTH. I won't report the data on  
16 ACTH -- we don't have it yet.

17 We also used a different  
18 approach -- liquid chromatography tandem mass  
19 spectrometry was used to measure the serum  
20 estrogens -- estrone, estradiol, and  
21 estriol -- as well as the androgens --  
22 androstenedione, testosterone, and

1 dihydrotestosterone -- and we have not yet  
2 obtained the data on aldosterone levels.

3           Now, why would we want to use the  
4 LCMS to measure steroid hormones? I think  
5 there's been recently a controversy regarding  
6 the ability to measure estrogens and androgens  
7 using antibody based approaches. There's some  
8 evidence that there's very low fidelity in the  
9 different assays that are used to measure  
10 these hormones, particularly when you get to  
11 low levels. And by low levels we mean about  
12 100 picograms or less. We also used  
13 deuterated steroids as internal standards so  
14 that we could identify exactly where peaks of  
15 these hormones ended up on the chromatograms.

16           Let me just briefly describe the  
17 biosynthesis of steroid hormones so you can  
18 which of these hormones we began to examine.  
19 All steroid hormones are derived from a common  
20 precursor, and that precursor is cholesterol,  
21 which is taken up into steroid synthesizing  
22 tissues. It's then transferred into the

1 mitochondria by this steroidogenic acute  
2 regulatory protein, and then it's acted upon  
3 by a number of enzymes. The rate limiting  
4 enzyme is P450 side chain cleavage. And, as  
5 a result, you can see that then flows downhill  
6 depending on the presence of these different  
7 enzymes in different tissues.

8 But what you can immediately see  
9 here is these hormones that are -- these  
10 steroids that are indicated in green are the  
11 progestins, and they actually give rise to all  
12 the other steroid hormones -- the  
13 mineralocorticoids, such as aldosterone, the  
14 glucocorticoids, such as cortisol, the  
15 androgens, such as androstenedione,  
16 testosterone, and DHT, which are the  
17 predominant androgens found in the rat. And  
18 androgens give rise to the estrogens --  
19 estrone, estradiol, and estriol -- which are  
20 the predominant estrogens also found in the  
21 rat.

22 So we measure plasma levels of

1 progesterone, of aldosterone, of  
2 corticosterone, androstenedione, testosterone,  
3 dihydrotestosterone, estrone, estradiol, and  
4 estriol.

5           And I'll show you the results of  
6 these studies. I should first tell you a  
7 little bit about some of the other results  
8 from this series of studies. Again, animals  
9 were kept on atrazine at least three doses for  
10 up to 28 days, and this is the result of  
11 results showing changes in body weight. I  
12 think someone from the panel asks whether  
13 atrazine alters body weight, and what you can  
14 see here is at the highest dose -- 100  
15 milligrams per kilogram -- per day there's a  
16 significant decrease in body weight. The  
17 changes that you see at the 6.5 and the 25  
18 milligram per kilogram dose did not reach  
19 significance.

20           Someone else also asked whether  
21 there are effects of atrazine on adrenal  
22 weight yesterday, and we will report now that

1 there was no effect of atrazine at any one of  
2 the three doses on adrenal weight, whether  
3 calculated on absolute adrenal weight or an  
4 adrenal weight to body weight ratio.

5 What we find if we look at some of  
6 these hormones -- for example,  
7 corticosterone -- we find that, in fact,  
8 following the initial treatment with atrazine,  
9 we see a very dramatic increase in  
10 corticosterone. Again, this is 30 minutes  
11 after gavage, and we see that there is a dose  
12 response curve. We have not yet found the no-  
13 effect level because 6.5 milligrams per  
14 kilogram effectively increases corticosterone,  
15 but albeit not to the degree seen following  
16 100 milligrams per kilogram.

17 Of interest is the fact that after  
18 seven daily doses of atrazine we see no  
19 increase in corticosterone in these animals.  
20 And this is maintained throughout day 14 -- or  
21 14 daily doses -- suggesting that the response  
22 of these animals -- of male Sprague Dawley

1 rats to atrazine is habituated somewhere  
2 between the first and the seventh day of  
3 treatment.

4 We continue on. We can measure  
5 progesterone, and progesterone is another  
6 hormone -- steroid hormone of adrenal origin  
7 in the male. Progesterone is largely secreted  
8 in response to ACTH administration. And what  
9 you can see is the same thing that happens for  
10 corticosterone also occurs for progesterone.  
11 Within 30 minutes after the first injection of  
12 atrazine, we see dramatic increases in  
13 progesterone, which are lost by the seventh  
14 and the fourteenth exposure to atrazine.

15 Interestingly, there are no  
16 changes in prolactin to response to atrazine  
17 administration at any of the doses for any of  
18 the time periods. And this suggests that the  
19 effects of atrazine on corticosterone and  
20 progesterone are not a generalized stress  
21 response because in most instances prolactin  
22 rises following a stressor.

1                   We also examined the androgens, as  
2                   I indicated, using LCMS. These are the  
3                   results shown here. We find no effect of  
4                   atrazine at 1 or 7 or 14 days of treatment at  
5                   any of the doses on plasma levels of  
6                   androstenedione, testosterone or  
7                   dihydrotestosterone. There is a trend for the  
8                   longest time point examined -- 14 days -- and  
9                   the highest dose -- 100 milligrams per  
10                  kilogram -- to reduce androstenedione levels.  
11                  But these did not reach significance.

12                  Similarly, we also measured the  
13                  estrogens -- estradiol, estrone, and estriol.  
14                  And what we report now is that for all the  
15                  groups there was a substantial number of them  
16                  below assay sensitivity -- more than 50  
17                  percent in every group. And as a result we  
18                  have to report that the average values are  
19                  below assay sensitivity.

20                  The sensitivity of this assay is  
21                  very low in terms of milligram -- or picograms  
22                  per ML. For estradiol and estrone it's 2

1 picograms per ML. For estriol it's 10  
2 picograms per ML. And for the rodent that's  
3 at the very low physiological end of the  
4 scale.

5 These chromatograms then show  
6 standards for each of these hormones -- and  
7 you can see it's very selective in terms of  
8 what we're measuring. And so we have an assay  
9 that is very specific and very sensitive, and  
10 we aren't measuring changes in any of the  
11 estrogens. This assay was originally  
12 developed by Steve Soldin at Georgetown  
13 University to measure low levels of estrogens  
14 and androgens.

15 So this suggests that, in fact,  
16 there are some changes in response to atrazine  
17 in the male. To be honest, we have not yet  
18 run as extensive an experiment in females.  
19 This is a little bit harder to address just  
20 because of the cyclicity of females. But,  
21 nonetheless, I'll try and piece together the  
22 results of several different studies to

1 demonstrate to you that, in fact, there may be  
2 similar changes that occur in females.

3           So in this study we examined the  
4 acute response of the components of the HPA  
5 axis, particularly corticosterone on --  
6 following atrazine administration at two  
7 different doses of 50 and 200 milligrams per  
8 kilogram -- and what we see, in fact, in  
9 females -- ovariectomized females that we find  
10 a very rapid increase in corticosterone that  
11 peaks within 20 minutes. And at the highest  
12 dose these levels of corticosterone are  
13 actually maintained elevated for up to 12  
14 hours. So this is a very unusual type of  
15 corticosterone response in that it's extended  
16 for a long period of time. At lower doses,  
17 the response is much briefer, and we get a  
18 peak which rapidly drops down to the levels of  
19 the controls. You can also see here that  
20 gavage by itself causes an increase in  
21 corticosterone.

22           Results taken from a different

1 study in which animals were exposed to five  
2 daily doses of atrazine at the 100 milligram  
3 per kilogram dose show that, in fact, after  
4 five daily doses, we seem to find also that  
5 there's an increase in corticosterone. In  
6 particularly, these animals were also measured  
7 for LH responses to estrogen, and we find no  
8 LH surge in response to estrogen.

9 And, lastly, in this series of  
10 slides, I want to introduce some studies  
11 performed by Dr. Pruett who will address these  
12 in more detail shortly in that he used female  
13 mice -- not rats. These animals were  
14 administered atrazine for up to 28 days. They  
15 were administered in a different route --  
16 intraperitoneally. But what you can see if  
17 after a single exposure to atrazine that  
18 there's a dramatic rise in corticosterone --  
19 the levels in mice are much greater than those  
20 achieved in rats -- and that this is  
21 maintained for over four hours and that 28  
22 days later -- after 28 daily exposures to

1 atrazine you find the same effect is present,  
2 suggesting that in females there's very little  
3 habituation to atrazine exposure in that  
4 corticosterone responds in a similar fashion  
5 through at least four weeks.

6 Okay. So this begs the question  
7 as to whether or not the product of the HPA  
8 axis -- that is corticosterone -- can  
9 influence the HPG axis. And we know from a  
10 number of studies that corticosterone and  
11 perhaps CRH can negatively impact the  
12 hypothalamic-pituitary-gonadal axis.

13 So we asked the question as to  
14 whether or not if we disrupted this axis,  
15 particularly if we adrenalectomized the  
16 animals, whether this would affect the ability  
17 of atrazine to disrupt the hypothalamic-  
18 pituitary-gonadal axis.

19 The design of the study was to  
20 adrenalectomize or sham adrenalectomize these  
21 animals and then begin treatment with 200 or  
22 50 milligrams per kilogram atrazine. And at

1 the end, initially we examined these animals  
2 for pulsatile hormone secretion. We used a in  
3 dwelling right atrial cannula to collect  
4 samples every five minutes for a three-hour  
5 period. If you remember from our previous  
6 results, atrazine normally decreases the  
7 frequency of these pulses and increases the  
8 amplitude of these pulses.

9           These are the results of this  
10 study in which in the sham animals, again, you  
11 can see following exposure to -- well,  
12 following exposure to atrazine at these two  
13 doses you see a decrease in pulse frequency  
14 coupled with an increase in pulse amplitude.  
15 And if we remove the adrenals you see no  
16 effects of atrazine on those hormonal changes,  
17 suggesting that pulsatile LH is driven by  
18 changes in corticosterone levels.

19           Of course, we also examined the  
20 hormonal induced surge of LH and asked the  
21 question as to whether adrenalectomy can block  
22 the effects of atrazine on the estrogen

1 induced LH surge. And remember that atrazine  
2 very potently inhibits the LH surge.

3           These are the results of that  
4 study. We can induce an LH surge with  
5 estrogen and progesterone. That treatment  
6 with atrazine reduces the peak amplitude and  
7 the area under the curve of LH secretion, and  
8 that in the adrenalectomized animals those  
9 effects of atrazine are identical, suggesting  
10 that for the LH surge generation that adrenal  
11 secretions are not responsible for the  
12 inhibition seen by atrazine treatment.

13           Okay. So let me summarize very  
14 quickly here. What we know is that atrazine  
15 increases corticosterone and progesterone  
16 secretion within 30 minutes after a single  
17 treatment. But this disappears by 7 or 14  
18 days in male Sprague Dawley rats. That in  
19 females, atrazine also increases  
20 corticosterone following a single dose and  
21 that this -- these levels may remain elevated  
22 for a long period of time and that females do

1 not seem to habituate to this effect as do  
2 males.

3 We find no effect of atrazine on  
4 prolactin, on any of the androgens measured,  
5 or on any of the estrogens measured. And this  
6 suggests that changes in vitro -- reported in  
7 in vitro studies showing increases in  
8 aromatase may not actually correspond to  
9 physiological changes in hormone levels.

10 And, lastly, we show that  
11 adrenalectomy blocks the effects of atrazine  
12 on the LH pulses, but doesn't block the  
13 effects of atrazine on the LH surge. And this  
14 suggests that the effects of corticosterone on  
15 the HPG axis may not come into play in terms  
16 of the loss of cyclicity seen in these animals  
17 with age.

18 So some key points I want you to  
19 remember when driving home tonight, and that  
20 is that high doses of atrazine can inhibit the  
21 HPG axis -- I know you're all going to be  
22 thinking about this on the way home -- and

1 that the effects on the HPG axis are reversed  
2 following cessation of treatment, that the  
3 effects of atrazine on the HPG axis are  
4 secondary, perhaps to changes in HPA axis  
5 activity in that adrenalectomy can block the  
6 effects of atrazine on pulsatile hormone  
7 secretions but not on the LH surge.

8 And the fact is that at this point  
9 in time we find no effects of atrazine on  
10 circulating androgen or estrogen levels in  
11 male rats using LCMS.

12 So some of the things that we're  
13 approaching in terms of identifying how this  
14 might work, we are testing the ability of  
15 atrazine to activate CFR neurons or the  
16 hypothalamic centers -- neurons involved in  
17 regulating the HPA axis. We can passively  
18 immunoneutralize HCTH and get HCTH out of the  
19 picture, and that will tell us whether  
20 atrazine can effectively activate the adrenal  
21 directly.

22 And we also want to determine

1       whether the effects of atrazine we see on  
2       hormone secretion are differences between our  
3       measurements and those of other labs are due  
4       to methodological considerations, and so we're  
5       going to measure using antibody based assays  
6       as well as LCMS assay to measure these  
7       changes. Are there any questions?

8                   SESSION CHAIR PORTIER: Yes. Dr.  
9       Horton?

10                   DR. HORTON: Thank you. Theresa  
11       Horton, Northwestern University. In the  
12       female estrocycle or menstrual cycle,  
13       whichever group of species you want to  
14       consider, there's a switch between a period of  
15       negative feedback and positive feedback. And  
16       it appears that what you have delineated in  
17       your work here is potentially a need to focus  
18       on those two separate components of the cycle  
19       independently, and that the HPA axis  
20       components may be, in fact, impacting the  
21       negative feedback components, if that is  
22       influencing the pulsatile secretion. Would

1 you agree with that?

2 DR. HANDA: I'm not sure --

3 DR. HORTON: Or suggest --

4 DR. HANDA: I'm not sure I would  
5 agree with that completely. The pulses that  
6 we measured in terms of pulsatile LH  
7 secretion, of course, were measured in the  
8 absence of negative feedback.

9 DR. HORTON: Right.

10 DR. HANDA: That's the only way we  
11 can actually see that.

12 DR. HORTON: Okay.

13 DR. HANDA: Okay. So we don't  
14 really know if, in fact, there's a change in  
15 sensitivity to estrogen negative feedback. We  
16 have to address that --

17 DR. HORTON: That's true.

18 DR. HANDA: -- by actually looking  
19 at the ability of estrogen to inhibit those  
20 pulses and then we will be able to answer  
21 that.

22 DR. HORTON: Okay. And the second

1 part to that is then the LH surge mechanism is  
2 a positive feedback mechanism. And since  
3 there's ample evidence that there is something  
4 altering that positive surge mechanism it  
5 appears the potential of that needs to be  
6 investigated independently and maybe a  
7 component of impacts that may be part of  
8 modification of the HPG regulatory mechanisms.

9 DR. HANDA: And I agree with that  
10 completely.

11 DR. HORTON: Okay.

12 DR. HANDA: I think we are looking  
13 at two different, although related, mechanisms  
14 driving LH and GnRH neural activities --

15 DR. HORTON: Okay.

16 DR. HANDA: -- and that just  
17 because we influence one doesn't necessarily  
18 say that we can influence the other.

19 DR. HORTON: Okay. Thank you.

20 DR. HANDA: So it appears that  
21 corticosterone may -- the system may be much  
22 more sensitive to corticosterone when we

1 measure pulsatile hormone secretion.

2 DR. HORTON: Thank you.

3 SESSION CHAIR PORTIER: Dr.

4 Selvage?

5 DR. SELVAGE: Yes. That was very  
6 nice. You addressed a lot of the questions  
7 that I've been asking myself in the past  
8 couple of weeks here. I just had a couple of  
9 questions, and you went pretty fast so if I  
10 just missed something forgive me.

11 So in your chronic studies when  
12 you gave atrazine chronically, did you ever  
13 measure cort levels, you know, like, say,  
14 prior to the atrazine application?

15 DR. HANDA: No, we didn't.

16 DR. SELVAGE: Okay.

17 DR. HANDA: No, we didn't. All  
18 the analyses were done as compared to the  
19 vehicle treated control at the same time.

20 DR. SELVAGE: Okay. I think that  
21 would be a useful measure.

22 DR. HANDA: It would add a number

1 of animals to the group --

2 DR. SELVAGE: Yes.

3 DR. HANDA: -- and so, you know, in  
4 order to save some animal --

5 DR. SELVAGE: Okay.

6 DR. HANDA: -- life we --

7 DR. SELVAGE: And just a technical  
8 question, in your ex vivo GnRH studies what  
9 was the media that you dissolved the atrazine  
10 in? You know, I've been thinking, well, you  
11 can shoot this stuff in ICV or whatever, but  
12 you'd probably get a -- you know, a vehicle  
13 effect if you tried to do that.

14 DR. HANDA: Right.

15 DR. SELVAGE: So what media did  
16 you use for that?

17 DR. HANDA: So that was using  
18 artificial CSF. Again, that was all in  
19 vitro --

20 DR. SELVAGE: Right.

21 DR. HANDA: -- that tissue was  
22 taken out.

1 DR. SELVAGE: Right.

2 DR. HANDA: We made sagittal

3 slices and then placed them into the

4 superfusion chambers and ran artificial CSF

5 over the top of that, either containing --

6 well, in this case there was nothing else in

7 that CSF. So the atrazine exposure became --

8 came earlier than the examination of pulses.

9 Okay?

10 DR. SELVAGE: That's it for now.

11 DR. HANDA: Okay. Thank you.

12 SESSION CHAIR PORTIER: Dr.

13 LeBlanc?

14 DR. LEBLANC: That was a very nice

15 presentation. So one of the take-home

16 messages that that I got from it was that

17 males habituate and females don't with respect

18 to corticosteroid -- or atrazine treatment

19 with respect to corticosteroid levels. It

20 wasn't obvious to me as to why. Is there an

21 obvious mechanism there or reason?

22 DR. HANDA: I don't think there's

1 an obvious mechanism. Obviously sex  
2 differences in stress responses have been  
3 explored for years and years. And one of the  
4 things that has come about if you look at the  
5 literature is that there are some sex  
6 differences in habituation to a stressor.  
7 And, again, females don't necessarily  
8 habituate as fast as males. That's stressor  
9 specific. It usually involved estrogen and  
10 testosterone being onboard. In this case  
11 we're using a very different system so we  
12 can't really say why males may habituate and  
13 females won't.

14 DR. LEBLANC: At least at face  
15 value, it seems that there's some lack of  
16 concordance between what we saw just now and  
17 some of the studies we were exposed to  
18 yesterday -- things like testosterone levels  
19 being affected or not being affected,  
20 estradiol levels being affected or not being  
21 affected.

22 And, again, I guess my question's

1 a general one. Have you -- is it obvious to  
2 you why we see these inconsistencies? Is  
3 it -- if I look more closely at the dosages,  
4 would that explain it or the sex differences  
5 or the duration of exposure?

6 DR. HANDA: What we believe is  
7 that when measuring -- and I should go back to  
8 a couple of recent reports, one by the College  
9 of American Pathologists, where they did a  
10 test and submitted samples to a number of  
11 different companies for measuring estrogen,  
12 testosterone by antibody based assays. They  
13 left it up to the companies.

14 They found a variation within what  
15 those companies produced using different  
16 antibodies of up to ninefold from the lowest  
17 to the highest, the idea being that when you  
18 use the antibody to measure something you're  
19 really dependent on the specificity and the  
20 sensitivity of that antibody to detect it.

21 And there have been some reports  
22 that antibodies may -- especially steroid

1 antibodies because they're directed against a  
2 very small molecule -- that they may interact  
3 with something that we call a matrix. Okay?  
4 And that's really a fancy word for something  
5 in the assay tube. And as a result we don't  
6 necessarily get the exact right levels,  
7 especially when we're looking at low levels.

8 But, again, we're going to test  
9 that by trying to directly compare our  
10 measurements using LCMS versus an antibody  
11 based approach.

12 SESSION CHAIR PORTIER: Dr. Schlenk  
13 and then Dr. Regal.

14 DR. SCHLENK: Yes. Just to follow  
15 up on Jerry's comment there. Am I right in  
16 terms of your slide saying that you didn't  
17 detect any estrogen in any group in the  
18 controls?

19 DR. HANDA: The majority of  
20 animals had levels below detectability. We  
21 did detect some.

22 DR. SCHLENK: Even the controls.

1 DR. HANDA: Even in the controls.  
2 And the idea is that circulating estrogen  
3 levels are not very high in males. They are  
4 in females -- well, in rats the highest level,  
5 physiological levels are in about the 50  
6 picogram per ml range and basal levels are in  
7 the 10 to 15 picogram range for estradiol,  
8 which means in males they're going to be way  
9 down there in the 2 picogram range -- very  
10 difficult to detect.

11 DR. SCHLENK: Okay. Because, I  
12 mean, if I compare slide 13 -- I mean, they're  
13 in the 20 to 40 picogram per ml range, and  
14 you're saying there's that much discrepancy  
15 between an RIA and your LCMS method?

16 DR. HANDA: I mean, basically  
17 there's that much discrepancy between RIAs.  
18 Okay. So if you examine different places that  
19 use different assays -- different  
20 antibodies --

21 DR. SCHLENK: Sure.

22 DR. HANDA: -- to detect estrogen

1 levels sometimes you'll see a 10 and sometimes  
2 you'll see an 80. And even if it's the same  
3 sample --

4 DR. SCHLENK: Well, I understand  
5 that. That's --

6 DR. HANDA: -- it's got much  
7 variation.

8 DR. SCHLENK: That's a pretty  
9 small variation I would think as opposed to a  
10 tenfold difference. That seems pretty  
11 dramatic actually, I mean, particularly when  
12 you're not seeing any estrogen in a --

13 DR. HANDA: And, again, I can only  
14 say, again, we measured estrogen levels in  
15 those females that we showed following -- up  
16 to 12 hours of increases following  
17 corticosterone. And, again, we see no  
18 detectable estrogen -- estradiol levels in  
19 those animals.

20 DR. BRECKENRIDGE: Mr. Chairman, I  
21 submit that this is an experimental question  
22 that we'll elucidate, and we'll do it by

1 making comparisons between the two  
2 methodologies and then we'll come back. Thank  
3 you.

4 SESSION CHAIR PORTIER: Dr. Regal  
5 and Dr. O'Byrne.

6 DR. REGAL: Just back to that  
7 habituation thing for a second, you know that  
8 male rats habituate but female mice don't.  
9 You don't know about -- so you've got two  
10 species in there too. Right?

11 DR. HANDA: Exactly. And that was  
12 the caveat with the study. We piecemealed  
13 together evidence from a number of different  
14 studies. We know that five days of treatment  
15 in rats -- they still show a response. But  
16 that's not inconsistent with the data we  
17 showed in the male because we only looked at  
18 seven.

19 DR. O'BYRNE: I was about to say a  
20 mouse is not a small rat. But can I ask you  
21 a question about Fos. It's a very powerful  
22 tool. And you showed complete obliteration of

1 the LH surge with your 50 milligram dose, but  
2 very little -- well, you don't show  
3 significant tenuation of the Fos activation.  
4 How do you account for that?

5 DR. HANDA: So we don't know for  
6 sure. And the idea with the Fos is we're  
7 taking a snapshot of Fos expression at one  
8 particular time. Okay?

9 DR. O'BYRNE: Of course.

10 DR. HANDA: Which was 1700 hours,  
11 which is what we estimated beforehand about  
12 the peak of the LH surge. Now, when the LH  
13 surge is reduced in amplitude, but perhaps not  
14 all the way, sometimes it shifted --  
15 oftentimes we see it shifted in time. Okay?  
16 So the induction of Fos expression in GnRH  
17 neurons is time locked so that it doesn't just  
18 pop on in all neurons. It slowly creeps up on  
19 all those neurons and you kind of see a wave  
20 of Fos expression occurring through the  
21 population of GnRH neurons. If we miss the  
22 peak we're going to hit something that's not

1 necessarily as robust.

2 DR. O'BYRNE: So delay in the  
3 surges is reasonable, and there's evidence for  
4 that as well.

5 DR. HANDA: In fact, every time  
6 we've measured the presence of an LH surge but  
7 reduce in size that surge is delayed in onset.  
8 The samples I showed you today -- it was  
9 basically obliterated so you couldn't tell  
10 that.

11 DR. O'BYRNE: I have one other  
12 question relating to the adrenalectomy. I  
13 mean, I'm fascinated that you can't block the  
14 effects of the surge. What do you think is  
15 going on there?

16 DR. HANDA: We were very surprised  
17 when that happened. I don't know. We have no  
18 idea --

19 DR. O'BYRNE: So it's quite  
20 critical, isn't it?

21 DR. HANDA: It is. It is. And so  
22 we are very happy when we saw that there was

1 a decrease of the obliteration of the effect  
2 on LH pulses. We expected to see a  
3 decrease -- or prevention of the inhibition of  
4 the LH surge following adrenalectomy -- didn't  
5 show up. And so we're scratching our heads  
6 and we've got to go back and figure out why  
7 that is.

8 DR. O'BYRNE: You're not only one.

9 SESSION CHAIR PORTIER: Last two  
10 questions and then we'll move on. Let me  
11 start with -- actually let's do Dr. Akana.  
12 You had one already.

13 DR. AKANA: On your reversal with  
14 the removal of atrazine did you measure  
15 corticosterone in those animals?

16 DR. HANDA: Unfortunately we  
17 didn't --

18 DR. AKANA: Okay.

19 DR. HANDA: -- because it was  
20 much earlier on before we began to explore the  
21 contribution of corticosterone.

22 DR. AKANA: And Part B, on your

1 long body weight studies where you had the  
2 per-fed controls -- okay, so these are running  
3 28 days -- have you started considering to  
4 measure leptin or to measure nasal-anal length  
5 to see what kind of growth you are getting in  
6 the two different -- the control food  
7 restricted and the high dose?

8 DR. HANDA: That's an excellent  
9 idea. I think we should consider that.

10 DR. SELVAGE: Dan Selvage again.  
11 Just one question. Hopefully I'm not going  
12 off on too much of a tangent. But considering  
13 your expertise in HPA and HPG axes, do you  
14 think there could be a disruption of the  
15 neuradrenergic -- central neuradrenergic  
16 system going on that could explain both of  
17 these effects?

18 DR. HANDA: That's a possibility.  
19 That's been suggested before actually by Dr.  
20 Cooper in terms of some of the data that he's  
21 been able to garnish over the last ten years.  
22 And so I would not want to misinterpret his

1 data. I guess I'd have to ask him more  
2 specifically after this.

3 SESSION CHAIR PORTIER: I think at  
4 this point we'll move on and forewarn Dr.  
5 Pruettt that he's going to face a lot of  
6 questions. Linda, do you have a quick  
7 question? I kept -- I thought I kept seeing  
8 something but I --

9 DR. YOUNG: No. I just -- I'm  
10 really surprised that some of these results  
11 aren't significant. So I was just questioning  
12 kind of what's -- whether you powered your  
13 study and what kind of numbers you had in your  
14 treatment groups along the way.

15 DR. HANDA: Which experiment  
16 are -- in particular are you referring to?

17 DR. YOUNG: This is one. I mean,  
18 over time when it -- the two lines are  
19 consistently below the control you would think  
20 you'd be picking up significance for most  
21 analyses, yes.

22 DR. BRECKENRIDGE: Okay. So

1 that's about a 5-1/2 percent reduction in gain  
2 on those ten animals in the group when you  
3 start to -- I mean, we're not discounting that  
4 those are probably treatment-related effects.  
5 But it's a statistical detection phenomenon.  
6 And so that's typical -- that statistical  
7 significance with that kind of -- and on body  
8 weight reaches levels when you start to get  
9 around 8, 9 percent reduction.

10 And that's -- clearly is a trend  
11 there that indicates there's a compound effect  
12 on body weight. It's interesting that they  
13 don't discriminate between each other at 25 or  
14 6.5 mgs per kg. And so there's other  
15 possibilities.

16 Mr. Chairman, if I could, I just  
17 want to kind of give a segue now to the  
18 immunotox presentation. So we've been  
19 spending a lot of time describing  
20 endocrinological characterization. And the  
21 immunotox area is a somewhat unique advantage  
22 to actually do a translational research from

1 end point measurement into -- things really  
2 matter for the well-being of the animal or the  
3 human. And this is systems impacts and  
4 adverse effect outcome.

5 So Dr. Pruett is especially in  
6 that topic, and I think you'll see a  
7 connection between the work on the cort  
8 systems and the immune system response.

9 DR. HANDA: We need Joseph Bailey  
10 here to to unlock the computer.

11 DR. YOUNG: It's just that it  
12 makes me question what methods you used in the  
13 analysis. If you have something with that  
14 many time points straight that's consistently  
15 below, to not pick that up indicates that --  
16 it makes me question statistical methodology.  
17 So just for a comment.

18 DR. BRECKENRIDGE: Thank you.  
19 We'll look at that very carefully. I should  
20 say that most of this data has come in over  
21 the last days, so that it's not exactly well-  
22 examined at this point. Thank you.

1 DR. PRUETT: Ready? Okay. Thank  
2 you very much for the opportunity to speak to  
3 you today. I want to thank Dr. Bob Luebke for  
4 setting the stage for this presentation. He  
5 gave us a very nice overview yesterday of the  
6 effects of atrazine on immunological  
7 parameters.

8 I'm not going to try to reiterate  
9 all of that, but I would like to focus on a --  
10 narrow down just a little on one of the  
11 components of that, particularly because it  
12 also ties into the discussion that we've just  
13 been having about endocrine effects of  
14 atrazine.

15 I should also tell you that these  
16 studies were not done on behalf of Syngenta.  
17 These were studies that were from an NIH-  
18 sponsored grant, and then also one of the  
19 experiments I'll show is from a project with  
20 Pfizer.

21 And really the basis for those  
22 studies -- the reason for those studies is

1 that, quite often, when chemicals are being  
2 tested for safety near the maximum tolerated  
3 dose there's often a non-specific stress  
4 response associated with that. And the exact  
5 quantitative contribution of that response to  
6 immunological end points had not been  
7 investigated previously. And that's really  
8 what this -- these experiments were designed  
9 to do. But it turns out I think they do have  
10 something to say about the questions at hand  
11 today with regard to atrazine.

12 You've seen the diagram of the HPA  
13 axis, so I won't go into that again. Suffice  
14 it to say that corticosterone, in addition to  
15 feeding back and controlling that axis and  
16 also contributing to effects in the HPG axis,  
17 also affects the immune system at both the  
18 organ, cellular, and functional levels.

19 I've indicated a couple of  
20 parameters by underlining them that I will  
21 mention again as we go through some data.  
22 Natural killer cell function and antibodies --

1 both of those have been selected. In fact,  
2 those are two of the ones that have been  
3 identified by EPA and FDA in their guidance  
4 documents as functional immunological  
5 parameters that would be useful in evaluating  
6 immunotoxicity.

7 First, the approach that we've  
8 taken has been a little different than what  
9 most investigations have done in terms of  
10 evaluating, not single time points of the  
11 corticosterone level, but rather looking at  
12 the area under the curve.

13 And the value of that can be  
14 illustrated in these graphs. You can see that  
15 we've dosed mice with 100, 200, and 300  
16 milligrams per kilogram, single dose, and then  
17 we follow them over a period of hours and  
18 measure corticosterone in the blood.

19 And what you can see is that, if  
20 you look at the hour one values, they are  
21 between 8- and 900 for all three dosages.  
22 That -- if that was the only information you

1 had you would conclude that corticosterone is  
2 affected very, very similarly by all three  
3 doses and that there was not really a dose  
4 response pattern. And, therefore, if you saw  
5 a dose response in immunological effects you  
6 would assume that it wasn't glucocorticoid  
7 related.

8           However, if you measure area under  
9 the curve -- and you can see those values up  
10 at the top of each graph -- those are very  
11 nicely dose dependent. And we have graphed  
12 those and they are for a number of different  
13 stressors over a considerable time period.

14           So one of the interesting  
15 parameters that we've evaluated is the  
16 expression of the major histocompatibility  
17 complex class 2 protein on spleen cells. This  
18 protein is involved in presenting foreign  
19 antigens to T cells and it's a critical  
20 component, both of the antibody response and  
21 the T cell mediated acquired immune response.  
22 And it turns out to be one of the most

1 sensitive parameters in terms of the effects  
2 of glucocorticoids.

3           What you can see on these graphs  
4 is that at 100, 200, and 300 milligrams per  
5 kilogram on the left, if we plot those data in  
6 terms of corticosterone area under the curve  
7 instead of using the milligram per kilogram  
8 dosage you can see that the effects of  
9 exogenous corticosterone, which are indicated  
10 by the dotted line, and restraint stress,  
11 those effects are quite similar to the effects  
12 that we see on an equivalent area under the  
13 corticosterone concentration versus time curve  
14 as we see with atrazine. Those values -- or  
15 the elevations and the slopes of those lines  
16 are not significantly different.

17           If we look at dose values and  
18 compare one-day and 28-day exposures, we also  
19 see there that there is really no difference  
20 in the corticosterone production one day as  
21 compared to 28 days. So, as has already been  
22 mentioned, no sign of habituation in these

1 female mice in this particular study.

2 I'd also point out that the low  
3 dose at the 28-day -- in the 28-day group is  
4 37.5 milligrams per kilogram, and if we just  
5 did a simple -- ANOVA comparing the doses in  
6 either of these studies we find that that  
7 difference between the control and the low  
8 dose is not significant. And, in fact, it  
9 doesn't get significant until we get to about  
10 100 milligrams per kilogram. And that's  
11 generally the case in -- for all of the  
12 immunological parameters that we've measured.  
13 This is the most sensitive immunological  
14 parameter that we've measured in this series  
15 of studies.

16 Natural killer cells I mentioned  
17 are an important parameter in determining  
18 overall immunotoxicity, and they are also  
19 decreased in a linear manner predictable by  
20 area under the corticosterone concentration  
21 versus time curve, and also quite similarly to  
22 the effects of corticosterone, exogenous

1 corticosterone, and restraint, which were  
2 designed to give similar area under the curve  
3 values.

4 This is an experiment where we're  
5 changing gears a bit and looking at male  
6 Sprague Dawley rats. And this is a project  
7 that I did with Pfizer. And the idea here was  
8 that new guidance documents indicated that the  
9 FDA would no longer take investigators' word  
10 for it that thymus decreases and other things  
11 that are typical -- other changes typical of  
12 stress responses are due to a non-specific  
13 stress response. They indicated that from now  
14 on there would need to be evidence of a stress  
15 response along with those immunological  
16 changes to make the case that there was, in  
17 fact, a stress response causing those  
18 immunological effects.

19 So one of the easy ways to measure  
20 a stress response, rather than bleeding, to  
21 get blood values for corticosterone is to take  
22 urine samples. And what we found is that a

1 six-hour urine sample from zero to six hours  
2 after dosing gives a very nice indication of  
3 the excess corticosterone produced during that  
4 period of time.

5 I think it's very analogous to  
6 area under the curve and we do have data on  
7 that. I don't have a slide here with me  
8 today. But we have compared area under the  
9 curve and urinary glucocorticoids and they do  
10 have a nice correlation.

11 So in this particular experiment  
12 we've evaluated several stressors. The  
13 experiments labeled 20 and 25 involve atrazine  
14 at quite high doses. But what you can see  
15 here is that they decrease lymphocyte  
16 differential and stressors in general --  
17 glucocorticoids in general have this effect.  
18 But you can see that the relationship is quite  
19 similar for all the different stressors and  
20 that the urine corticosterone values seem to  
21 be quite predictive of that effect.

22 And there are several other

1 parameters. In the interest of time I don't  
2 have those shown. But there are several other  
3 parameters with similar relationships.

4 So you've seen this before. This  
5 is a study that is in progress that Syngenta  
6 has commissioned. And the last column under  
7 28 days will be used for evaluation of dose  
8 response relationship in the -- in terms of  
9 immunological effects.

10 And we have some groups in  
11 there -- the NK assay anti-asialo GM1 and the  
12 AFC assay cyclophosphamide. Those are  
13 positive control groups where we should  
14 definitely see an effect just to make sure  
15 that the assay's working properly, and we  
16 should be able to get a much better idea than  
17 we have now about the dose response pattern.

18 As already mentioned, these  
19 animals will also be used to evaluate  
20 endocrine effects, and we will take urine  
21 samples from these animals to evaluate  
22 corticosterone. So those results, the plan is

1 to report those in July.

2 And similarly, one of the areas  
3 where there is some uncertainty because the  
4 two major studies didn't reach quite the same  
5 conclusion is the effects of atrazine on  
6 development of the immune system. And a  
7 developmental study was already planned when  
8 I came -- when I became involved in this  
9 process. And it became clear that we could  
10 probably get some useful immunological  
11 information from this study as well.

12 Now, the ovariectomy, admittedly,  
13 may have some effects on immune system  
14 parameters, but the parameters that I've been  
15 talking about typically are not drastically  
16 affected in adult animals by ovariectomy. And  
17 I think this would give us some useful  
18 information. So we would check urine  
19 corticosterone shortly before the ovariectomy  
20 in both the animals that are exposed  
21 throughout gestation and early development,  
22 and then we would do the same thing for

1 animals on the -- in Cohort 2 that are exposed  
2 for a lesser period of time.

3 Then we would measure  
4 immunological parameters, both immediately  
5 after that at the time indicated on the chart  
6 there for blood collection, and then we would  
7 also let them recover for three weeks and then  
8 also evaluate immunological parameters at that  
9 time.

10 I believe we can evaluate not  
11 perhaps exactly the same parameters that were  
12 evaluated in the Rooney and Rowe studies, but  
13 we can evaluate parameters that are very  
14 comparable that should give us a similar  
15 answer -- like instead of the -- we can do  
16 mixed lymphocyte culture, which should give us  
17 an idea of the T cell -- specific T cell  
18 response, even though that different assay was  
19 done in those investigations, as well as we  
20 can measure all of the typical immunological  
21 basal data that was measured in both of those  
22 studies. And that, again, should be available

1 in July.

2 To summarize, high doses of  
3 atrazine increase circulating levels of  
4 corticosterone in rodents. Elevated  
5 corticosterone levels have been reported for  
6 atrazine doses associated with immunological  
7 effects. The effects of the immune system may  
8 be caused by elevated corticosterone levels --  
9 the effects of atrazine on the immune system.

10 Urinary corticosterone at zero to  
11 six hours and area under the plasma  
12 corticosterone concentration versus time curve  
13 are good predictors of immune system effects.  
14 And studies in progress should provide us a  
15 description of the dose response relationship  
16 for the urinary corticosterone levels and  
17 immunological changes, and also should give us  
18 some more information about developmental  
19 effects of atrazine exposure in terms of dose  
20 response.

21 And I'd be glad to address any  
22 questions that you might have.

1                   SESSION CHAIR PORTIER: Dr. Regal.

2                   DR. REGAL: Yes. So are you  
3 planning on looking at the male and female  
4 offspring?

5                   DR. PRUETT: I think if you go to  
6 those -- back to those --

7                   DR. BRECKENRIDGE: I can address  
8 that quickly. Charles Breckenridge. So we're  
9 only carrying the females because originally  
10 that was designed as a study to look at the  
11 impact on LH mechanisms. So that's all we  
12 have running in that study.

13                  DR. REGAL: Yes. Because the  
14 other two studies in the literature saw the  
15 primary effects in the males.

16                  DR. PRUETT: Right.

17                  DR. BRECKENRIDGE: We understand  
18 that. And we may have to go back.

19                  DR. REGAL: And then is -- how --  
20 so 111-day old rat -- most of the other  
21 studies also use slightly younger animals.  
22 Right?

1 DR. BRECKENRIDGE: Yes.

2 DR. REGAL: Okay.

3 DR. BRECKENRIDGE: Yes. Yes.

4 This won't be an exact replica of either of  
5 those studies -- absolutely.

6 DR. REGAL: Okay.

7 DR. BRECKENRIDGE: No, it won't.

8 And that -- and it may be necessary to do an  
9 additional study to clarify what's still  
10 uncertain.

11 SESSION CHAIR PORTIER: Dr. Akana?

12 DR. AKANA: Is the urine  
13 collection -- is it a nighttime or a light  
14 time collection? What time of the day in the  
15 cycle?

16 DR. BRECKENRIDGE: Yes, the urine  
17 will be collected during the interval of time  
18 from lights on for six hours. And it  
19 coincides with the time when dose is  
20 administered actually.

21 DR. PRUETT: We've evaluated other  
22 times, and we've also evaluated longer

1 collection times -- zero to 24 hours. And  
2 zero to 6 gives us the least noise in the  
3 system -- less error within groups. So that's  
4 the basis for that.

5 DR. AKANA: That probably also  
6 gives you the least urine volume.

7 DR. PRUETT: Yes, it does. Yes.  
8 That's right. We do adjust. We also -- we do  
9 an adjustment for creatinine, which should  
10 account for differences in urine output. And  
11 that also does help to decrease the  
12 variability in the numbers.

13 SESSION CHAIR PORTIER: Dr.  
14 Selvage?

15 DR. SELVAGE: I have  
16 catecholamines on the brain. But some of  
17 these -- some of the results you've seen, like  
18 with NK cells in the spleen, could that be  
19 explained by catecholamine action at the level  
20 of the spleen?

21 DR. PRUETT: Yes. Some portion of  
22 the effects of these stressors is almost

1 certainly due to catecholamines. There are  
2 some data that I didn't show you where the  
3 effects of the chemicals and restraint stress  
4 depart considerably from the effect of  
5 exogenous corticosterone. Now, exogenous  
6 corticosterone -- there isn't a big  
7 catecholamine response because the only stress  
8 there is brief handling to do the dosing.

9           The others -- the chemicals  
10 themselves where the restraint induce is a  
11 major catecholamine response -- and for some  
12 parameters we see that all the chemicals and  
13 the restraint track much closer to each other  
14 than they do to corticosterone, suggesting  
15 that probably it's catecholamines or some  
16 other stress mediator that is driving that  
17 particular effect.

18           Most of these we didn't -- we ones  
19 that I showed you we didn't see that pattern,  
20 but we have seen it for other parameters.

21           SESSION CHAIR PORTIER: Dr.  
22 LeBlanc?

1 DR. LEBLANC: You showed rather  
2 nicely that at these dosages the area under  
3 the curve is very informative with respect to  
4 corticosterone levels. But these are high  
5 dosages. And I was just wondering if you  
6 titrated down to levels that are more  
7 representative -- the NOEL, the LOEL for  
8 atrazine -- whether the peaks might be more  
9 informative -- or at least as informative.

10 DR. PRUETT: That is possible. We  
11 have done some studies at lower levels and  
12 also a number of vehicle studies. And below  
13 a certain value -- and it's not far from the  
14 lowest value that I showed you up there -- the  
15 100 milligram per kilogram -- it's not far  
16 from that. We don't see any immunological  
17 effects.

18 However, we have not looked at  
19 some parameters that some people have reported  
20 to be enhanced if there is a very brief stress  
21 response. So one example might be cocaine,  
22 which induces a very brief, but high

1 amplitude, stress response in rodents. And  
2 that actually doesn't cause immuno  
3 suppression; it enhances some immunological  
4 end points, similarly with certain physical  
5 stressors or restraint stress if it's just a  
6 very short duration.

7 SESSION CHAIR PORTIER: Dr. Akana?

8 DR. AKANA: Have you carried  
9 adrenalectomized animals through this  
10 protocol?

11 DR. BRECKENRIDGE: No, we have  
12 not. I think it's a rather arduous task to  
13 maintain animals for any duration of time.  
14 And actually it's the in-dwelling catheters  
15 that Dr. Handa uses that permit us to do those  
16 kind of experiments because we can provide  
17 back saline to those animals.

18 DR. PRUETT: We've done some  
19 experiments like that with other chemicals,  
20 not atrazine. And for a number of the  
21 parameters that I've shown you here,  
22 particularly MHC Class 2, the effect

1 completely disappears in the adrenalectomized  
2 animals. We've also used glucocorticoid  
3 synthesis inhibitor and a glucocorticoid  
4 antagonist and we get the same answer using  
5 all three methods.

6 SESSION CHAIR PORTIER: Okay. I  
7 think we're going to move the token to the  
8 other side of the table for a while.

9 DR. BRECKENRIDGE: That's correct.  
10 And I had a summary. I'll just give that out  
11 in paper copy.

12 And I'm only going to make two  
13 comments just making an introduction. Dr.  
14 Pastoor is going to present a margin of  
15 exposure assessment using NOELs that exist at  
16 the present time in the regulation of  
17 atrazine. So the acute NOEL is 10 mgs per kg  
18 short term, 6.25 in long term, 1.8 mgs per kg.  
19 These are obviously subject to a new research  
20 when some of these other parameters get  
21 investigated.

22 And, just in general, to say that

1 Syngenta's committed to continuing to conduct  
2 research to elucidate the mechanisms of  
3 actions of atrazine on all aspects of  
4 endocrine and impact functions in toxicology.

5 So, with that, I'll ask the  
6 colleagues from the other side to come up and  
7 we'll abandon the table. Thank you very much  
8 for your patience.

9 SESSION CHAIR PORTIER: Before you  
10 all leave I think Dr. Bucher's got a quick  
11 question.

12 DR. BUCHER: Sorry. I just wanted  
13 a quick question. Is this the only study the  
14 one that's going on now with the in utero  
15 exposure that you know of with atrazine?

16 DR. BRECKENRIDGE: Could you  
17 repeat please?

18 DR. BUCHER: You have a study  
19 going on with in utero lactational exposure.  
20 Is this only one that you're aware of that's  
21 been done this way so far?

22 DR. BRECKENRIDGE: I'm the only

1 one that -- I haven't directly involved with  
2 conducting so I don't know what others may be  
3 doing. I think there could be programs  
4 similar to that elsewhere, but I don't know of  
5 those.

6 DR. BUCHER: So there's no --  
7 given the neurological effects that have been  
8 seen in all of these other studies has any  
9 thought been given to neural behavioral  
10 studies or assessments of the developing  
11 nervous system in these animals?

12 DR. BRECKENRIDGE: We're listening  
13 with interest to the discussion of the neural  
14 toxicity sections that were brought forward in  
15 this meeting in the last few days. And we  
16 have been investigating that model for two  
17 years for other reasons. We are aware --  
18 brutally aware of its limitations, and so  
19 we're reluctant to do those kind of high dose  
20 types of experimentations. If we thought  
21 there was a need to investigate those kinds of  
22 outcomes we would. Thank you.

1 DR. HENDLEY: Okay, thank you, Mr.  
2 Chairman. My name is Paul Hendley. I'm a  
3 senior Syngenta fellow from the product safety  
4 department in Syngenta. My interests are in  
5 exposure assessment. And what Dr. Pastoor and  
6 I will be talking about over the next few  
7 minutes is moving from toxicology into the  
8 exposure assessment and leading to talking  
9 about the risk assessment part of the  
10 challenge to understand that.

11 Okay. We're looking forward to  
12 giving the panel some more information that's  
13 going to compliment that they've already seen.  
14 And the first part of that is going to refer  
15 back to the atrazine drinking water monitoring  
16 databases and show how they indicate that the  
17 current monitoring frequency is sufficient to  
18 estimate exposure profiles for the end points  
19 and duration.

20 And then we'll move to Dr. Pastoor  
21 talking about the margins of safety -- and  
22 they're extremely large for the exposures in

1 toxicological end points. And he will go into  
2 the issues of some of the thresholds in  
3 detail.

4 But I would like to take the  
5 opportunity now to talk about a little sort of  
6 safety warning because I'm going to use the  
7 word peaks and maxima and high centiles. But  
8 the important thing to bear in mind when I'm  
9 saying that is the drinking water supply is  
10 indicated as safe. No finished drinking water  
11 samples have ever exceeded 100 parts per  
12 billion, which is the one-day HAL. And Dr.  
13 Pastoor will go into the background of that.

14 In the atrazine monitoring program  
15 with high frequency, no system has had a  
16 finished water annual average greater than 3  
17 parts per billion of atrazine from 2006 to  
18 2009, which is the current MCL or MCLG as the  
19 running annual average. And also, no 90-day  
20 rolling average has exceeded the drinking  
21 water level of -- I always want to say  
22 concern, and, of course, it isn't -- it's

1 comparison -- of 37.5 parts per billion total  
2 chlorotriazines in rural finished water in the  
3 atrazine monitoring program. So that's the  
4 background against which we're going to talk  
5 about peaks and maxima.

6 So the two features of my talk are  
7 about the atrazine monitoring programs and the  
8 magnitude, the focus, and the frequency that  
9 has produced a massive database, and then  
10 some of the analyses that have been done on  
11 that database that have indicated the  
12 trends -- and they're trending downwards --  
13 the confidence with which we understand the  
14 peak values and the high centiles, and some  
15 sampling performance of some alternative and  
16 additional sampling designs to those that  
17 you've seen already from EPA.

18 But I think the keynote word for  
19 my presentation is going to be database  
20 because when I sum up I'm going to use the  
21 word exceptional for this database. And I  
22 hope by then you'll realize why I'm absolutely

1 certain that's the right word to use in how it  
2 provides a unique resource for actually  
3 answering some of the questions that the panel  
4 has been challenged with.

5 So the magnitude of the surface  
6 water programs is where I'd like to start.  
7 There's essentially two types of surface  
8 water, non-drinking water and drinking water.  
9 Let's deal with the non-drinking water first.  
10 And by that I'm talking about all water  
11 bodies -- streams, rivers, lakes -- not  
12 associated with drinking water finished  
13 analyses.

14 There's about 180,000 atrazine  
15 analyses in that database. Probably one of  
16 the best and most consistent databases,  
17 particularly because it analyzes multiple  
18 compounds, is the NAWQA program that Dr.  
19 Gilliom supervises.

20 You've heard about the Heidelberg  
21 College program -- we'll come back to it  
22 briefly. That is characterized by superb

1 daily information, so very relevant to sample  
2 frequency work.

3 The ecomonitoring program many of  
4 you know quite well from several presentations  
5 in the past. And, in addition, there's a  
6 massive database on over 100,000 analyses on  
7 other non-drinking water.

8 However, the rest of the  
9 presentation is going to be on the topic of  
10 drinking water -- community water systems that  
11 are using surface water as sources. And  
12 there's going to be three sets of acronyms  
13 that we'll use extensively. The Safe Drinking  
14 Water Act program, which is a program managed  
15 by the states -- and we will keep calling it  
16 SDWA from now on -- and the Syngenta managed  
17 voluntary monitoring program, which we will be  
18 calling VMP, and the Syngenta managed atrazine  
19 monitoring program, AMP.

20 So what do I mean by that? The  
21 SDWA program has been running since 1993, and  
22 it's a regulatory compliance program that's

1 roughly 90 regulated compounds -- atrazine is  
2 one of them. And the 12,000 community water  
3 systems on surface water have to meet  
4 compliance.

5 Typically sampling for atrazine is  
6 up to four samples per year, and that has led  
7 to the accumulation of 50,000 or so samples  
8 since 1993. And that's coming from 4,400  
9 community water systems. The SDWA program  
10 only looks at finished water.

11 So the next part of the program is  
12 the Syngenta voluntary monitoring program.  
13 And that little icon has appeared at the top  
14 of the pyramid for a reason -- because the  
15 community water systems that move into the  
16 voluntary program are moved in because this  
17 ran from '93 to 2003 are those with a  
18 significant history of atrazine detections.

19 And 132 community water systems  
20 eventually became part of the voluntary  
21 monitoring program, covering ten states. And  
22 the voluntary monitoring program typically

1 used 26 to 30 samples a year. And those  
2 samples were stratified towards the peak  
3 runoff time in the growing season.

4 Now, in addition to finished  
5 water, sort of -- let's say 26 raw samples and  
6 26 finished samples taken a year. And that  
7 has accumulated a database of over 22,500  
8 finished water samples.

9 The second program is the atrazine  
10 monitoring program, and that was mandated in  
11 2003. The way it was set up was it had to  
12 capture all the community water systems with  
13 annual average atrazine concentrations in  
14 excess of 1.6 parts per billion, which is half  
15 of this MCL level.

16 But that was going back to 1997,  
17 so it looked back over the records for the  
18 last six years to pull in all the community  
19 water systems that had a history of  
20 atrazine -- interesting atrazine residues --  
21 and that's why we also have an icon at the top  
22 of the pyramid. We're focusing in on those

1 sites of most interest.

2 In the end, 152 community water  
3 systems are in that database from ten states.  
4 The sampling frequency is higher than the  
5 voluntary program. The timing is very  
6 similar. And, again, you have a full set of  
7 raw and finished samples. And that's amassed  
8 about 26,500 finished water samples.

9 Some people find this format  
10 easier to look at, and I think it deals  
11 directly with the word Dr. Gilliom used early,  
12 which was density of sampling. What this  
13 shows is a -- the time course from zero to 365  
14 days. And what it shows is for each day  
15 within the entire SDWA database how many  
16 measurements there are in the database.

17 And because atrazine runoff is  
18 stochastic -- it's due to the timing of  
19 rainfall application, complex interrelated  
20 factors. What we see here is how well we've  
21 sampled that universe of possible actions. We  
22 also happen to see that apparently in the

1 Midwest, sampling on Christmas Day and New  
2 Year's Day are not popular activities.

3 In addition to the SDWA  
4 distribution we see the same thing for the VMP  
5 and AMP. And what you can see here is April  
6 1 to July 31 is -- if you like the growing  
7 season when we know you're likely to get  
8 higher residues -- higher runoff occurring --  
9 and you can see how VMP, AMP selectively  
10 samples from that period.

11 But think about the total sum of  
12 the database. If you think of that, say,  
13 April 15 you have around 200 -- well, 150  
14 samples to 250 samples perhaps. And, again,  
15 you add in the AMP samples, the amount of data  
16 and information in our database is really  
17 quite remarkable.

18 So that gives us a database of  
19 enormous magnitude. It's focused on sites of  
20 interest and it has high frequency monitoring  
21 data. So Dr. Heeringa used the phrase "prior  
22 information." This is a pool of prior

1 information of some considerable power. And  
2 it also perhaps also ought to be in the list  
3 of what do we know now, which is a question  
4 that Dr. Thurman asked in one of his slides.

5 So the first thing we did with the  
6 database was we looked at trends. And what we  
7 have here -- what are we doing from now is  
8 giving you a one-page summary, a very short  
9 introduction and some conclusions, and you  
10 will see the reference, in fact, up in the top  
11 left-hand corner here. That is on the  
12 docket -- that report -- but with just too  
13 detail and too little time to go through it in  
14 detail I'm afraid.

15 So what we see here is across the  
16 period 1994 to 2006 there is a downward trend  
17 in time weighted annual mean concentrations of  
18 atrazine. And there's two lines on there  
19 because the sites where the raw annual mean  
20 greater than 3 at some point within that  
21 historical database are actually seen to be  
22 trending downwards at a faster trend than

1 those without such a history.

2 And that's encouraging. And one  
3 of the reasons to note is that across the top  
4 line here you see the total atrazine use in  
5 millions of pounds. And that hasn't changed  
6 significantly over the 1994 to 2006 period.  
7 So the decrease and the trend downwards  
8 largely reflects activities by the growers,  
9 improvements in stewardship for atrazine use.

10 In addition to this for the annual  
11 mean is a similar and somewhat steeper trend  
12 for the high centile peak values. And USGS  
13 also reported a similar trend in their NAWQA  
14 decadal review.

15 The second thing we did with the  
16 database was look at both peak and high  
17 centile atrazine drinking water  
18 concentrations. And here obviously with  
19 sample sizes in the order of 50,000 data  
20 points they're large enough to estimate the  
21 high centile population measurements with  
22 extreme confidence.

1                   And what this table does is  
2                   summarize those measurements. The actual  
3                   confidence limits are in the detailed report.  
4                   And Dr. Mosquin from RTI International is with  
5                   us on the table should you have any questions  
6                   on the detail of this piece of work. Dr.  
7                   Mosquin is down there.

8                   On the top line you can see the  
9                   SDWA data. And what you have is a 99.9th  
10                  centile value of 6.7 parts per billion from  
11                  our 4,400 community water systems. For the  
12                  VMP, AMP we have 22.7 ppb as the 99.9th  
13                  centile.

14                 Interestingly, if you take from  
15                 SDWA the data corresponding to those community  
16                 water systems in VMP and AMP you see that the  
17                 99.9th centile moves from the 6.7 of the total  
18                 population to 17 parts per billion. In other  
19                 words, SDWA sampling across the years does a  
20                 good job of capturing the community water  
21                 systems with a history of higher atrazine  
22                 occurrence.

1                   The panel also asked the question  
2                   earlier about sourcing for community water  
3                   systems. So what was done here was the  
4                   database was broken down into subsets, the  
5                   first of which is community water systems  
6                   using static water bodies as the source.  
7                   There's 134 -- about two-thirds of that  
8                   population in the VMP and AMP. And there, the  
9                   99.9th centile and the 99th are higher than  
10                  the whole population, and correspondingly the  
11                  flowing water subset, the high centile values  
12                  are lower. In other words, the static water  
13                  bodies actually tend to have higher residue  
14                  patents, and that is unsurprising when you  
15                  think about the hydrology.

16                  Additionally on here, and  
17                  unsurprisingly as well, is when you look at  
18                  the April to July period, you come out with  
19                  centile estimates that are considerably higher  
20                  than the whole population.

21                  Okay. That led us to the question  
22                  before -- some of the questions before the

1 panel about sampling frequency and confidence  
2 intervals. What I'm going to do now is show  
3 three more approaches in addition to those  
4 you've seen from EPA.

5 The first of those deals with the  
6 longer term exposures -- the 90-day exposures.  
7 And in all these cases again I'm going to give  
8 a very brief summary. The reference -- or the  
9 handout material you have will provide details  
10 should you want more, or, indeed, our experts  
11 around the table with us.

12 So in this approach we used raw  
13 water from 400 community water systems from  
14 the AMP program from 2003 to 2006, and we  
15 looked at four sampling frequencies. Thirty-  
16 five samples a year stratified to the runoff  
17 season, 17, nine and six. We looked at both  
18 the full data set and the flowing water/static  
19 water subsets -- either source subsets. We  
20 simulated a set of samples, calculated the  
21 maximum 90-day rolling averages, and compared  
22 the predictions with the measured values.

1           The conclusions from that work are  
2           for the 90-day rolling averages maxima both  
3           the AMP schedule of 35 samples a year and the  
4           17 samples per year approach are almost  
5           indistinguishable. And what's more the static  
6           water systems' lower frequency sampling is  
7           effective.

8           But I think to answer a thought  
9           that was almost voiced by the panel, the  
10          correct -- I think it was -- the correct sort  
11          of suitable frequency for community water  
12          systems can be a sign based on history and  
13          knowledge about the source water, the atrazine  
14          trends, flows, et cetera.

15          The next two approaches deal with  
16          the question of the confidence associated with  
17          various sampling approaches if shorter  
18          exposures become of interest. And the first  
19          of these -- and here Dr. Sielken from Sielken  
20          Associates is on the table with us to answer  
21          any questions -- the approach was using 202  
22          community water system finished water profiles

1 which were up to eleven years in duration.

2 Each of those was linear  
3 interpolated across the entire length of the  
4 multi-year profile. And then fixed sampling  
5 intervals -- two day intervals, three day  
6 intervals, four day intervals -- were applied.  
7 And the sampled maxima from those samples were  
8 compared with the observed peak maxima for the  
9 entire community water system profile.

10 The combined ratios of those  
11 comparisons for each of the 202 individual  
12 profile analyses were built into a  
13 distribution. And that led to conclusions  
14 across all the community water systems. And  
15 I'll give you the example for the seven-day  
16 frequency. And you can be 95 percent  
17 confident that the sampled maximum from your  
18 seven-day sampling profile is greater than or  
19 equal to 78 percent of the maximum.

20 You can turn that around into what  
21 you could call a performance factor and say,  
22 if I multiply my sampled value by 1.28, which

1 is the reciprocal of .78 or 78 percent, you  
2 would be confident that you were trying to  
3 estimate -- managing to estimate the observed  
4 maxima.

5 Similar conclusions are in the  
6 handout for various intervals and time  
7 weighted periods. And the approach was also  
8 applied to daily data sets -- and I'll come to  
9 how that's helpful in a moment.

10 The second and last experiment I'm  
11 going to tell you about also deals with the  
12 question of the shorter exposure periods and  
13 sampling frequency. In this case, rather than  
14 using the power of the history from the VMP  
15 and database what was used were the daily data  
16 sets that are available, where true daily day  
17 after day after day samples were taken.

18 And I'll just sort of briefly  
19 dwell on these because there is one very late  
20 breaking item, as Dr. Breckenridge sort of  
21 mentioned. Data always seem to come in at the  
22 last minute. And a few weeks ago we became

1 aware of a community water system in Missouri  
2 between 1993 and 2000 took -- well, I think  
3 five years with more than 300 samples.

4 This is truly a valuable resource.  
5 If you really want to understanding drinking  
6 water variability you want to deal with  
7 measurements made in drinking water. This was  
8 something we were unaware of until very  
9 recently. This is a community water system  
10 that samples the Missouri River. It's a big  
11 system. So that's the most relevant one we  
12 have.

13 The Heidelberg College data set  
14 you've heard about from EPA. The key point I  
15 want to make is that there are four watersheds  
16 and they vary in area between about 34 square  
17 miles and 6,300. And somebody mentioned basin  
18 area earlier. And so this is a very  
19 convenient set for understanding some of the  
20 implications of basin area -- all of these  
21 heavily agricultural 60 to 80 percent raw  
22 crop.

1                   But the important think to note is  
2 both Heidelberg College and the eco programs  
3 are raw water. They're not drinking water.

4                   So the last group of data is the  
5 eco program data. And, remember, for those  
6 who haven't spent many hours on this these are  
7 very small streams -- some of them are six  
8 feet wide -- but certainly they're all very  
9 small on small watersheds -- typically nine  
10 to -- well, up to 100 square miles is the very  
11 most.

12                  We looked at 2009 data taken  
13 daily -- composite samples actually -- ten  
14 sites. And in addition, of course, there are  
15 some ongoing programs -- there will be 30-plus  
16 sites of daily data coming in in 2010. I  
17 won't dwell more on that.

18                  But I will raise a point that a  
19 panel member made yesterday. And the question  
20 was are there drinking water community water  
21 systems in some of these upstream small  
22 watersheds? And the answer is yes there is.

1 But there's a twist because the community  
2 water system's job is to provide a continuous  
3 supply to their customers. So if you have a  
4 very small stream that's prone to drying up or  
5 going very low you have to do something about  
6 it. And what you can see on this diagram is  
7 a watershed that's actually coming down  
8 here -- there's a creek -- doesn't look unlike  
9 some of the eco creeks.

10 But what they do is they pump from  
11 this creek, typically not in the worst runoff  
12 events because they don't want to put sediment  
13 and stuff in there, and they pump into a 30  
14 mega gallon kind of settling reservoir --  
15 that's million gallons. And then they pump it  
16 into a 90 mega gallon storage reservoir.  
17 That's actually got 150 days of supply for  
18 that community water system in there.

19 And so the raw water that actually  
20 feeds the treatment plant comes from this  
21 storage reservoir. It doesn't come from the  
22 creek. Now, the reason why I raise that is

1 because in May 2006 -- May 23 actually -- was  
2 a residue reported that 227 parts per billion  
3 in the creek. On the same day the raw water  
4 that was going into the plant was .09 parts  
5 per billion. And then the finished water that  
6 came out was .05 parts per billion.

7 In your handout there are two high  
8 numbers. One of them is this 227 as raw water  
9 feeding a community water system. This is in  
10 the white paper -- sorry -- from the EPA. And  
11 so the value that is of 227 is a true value  
12 for the creek. It is not relevant for what is  
13 going into the plant. And, in fact, another  
14 value -- 73 ppb -- was reported in 2008. And  
15 that is also in the database. It's got a  
16 different CWS code number in the EPA white  
17 paper. And that was also not representative  
18 by about the same ratio of the true raw water  
19 that's actually feeding the plant.

20 So the important thing to realize  
21 is these what are called side channel  
22 reservoirs have no watershed of their own.

1 There's no water drains in there barring  
2 actual rainfall. You've got to pump water  
3 uphill to get them in there.

4 So looking at our daily data set  
5 the same sort of simulation approach that Dr.  
6 Frankenberry discussed generated simulated  
7 sampling ranges including the every seven days  
8 AMP ranging. And then it compared the  
9 simulated data with the true values -- the  
10 full daily data set -- and estimated the  
11 ratios between the true and the simulated  
12 values.

13 And these, again, are sampling  
14 performance factors -- and Dr. Mosquin  
15 actually did this work and so, again, he can  
16 answer the questions on this. And those  
17 performance factors for estimating maximum  
18 daily values from seven day in season sampling  
19 programs range for the community water system  
20 between 1.2 and 1.8 and for the Heidelberg  
21 College set of watersheds -- there's four,  
22 remember -- between 1.1 and 2.6. But I'll

1 hasten to point out that's not drinking water,  
2 so its relevance has to be carefully  
3 considered.

4 And, again, for the eco programs,  
5 which I believe are representative merely of  
6 understanding how extremely flashy systems  
7 behave and really have very little relevance  
8 to drinking water, the range was 2.1 to 2.6.

9 So what can we conclude about  
10 sampling frequency and confidence? The data  
11 support lower frequencies than current AMP  
12 programs, but 90 day for the longer averaging  
13 periods, community water systems characterized  
14 by static source water require fewer samples  
15 than flowing, and you can use knowledge --  
16 prior knowledge to come up with suitable  
17 frequencies for sampling such watersheds.

18 The huge available monitoring  
19 database address current SAP questions, and  
20 the daily data sets are very important to help  
21 us kind of validate our thinking about  
22 sampling frequency.

1                   We used two complimentary sampling  
2 performance estimation approaches. One was  
3 the one from the VMP data looking down at the  
4 entire profiles across history, sampling many  
5 years, many circumstances. The other was  
6 working up from true daily measured data sets.  
7 Both of those gave similar results for the  
8 daily data sets that are available. And those  
9 two converged to suggest that sampling  
10 performance factors for estimating maximum  
11 daily values from seven-day sampling regimes  
12 range between 1.1 and 2.6.

13                   And why is that a useful number?  
14 Well, it's consistent with the 3X sampling  
15 uncertainty factor that's already in the  
16 drinking water level of comparison. So the  
17 numbers are coming out and, again, making  
18 sense within the context of the existing risk  
19 assessment process. And Dr. Pastoor will  
20 mention that later.

21                   Additionally, in turning very  
22 briefly to the modeling questions, a variable

1 data permit confident analyses of sampling  
2 uncertainty. Direct analysis of relevant data  
3 sets that have historical relevance are  
4 true -- feasible. And so I would suggest that  
5 developing models to interpolate between less  
6 frequent samples may be unnecessary given the  
7 unique qualities of the atrazine database.

8 I would also suggest -- just  
9 popping back to the first point on community  
10 water systems, I would submit to the panel  
11 that considering the source of the community  
12 water systems may be an easier way of  
13 classifying than worrying about peak shape,  
14 but I think both need to be examined  
15 carefully.

16 So, in wrapping up, we have a  
17 truly exceptional database of monitoring that  
18 provides very effective way of getting into  
19 some of the questions being asked due to its  
20 temporal and spatial coverage. It gives us  
21 high certainty that 99.9th centile can be  
22 determined and other high centile values, and

1 we can understand trends that are declining.

2 The current seven-day regime being  
3 used in AMP is sufficient for estimating  
4 short, intermediate, and long-term exposures  
5 with high confidence using some of the  
6 approaches we've show you. No additional  
7 uncertainty factor is needed based on sampling  
8 performance.

9 We recommend that you should use  
10 finished drinking water for all aspects of  
11 human exposure assessment, and we would also  
12 suggest that the data available -- the  
13 relevant data available, and full use of that  
14 is preferable to developing models.

15 And, with that, after questions I  
16 will turn you over to Dr. Pastoor.

17 SESSION CHAIR PORTIER: Panel?  
18 Questions? Dr. Horton.

19 DR. HORTON: I have a question for  
20 you. I'm a neuroendocrinologist so I'm going  
21 to ask you some naive question regarding  
22 hydrology. Most of what I've heard regard

1 surface water runoff -- what is done regarding  
2 sampling of deeper water supplies -- aquifers,  
3 wells, and such things?

4 DR. HENDLEY: Okay. Very good  
5 question. There are approximately 212,000  
6 ground water samples also from the SDWA  
7 program. So from that database plus some very  
8 focused studies done on both community water  
9 systems on drinking water, as well as rural  
10 wells, which are the smaller wells that maybe  
11 an individual family may use, there was a  
12 great deal of work done between the mid-  
13 nineties and the early 2000s.

14 EPA reviewed all of the water data  
15 in roughly 2002. They concluded that the  
16 exposure through groundwater was limited. And  
17 then they actually -- that's -- they then  
18 moved towards these programs on surface water.  
19 So the data show that surface water is what to  
20 concentrate on.

21 As I pointed out, none of the  
22 surface water samples are exceeding the health

1 standard. Groundwater residues are so much  
2 lower than surface water residues that EPA  
3 judged surface water to be the focus.

4 SESSION CHAIR PORTIER: Dr.  
5 Gilliom.

6 DR. GILLIOM: On the -- on that  
7 trend analysis graph, which was slide eight,  
8 is -- I wasn't able to catch up totally on the  
9 background documents so I apologize for that.  
10 But how was the -- was the trend analysis that  
11 Syngenta did based on the aggregated data or  
12 was it a site-by-site analysis that this is  
13 summarizing?

14 DR. HENDLEY: This is summarizing  
15 the data from 103 water -- raw water bodies  
16 from 96 community water systems. And I think  
17 it was -- there were two communities we looked  
18 at. One was a population with I think more  
19 than nine years of continuous data and the  
20 other was a population with more than five  
21 years of continuous data.

22 And so those were looked at within

1 the categories, as we said, of source water  
2 type and also the, if you like, the low  
3 series, the ones with history never exceeding  
4 three ppb, and ones with the high, higher than  
5 three ppb. So those community water system  
6 data sets were looked at in various clusters.

7 DR. GILLIOM: So the lines on the  
8 graph are kind of a generalization of that?

9 DR. HENDLEY: They are absolutely  
10 a generalization. If you saw the original  
11 graphics you would all have screamed and run  
12 out of the room because they are a series of  
13 distributions for each of the years of the  
14 data within the year. And you really can't  
15 explain them in a 20-minute presentation.

16 However, I would commend you to  
17 have a look at the report, because it's very  
18 relevant to some of the work that you and  
19 Recio have done.

20 DR. GILLIOM: Yes. Because you --  
21 I mean, you guys are -- I haven't caught up to  
22 the fact of trying to resolve the differences.

1 But you're aware that that's a different  
2 result than what that work shows for the large  
3 rivers?

4 DR. HENDLEY: I think that was  
5 actually why you probably wanted to talk to  
6 Dr. Chen.

7 DR. GILLIOM: Yes.

8 DR. HENDLEY: I would defer to Dr.  
9 Herschel and Dr. Chen who are both in the  
10 room. And perhaps after this session it will  
11 be best if you spoke to them about that.

12 DR. GILLIOM: Okay. And one other  
13 just while I have the mike here. On the slide  
14 12 where you did the comparison for the 90-day  
15 exposures, was -- am I correct in  
16 understanding that this was done by  
17 essentially resampling distributions from the  
18 AMP data which was on the order of 30 to 35  
19 samples a year?

20 DR. HENDLEY: Correct.

21 DR. GILLIOM: So I guess -- and  
22 the only point, which was the same point we

1 talked about some with the EPA simulated data  
2 experiments, was that -- and it's mostly  
3 relevant to shorter-term occurrences. But you  
4 don't have -- in the original data set used to  
5 build the relations, you don't have the  
6 highest peak from more frequent sampling. In  
7 other words, it's limited by the original  
8 data.

9 DR. HENDLEY: I think that's an  
10 accurate statement. Of course, this analysis  
11 was looking at the success against the 90-day  
12 rolling average end points.

13 DR. GILLIOM: True enough. It's  
14 just that some of the 90-day ones can be  
15 pretty affected by relatively short-term  
16 runoff events and so forth. That would be the  
17 only --

18 DR. HENDLEY: But, again, this is  
19 over 440 community water system years. So  
20 it's sampled pretty thoroughly across time.

21 DR. GILLIOM: With all the sites  
22 aggregated, you mean, or you mean --

1 DR. HENDLEY: I'm just trying  
2 to --

3 DR. GILLIOM: I was getting a  
4 little confused at some points in here where  
5 we had aggregated across sites -- kind of  
6 the --

7 DR. HENDLEY: Right.

8 DR. GILLIOM: -- grand data set,  
9 because it's a mixture of approaches that  
10 makes a difference. Because some of these  
11 questions are being targeted to the most  
12 vulnerable systems, so it's more that  
13 individual system versus the global.

14 DR. HENDLEY: I think the point --  
15 well, one of the points here is, of course,  
16 the AMP programs are already the most  
17 vulnerable systems.

18 DR. GILLIOM: Right.

19 DR. HENDLEY: So, you know, the  
20 entire analysis was on the most vulnerable  
21 systems.

22 DR. GILLIOM: Right.

1                   SESSION CHAIR PORTIER: Dr. Young?

2                   DR. YOUNG: But just to follow up,  
3 if I understand correctly you took these and  
4 you did just linear interpolations. So any  
5 peaks that were missed are still missed. And  
6 so, in fact, it's a very great smoothing. And  
7 so -- and then things are aggregated, so we're  
8 losing things over space and time. And then  
9 to draw conclusions like that seems just very  
10 counter-intuitive. So --

11                  DR. MOSQUIN: Paul Mosquin, RTI.  
12 There's two different approaches used. One  
13 uses the linear interpolation. And when the  
14 linear interpolation was used that was for  
15 data sets that were, let's say, essentially --  
16 had a large number of observations relative to  
17 the others -- the Heidelberg, the ECHO and the  
18 St. Louis. So there was less interpolation,  
19 let's say, than you would if you'd used a VMP  
20 or an AMP site.

21                  For -- in the case of aggregation  
22 the interpolation, if you will, was by a

1 weighting, which is a constant value weighting  
2 over a particular interval centered on the  
3 measurement, which is then a finite population  
4 approach. So they are separate techniques in  
5 that sense.

6 DR. SIELKEN: Can I add to that  
7 response a little bit? This is Bob Sielken.  
8 When we did the analysis looking at the CWSes  
9 it is true that we used the available  
10 realistic data, interpolated it linearly  
11 stepwise and it didn't make much difference  
12 which we did to create a test profile for the  
13 202 CWSes over about 1,400 years. So we had  
14 a large CWS/year combination.

15 So we took those real data set --  
16 realistic data set for year-to-year  
17 variability that was discussed earlier -- took  
18 those as tests to see how well our performance  
19 would do -- not necessarily how well they  
20 would have captured some unknown maximum. But  
21 when we went back and sampled those profiles  
22 whatever scheme we used -- would it have

1 captured what was known to be there.

2 So they're really just used as  
3 test cases when we're going back to those 202  
4 CWSes. And, you know, we got really good  
5 performance. Paul Hendley mentioned that, you  
6 know, you got at the 95 percent confidence  
7 limit -- the ratio of the sample max to the  
8 true profile max in your test case was 78  
9 percent. And that was at one day. We got --  
10 we did the analysis for three-day rollings and  
11 seven-day and ten-day and others. And we  
12 could show that -- of course, the level of  
13 performance improved. So there were none of  
14 those that were really bad even looking at the  
15 short durations down to one day.

16 The follow up to that is is that  
17 in addition to using those representatives  
18 test cases based on real data we went to the  
19 Heidelberg, the Missouri, and then looked at  
20 partitioning the data sets. And we found that  
21 in all of those separate analysis, which were  
22 closer to having a raw database that was

1 nearly daily sampling, that we got the same  
2 sort of performance.

3 And I think that that's really  
4 germane to the question about what about short  
5 durations. And in that analysis we show that  
6 even down to one day your current sampling  
7 plan is really on top of things.

8 DR. YOUNG: But the -- I need to  
9 do some more reading on it because there's a  
10 logical disconnect here. The things that you  
11 see -- if you sample every fourth day and your  
12 peaks occur in between you're going to miss  
13 something. It -- that's just a fact. You  
14 know, you can't get away -- that if you want  
15 short time scales you've got to sample on  
16 short time scales.

17 So -- now, that's a fact. It's  
18 just -- it doesn't matter whether you're in  
19 space or time. If you want fine resolution  
20 you've got to sample at that fine resolution.  
21 Now, I can't quite -- haven't quite figured  
22 out what's happening here, but that fact

1 can't -- it's just solid. So help me  
2 understand why all of a sudden this is going  
3 to work when I know that last fact's a fact.

4 DR. HENDLEY: I'll make out,  
5 though, is I think that's why I'm happy that  
6 we had the two-pronged approach working  
7 upwards from true daily data, which addresses  
8 your question, as well as downwards from the  
9 extent of data collected across many years and  
10 many sites.

11 Dr. Mosquin?

12 DR. MOSQUIN: Thank you. Yes,  
13 certainty at a given site you're not going to  
14 capture all the peaks if you sample  
15 intermittently. The argument for the  
16 weighting approach is -- relies on a belief  
17 that the sites are comparable in some manner  
18 so that for some sites you do sample the peak.  
19 For other sites you don't. And yet because  
20 there are enough sites that are of comparable  
21 nature the times when you do sample the peaks  
22 the weight is going to contribute that site's

1 maximum a certain number of days.

2 DR. YOUNG: But aren't you then --  
3 I mean, that seems to me to be changing the  
4 question, because aren't -- I mean, and maybe  
5 I need guidance here. I just don't know. I  
6 don't think we're trying to find the peak of  
7 the whole population. Aren't we trying to  
8 think about each site and what we can say  
9 about a site? Or are we just kind of talking  
10 about for all of those blue dots out there?  
11 I mean, because that's -- I mean, you're  
12 looking at all blue dots.

13 DR. MOSQUIN: Right. That's --

14 DR. YOUNG: And I thought we  
15 wanted to be able to draw inferences at  
16 locations. And those are two very different  
17 questions.

18 DR. MOSQUIN: Right. So you  
19 might -- I mean, that's why the two analyses  
20 are performed. And one way to view it perhaps  
21 in terms of the -- you know, the finite  
22 population methods is that you ultimately

1 arrive at estimates that might represent, say,  
2 your prior belief for sites of this kind in  
3 terms of centiles.

4 DR. SIELKEN: I'd like to add two  
5 things here. One is that in the profile that  
6 you're sampling from those data are related to  
7 each other. I mean, if you have admittedly a  
8 peak that went up in a minute and came back  
9 down by the end of the day you'd probably miss  
10 it even with daily sampling.

11 But you've got a profile where  
12 yesterday is a little bit related to the day  
13 before and today is a little bit related to  
14 yesterday and tomorrow will have this relation  
15 over days. So that's one point -- that this  
16 data is related and not isolated from each  
17 other.

18 The second point regards to this  
19 aggregation point -- really what we did was --  
20 when we were, say, talking about the 202 CWSes  
21 was we tested the procedure individually on a  
22 CWS, got an answer, and then said, well,

1 either put up a table of 202 answers or  
2 characterize the distribution of those  
3 answers, which you would do in a statistical  
4 analysis. You'd look at the performance of  
5 your procedure and you'd evaluate it  
6 individually and then report the distribution  
7 of those performances. And that's all we're  
8 doing.

9 DR. YOUNG: Again, I think -- I'd  
10 like clarification. Are we going to be  
11 looking at locations and want to be able to  
12 draw inference at locations or across the  
13 whole area?

14 SESSION CHAIR PORTIER: Linda, I  
15 think you can save that question. When EPA  
16 reads the question to the panel you can ask  
17 for clarification again at that time and we'll  
18 get staff to come up and clarify it, because  
19 I understand what you're talking about. It's  
20 a matter of exactly what data you're  
21 estimating for the decision role and there's  
22 a lot of ways to look at that.

1 I don't want to drag this out for  
2 too much longer, but Dr. Horton's been waiting  
3 patiently for her question.

4 DR. HORTON: I have another  
5 question of just how community water systems  
6 are making decisions about how to pump and  
7 when to pump. And going back to your slide  
8 16, you're showing the model system and you're  
9 saying, you know, the communities are not  
10 pumping all the time from their sources, but  
11 yet they're sampling -- or oftentimes their  
12 samples are being taken even when pumping is  
13 not occurring.

14 I'm wondering if information from  
15 sampling can be used by communities to make  
16 decision as to when to pump or not in order to  
17 keep their side channel reservoirs cleaner.

18 DR. HENDLEY: I think there's two  
19 answers to that. It depends on the community  
20 water system. If you're on the Missouri or  
21 the Mississippi, you have a constant stream of  
22 water that you're pretty confident about, and

1 I understand it's efficient for them to pump  
2 continuously under those circumstances.

3 For this type of smaller community  
4 water system on a more variable water source  
5 my understanding -- and these are individuals.  
6 They all have their own characteristics,  
7 communities, numbers of people to supply, and  
8 jurisdictions within which they work -- but I  
9 understand that the reason why they don't like  
10 to pump during runoff events is sediment  
11 organic matter, as well as synthetic organic  
12 chemicals.

13 And so they will try and avoid  
14 that where they can. And in fact you could do  
15 it by chemical analysis. I think it's an  
16 interesting suggestion. The problem is time,  
17 because you've got to get that information  
18 somehow in real time if you're going to use it  
19 in real time. I think with what we know and  
20 what they know about runoff they know, and  
21 that's why they do tend to avoid peak events.

22 So they're very clever guys.

1 They're good at doing their job. And they  
2 minimize their own difficulties. And that's,  
3 in fact, why there's this sedimentation  
4 reservoir.

5 And we didn't go into it, but  
6 there are aspects to do with blending. And I  
7 understand from people much more expert than  
8 I that there are actually other legislations  
9 to do with blending and getting a more sort of  
10 homogenous supply in terms of the way their  
11 plant's going to work. You know, they don't  
12 want peaks going into the plant -- much easier  
13 to have a smooth constant set of  
14 concentration. So they do their best to  
15 simplify things for themselves like all of us.

16 VOICE: Just to add one little  
17 thing to that, that points out the difference  
18 between using finished water concentrations to  
19 characterize the drinking water than it would  
20 to take an ambient water out of the creek as  
21 a measure of drinking water -- just greatly  
22 illustrates that difference.

1                   SESSION CHAIR PORTIER:  Dr.

2           Heeringa asked for the last question here.

3                   CHAIR HEERINGA:  I'll do this  
4           quickly, and if it doesn't come across, I'll  
5           have a side conversation.  So getting back to  
6           Linda's question, think of the 202 community  
7           water systems.  I'll start out and I'll take  
8           the maximum observed value in that community  
9           water system and I'll plot that on -- one to  
10          202.  There are 202 points and it's 78 percent  
11          of the maximum value.  I plot that for every  
12          community water system, and those are the --  
13          and then I do a bootstrap sample from the  
14          observed sample data for each community water  
15          system.  And I resample according to  
16          frequency.  So I get a distribution for each  
17          of those community water systems.

18                          And what you're saying is that in  
19          95 out of 100 community water systems that the  
20          sample point exceeded that 78 percent of the  
21          observed maximum, not that five percent of the  
22          generated samples for a community water system

1 exceeded --

2 DR. HENDLEY: Dr. Sielken will  
3 address that.

4 DR. SIELKEN: Thank you, Paul.  
5 This is Dr. Sielken. Yes, Dr. Heeringa, you  
6 have the example right. You're looking at all  
7 202, how they performed, simulated each one,  
8 and then you looked to see the -- what you  
9 would have expected across that group. And  
10 you would have expected in 95 percent of the  
11 cases that your sample max would have been  
12 bigger than about 80 percent of that.

13 CHAIR HEERINGA: So you're looking  
14 along this axis. I think Linda's looking  
15 vertically at the distribution of the  
16 simulation samples within a community.

17 DR. SIELKEN: Yes. I am looking  
18 across the CWS axis.

19 SESSION CHAIR PORTIER: Frigid  
20 factor is going up in the audience. We're  
21 looking for a break, but we have about 13  
22 slides -- right? -- for the last presentation

1 here.

2 DR. PASTOOR: I promise not to be  
3 too boring. Okay? All right. Let me just  
4 first of all get my slides up here. Just one  
5 second here.

6 (Pause.)

7 DR. PASTOOR: All right.  
8 Everybody stand up and do calisthenics now.  
9 Okay.

10 Tim Pastoor. I'm a toxicologist  
11 and principal scientist with Syngenta, and I'm  
12 battling cleanup today. And it's my pleasure  
13 to try and bring us back to what this all  
14 means in context.

15 And, Dr. Portier, you've been  
16 mentioning that there seems to be one side of  
17 the table over here that gets all excited  
18 about things like corticosterone increases,  
19 whereas the other side of the table gets  
20 excited about, you know, 95th percentile of  
21 the 99.9 percentile of confidence. So what my  
22 job has been over the last number of weeks is

1 to spent time in both of those rooms, and I  
2 think I get a higher place in heaven for that.

3 But the point is is that I was  
4 able to sit with the neurobiologists, Dr.  
5 Handa and Dr. Simpkins, as well as to sit with  
6 Dr. Chen and with Dr. Hendley and also with  
7 Bob Sielken, RTI. And, believe me, I've  
8 learned more about statistics than I've ever  
9 wanted to know. And I know more about  
10 neurobiology than I should know.

11 But collectively we're trying to  
12 answer a question that I think Anna Lowit --  
13 Dr. Lowit brought up the other day is -- where  
14 does the rubber hit the road. And someone  
15 else -- I think it was Dr. Hayton -- asked,  
16 well, what's coming out of my tap and what  
17 does that mean for health? And for me it's a  
18 matter of how do you answer your friends and  
19 family. And when they say, well, atrazine --  
20 you find it in water -- what does that really  
21 mean.

22 So my job is to take the

1 neurobiology and the statistics and bring that  
2 together in something that resembles something  
3 of a risk assessment. Now, this is a risk  
4 characterization, and it's a contextual one.  
5 It's not a true risk assessment. It's just a  
6 way of giving you some sense of where we are.

7 Now, one of the first things we've  
8 got to do is take a look at exposure. I'm  
9 going to take a look at exposure and I'm going  
10 to bring the toxicology back in again. And in  
11 order to do that we have to take a look at all  
12 those data points. And Dr. Sielken graciously  
13 gave me one example of how we do the linear  
14 interpolation to get at how much exposure  
15 might occur in a particular CWS or overall  
16 anyway.

17 And the first thing you have to do  
18 to establish an exposure is take all of these  
19 data points and do a linear interpolation.  
20 Why would you do that? It's because you now  
21 have from these data points -- this is over  
22 quite a number of years you can see here on

1 the X axis. You can actually do a linear  
2 interpolation and you can begin getting an  
3 idea of the 365-day pattern -- or 365-day  
4 profile for the atrazine concentrations in  
5 each individual CWS.

6 The value to that is that you can  
7 then start taking slices of that and saying,  
8 well, what's the average concentration that  
9 you'd have for 90 days, for 30 days, for 10  
10 days, and, of course, you can also take a look  
11 at it on the basis of single-day peaks. And  
12 you can compare that then to no-effect levels,  
13 which is what I'm going to do next.

14 So the real thing here is when you  
15 take a look at all the information that we  
16 have -- and this is in finished water from the  
17 CWSes primarily in the Midwest that have been  
18 in this intensive monitoring programs. So  
19 these are the CWSes where you'd expect to find  
20 atrazine in the first place. And, indeed,  
21 that's where we focus our attention.

22 We've got over 40,000 individual

1 data points which are then taken, and we've  
2 made this linear interpolation for 365 yearly  
3 points. That gives us a half-a-million points  
4 to work with from the standpoint of  
5 understanding what the distribution of  
6 concentrations are in water in the Midwest in  
7 finished drinking water.

8 So when we do that you can then  
9 take a look at what that shows us. And I like  
10 this because this box and whiskers diagram  
11 kind of pulls it back from all the stuff that  
12 we've been listening to -- well, how much is  
13 where.

14 If you take a look at the one-day  
15 concentrations and you look at the -- this is  
16 the mean right here which is less than 1. You  
17 look at the 75th percentile, of course, and  
18 99.9th percentile -- you can look at that over  
19 these rolling averages as well -- so 10 day,  
20 30 day, and 90 day.

21 And you get an idea of what the  
22 concentrations actually are in the water

1 supplies that we've been sampling with a large  
2 degree of intensity that we've been doing.

3 And you can see here that the -- we know with  
4 a significant degree of confidence that the  
5 top value there -- 99.9th percentile anyway --  
6 is right around 15. Fifteen drops down as you  
7 start averaging your 365-day profile. So you  
8 can kind of get an idea of how much atrazine  
9 is in the water.

10 Now, that's all well and good,  
11 but, again, what does that really mean? What  
12 kind of context can we put that in relative to  
13 water limits that EPA has already set? And  
14 there are actually limits that you can compare  
15 that to. Let me give you that so that you can  
16 put it in relative context.

17 EPA has two sets of values that  
18 have been developed. One is by the Office of  
19 Water, and these are health advisory limits.  
20 And they're duration specific. You can see  
21 here seven-day HAL for adults, one-day HAL for  
22 children, and, of course, you've heard already

1 about the three part per billion maximum  
2 contaminant limit which is a lifetime health  
3 advisory as well. That was established back  
4 in 1988.

5 That particular value is based on  
6 .5 milligram per kilogram per day no-effect  
7 level, a thousandfold uncertainty factor, and  
8 also a contribution of 20 percent of water to  
9 a dietary contribution. I'll get back to  
10 that. But, anyway, that's where that number  
11 comes from.

12 And in actuality it is the  
13 statutory limit for atrazine. If you look at  
14 the SDWA code you'll actually see that the  
15 maximum contaminant limit, or the maximum  
16 contaminant limit goal of three parts per  
17 billion, actually has a statutory statement  
18 that surrounds it. And I'll leave it at that,  
19 but that's what the official level is that we  
20 cannot exceed. But there are other levels  
21 that are duration specific.

22 The Office of Pesticide Programs

1 also had what are called drinking water levels  
2 of comparison, which are also duration  
3 dependent. This is a 90-day DWLOC -- this for  
4 infants. We have an annual one here -- 90-day  
5 and so forth. So these are duration specific.

6 This particular value here is  
7 based on a ten -- I'm sorry -- a 1.8 milligram  
8 per kilogram per day study. That was the  
9 Morseth study that Dr. Breckenridge referred  
10 to. I believe it's also a study that Dr.  
11 Mendez referred to as one of the end points of  
12 interest.

13 That also has a thousandfold  
14 safety factor built into it. Why? There's  
15 the typical hundredfold safety factor built  
16 in, and then there's an additional tenfold  
17 safety factor. That tenfold safety factor  
18 that's added onto it is for two reasons --  
19 threefold for uncertainties with a drinking  
20 water program and threefold for uncertainties  
21 with regard to children. Now, I think we're  
22 answering both of those question, but suffice

1 it to say that's the basis for a thousandfold  
2 uncertainty factor. So that's 12.5 parts per  
3 billion.

4 There's also a value here of 298.  
5 That's a one-day drinking water level of  
6 comparison that's used by EPA as a way of  
7 giving yourself a level to compare against  
8 measurements that you would find in community  
9 water systems. That value is based on a 10  
10 milligram per kilogram no-effect level. It  
11 also has a one thousandfold safety factor  
12 applied to it.

13 Okay. So what happens when you  
14 take what I showed you before on the box and  
15 whiskers diagram here? And if we rescale the  
16 y-axis now, because we've got to put in those  
17 larger values -- so we now have this axis  
18 here -- same box and whiskers diagram. But  
19 now we're going to put the values in for the  
20 one day or the shorter term values.

21 You can see that the information  
22 that we've achieved from the water monitoring

1 program in the Midwest has clearly shown that  
2 we're well below these levels which already  
3 have a one thousandfold safety factor built  
4 in.

5 Now, if you take a look at the  
6 longer term, which is the 90-day -- here's  
7 some values just to give you some context to  
8 it -- there is, of course, the seven-year  
9 adult health advisory limits, seven-year  
10 child, and, of course, the 90-day drinking  
11 water level comparison just to give you an  
12 idea of where these 90-day rolling average  
13 values are falling out relative to EPA's  
14 already established comparison levels. That's  
15 just to give you some comparison to  
16 established levels that EPA can use.

17 The other way as a toxicologist  
18 that I can do it -- and you've been hearing a  
19 lot of about corticosterone up and down and  
20 no-effect levels and dosages at 200 milligram  
21 per kilogram, 50, and so forth. I've also  
22 mentioned that there's a short term limit for

1 NOEL for 10 and longer term NOELs.

2 How do they all fit together?

3 Well, they fit together in the following way.

4 If you look at the top over here you can see  
5 the no-level levels of 10 for short term, 6.25  
6 for intermediate, and longer term is the 1.8  
7 milligram per kilogram per day. These are  
8 values that Dr. Mendez was referring to  
9 yesterday and are the values that underpin  
10 these limits down here.

11 And I did a calculation just to  
12 get an idea of what that means in parts per  
13 billion. So what -- if someone were to  
14 actually be drinking water that would give  
15 them a 10 milligram per kilogram dosage on  
16 that particular day what does that convert to?  
17 And the conversion factor that I use, which is  
18 down here on the bottom, is a 70 kilogram body  
19 weight, somebody drinking two liters a day.  
20 And what that converts to in this particular  
21 case is 350,000 parts per billion. And,  
22 likewise, if you look at the lower value for

1 longer term exposure of 1.8 milligrams per  
2 kilogram per day -- if you do that same  
3 conversion it comes out to 63,000 parts per  
4 billion.

5 Why am I doing this? I'm trying  
6 to give us a context for a question that  
7 actually came up yesterday, which is what's  
8 the gap between what we're finding in these  
9 water supplies with great confidence and the  
10 toxicological testing levels that we're using.  
11 What can we say about that? That's why I did  
12 these calculations.

13 And I went one step further and I  
14 said, Well, what if you compared the gap  
15 here -- what kind of levels do you get? If  
16 you compare the 99.9th percentile in the case  
17 of one day you're dealing with something close  
18 to 23,000 fold difference. If you look at the  
19 75th percentile the gap is obviously quite a  
20 big larger to the tune of 410,000 for one day,  
21 69,000 for 90 day.

22 And if you take the mean values

1 and compare that against those no-effect  
2 levels you're talking about nearly a  
3 millionfold difference between the no-effect  
4 level that's seen here and the mean value  
5 that's found in the water supplies that we're  
6 detecting, which is somewhere less than one  
7 part per billion.

8           Likewise, for the longer term  
9 value you're still looking at something like  
10 150,000 fold difference between the no-effect  
11 level and the 50th percentile that's found in  
12 the 90-day rolling average.

13           So overall what we can say by this  
14 that you've heard from Dr. Hendley, that  
15 you've heard from the neurobiologists and so  
16 forth, is that with regard to the water  
17 monitoring programs it's extraordinary  
18 extensive. We've got 100,000 finished  
19 drinking water samples to work with, which for  
20 the statisticians has been like kids in a  
21 candy store with all that data to work with.  
22 They've had a great time with it.

1           It's also been focused. We've got  
2           50,000 samples from CWSes that have been  
3           triggered into the extensive monitoring  
4           program, which is based on these criteria of  
5           half the MCL. And on top of that it's a  
6           frequent program. It's weekly during the  
7           planting season when you're likely to find  
8           atrazine in the water.

9           On top of that the results are  
10          then showing that there's a sufficient  
11          database to start making estimates of what you  
12          believe to be the highest values. And we can  
13          say with certainty what we know they are at  
14          the 99.9th percentile because of the extensive  
15          database.

16          On top of that, and because of  
17          this large database that we're working with,  
18          it's our opinion -- and I think Dr. Hendley  
19          articulated this -- is that models are really  
20          unnecessary. If you've got the data you don't  
21          need the models.

22          Finally, I think I'd like to leave

1 us all with this final message here -- that  
2 the drinking water is safe. The margins of  
3 exposure are very, very large and substantial.  
4 And I think that is a good indication that for  
5 as much as we want to know a great detail  
6 about the mode of action and the levels at  
7 which it can occur, we need to put that in a  
8 context of exactly what can people be exposed  
9 to.

10 And I got to thinking as well the  
11 other day when I was talking to Dr. Simpkins  
12 about that one slide -- I don't know if you  
13 remember that where they saw the atrazine  
14 precipitating out in solution. And so I asked  
15 our chemist, well, what's the water solubility  
16 limit for atrazine?

17 And so I went back to this  
18 slide -- and I'm going to leave you with this  
19 last slide here. And I said, well, what's the  
20 water solubility limit if I were to look at it  
21 on this scale. And that's what the atrazine  
22 water solubility limit is; it's about 33,000

1 parts per billion.

2 And I sat there and thought about  
3 that for a minute, and I thought, you know,  
4 the fact of the matter is we're establishing  
5 that no one is getting exposed to atrazine in  
6 excessive amounts, nor could they because you  
7 simply can't get enough atrazine in the water  
8 to get that kind of a dose.

9 Now, the last thing I want to  
10 leave you with too is that we are still in the  
11 process of refining these no-effect levels.  
12 We will understand them better and better as  
13 we go through the information. And I think  
14 when it comes to atrazine there has been a lot  
15 of work, not just on the mode of action level,  
16 but I believe on the mechanistic level to  
17 understand how it works. And we'll get a  
18 better idea of what these no-effect levels are  
19 and how they compare with these water  
20 monitoring limits.

21 So I hope what I've done here  
22 today is give us a contextual reference to

1 what we're finding in these toxicology studies  
2 relevant to the levels that we're finding in  
3 the monitoring program. Okay? And I'll take  
4 questions.

5 SESSION CHAIR PORTIER: Questions?  
6 Dr. Krishnan?

7 DR. KRISHNAN: I have a couple of  
8 questions. Maybe with this slide. Here, this  
9 is similar to your slide on page five also  
10 where you showed the margin of exposure of  
11 about 6,000 at the last set of data --  
12 right? -- 1.8? Maybe -- just to be sure that  
13 you mentioned -- would this set of data, the  
14 1.8 as the RfD, the uncertainty factor was  
15 thousand.

16 DR. PASTOOR: Yes, that's correct.

17 DR. KRISHNAN: And the relative  
18 source contribution used was 20 percent as in  
19 other risk assessments. So it should be about  
20 a 5,000 is the expected margin of safety  
21 because we can't just compare those 63,000  
22 directly with the water concentration that

1 doesn't have any -- I'm trying to --

2 DR. PASTOOR: Yes.

3 DR. KRISHNAN: -- be sure that I  
4 understand it correctly.

5 DR. PASTOOR: You're absolutely  
6 correct. And, in fact, I think it's more  
7 appropriate to go back to this slide right  
8 here. And if, for example, we compare to the  
9 12.5 -- just for an example -- this is based  
10 on 1.8 milligrams per kilogram per day divided  
11 by the 1,000 uncertainty factor and multiplied  
12 by the 20 percent contribution of water to the  
13 diet. Now, the other 80 percent is considered  
14 to be foodborne atrazine. And I should point  
15 out there is no atrazine exposure through the  
16 food.

17 What EPA has in their document to  
18 account for food is actually -- let's see, the  
19 number is .000041 milligrams per kilogram per  
20 day by food contribution. So the source  
21 contribution is actually going to be 100  
22 percent water. If you're going to get exposed

1 it will be by this route. Does that answer  
2 your question?

3 DR. KRISHNAN: Thanks for the  
4 clarification on the reassessing of the water  
5 source contribution. But what I wanted to be  
6 sure is that the margin of about 6,000 or so  
7 that you showed with the last one that  
8 compares with an expected margin of 5,000  
9 based on the same assessments that you were  
10 comparing to that's what I wanted to be sure  
11 about -- thousand of uncertainty factor and  
12 five for the water source contribution, which  
13 would mean -- because there's no benchmark of  
14 what is expected, so that's why I'm saying.  
15 Because the margin of exposure is usually  
16 interpolated based on the applied uncertainty  
17 factors to an assessment. So --

18 DR. PASTOOR: That would be true --  
19 well, yes. You're absolutely right. I think  
20 we're saying the same thing here unless I'm  
21 wrong here. These already have built-in  
22 they're uncertainty factors. So you're

1 comparing uncertainty factored levels to the  
2 existing concentrations.

3 Let me correct this. This does  
4 not have the 20 percent correction here. It's  
5 actually built in to the 298. Do I have that  
6 one right?

7 DR. KRISHNAN: The 20 percent  
8 is --

9 DR. PASTOOR: Right. Only in the  
10 MCL values that are calculated is a 20 percent  
11 calculation made for relative source  
12 contribution in the health advisories -- the  
13 Office of Water calculations that are made.

14 DR. KRISHNAN: Not with these  
15 numbers that are presented as the pbbs?

16 DR. PASTOOR: No. This has got  
17 a -- this is a 1.8 divided by what the 1,000  
18 for the uncertainty factor, and then the  
19 according body weight for either an adult or  
20 a child. So the adult would be 70 divided by  
21 two liters -- 70 kilograms divided by two  
22 liters. For the child it's 10 kilograms

1 divided by one liter per day consumption. So  
2 sorry for that.

3 SESSION CHAIR PORTIER: I think the  
4 rest of us are going to take a break and  
5 you're going to keep working on this.

6 DR. PASTOOR: Right.

7 SESSION CHAIR PORTIER: Dr.  
8 Breckenridge, do you have any final words?  
9 Because after this we're going to switch to  
10 the rest of the public commentators.

11 DR. BRECKENRIDGE: No, Mr.  
12 Chairman. Thank you very much for your  
13 continued patience and the time you spent with  
14 us this afternoon. We greatly appreciate the  
15 opportunity to share new information. Thank  
16 you very much.

17 SESSION CHAIR PORTIER: We're going  
18 to take a 15-minute break and reconvene at  
19 four o'clock.

20 (Whereupon, the above-entitled  
21 matter went off the record at 3:45 p.m. and  
22 resumed at 4:02 p.m.)

1                   SESSION CHAIR PORTIER: Okay. We  
2                   have -- yes, I know -- my bell. I left my  
3                   bell at the other meeting room. We have  
4                   remaining four public commentors. It will  
5                   take a little over a half-hour. These are  
6                   relatively short compared to the two sets of  
7                   public comments we've heard before. So, Joe,  
8                   what's the order here? Just like it is?

9                   MR. BAILEY: Yes.

10                  SESSION CHAIR PORTIER: So I guess  
11                  the first commentor is Alan Roberson with the  
12                  American Water Works Association.

13                  MR. ROBERSON: Well, my comments  
14                  start off by saying good morning, but I'll  
15                  switch that to good afternoon. And while I  
16                  was in the audience, I made up 60 slides that  
17                  I'll start off with.

18                  (Laughter.)

19                  MR. ROBERSON: I do have one thing  
20                  that's real short.

21                  SESSION CHAIR PORTIER: As long as  
22                  you can do it in the five minutes we've got.

1 MR. ROBERSON: I'll talk really  
2 fast. So, anyway, I want to thank EPA and SAP  
3 for the opportunity to present the perspective  
4 of the American Water Works Association. This  
5 is an important issue to us.

6 We're an international non-profit  
7 scientific and technical association  
8 representing drinking water -- primarily  
9 drinking water utilities. So some of the  
10 questions I've heard earlier about water  
11 utilities I'd be happy to answer. We've got  
12 almost 50,000 members, 4,200 member utilities  
13 that serve about 80 percent of the water in  
14 the U.S.

15 So we're dedicated to safe water  
16 and we appreciate the opportunity to comment  
17 on the statistical approaches for the drinking  
18 water monitoring frequency.

19 Our staff -- me -- and our member  
20 utilities -- we're not expert on the health  
21 effects issues, and we'll leave those issues  
22 to the appropriate experts -- and a lot of

1 those are around the table.

2 We have reached out to some of our  
3 members that have statistical expertise to  
4 develop these verbal comments. And these  
5 comments focus on the drinking water  
6 monitoring frequency as opposed to the  
7 ecological monitoring. There's two separate  
8 issues there and we recognize that.

9 So -- and the other caveat I want  
10 to make is that I'm not a statistician but I  
11 play one on T.V. I'm an engineer by training  
12 so I've had to go out to my members to do  
13 this. So these verbal comments mirror our  
14 written comments that we submitted to EPA on  
15 April seven that are in the docket -- little  
16 more detail in those comments.

17 So we've been following the  
18 regulatory process for atrazine, simazine, and  
19 the other triazines since the MCLs came out in  
20 the early nineties. As you know, compliance  
21 with the atrazine MCL of three parts per  
22 billion is based on annual average of

1 quarterly samples.

2 And one sort of side comment I  
3 want to make is that sampling is taken as what  
4 is known as the entry point to the  
5 distribution system -- so it's the finished  
6 water after any treatment. If you hear about  
7 raw water samples -- utilities may take those  
8 as part of the participation in the Syngenta  
9 program or they may be doing that as part of  
10 their process control if they're trying to  
11 determine how much carbon they might need to  
12 add to comply with the MCL.

13 So atrazine and the other triazine  
14 herbicides have been a major issue for us and  
15 our members for the past 20 years due to this  
16 potential to contaminate groundwater and  
17 surface water. Over the past 20 years we've  
18 written many comments to EPA as part of the  
19 atrazine re-registration process.

20 In the past we were concerned  
21 about the lack of data to make regulatory  
22 decisions. But the recent IRED has been a

1 step in the right direction in requiring the  
2 registrants to conduct monitoring in source  
3 water. We think that's very important to have  
4 that information. And we think those  
5 registrant monitoring requirements should be  
6 a requirement for any pesticide with the  
7 potential to contaminate drinking water.

8 So our past written comments have  
9 focused on several issues, but primarily our  
10 main concern has been the additional treatment  
11 burden that our utility members and ultimately  
12 their customers continue to shoulder in order  
13 to comply with the current atrazine standard.

14 Many service water utilities  
15 installed additional treatment, either  
16 granular activated carbon or powdered  
17 activated carbon or both, soon after the MCL  
18 was finalized in 1991 to comply with the new  
19 standard. In fact, I would say from sort of  
20 anecdotal evidence most service water  
21 utilities now have carbon treatment in one  
22 form or another to comply with the atrazine

1 MCL and to address other issues such as taste  
2 and odor issues.

3 The registrant and the growers  
4 have made some progress in controlling  
5 atrazine at the source. And this stewardship,  
6 combined with the additional carbon treatment  
7 by utilities, have contributed to atrazine  
8 violations in community water systems  
9 decreasing from 81 in 1995 to three in 2007.  
10 And that data came from the EPA's data system.

11 Any potential change in compliance  
12 monitoring has implication for our members,  
13 particularly the small and medium systems in  
14 the Midwest that are subject to the wide  
15 variability of atrazine concentrations in  
16 their source waters.

17 Without restating the obvious in  
18 the extensive literature you've seen the  
19 service water utilities get that flush in the  
20 runoff, and that depends on a lot of factors  
21 such as the application date, the intensity  
22 and direction of the rainfall, the type of the

1 watershed, several other factors. In some  
2 Midwestern reservoirs the spring flush will  
3 remain in the reservoir so that the atrazine  
4 levels remain elevated year round.

5 I want to talk a little bit about  
6 the economic implications for a required  
7 increase in compliance monitoring. For  
8 example, assume you have a small service water  
9 system in the Midwest that serves 500  
10 connections -- that's about 1,500 people. And  
11 for this example let's assume an average  
12 monthly water bill of \$30 a month, so that the  
13 total annual revenue for this system would be  
14 about \$180,000 a year.

15 So the analysis for a single  
16 compliance sample using the approved GCMS  
17 method costs about \$200. And it should be  
18 noted that the amino assay analytical method  
19 has not been approved for drinking water  
20 compliance monitoring. It's good for  
21 screening. It's just not sensitive and  
22 accurate enough for the compliance monitoring.

1 Assume an additional \$100 for sample  
2 collection. That gives a total cost of \$300  
3 for each additional compliance sample.

4 So doubling the samples for this  
5 water system from four to eight would increase  
6 the monitoring cost by about \$1,200 a year.

7 That's about one percent of the revenue for  
8 that system. So there's a significant impact  
9 for any change in compliance monitoring. And,  
10 again, that's for the drinking water side.

11 The ecological from my point of view will be  
12 done by the registrant and our utilities would  
13 not be involved with that.

14 At the same time, due to this  
15 application in right-of-ways and other  
16 widespread uses, atrazine is ubiquitous is  
17 almost all surface waters and many  
18 groundwaters, albeit in low concentrations.

19 In a recent study by USGS out of 4,600 samples  
20 only eight were non-detects. In other words,  
21 atrazine was detected in 99.8 percent of the  
22 USGS samples of potential sources in drinking

1 water. This study did have a relatively low  
2 detection limit of .004 parts per billion, and  
3 the samples were taken in might be considered  
4 vulnerable areas.

5 EPA's recent release of finished  
6 water monitoring data from 44 states is part  
7 of it's six-year review of drinking water  
8 regulations. So EPA's required to go back and  
9 look at the drinking water standards every six  
10 years. That basically parallels the  
11 previously mentioned violation data.

12 Atrazine was detected in 4.23  
13 percent of about 161,000 samples. And I'm  
14 going to give some ranges of the median, the  
15 90th percentile, and the maximum levels from  
16 that data set. And that's from each state, so  
17 when you see the range it's -- you know,  
18 here's the lowest in one state and here's the  
19 highest.

20 The median range from .1 to 1.61  
21 part per billion, the 90th percentile range  
22 from 0.4 to four parts per billion, and the

1 maximum range from .1 to 27 parts per billion.  
2 Generally atrazine is found less frequently in  
3 finished drinking water as opposed to drinking  
4 water sources due to existing carbon treatment  
5 to comply with the MCL.

6 So we have four general  
7 recommendations for the EPA and the SAP. EPA  
8 should use its authority under FIFRA to  
9 require environmental monitoring for any  
10 pesticide with the potential for being water  
11 contamination. EPA should complete this  
12 reevaluation of atrazine as soon as possible  
13 and to continue to hold to its principles of  
14 good science and transparency.

15 EPA should use its toxicological,  
16 epidemiological, and cost benefit expertise to  
17 develop the appropriate risk management option  
18 for drinking water as soon as possible. And  
19 the registrants, or the users, should pay for  
20 any additional compliance monitoring if needed  
21 for water utilities.

22 Finally, I want to comment a

1 little bit on the basis of drinking water  
2 monitoring frequency due to the potential  
3 implications to compliance monitoring for  
4 service water utilities.

5 A two-step process is needed to  
6 make the decision if any additional monitoring  
7 is necessary. First, EPA needs to determine  
8 the appropriate concentration and time frame  
9 that protects public health. It is important  
10 to decide what criteria are before any attempt  
11 to made to define a sampling strategy.

12 To do this some basic decisions  
13 need to be made regarding what causes the  
14 risks that are being mitigated. Are the risks  
15 acute, chronic, sub-chronic, semi-chronic --  
16 there are different words you can use. If  
17 chronic then what levels over what duration  
18 are implicated in the health end point of  
19 concern.

20 These fundamental questions need  
21 to be answered, and we are looking at EPA to  
22 answer these questions. Then a sampling plan

1 can be developed to meet those objectives.

2           Again, the current atrazine MCL of  
3 3 parts per billion in compliance is based on  
4 an annual average of quarterly samples. This  
5 may or may not be the bright line for shorter  
6 term exposures to atrazine. I have seen other  
7 numbers mentioned such as 12, 12-1/2, 20, 30,  
8 37-1/2 parts per billion and others -- there  
9 was a whole list in the previous  
10 presentation -- along with time frames of one,  
11 seven, 30, and 90 days.

12           At this point we recommend that  
13 the EPA make the decision as soon as possible  
14 on a bright line for the appropriate  
15 concentration and time frame for public health  
16 protection noting that the ecological issues  
17 may require a different set of criteria.

18           Then once the appropriate  
19 concentration and time frame is set the  
20 appropriate monitoring strategy can be  
21 designed for water utilities, noting that the  
22 current framework may or may not be

1 appropriate.

2 We think that the artificial  
3 neural network approach developed by EPA is  
4 too complex for water utilities and state  
5 primacy agencies to use in developing  
6 compliance monitoring strategies for specific  
7 utilities.

8 It may be useful in evaluating  
9 possible sampling structures during the  
10 development of alternative rules, but even  
11 before this application there are other  
12 methods that have been explored, like  
13 bootstrap sampling that are as effective and  
14 much simpler than the ANN approach.

15 We've developed an approach that  
16 focuses on developing a high confidence that  
17 a measured value does not exceed specific  
18 values established in the regulation, whatever  
19 those values might be.

20 This approach found that the  
21 number of samples needed to characterize a  
22 spring flush and understand its potential

1 impacts on compliance for a specific level of  
2 concern -- in this case we used three parts  
3 per billion on an annual average because  
4 that's what we were -- we knew to be a set  
5 value for drinking water. That level of  
6 concern is weighted to the mean and the  
7 standard deviation of historical data for each  
8 site.

9 These potential monitoring  
10 requirements can be very succinctly and  
11 summarized on the approach shown on the next  
12 page -- and that's the graph -- I think it's  
13 on the back of what everybody's gotten.

14 The results from this approach  
15 suggest that using historical data -- and,  
16 again, that's really looking at the mean and  
17 standard deviation -- sampling can be designed  
18 so that surface water systems that are  
19 vulnerable with high means and high  
20 variability sample more frequently while  
21 systems that have low means and are little  
22 variability sample less frequently. And I've

1 given a electronics copy of this spreadsheet  
2 on stick drive to EPA staff, and that's  
3 available for anyone to use. It's really a --  
4 I think a pretty simply tool that might be  
5 effective.

6 So that's the end of my comments.  
7 If there are any questions?

8 SESSION CHAIR PORTIER: Any  
9 questions from the panel?

10 MR. ROBERSON: Wow.

11 SESSION CHAIR PORTIER: I don't see  
12 any. Could be a factor that you're very clear  
13 or a factor that we're very tired.

14 MR. ROBERSON: You've had a long  
15 day. Okay.

16 SESSION CHAIR PORTIER: I suspect  
17 it was clear.

18 MR. ROBERSON: Okay. And I will  
19 be around for some of the discussion tomorrow  
20 afternoon and Thursday when you start talking  
21 about this issue. My toxicological background  
22 is pretty thin so I'm going to pass on that

1 tomorrow morning.

2 SESSION CHAIR PORTIER: An  
3 opportunity to learn more.

4 MR. ROBERSON: I learned a lot  
5 today.

6 SESSION CHAIR PORTIER: The next  
7 speaker is Dr. Sass with the National  
8 Resources Defense Council. Dr. Sass provided  
9 two handouts this morning to the panel.

10 DR. SASS: Thank you very much for  
11 your indulgence. I know it's been a really  
12 long two days and I know it's not going to get  
13 shorter.

14 My name is Jennifer Sass. I'm a  
15 scientist with the National Resources Defense  
16 Council, which is an environmental non-profit.  
17 And I'm in the health program. I'm located  
18 here in Washington, D.C., and my background is  
19 molecular, developmental, and toxicology.

20 I have two handouts for you. So  
21 one is this report. It's an update from a  
22 report that we actually did, I think, in

1 August of '09 -- doesn't seem that long ago to  
2 me. And we analyzed the data and crunched it  
3 and sort of came up with different tables of  
4 the individual community water systems as well  
5 as drinking water and watershed both from the  
6 Syngenta -- I'll call it Syngenta EPA data --  
7 from the monitoring programs that you've been  
8 hearing about.

9 So we presented that in a report  
10 in August and this is an update of the more  
11 recent years from that data set. But the  
12 summary of that -- there's some executive  
13 summary, but the summary of that is in my  
14 comments.

15 My comments, which have also been  
16 passed to you -- I'm not going to read all of  
17 it obviously; I think it's about 17 pages.  
18 But I did respond to the actual charge  
19 questions that you've been given and I slotted  
20 my answers -- I read those charge questions  
21 and tried to answer those and give you what I  
22 think are my answers. So feel free to sleep

1 through this presentation, and then when you  
2 get to those charge questions you can pop open  
3 this handy list and see what Jennifer would  
4 have said.

5 And a lot of them -- again, the  
6 toxicology is really very expert, and you know  
7 that, and you've heard from the experts  
8 actually. So in a lot of them, I just say  
9 that I don't have an answer for that and I  
10 look forward to seeing what you guys come up  
11 with. So I haven't stretched myself -- I  
12 haven't made up anything -- I haven't  
13 stretched myself beyond what I actually can  
14 comment on.

15 So question 1.1 -- this is the  
16 issue of the carcinogen -- whether -- how to  
17 classify it as -- what its potential is to be  
18 a human carcinogen. This is something that  
19 EPA and I have been going back and forth on  
20 since I started this job in 2001, in January.

21 So my answer to this hasn't  
22 changed that much, which is that I think

1 classifying it as not likely a human  
2 carcinogen, which is what EPA is proposing  
3 here, is inconsistent with EPA's cancer  
4 guidelines and supplemental, which were  
5 published and finalized in '05, and as well  
6 with the criteria of the International Agency  
7 for Research on Cancer, IARC, which is  
8 probably the premier cancer classification  
9 body located in France. They've reviewed  
10 atrazine twice. And I also say it would be  
11 scientific ignorance and dangerous public  
12 health policy to classify atrazine in the way  
13 that EPA proposes here.

14 I want to read you the IARC  
15 guidelines for classifying something as not  
16 likely -- that would be a Group 4 for IARC.  
17 IARC has evaluated about 900 agents since the  
18 mid -- since 1971 -- since the 1970s. And of  
19 those only one has ever been categorized as a  
20 Group 4, not likely. And that's because the  
21 burden of proof required to put something into  
22 not likely, to actually know, to be able to

1 state with scientific certainty -- scientific  
2 confidence that you know that it's not going  
3 to cause human cancer is a threshold that's  
4 very hard to meet for the World Health  
5 Organization, which is who IARC advises.

6 On the other hand the EPA doesn't  
7 seem to have too much trouble bumping things  
8 into that category. And I think that's really  
9 poor public health policy for an agency that's  
10 charged with protecting public health.

11 Atrazine, as I said, has been  
12 twice reviewed by IARC in '91 and again in  
13 '99. It's classified as Group 3, unable to  
14 determine. And that's based on sufficient  
15 evidence of causing cancer in experimental  
16 animals, but inadequate evidence in humans.

17 It was downgraded in -- from its  
18 1991, from its earlier classification, which  
19 was a 2B -- Group 2B, possibly carcinogenic to  
20 humans. And that's because in the '99 the  
21 second work group felt that the mechanism by  
22 which it was causing tumors in animals might

1 not be relevant to humans. Nobody questions,  
2 though, that it caused cancer in animals.

3 Okay. Dr. Lorenzo Tomatis, who, I  
4 point out here, was probably one of the  
5 greatest public health experts of our  
6 lifetime, a former director of the IARC, as  
7 well as chief of the IARC monograph program,  
8 wrote, in referring to the decision to  
9 classify atrazine as unable to determine,  
10 Group 3, "Evidence of carcinogenicity provided  
11 by the results of experimental bioassays  
12 appears too often to have been disregarded on  
13 the basis of suggested mechanistic hypotheses.  
14 Ominous consequences on public health may  
15 follow if such hypotheses, once actually  
16 tested experimentally, are shown to be  
17 incorrect or if they do not account adequately  
18 for the wide range of susceptibility that is  
19 known to exist in human populations."

20 Atrazine has not been adequately  
21 tested in studies covering a full range of  
22 human exposures, including pre-birth and early

1 life exposures for its potential to cause  
2 cancer in humans and it should not be  
3 classified as not likely.

4 I have some more on that but I'm  
5 not going to read it to you at this time  
6 except to say that we would like EPA to follow  
7 the advice of earlier scientific advisory  
8 panels in 2000 and in 2003 that reviewed this  
9 question. In both those panels the final  
10 report recommended that EPA consider all of  
11 the relevant science relating to atrazine  
12 carcinogenicity including whether hormonal  
13 effects in childhood or adolescence may have  
14 an impact on cancer occurrence in later years.

15 But, unfortunately, this panel has  
16 not been asked to look at all that data and  
17 has not been charged, actually, with a full  
18 review of data for that question. And so I  
19 would suggest that the suggestions of earlier  
20 panels be heeded.

21 The regulation of hazardous  
22 materials in the U.S. is generally based on

1 the scientific dogma that the dose makes the  
2 poison -- the notion that a larger doses are  
3 more toxic and that smaller doses are less  
4 toxic. This belief leads to the presumption  
5 that a chemical is safer at lower doses. And  
6 for this reason, and also because testing with  
7 low doses is often not done for practical  
8 reasons, which you all know, we rarely have  
9 reliable toxicity data of potential hazardous  
10 effects at very low doses.

11 Moreover, for chemicals that  
12 interfere with the development of critical  
13 organ systems, such as the immune system,  
14 reproductive systems, and the nervous system,  
15 there is now a substantial amount of  
16 scientific proof than when exposure occurs at  
17 the same time as these critical systems are  
18 developing during early life stages even  
19 transient low dose exposures can cause  
20 irreparable harm -- that is, the timing of  
21 exposure may be as important or even more  
22 important than the dose.

1                   For example, pre-birth exposure to  
2 mercury at levels so low that you can't detect  
3 effects in the pregnant mother could cause  
4 improper connections between the brain cells  
5 that are forming synapses in her fetus and  
6 result in lifelong alterations in brain  
7 structures and function. We know that.

8                   Exposure to endocrine or hormone-  
9 disrupting chemicals such as atrazine during  
10 critical windows of development has also been  
11 shown to have permanent effects in laboratory  
12 animal studies. Some of these effects, such  
13 as infertility or cancer, may not be obvious  
14 until adulthood even though the exposure  
15 occurred during fetal or neonatal life.

16                   This phenomenon has been  
17 demonstrated for atrazine in laboratory  
18 animals, such as amphibians, where short  
19 exposures during early development stages have  
20 had long-lasting or even permanent  
21 irreversible effects on adult behavior and  
22 longevity, including increased susceptibility

1 to infection -- the immune tox data --  
2 alternations in survival behavior -- also  
3 shown there -- and reduced long-term survival.  
4 Some of these data were mentioned by your  
5 expert speakers that addressed you yesterday.  
6 I know because I was here -- something to  
7 consider.

8           Jumping to question 1.4,  
9           commenting on the agency's preliminary  
10          conclusion regarding the aromatase mechanism,  
11          I just want to point out there is data, and I  
12          don't want to go through the data -- actually  
13          Pia summed it up for you and as well I'm sure  
14          some of you know it independently.

15                 I just want to point out that  
16          atrazine is associated with numerous diverse  
17          health end points related to endocrine  
18          disruption. For example, it's an endocrine  
19          disruptor. It impairs the immune system and  
20          it is associated with birth defects. It's  
21          associated -- it's been associated in male  
22          frogs with eggs in their testes, with impaired

1 sperm production and frogs -- in animals --  
2 sorry -- and in humans and with birth defects  
3 in human infant gut wall.

4 Giving the experimental evidence  
5 of such diverse outcomes it is unclear to me  
6 how EPA can determine with confidence that a  
7 particular mechanism of toxicity is not  
8 relevant until it has been thoroughly tested  
9 in multiple, mutually consistent, adequately  
10 powered studies that exclude with reasonable  
11 certainty bias, confounding, and chance. And  
12 I don't think that bar has been met.

13 A 2010 article published by  
14 University of South Florida researchers Rohr  
15 and McCoy analyzed the findings of over 125  
16 independently published research studies of  
17 atrazine effects on freshwater fish and  
18 amphibians. Their meta-analysis found that  
19 many of the studies reported the same health  
20 outcomes, even though the studies were in  
21 several different wildlife species and used  
22 different research methods.

1           In particular, atrazine affected  
2           the hormone system of freshwater fish and  
3           amphibians in most studies, including effects  
4           such as altered time of metamorphosis --  
5           sometimes it was a delayed and sometimes it  
6           was accelerated, it wasn't always the same --  
7           impaired sperm production and abnormal gonadal  
8           development.

9           These reports of diverse endocrine  
10          disruption effects on atrazine across diverse  
11          species and in different independent studies  
12          suggests that the mechanisms of toxicity for  
13          atrazine are likely also diverse, including  
14          several mechanisms of action potentially and  
15          possibly including aromatase catalysis.

16          Question 1.6, the agency has also  
17          concluded that there's no association between  
18          atrazine and the development of Parkinson's  
19          disease. You heard their presentations  
20          yesterday; I also did. Please comment.

21          So my comment is this. A  
22          potential association between atrazine and

1        Parkinson's disease has not yet been tested  
2        with multiple, mutually consistent, adequately  
3        powered studies covering a full range of human  
4        exposures that exclude, with reasonable  
5        certainty bias, confounding, and chance to  
6        provide individual and pooled estimates of  
7        risk in near unity with narrow confidence  
8        intervals. It has not been tested, in other  
9        words.

10                    However, a number of well-  
11        conducted studies have reported a  
12        statistically significant link between  
13        Parkinson's disease and exposure to pesticides  
14        generally, and including some herbicides and  
15        organochlorines like atrazine.

16                    For example, in 2010 a Portuguese  
17        team reported that among 86 cases of  
18        Parkinson's disease, sex- and age-adjusted  
19        logistic regression showed a potential risk  
20        factor, included pesticides, herbicides, and  
21        insecticides. It's in my comments: The odds  
22        ratio is 2.6, and the 95% confidence interval

1 range is 1.17 to 5.86.

2 The 2009 epi study from California  
3 reported a correlation between well water  
4 possibly contaminated with agriculture  
5 pesticides, possibly because they used GIS-  
6 based models and state pesticide use reports  
7 in order to estimate contamination levels, and  
8 Parkinson's disease specifically.

9 Although atrazine was not one of  
10 the pesticides that was selected for  
11 examination in that study, they did find a  
12 high level of possible well water  
13 contamination with methomyl -- odds ratio is  
14 1.67 -- it was statistically significant --  
15 with chlopyrifos -- and the odds ratio of  
16 1.87, again statistically significant -- and  
17 propargite -- odds ratio 1.92, again  
18 statistically significant -- resulting in  
19 approximately 70 to 90 percent increases in  
20 relative risk of Parkinson's disease.

21 And more recently a 2010 study  
22 published in the Journal of Neurology reported

1 on a correlation between blood serum levels of  
2 dieldrin, which is also an organochlorine like  
3 atrazine, and Parkinson's disease. I also  
4 have the odds ratios here. Atrazine may also  
5 be found to have similar health outcomes if it  
6 were examined properly.

7           These findings are in agreement  
8 with an NIH agriculture health study which  
9 reported in 2006 a nearly twofold increase in  
10 the risk of Parkinson's among applicators.  
11 Incident Parkinson's was associated with  
12 cumulative days of pesticide use at  
13 enrollment. So the more days that you applied  
14 the more your risk went up. And they divided  
15 them into quartiles. And when the highest  
16 quartile, which was 400-plus days, was  
17 compared to the lowest the odds ratio was 2.3,  
18 and it was statistically significant for  
19 persons applying pesticides.

20           For persons applying pesticides  
21 more than half the time the odds ratio is 1.9.  
22 While this study reported a link between

1 atrazine and incident Parkinson's it was not  
2 significant at the 95th percentile. It  
3 probably would have been significant at the  
4 90th percentile -- the odds ratio is 1.1 and  
5 the confidence sensor was -- spanned .5 to  
6 2.2, but they didn't present 90th  
7 percentile -- or 90 percent confidence  
8 intervals. I wish they did. Moreover, the  
9 authors reported a link between the  
10 organochlorine lending and also incident  
11 Parkinson's -- statistically significant.

12           Unfortunately, there was a low  
13 number of cases -- 43 percent with atrazine  
14 and 19 cases with lindane. It's -- because  
15 it's a prospective epidemiology study they're  
16 still following it. And it compromises the  
17 statistical power of the study at this point,  
18 but they're still following up these  
19 applicators and I think there may be things we  
20 can learn in future iterations -- future  
21 reports.

22           These studies and others provide

1 suggestive evidence, though, that a possible  
2 link may exist between atrazine exposure and  
3 risk of Parkinson's disease. And therefore,  
4 a lack of an association cannot be asserted  
5 with scientific confidence.

6 I have some answers to 1.8 on the  
7 immune system but I actually don't think I'm  
8 going to read them for you today. Oh, except  
9 to sum up at the end because I read a little  
10 bit of the Jason Rohr study -- the meta-  
11 analysis and a few things -- except to sum up,  
12 that atrazine has been shown to act  
13 synergistically with other chemicals to  
14 increase their toxic impairing of the immune  
15 system.

16 In a 2009 study when tiger  
17 salamander larvae were raised for two weeks in  
18 atrazine containing -- or in water containing  
19 atrazine at 20 or 200 part per billion or  
20 chlorpyrifos at 220 or 200 part per billion,  
21 no increase in death was observed. But when  
22 the larvae were exposed to the combination of

1 atrazine and chlorpyrifos together there was  
2 a significant increase in larval death from  
3 increased viral infection and disease, so  
4 presumably a compromised immune system.

5 This study suggested the two  
6 chemicals acting together can harm immune  
7 function, whereas either one alone may not.  
8 This is significant because these pesticides  
9 are commonly found together. USGS finds them  
10 up to seven or more at the time routinely in  
11 water bodies, and, as well, because many of  
12 the pesticide products, including atrazine,  
13 are packaged and sold as mixtures with other  
14 pesticides.

15 Question 1.9: I sort of use that  
16 question as an opportunity to jump in and say  
17 that I think EPA failed to consider a number  
18 of important studies that are directly  
19 relevant to the understanding of human health  
20 risks associated with atrazine, and I've  
21 identified some of those.

22 One of them that I think is really

1 important and that was mentioned at the -- by  
2 the scientific advisory panel you guys in --  
3 I think February was your last meeting -- is  
4 one on poor birth outcomes -- it's a 2009  
5 study. It found a significant correlation  
6 between prenatal atrazine exposure and reduced  
7 birth weight -- reduced body weight at birth.

8 They reviewed over 24,000 babies  
9 born in Indiana and localized them to  
10 particular water systems. I've summed it up  
11 for you with a little more data. I think it  
12 should be considered.

13 There's also a 2009 study that  
14 analyzed over 30 million births across the  
15 U.S. and reported an increased risk of birth  
16 defects associated with mothers who became  
17 pregnant in April to July, when pesticides are  
18 at their highest in the waterways. These  
19 ecological epidemiology studies, as you know,  
20 are more like hypothesis testing rather than  
21 conclusive.

22 But what I think is interesting

1 about this is that in spring when other --  
2 where pesticides may fluctuate in the water  
3 and might be considered to be highest, other  
4 contaminants wouldn't be expected to fluctuate  
5 in spring. So, for example, pharmaceuticals  
6 that are in our water, other kinds of  
7 endocrine disruptors that are in drinking  
8 water -- so you wouldn't be expecting them to  
9 have seasonal spikes like pesticides. So I  
10 think it's worth looking at. I think it's  
11 significant. They found a birth defect in the  
12 gut wall of newborn babies associated with  
13 early life exposures during this time.

14 The other thing I want to point  
15 out -- in digging through the RED, which is  
16 the Registration Eligibility Decision that  
17 EPA -- EPA's final decision to register  
18 atrazine -- is that they actually determined  
19 that it was likely that workers and homeowners  
20 and their families may be exposed to unsafe  
21 levels of atrazine because of lawn uses. For  
22 workers, that included farmers who mix, load,

1 and apply the pesticides like atrazine -- this  
2 is in atrazine RED -- and I have page numbers  
3 and references.

4 What they found -- we know that  
5 exposures can occur from accidental spills and  
6 splashes onto skin or clothing as well as  
7 inhalation and droplets being applied directly  
8 to the skin. And EPA noted all that and that  
9 exposure can also occur when applicators  
10 follow all the label requirements and use  
11 protection clothing and equipment, that you  
12 can still have exposures.

13 We also know that because we have  
14 data showing that farmers have it in their  
15 urine when they apply atrazine -- and that's  
16 data from CDC researchers -- and I've cited  
17 all of those studies. As well, we know that  
18 there's been links between atrazine levels in  
19 the urine and poor sperm quality in rural men  
20 associated with atrazine exposure --  
21 statistically significant.

22 And we also know that if you

1 reduce the amount of atrazine that's being  
2 applied then you can actually reduce the  
3 amount that's in the urine. So we know that  
4 there's a direct correlation if we take action  
5 that we can actually protect direct exposures  
6 to those workers.

7 And in 2006 in its RED in its  
8 final decision EPA acknowledged concerns about  
9 these human exposures. EPA classified  
10 atrazine as an RUP, or restricted use  
11 pesticide. That's because of its hazards to  
12 ground and surface water, and it means that  
13 only applicators can apply it.

14 But there's an exception for lawn  
15 care, turf, and conifer trees and it allows  
16 homeowners to apply the chemical themselves.  
17 And according to EPA's own assessment in its  
18 RED, this exception may lead to unsafe  
19 exposures that exceed EPA's own levels of  
20 concern for homeowners who apply the products  
21 for their lawn. And EPA also expressed  
22 concern that children who play on these

1 atrazine-treated lawns may also be at risk for  
2 potentially unsafe exposures. So the idea of  
3 needing to consider these early life exposures  
4 is very relevant. It's very real.

5 We have some recommendations. I  
6 used question 2.1 to take advantage of some  
7 extra space at the end and make some  
8 recommendations. So, first of all, the  
9 watershed and monitoring programs of watershed  
10 and drinking water -- actually our analysis of  
11 EPA's atrazine monitoring program taken from  
12 20 watersheds between 2007 and 2008, which is  
13 our updated report which I've provided to you,  
14 confirms that waters are contaminated. They  
15 continue to be contaminated.

16 Actually they did 20 watersheds  
17 and they all showed detectable levels of  
18 atrazine. 16 had average concentrations above  
19 1 part per billion. 1 part per billion is the  
20 level that EPA has been determined to show --  
21 is determined to be harmful and plants and  
22 wildlife -- aquatic plants and wildlife.

1                   18 of the monitored watersheds  
2 were intermittently severely contaminated  
3 where at least one sample was above 20 -- this  
4 is watersheds, not drinking water, remember --  
5 above 20 part per billion. And nine had peaks  
6 that were above 50 part per billion. Three  
7 had maximums that exceeded 100 part per  
8 billion. One, the Big Blue River watershed in  
9 Nebraska, had 147 part per billion in May of  
10 2008.

11                   The drinking water data, which we  
12 also analyzed and provided an update, was  
13 taken between 2005 and 2008. 80 percent of  
14 the samples from 153 drinking water systems  
15 contain atrazine -- that's raw and finished --  
16 that's 80 percent of total samples. But of  
17 the 153 drinking water systems that were  
18 monitored, 100 had peaks in the raw water that  
19 exceeded 3 part per billion, and two-thirds of  
20 these 100 systems also had peaks that exceeded  
21 3 in the finished water. Again, they don't  
22 exceed the MCL because it's averaged over a

1 year, but they're spiking.

2 Six had high enough atrazine  
3 levels to actually exceed the MCL. But what  
4 happens is, the utilities put in all the data,  
5 and so when you get a lot more non-detects or  
6 low levels of the year, you can average away  
7 those peaks. But if they just took the  
8 quarterlies it would actually exceed the MCL  
9 in the finished tap water.

10 But the problem -- and my  
11 recommendations as a scientific advisory panel  
12 that you can pass on to the EPA -- is that EPA  
13 actually identified 1,172 watersheds that were  
14 at high risk. They, however, negotiated a  
15 monitoring program with the registrant that  
16 would only monitor 40 of the 1,172. So  
17 everything you've been hearing about and all  
18 the data we've collected and everything that  
19 EPA has is on about 4 percent of what EPA  
20 recognizes as the high risk watersheds.

21 Okay. So we think that that  
22 monitoring program should be broadened. For

1 one thing EPA doesn't have any plan to deal  
2 with the other ones. So actually everything  
3 they're finding and everything they're telling  
4 you that they're taking action on is in that  
5 40 and the other, you know, 1,060 are being  
6 ignored. And I agree with Alan Roberson that  
7 that should be paid for by the registrant.

8 And we also think that the  
9 scientific advisory panel could recommend to  
10 EPA that they publish the monitoring data so  
11 that we don't have to keep doing report  
12 updates. And they should publish it in a way  
13 that the public can look up their data, like  
14 they can on our website now, and they can look  
15 up their community water system and see what  
16 the numbers are. That shouldn't be our job.  
17 Thank you.

18 SESSION CHAIR PORTIER: Any  
19 questions from the panel? Yes, Dr. Gilliom.

20 DR. GILLIOM: It's partly a  
21 question on protocol. Are the reports that  
22 are referenced in Dr. Sass' testimony with

1 your notes -- are those automatically included  
2 in the record? And part of this is also  
3 intermixed with a question that some of the  
4 input we've received is based on the  
5 epidemiological type of studies -- more the  
6 correlation things and sometimes involving  
7 mixtures, which is kind of in this gray area  
8 of scope for our panel. So it makes it kind  
9 of difficult of how to factor everything in.  
10 Is there some guidance from -- is it included  
11 in --

12 MR. BAILEY: I don't have the  
13 studies. I only have the citations that  
14 Jennifer has provided. If you -- I suppose if  
15 you want copies of them we could try to get  
16 them for you -- work with Jennifer to get  
17 copies of them.

18 DR. SASS: I was being polite I  
19 guess. I can provide those with you. I think  
20 that your rules are that you don't put  
21 published manuscripts in the docket because it  
22 violates the copyright of the journal. So --

1 but I can e-mail them to you and then you can  
2 provide them to the committee I believe. Is  
3 that correct?

4 MR. BAILEY: We do provide them on  
5 an as-requested basis.

6 DR. SASS: So, tomorrow morning  
7 I'll bring our thumb drive with all of the  
8 atrazine papers as well as the report. Is  
9 that okay with you?

10 SESSION CHAIR PORTIER: And the --  
11 I think as of today the minutes from our  
12 February meeting are on the February docket  
13 where we discuss a lot of the epidemiology  
14 studies, the exploratory correlation studies  
15 that the panel reviewed back in February. And  
16 I think that -- a draft of that report was  
17 provided to the panel. Is that right? I  
18 think that's right. Dr. Fenner-Crisp?

19 DR. FENNER-CRISP: The report from  
20 the February meeting is in the docket and I  
21 downloaded it last night. So it's publicly  
22 available.

1 DR. GILLIOM: So just -- did we  
2 get that one yet for the panel package or is  
3 it just on the docket that I should get it if  
4 I want it?

5 MR. BAILEY: Actually, I think  
6 that one just came out last week.

7 DR. GILLIOM: Okay.

8 MR. BAILEY: Within the last few  
9 days. We can e-mail that -- I can e-mail that  
10 to you because it is in the docket -- should  
11 be in the docket.

12 SESSION CHAIR PORTIER: I think you  
13 have to pull it down because it's a pretty big  
14 report. We were having problem e-mailing even  
15 the panel members the report. So it's better  
16 to go to the docket and download it at that  
17 point.

18 DR. FENNER-CRISP: It's 80-  
19 something pages -- 82 pages.

20 SESSION CHAIR PORTIER: Yes, it  
21 was -- we reviewed it pretty thoroughly.

22 DR. FENNER-CRISP: The other point

1 is, I think we have been asked today, in this  
2 panel, to focus on the animal studies and not  
3 on the epidemiology at this point in time,  
4 because it isn't all available.

5 SESSION CHAIR PORTIER: And I think  
6 we'll be ruling on that as the conversation  
7 goes along. I'll help say whether this is in  
8 the discussion. I mean, again, we're going to  
9 have more discussion later on in the year,  
10 it's going to come back to epidemiology. So  
11 thank you very much.

12 The next public commenter is Scott  
13 Slaughter, the Center for Regulatory  
14 Effectiveness. And then following him is Jay  
15 Vroom of Crop Life America. So maybe the two  
16 of you can stage up.

17 I do want to get one question in  
18 today. We're going to do one question if it  
19 kills me.

20 MR. SLAUGHTER: I'm Scott  
21 Slaughter and I'm commenting today on behalf  
22 of the Center for Regulatory Effectiveness.

1 I met Dr. Portier in the hall at the beginning  
2 of the last break, and he looked at me and  
3 said, "Well, you wanted to be last." And I  
4 told him it was one of my many errors in  
5 judgment.

6 I beg your indulgence for just a  
7 few minutes while I talk to you briefly about  
8 the quality of the information that EPA's  
9 asked you to consider in this SAP. The  
10 February minutes of the February -- the  
11 minutes of the February atrazine SAP were  
12 mentioned just a minute ago. And those  
13 minutes state, and I quote, "Like all  
14 information considered in risk assessments,  
15 the quality and reliability of the information  
16 provided by epidemiologic studies needs to be  
17 closely scrutinized."

18 That's good advice, and it's not  
19 limited to epi studies. It also applies to  
20 the other studies which EPA has asked this SAP  
21 to review and which EPA is considering for use  
22 in a new atrazine risk assessment.

1                   There are several regulatory  
2 requirements and guidelines that govern EPA's  
3 use of these studies. EPA cannot base an  
4 atrazine risk assessment on studies that do  
5 not meet and comply with these requirements  
6 and guidelines. The guidelines and  
7 requirements include reproducibility.

8                   For example, EPA's information  
9 quality guidelines require EPA to "ensure the  
10 reproducibility of influential information."  
11 An atrazine risk assessment is influential  
12 information.

13                   As another example, EPA is a  
14 member of the international coordinating  
15 committee for the validation of analytical  
16 methods. We groupies know it as ICCVAM.  
17 ICCVAM has established test validation and  
18 acceptance criteria which require that -- and  
19 I quote -- "the extent of within-test  
20 variability and the reproducibility of the  
21 test within and among laboratories must have  
22 been demonstrated. Data must be provided

1 describing the level of inter- and intra-  
2 laboratory reproducibility and how it varies  
3 over time. The degree to which biological  
4 variability affects the test reproducibility  
5 should be addressed."

6 As still another example, EPA's  
7 FIFRA data rules state that EPA "will evaluate  
8 the conduct of each experiment in terms of  
9 whether the study was conducted in conformance  
10 with the design, good laboratory practices  
11 were observed, and the results were  
12 reproducible."

13 As a final example, CRE's comments  
14 on the 2002 atrazine risk assessment raised  
15 validation issues about some of the test data  
16 which EPA wanted to use and which allegedly  
17 showed endocrine effects from exposure to  
18 atrazine. EPA's response to CRE's comments  
19 said, and I quote, "In determining whether  
20 data are acceptable the agency considers a  
21 number of factors: for example, study design,  
22 including sample size, replication, use of

1 appropriate controls, et cetera."

2 In light of these regulatory data  
3 quality requirements we ask EPA to answer two  
4 questions. First, where is the record  
5 demonstrating the reproducibility of the  
6 studies the agency wants to use in atrazine  
7 risk assessment? Second, where is the record  
8 demonstrating that these studies meet EPA's  
9 other data quality requirements?

10 EPA has dumped a large number of  
11 studies and data on the public and has  
12 provided very little time for the public to  
13 review and comment on these studies and data.  
14 EPA's answers to these two questions would  
15 greatly improve the transparency and user  
16 friendliness of this proceeding.

17 Thank you. And I'll try to answer  
18 any questions you might have.

19 SESSION CHAIR PORTIER: Any panel  
20 questions?

21 (No response.)

22 MR. SLAUGHTER: Oh, that's good.

1 Thank you.

2 SESSION CHAIR PORTIER: Thank you,  
3 Scott. The last public commenter is Jay  
4 Vroom.

5 MR. VROOM: Thank you, Mr.  
6 Chairman and members of the panel. My name is  
7 Jay Vroom. I'm president of Crop Life  
8 America, a trade association that represents  
9 virtually all of the manufacturers, discovery  
10 firms, distributors, and formulators of crop  
11 protection products used by American farmers.

12 I submitted my four-page letter  
13 for the staff to put in the record and I'd  
14 prefer to summarize if I might.

15 I begin by saying good evening,  
16 taking a different temporal approach --  
17 perhaps more optimistic with the notion that  
18 some of us may have been contemplating  
19 exposing ourselves to water contaminated by  
20 alcohol after a day like this.

21 Crop Life does not advocate on  
22 behalf of any one individual member company or

1 any one particular product provided by our  
2 industry to be a tool for American farmers.  
3 We do try to take opportunities like this  
4 public comment period to articulate specific  
5 thoughts with regard to policy that has a  
6 precedent that is important for our members  
7 and others in the industry from a policy  
8 standpoint and of ultimate impact and  
9 importance to our customer, the American  
10 farmer.

11 With respect to our understanding  
12 at Crop Life of what's before this SAP, I was  
13 struck by Dr. Sass's presentation that also  
14 mentioned a number of other issues that, from  
15 my understanding are not before this  
16 committee, but, in fact, are also very  
17 important issues. And it just, to me,  
18 reinforced the reaction that we had when this  
19 administration decided to convene the SAP on  
20 these issues particular to atrazine, which we  
21 believe have been rather thoroughly examined  
22 by the agency and with input from previous

1 SAPs in the past.

2 And our preference, of course,  
3 would be that the kinds of resources  
4 represented by you on this panel and the  
5 support of the agency would be actually  
6 attentive to many of those other issues that  
7 Dr. Sass referenced. And so, in fact, we  
8 believe that this is an unfortunate focus of  
9 resource that otherwise could perhaps  
10 otherwise be allowed to have you spending time  
11 on that range of other issues that are on down  
12 the road and in front of us.

13 The one specific issue that I'd  
14 like to address here is the importance of  
15 focusing on those sources of data that are  
16 specific to finished drinking water. That is  
17 our understanding as to what the issues are  
18 really in front of this SAP with regard to  
19 that route of exposure and that particular  
20 concern with regard to human health effects  
21 and the compound atrazine.

22 And I really think it really gets

1 down to the matter of communication. And I  
2 would draw another parallel to activity that  
3 EPA has undertaken with regard to the  
4 requirement under the Safe Drinking Water Act  
5 as well as the Food Quality Protection Act  
6 passed by Congress in 1996 and that has to do  
7 with the evaluation of endocrine effects and  
8 crop protection products and other chemicals  
9 that humans may be exposed to.

10 And the parallel that I think is  
11 important to draw here is how careful EPA has  
12 been to explain what they are doing with  
13 regard to the very careful and deliberate  
14 science-based stepwise approach to  
15 implementing the endocrine disruption  
16 provisions in the Safe Drinking Water and Food  
17 Quality Protection Acts, and more particularly  
18 what they are not doing at particular stages.

19 And I think that's been a model  
20 with regard to communication by the agency and  
21 their advisors that would serve this SAP  
22 working with the agency going forward to be

1 extra careful about how you communicate, what  
2 you're doing, what you're considering, and,  
3 just as importantly, what is not on the table  
4 in front of you.

5 And so, again, I would go back to  
6 the core presentation that we wish to  
7 emphasize here today with these remarks, which  
8 is that -- the matter before this SAP has  
9 nothing to do with human consumption of raw  
10 water and that the data that should be  
11 examined and the risk factors that should be  
12 considered by this SAP in providing advice  
13 back to the agency have to do with the risk  
14 factors associated with the presence of this  
15 compound in finished drinking water.

16 The record is clear with regard to  
17 Congressional intent. In our view, having to  
18 do with the scientific validity of information  
19 that comes before and consideration of the  
20 agency, that it needs to be science-based, and  
21 when it is science-based there are a number of  
22 criterion that the law is specific with regard

1 to how the agency should consider it and how  
2 it should communicate to the public.

3 And I believe, again, that that  
4 kind of consideration with regard to  
5 communication is an obligation that the SAP  
6 over the years has taken seriously and been  
7 effective with. And at the end of the day,  
8 with regard to the kinds of risks that are  
9 being assessed and advice being given to the  
10 agency with regard to exposure in water to  
11 human beings with regard to atrazine, it's  
12 only around the exposure on finished drinking  
13 water and that humans are not intentionally  
14 drinking unfinished or raw water provided to  
15 them by community water systems.

16 So, once again, I thank you for  
17 this opportunity to share that perspective.  
18 I would also share with you that having been  
19 here for much of today I was struck by how  
20 lucky we are as citizens of the United States  
21 to have the service of committed volunteers,  
22 such as yourselves, with scientific expertise

1 that you represent for the SAP in looking at  
2 these kinds of issues, serving not only the  
3 interest of the general public but my industry  
4 and ultimately the American farmer who uses  
5 these tools effectively to conduct modern  
6 agriculture and to provide us with a safe and  
7 abundant food supply. Thank you very much.

8 SESSION CHAIR PORTIER: Thank you.  
9 Any additional questions from panelists? Yes,  
10 Dr. Coupe.

11 DR. COUPE: I just had a comment  
12 mostly, and it's kind of a little bit of  
13 different thinking. I think I was more in  
14 line with you last week before I got here and  
15 heard the discussion.

16 But now I think I understand why  
17 we want to look at surface water as opposed to  
18 just concentrating on finished water, now that  
19 I'm thinking about it, because the sampling  
20 the surface water -- examining the surface  
21 water gives us a conservative estimate. And  
22 it also shows us, you know, sometimes these

1 treatment plants can fail, and it kind of  
2 gives us a backup on how much we need to be  
3 careful with.

4 But, additionally, listening to  
5 some of the other people I was struck by, why  
6 should these treatment plants have to install  
7 equipment to take care of something that  
8 shouldn't naturally be in there? They do  
9 their work looking on -- you know, they're  
10 meant to take out chemicals that absorb to  
11 sediment and to disinfect. They're not meant  
12 to take out water-soluble chemicals.

13 So we're applying these water-  
14 soluble chemicals. And there's always a  
15 chance that they might get through. I know  
16 I'm not a toxicologist, so I can't say what  
17 the epidemiological work on it is, but it just  
18 seems to me that perhaps we should be looking  
19 and continue to look in the surface water, as  
20 well as the drinking water.

21 MR. VROOM: Thank you. It should  
22 be clear that as an industry we are not

1       opposed to testing of other water besides  
2       finished drinking water for certain crop  
3       protection products.

4                   But in terms of the level of the  
5       magnitude of testing that has been reviewed  
6       here today by any number of presenters,  
7       particularly all those representing the data  
8       that Syngenta have produced, we think that  
9       that's the right place where that kind of  
10      resource has been focused in addition to all  
11      of the resources that have been put into,  
12      number one, innovating other products that  
13      have displaced older compounds, but, number  
14      two, also allowing for education on how older  
15      compounds like atrazine can be more  
16      effectively used by growers and other  
17      pesticide users -- that the combination of all  
18      of those resources coming together have  
19      allowed the kinds of trend lines with regard  
20      to reduction of exposure and reduction of risk  
21      to occur over time.

22                   And there are other reasons to

1 sample water for other considerations,  
2 including ecological effects, but the level of  
3 resource and intensity of volume of sampling  
4 seems to be, you know, completely different in  
5 those contexts and ought to be approached that  
6 way.

7           Lastly, I would say that it's my  
8 understanding that community water systems do  
9 filter for a wide range of contaminants and  
10 that crop protection products, including  
11 atrazine, are only, you know, one category,  
12 and there are other soluble chemicals that are  
13 out there.

14           We think that, you know, the  
15 systems are adequate and are working quite  
16 well -- always room for improvement. And,  
17 once again, the kind of scientific robustness  
18 that a group such as the SAP can bring to  
19 thinking through those sorts of considerations  
20 in EPA's context here as well as for the  
21 Office of Water and the Safe Drinking Water  
22 programs continues to, I think, advance the

1 science and the practical safety of our water  
2 supply.

3 SESSION CHAIR PORTIER: Thank you.  
4 We did receive electronically -- and you have  
5 copies of a comment from an M. J. Quinn -- no  
6 address, no other information -- recommending  
7 banning of atrazine. And you can read this.

8 At this point I'm going to make a  
9 last call for any additional public  
10 commenters. Anyone wishing to provide a  
11 comment before the panel? Going once, going  
12 twice.

13 I think at this point I'm going to  
14 close the period of public comment and we're  
15 going to proceed to the panel discussion.  
16 We're about three hours late. I guess that's  
17 not too bad. For an important meeting like  
18 this, that isn't that bad.

19 So I'm going to invite EPA back up  
20 to the front table here to read the first  
21 question. For the panel, we're going to begin  
22 the discussion. I don't think we're going to

1 probably end the discussion, but we're going  
2 to at least spend the next 45 minutes on this  
3 topic. When we get to about 4:40 we're going  
4 to reconsider how much we've got left and then  
5 move on -- 5:40 -- I'm sorry. Yes, 45 more  
6 minutes -- 5:40 -- 5:40, 5:45.

7 DR. MENDEZ: Good afternoon. This  
8 is Elizabeth Mendez again for the U.S. EPA.  
9 I'm going to start reading the charge  
10 questions to the FIFRA Scientific Advisory  
11 Panel.

12 Charge question 1.0 -- in 2003 the  
13 human health risk assessment was based on a  
14 mode of action in which exposure to atrazine  
15 leads to a reduced release of gonadotropin  
16 releasing hormone (GnRH) from the  
17 hypothalamus, thereby lessening the afternoon  
18 pituitary luteinizing hormone (LH) surge in  
19 female Sprague Dawley rats. As a result, the  
20 estrous cycle lengthens. This, in turn, leads  
21 to increased estrogen levels and an increased  
22 incidence of mammary tumors in female Sprague

1 Dawley rats.

2 EPA determined that atrazine's  
3 cancer mode of action (i.e., premature  
4 reproductive aging) in the Sprague Dawley rat  
5 is not likely to be operative in humans (a  
6 conclusion consistent with the SAP  
7 recommendation in 2000). The agency will be  
8 evaluating the cancer classification further  
9 as the experimental toxicology data are  
10 integrated with the epidemiology data. New  
11 experimental toxicology studies (Section 3.6  
12 of the draft issue paper) do not suggest a  
13 change to the agency's previous conclusion  
14 that atrazine is not likely to be carcinogenic  
15 to humans.

16 Next please. Although the cancer  
17 mode of action may not be operative in humans,  
18 it is not unreasonable to assume that atrazine  
19 might cause adverse effects on hypothalamic-  
20 pituitary function in humans. Thus, the same  
21 endocrine perturbations that induce tumors in  
22 rats may play a role in at least some

1 reproductive/developmental effects (not  
2 associated with reproductive aging) that may  
3 be relevant to humans.

4 Accordingly, the agency identified  
5 disruption of estrous cyclicity and delays in  
6 puberty onset (males and females) occurring as  
7 a consequence of disruptions to the  
8 hypothalamic-pituitary-gonadal (HPG) axis as  
9 the critical end points of concern (Sections  
10 2.0 and 3.2 of the draft issue paper).

11 The agency continues to believe  
12 that this disruption of the HPG axis is  
13 critical to affecting estrous cyclicity and  
14 delayed puberty onset. However, as discussed  
15 in questions 1.2 through 1.6 below (see figure  
16 3 of the draft issue paper), new information  
17 has been published that indicates a more  
18 expanded understanding of how atrazine may  
19 perturb the pathway leading to reproductive  
20 effects.

21 These new data indicate that  
22 atrazine disrupts the hypothalamic-pituitary-

1       adrenal (HPA) axis altering the central  
2       nervous system's control of the pituitary and  
3       adrenal which, in turn, disrupts the HPG axis.  
4       Furthermore, a hypothesis for a direct effect  
5       of atrazine on the adrenal cortex and the  
6       gonads which may impact steroidogenesis  
7       directly is also supported by the available  
8       data.

9                       Now we get to the question. With  
10       the caveat that the review of the  
11       epidemiological literature is still ongoing,  
12       please comment on the agency's preliminary  
13       conclusion that new experimental data from in  
14       vitro and in vivo laboratory animal studies do  
15       not support a change in the conclusions from  
16       the 2003 risk assessment that atrazine is  
17       unlikely to be a human carcinogen.

18                      SESSION CHAIR PORTIER: So we start  
19       with a big question here. Dr. Fenner-Crisp as  
20       the lead discussant.

21                      DR. FENNER-CRISP: I could give a  
22       very short answer, but now being on a panel,

1 I can't do that. I've got to write a lot,  
2 give folks more to read.

3 I'll essentially summarize two  
4 documents, and I'll start out with saying, in  
5 the 2000 draft risk assessment, MOA thing --  
6 that's this one that went to the 2000 SAP and  
7 later finalized in the IRED and RED -- the  
8 agency presented its analysis of the human  
9 carcinogenic potential of atrazine. Rodent  
10 bioassay results revealed no increase in any  
11 tumor type in male Sprague Dawley rats or in  
12 Fischer 344 rats or CD1 or other mice strains  
13 of either sex. However, there was an  
14 increased incident and/or early onset of  
15 mammary adenomas, carcinomas, fibroadenomas,  
16 and pituitary adenomas in the females of  
17 Sprague Dawleys.

18 EPA conducted an in-depth analysis  
19 of these tumors, particularly the mammary  
20 adenomas and carcinomas, which included the  
21 development of additional data used to  
22 describe possible modes of action by which

1 these tumors arose and presentation and  
2 conclusions as to the relevance of the  
3 hypothesized modes of action with regard to  
4 the chemical's human carcinogenic potential.

5 Based primarily on the work of the  
6 ORD researchers, a non-genotoxic mode of  
7 action was postulated for effects of atrazine  
8 on components of the HPG axis and the  
9 development of the mammary and to some extent  
10 the pituitary tumors in these -- the strain of  
11 female rats.

12 An alternative possible genotoxic  
13 mutagenic mode of action was not supported  
14 based upon the weight of evidence evaluation  
15 of a variety of short-term genotoxicity  
16 assays.

17 The figure and the text below  
18 taken from the 2000 document present the key  
19 postulated events. And I pulled the figure  
20 off of page 33 in here and the text that  
21 surrounds that particular page. I won't go  
22 through the figure but remind folks they don't

1 have that document of what the key events  
2 were.

3 Key event one was: atrazine  
4 exposure affects either directly or indirectly  
5 the hypothalamus, leading to decreased  
6 secretion of hypothalamic norepinephrine.

7 The second key event: hypothalamic  
8 norepinephrine normally modulates the release  
9 of gonadotropin-releasing hormone, but with  
10 the decreased norepinephrine, one saw a result  
11 in a decreased release of GnRH.

12 Key event three: GnRH is  
13 responsible for inducing the pituitary gland  
14 to release LH. If you have decreased GnRH,  
15 you have decreased LH. We've been hearing  
16 this from several parties the last two days.

17 Fourth key event: LH normally  
18 provides a signal to the ovaries prompting  
19 ovulation, but below some critical level the  
20 decreased serum levels of LH are insufficient  
21 to stimulate ovulation.

22 The fifth key event essentially

1 describes that the feedback loop has been  
2 interrupted and you don't get the normal  
3 feedback.

4 Key event six was with the  
5 increased -- circulating estrogen acts on the  
6 mammary gland to increase the risk of mammary  
7 tumors.

8 And the last step in there dealt  
9 with the fact that there was not a genotoxic  
10 mode of action.

11 As will be discussed at greater  
12 length below much of the EPA research  
13 conducted since that time has been targeted  
14 toward improving the understanding of the  
15 nature of the reproductive and developmental  
16 effects of atrazine. Pursuit of the  
17 characterizations of the mode of mechanisms by  
18 which these effects occur has revealed at  
19 least one major aspect not identified earlier  
20 while characterizing the mammary tumor mode of  
21 action. And that's activation of the HPA  
22 axis.

1           The key events for this phenomenon  
2           have now been described -- and that's on  
3           page -- I think it's 33 in the current  
4           document -- those four key events.

5           Hypothalamic changes resulting in  
6           an increase in CRH release --

7           DR. KRISHNAN: Which document are  
8           you referencing? Is that a white paper or --

9           DR. FENNER-CRISP: The current  
10          document, yes, white paper. Key event two:  
11          increased release of adrenocorticotropic  
12          hormone (ACTH) from the pituitary. Key event  
13          three: increased production of the  
14          corticosterone and progesterone by the  
15          adrenals. And key event four: decrease in GNR  
16          release from the hypothalamus as a result of  
17          one or more of those key events. So we're  
18          seeing a circling back.

19          I've stuck Liz's favorite figure  
20          in here because I couldn't find that just  
21          shows the key events numbered in anybody's  
22          presentation for the HPA. And unfortunately

1 the numbers in your favorite thing don't match  
2 up with the four key events, but that's okay.

3 The bottom line here is the  
4 convergence of key events two and three in the  
5 original mammary tumor mode of action and key  
6 event four in the HPA activation pathway  
7 component are obvious. Discovery that an  
8 additional component or pathway may be in play  
9 neither negates nor diminishes the conclusions  
10 reached earlier with regard to the  
11 characterization of the mammary tumor mode of  
12 action, or its relevance to human health risk  
13 assessment.

14 Even though I was listening very  
15 carefully to the presentations today, I'm not  
16 completely satisfied with the answer we got.  
17 So I kept in here a statement that says, One  
18 aspect that remains unclear is whether  
19 atrazine can directly affect the hypothalamus,  
20 setting off the cascade of effects, or  
21 indirectly through the HPA axis or both.  
22 That's still unclear, so I'm raising that as

1 something to be --

2 And then I ask another question to  
3 think about. Is it possible to incapacitate  
4 the HPA pathway and determine if the HPG axis  
5 is impacted in same or different manner? I  
6 think some of the discussion studies ongoing  
7 today led some light on that possibly. That's  
8 what I've done so far.

9 SESSION CHAIR PORTIER: Okay. Dr.  
10 Bucher as an associate discussant.

11 DR. BUCHER: So I'm in general  
12 agreement with the findings from the recent  
13 studies on the interrelationships of the HPA  
14 and HPG axes do not fundamentally change the  
15 conclusions of the 2003 risk assessment  
16 concerning the likelihood that atrazine is or  
17 is not a human carcinogen.

18 The critical role of inhibitor of  
19 LH surge in suppressing the estrous cycling in  
20 the SD rat seems to be supported by the recent  
21 literature in the sensitivity of the SD rat to  
22 increases in mammary tumors with increases in

1 endogenous estrogens or from treatment with  
2 estrogenic substances is well recognized.

3           However, I'd caution that the  
4 demonstration of the involvement of the HPA  
5 axis and the mammary tumor response of the SD  
6 rat may, in the eyes of some, diminish its  
7 biological significance as an indicator of  
8 disruption of the HPG axis.

9           EPA's clearly not doing this in  
10 their background document, and the recent  
11 findings that Dr. Handa reported today  
12 concerning the maintenance of the suppression  
13 of the LH surge in adrenalectomized animals  
14 certainly supports the EPA's stance here. But  
15 I wouldn't be a bit surprised to see papers  
16 begin showing up in the literature  
17 hypothesizing that this particular event is  
18 maybe just a rat strain specific effect that  
19 results from a unique or abnormal sensitivity  
20 to a general stress response.

21           I've seen a strong tendency, when  
22 interpreting chronic rodent cancer studies, to

1 attribute difficult to explain tumor  
2 incidences to, quote-unquote, "differential  
3 stress across treatment groups." But, in  
4 fact, there's hardly ever any data to back  
5 this up.

6 Different routes of exposure do  
7 result in different rates of tumors in some  
8 sites in control animals. And there is a  
9 general perception that the levels of stress  
10 to animals might be different or greater in  
11 inhalation studies where animals are housed  
12 for two years in metal chambers with  
13 significant air flows and presumably more  
14 noise than, say, in studies where animals were  
15 simply held in enclosed polycarbonate cages.

16 And we do see somewhat higher  
17 rates of adrenal chromocytomas in control male  
18 Fischer rats in our NTP studies in inhalation  
19 studies than in dose feed studies. The  
20 mammary tumors in female Fischer rats are not  
21 different. And, of course, according to the  
22 prevailing hypothesis they wouldn't be

1 expected to differ as they don't senesce into  
2 a persistent estrous state.

3           Unfortunately we don't have any  
4 NTP studies in our database where we're used  
5 SD rats in inhalation studies. But a brief  
6 review of the SD rat inhalation studies in the  
7 literature comparing the mammary tumor rates  
8 in control females with the rates that were  
9 reported in the controls in the dose feed  
10 studies that were done by Syngenta on  
11 atrazine, you'll find that the tumor rates are  
12 actually very similar.

13           So what's the point of this?  
14 Well, again, if considerations of the  
15 potential health affects of atrazine are in  
16 any way diminished by the perception that the  
17 responses seen in the Sprague Dawley rat are  
18 because of an enhanced susceptibility of this  
19 animal to non-specific stress. And not that  
20 EPA is doing this in this current review, but  
21 strange things do happen over time. I would  
22 simply urge that the agency resist this line

1 of reasoning.

2 But the bottom line is, I don't  
3 see anything in the recent information that's  
4 come out that would change my perception of  
5 the original 2003 conclusion. Thank you.

6 SESSION CHAIR PORTIER: Dr.  
7 Krishnan?

8 DR. KRISHNAN: In considering the  
9 new lab animal studies that the agency's  
10 preliminary conclusion is the same as in 2003  
11 assessment, which is, atrazine is not likely  
12 to be a human carcinogen, this descriptive of  
13 "not likely to be a human carcinogen" is  
14 appropriate when there's evidence that the  
15 mode of action in experimental animals does  
16 not operate in humans.

17 The white paper lays -- well,  
18 emphasizes the initial reasoning that my  
19 colleagues just referred to, which is mammary  
20 tumors in female SD rats being a consequence  
21 of elevated levels of circulating estrogen and  
22 prolactin. And that remains unchanged.

1                   So the fundamental question of  
2                   human relevance still remains. And so  
3                   basically the new studies included here do not  
4                   provide any compelling evidence to change the  
5                   classification of atrazine.

6                   There's no new evidence that I see  
7                   that changes the conclusions regarding  
8                   atrazine's ability to act as an initiator;  
9                   that is, evidence of mutagenicity or  
10                  genotoxicity. And also the new studies on  
11                  tumor promotion progression, in my opinion, do  
12                  not provide sufficient strength of evidence to  
13                  change the classification for atrazine.

14                 So I agree with the agency's  
15                 initial conclusion -- or preliminary  
16                 conclusion that it still be considered not  
17                 likely to be carcinogenic to humans.

18                 However, one aspect that I think  
19                 could be of concern is the temporal  
20                 relationship of the early life exposure in  
21                 light of the revised cancer guidelines of  
22                 2005. That doesn't come out very well, and I

1 hope in the -- based on epi studies, the  
2 analysis that might be ongoing -- I'm not  
3 aware of the details of where those studies  
4 are -- and I hope there will be some  
5 consideration of time since first exposure,  
6 duration of window of exposure, and so on, in  
7 such analysis to be able to address whether  
8 there's any concern for early-life exposures  
9 and their relationship to tumorigenesis or the  
10 overall weight of evidence. And that's  
11 something that I'll be looking forward in the  
12 future work.

13 So the answer is yes.

14 SESSION CHAIR PORTIER: Okay. Dr.  
15 Reed.

16 DR. REED: It's true that I also  
17 have not heard of any presentation that could  
18 support any new mode of action within the  
19 framework that we're talking about -- I mean,  
20 the HPG and HPA axis.

21 However, I'm not I guess ready to  
22 rule out the relevance of the two in vivo

1 studies reviewed by the agency -- the  
2 promotional -- possible promotional mechanism  
3 of atrazine as presented in the Fukamachi et.  
4 al., 2004 and Ueda et. al., 2005 pertaining to  
5 mammary gland tumors.

6 I don't disagree with some of the  
7 uncertainties and limitations presented by the  
8 agency review. But I have a slightly  
9 different opinion about these two studies.  
10 With the Fukamachi study, it's true that  
11 there's uncertainties about the transgenic  
12 nature of these rats.

13 But the agency considered this  
14 study presented no dose response, and I looked  
15 at it and I felt sure -- you know, there's  
16 this small sample size, and particularly the  
17 high control incidence -- I think it's around  
18 about 50 percent -- that could cloud the  
19 conclusion coming from this study.

20 But when I look at it, I felt  
21 there is an apparent increase with the  
22 atrazine treatment in both female and male

1 rats. And I guess I'm a little bit more  
2 concerned because it was at the range of 5 and  
3 50 milligrams per kilogram.

4 I, frankly, am not as concerned  
5 about the high dose being -- the incidence at  
6 the high dose being dropped off because it's  
7 500 milligrams per kilogram and that could be  
8 some kind of a high dose effect that I'm not  
9 sure that I'm willing to take it in and to say  
10 that there is no dose response. The other  
11 study -- the other 2005 study was also very  
12 interesting, although the effects are now at  
13 50 to 500 milligrams per kilogram.

14 It's -- so looking at these two  
15 studies I come with a different -- slightly  
16 different conclusion. EPA concluded that  
17 these two sets of data suggest that estrogen  
18 does not induce mammary gland tumors in  
19 transgenic rats or ovariectomized rats treated  
20 with a mammary tumor inducer, thus  
21 highlighting the importance of ovarian  
22 hormones in the development of tumors in the

1 mammary gland.

2           And I would have said that you  
3 highlighted the possibility of a promotional  
4 potential -- not initiating, but promoting.  
5 So, frankly, I'm kind of curious that these  
6 two studies were from 2004 and '5, but there's  
7 no -- as far as I know no other follow-up  
8 studies along the same line of promotion.

9           Nevertheless, I would suggest that  
10 the agency expand on the discussion to include  
11 the significance of these two datasets on  
12 tumor promotion and perhaps look at the data  
13 in the context of mode of action and perhaps  
14 that house might have a little shed or  
15 something. I don't know.

16           Anyway, a possibility of, you  
17 know, branching it out that might not, you  
18 know, at least partly -- not directly  
19 associated with the endogenous estrogen at  
20 this point.

21           I would also suggest that, you  
22 know, if it is possible that the agency would

1 park these issues until all data for cancer  
2 risk assessment is ready next year. At such  
3 time, I'm sure these data and any other data  
4 fitting within the HPG/HPA mode of action  
5 would all come into play together with the epi  
6 data.

7 SESSION CHAIR PORTIER: Thank you.

8 At this point we open it up to any comments  
9 from anyone on the panel. Anybody want to  
10 jump in on this question? Add to it? The  
11 promoter issue? Dr. Williams?

12 DR. WILLIAMS: I just wondered  
13 what you really mean by not likely. So I  
14 thought there were some good points raised by  
15 the NRDC person regarding, you know, this  
16 other commission specific designations. They  
17 have a certain definition of not likely or  
18 likely or whatever. What do you really mean  
19 by not likely?

20 DR. MENDEZ: Our definition for  
21 not likely or unlikely to be carcinogenic to  
22 human is when they have a mode of action that

1 we feel it's not appropriate to the human  
2 condition. Having said that, let's keep in  
3 mind that we're going to be looking at the  
4 cancer issue in greater detail in 2011. So  
5 let's just kind of keep that in mind.

6 SESSION CHAIR PORTIER: Dr.  
7 Krishnan, did you want to comment?

8 DR. KRISHNAN: I'm going to leave  
9 it off. No, that's fine.

10 SESSION CHAIR PORTIER: But it --  
11 this is Ken Portier. But the definition means  
12 you've looked and you don't see anything  
13 rather than not look. One of the implications  
14 is, you know, you haven't looked for it. And  
15 you can't say it's not likely if you haven't  
16 looked for it. And I think what EPA is  
17 saying, we've looked for it and we see  
18 something; we discount it because it's a  
19 mechanism that's not related, therefore, it's  
20 something else.

21 DR. MENDEZ: And we have also not  
22 only looked at the mode of action, we've also

1 evaluated other potential modes of action and  
2 have ruled them out. So it's important to  
3 keep in mind that we don't just look at one  
4 component and just latch onto that. We then  
5 move on to disprove, so to speak, other  
6 potential MOAs.

7 DR. LOWIT: And the one piece to  
8 add to that. The 2003 SAP on epidemiology and  
9 atrazine really dealt with some of the  
10 epidemiology data at the time for cancer. And  
11 so that finding at that time incorporated both  
12 the animal mode of action and the epi data  
13 available at the time. And as we move towards  
14 what will now be 2011 we'll rethink that whole  
15 process again.

16 SESSION CHAIR PORTIER: Dr.  
17 Holladay?

18 DR. HOLLADAY: I think we kind of  
19 said it, but I want to make sure that I  
20 understand. My understanding is that, as  
21 least formally, EPA's definition of  
22 classification of carcinogens is different

1 than IARC's. And we had an IARC definition  
2 read to us earlier, but EPA's definition is  
3 not the same. Is that correct? So we're not  
4 working under the IARC definition per se?

5 DR. MENDEZ: It's important to  
6 point out that in 1999 -- I believe it's  
7 1999 -- IARC evaluated this very same mode of  
8 action and they consider that it was not  
9 likely to be relevant to humans. But in their  
10 definitions and in their framework they think  
11 about it a little bit different. Having said  
12 that, the MOA was actually considered and  
13 considered to be believable by the IARC.

14 SESSION CHAIR PORTIER: Dr.  
15 LeBlanc?

16 DR. LEBLANC: Considering our  
17 increasing understanding of the mode of action  
18 of atrazine my -- the only recommendation that  
19 I have is that as we reevaluate the  
20 epidemiological data that perhaps we're  
21 sensitive to cancers that might be more  
22 prominent in immunosuppressed individuals, not

1 suggesting that atrazine is going to cause  
2 immunosuppression in the population, but that  
3 would be consistent with the mode of action  
4 and it should be considered.

5 SESSION CHAIR PORTIER: Anyone  
6 else wish to join in? The issue of promotion,  
7 the issue of initiation -- those are always  
8 good ones. I don't see -- Dr. Reed.

9 DR. REED: Would it help if you  
10 have a copy of the 2005 cancer risk assessment  
11 guideline that has the narratives for -- there  
12 is a category called not likely to be  
13 carcinogen to humans? Because we can provide  
14 the panel with that. And I have a copy of the  
15 guidelines so maybe I'll give it to Joe.

16 DR. HORTON: I think it would be  
17 helpful.

18 SESSION CHAIR PORTIER: Dr.  
19 Horton?

20 DR. HORTON: Yes. I was going to  
21 say I think it would be helpful to know  
22 exactly which guidelines we're working under

1 if we're defining whether it's carcinogenic or  
2 not. And also, if this is going to be  
3 evaluated under the 2011 SAP under the  
4 carcinogen -- under another set of data what  
5 other -- I mean, how is this going to be  
6 reevaluated? Could you -- what will happen in  
7 2011 if we say -- or make a recommendation now  
8 that it may not be? What are the consequences  
9 of anything -- any recommendations that we  
10 make at this point?

11 DR. LOWIT: Well, I'm actually  
12 hearing -- I've heard from the -- from most of  
13 the respondents that as the question's worded,  
14 what's new since 2003 that would change those  
15 conclusions. And I've actually heard a  
16 consensus that no one's heard anything that  
17 really changes those conclusions. So I'd be  
18 surprised if we turn that upside down.

19 But in 2011, we will do some more  
20 update to the animal. We'll continue to  
21 monitor the literature to see if anything new  
22 appears in the animal literature that does

1 turn that upside down. And we will also be  
2 bringing the epidemiology with the animal to  
3 the degree to which there's a concordance with  
4 those conclusions.

5 DR. KRISHNAN: Can I --

6 SESSION CHAIR PORTIER: Yes, Dr.  
7 Krishnan?

8 DR. KRISHNAN: Yes.

9 DR. LOWIT: Yes. So, I mean, the  
10 one thing that's important for people to know  
11 about the atrazine risk assessment, it is a  
12 very dynamic thing. It's -- the agency's  
13 constantly monitoring the literature on  
14 atrazine. So we'll keep up.

15 SESSION CHAIR PORTIER: Yes. I  
16 would also say that all we're doing is  
17 recommending to the agency. We're not making  
18 any final decisions here. And the agency  
19 takes our recommendations and incorporates it  
20 with everything else and then moves forward  
21 from that. So just because we recommend that  
22 that holds doesn't necessarily mean they

1 believe us for the next two or three stages of  
2 this.

3 DR. LOWIT: And it is worth adding  
4 as -- it is worth adding to this piece that a  
5 major component of the decision to separate  
6 the cancer 2011 was -- with our colleagues at  
7 NCI -- and if you're not aware of the  
8 Agricultural Health Study, it's a very large  
9 robust study upwards of 90,000 people. And I  
10 don't know the exact number of people who are  
11 atrazine users, but I think it's upwards of  
12 50,000, maybe 60,000.

13 So it's a very large data set and  
14 it's a very large robust. So we feel like  
15 because of the large size of that it will  
16 really play a lot of weight, and it's really  
17 worth waiting to make sure that the results  
18 are very strong and robust.

19 SESSION CHAIR PORTIER: Dr.  
20 Krishnan?

21 DR. KRISHNAN: We talked about the  
22 revised guidelines of the EPA and this

1 particular clause of not likely to be  
2 carcinogenic. The classical example of the  
3 description that they give is that there can  
4 be positive results in experimental animals  
5 when there's consistent evidence -- consistent  
6 and strong evidence that the mode of action in  
7 experimental animals do not operate in humans,  
8 in which case it can be concluded as not  
9 likely.

10 But we can draw essentially a  
11 parallel between this and the IARC group. I  
12 suggest that we don't mix both of them even in  
13 our comments. I don't think it's in our  
14 purview. Because in IARC's number 4 you have  
15 to have evidence suggesting lack of  
16 carcinogenicity in experimental animals and  
17 lack of carcinogenicity in humans, which is  
18 not the case.

19 So I wouldn't -- but this  
20 classification -- the way it's termed is  
21 consistent with the criteria that EPA  
22 considers. And we haven't really seen any

1 convincing animal data that changed the  
2 classification, I don't think. The promoter  
3 studies can add to the strength of existing  
4 evidence, but I don't see how, by in itself,  
5 would suggest the chemical to be a carcinogen  
6 as a free-standing evidence of information.

7 SESSION CHAIR PORTIER: Dr. Reed?

8 DR. REED: Well, maybe I didn't  
9 make myself clear. Let me try it again. What  
10 I think we're looking at is that we have found  
11 a mode of action that looked very good to  
12 interpret the Sprague Dawley rats data. But  
13 I'm not ruling out the possibility that other  
14 mode of action which is not initiation, but  
15 promotion, might be a part of the oncogenic  
16 potential that have been sort of indicated by  
17 the two promotional studies.

18 The two promotional studies have  
19 some problems, but in my mind they do not  
20 deserve, I guess, to be put aside to say that,  
21 ah, you know, there's a lot of problem with  
22 this; we didn't see any potential or support

1 for initiation.

2 But how about promotion, is what I  
3 guess I'm saying. That I'd much rather that  
4 we take a better look at these two studies and  
5 see if we can or cannot fit these two pieces  
6 of information into the overall -- this well-  
7 put-together mode of action. And if we cannot  
8 then we need to set aside another possibility  
9 with a lot of question marks.

10 But I felt that these two studies  
11 can be looked at in a slightly different light  
12 than the way they have been looked at right  
13 now according to their reviews by the agency.  
14 So as I say, when I look at the Fukamachi  
15 study I didn't feel like it was a clear-cut no  
16 dose response. And going from a background  
17 control incidence and since these are, you  
18 know, transgenic in their prime, that the  
19 background is 50 percent.

20 When you get to the atrazine dose  
21 the lowest dose of 5 milligrams per kilometer  
22 you're seeing 100 percent. And so from 50

1 percent to 100 percent with small sample size  
2 you could say that there is no statistical  
3 significance. But, you know, how statistics  
4 come into play is, you know, kind of not very  
5 relevant with the sample size.

6 But I am alarmed that there is a  
7 50 percent to 100 percent increase from zero  
8 to five. And since you have the 5 milligram  
9 per kilogram at 100 percent when you get to a  
10 50 milligram per kilogram data of course it's  
11 another 100 percent. And so to say that, you  
12 know, 50, 100, 100 is no dose response it's a  
13 little bit kind of not satisfying to me.

14 And then, you know, the agency  
15 review saying that, okay, when you get another  
16 tenfold increasing dose it dropped off a  
17 little bit. Well, I mean, you might have some  
18 high dose effects. So I'm not putting a lot  
19 of weight on the lack of quote-unquote, "lack  
20 of dose response" at the high dose and the  
21 fact that, you know, you have high background.

22 So I'd like to see a little bit

1 more rigor in this discussion. I don't know  
2 what is this going to lead to -- whether it's  
3 going to fit into the current beautiful house  
4 or whether it's going to be a slightly  
5 different version or possibility. I just  
6 personally like to see a little bit more  
7 rigor.

8 And apparently, you know, my take  
9 on the promotional -- the two promotional  
10 studies will be different from Dr. Krishnan's  
11 comments. But maybe I'd like to hear, you  
12 know, other people who have looked at these  
13 two studies in terms of what they think about  
14 whether they fit or not fit or irrelevant or  
15 anything of that sort.

16 SESSION CHAIR PORTIER: This is Ken  
17 Portier. I make the recommendations that the  
18 statisticians are thinking, which is, do the  
19 study right. Power it up and do it right.  
20 And then we don't have these kinds of  
21 uncertainties and interpretation. I mean, I  
22 agree, a 50 to 100 percent increase is -- you

1 know, it's a big jump. And the fact that it's  
2 not statistically significant tells me it was  
3 way underpowered. So why did they do the  
4 study?

5 And what you're saying is, they  
6 did the study because they had some hypothesis  
7 that they really think needed to be looking  
8 at, and I wish they would have looked at it  
9 with sufficient resources to be able to answer  
10 the question the first time around.

11 It comes back to this whole  
12 repeatability of information issue. EPA can't  
13 look at it because we can't assess the  
14 repeatability of the experiment with the  
15 sample size and the power that they did. My  
16 recommendation would always be do it right, do  
17 it right the first time.

18 DR. REED: Well, I mean, as a risk  
19 assessors, I mean, you know, I feel like -- a  
20 lot of times I feel like -- I don't know --  
21 that robot's name is R2D2? It's always  
22 information, information, I need more.

1                   But when you look at what's out  
2                   there and, you know, there's times that you  
3                   say, well, I feel very comfortable to dismiss  
4                   this -- you know, it's not there. But in this  
5                   case I feel like there might be something  
6                   there and I just can't say go back and do some  
7                   more study because, you know, the agency is  
8                   not in the business of going and do some study  
9                   in that sense.

10                   But as a risk assessor I feel like  
11                   I cannot ignore that kind of information. To  
12                   say that, well, nobody repeated it and so  
13                   forth and, you know, it's low powered so let's  
14                   forget about it.

15                   SESSION CHAIR PORTIER: Dr.  
16                   Horton?

17                   DR. HORTON: This is a general  
18                   comment that I would like to add that tags on  
19                   with Ruby's, is, I felt that there were many  
20                   times that I understand the need for looking  
21                   at the quality of data. But as a practicing  
22                   scientist, there are two things I run into.

1           One is, molecular biologists don't  
2 understand statistics, but having been trained  
3 as an ecologist generally I do. And so I beat  
4 my head against the wall against this all the  
5 time. And the other is that you often just  
6 don't get the chance to repeat the study.

7           However, the more that the agency  
8 can ask people to go out and repeat the study  
9 that's great. But I felt that in the review  
10 of many of these papers, many of them were  
11 dismissed as not providing information when  
12 they were being dismissed on a technical basis  
13 of not meeting some criterion when they had  
14 passed scientific review.

15           And, in fact, they do suggest  
16 something and you have to take into this  
17 criterion of what is your risk assessment. So  
18 I think --

19           SESSION CHAIR PORTIER: Anyone  
20 else? Having spent a lot of time working both  
21 with microbiologists and trying to get them to  
22 understand statistics, but also reviewing a

1 lot of these kinds of studies it's very  
2 frustrating to -- because, you know, EPA did  
3 look through the literature, and I think two-  
4 thirds of the studies kind of got laid aside.

5 And the fact that this study got  
6 considered tells me that the ones they laid  
7 aside were even poorer. And that -- you know,  
8 as a scientist that really discourages me  
9 because that tells me we're doing a lot of  
10 under-powered research that's not answering  
11 the questions. It just raises more questions.  
12 And I get very frustrated with this though.  
13 Linda?

14 DR. YOUNG: I have to agree. And  
15 I just wonder if there's some way to go back.  
16 Because even the studies that I've seen  
17 presented by both EPA and Syngenta here, you  
18 look at it, and unless they have about two  
19 animals in the group, something's happening  
20 there.

21 I'm also concerned about the  
22 statistical methods they're using, given the

1 study design. I think a lot of this period-  
2 by-period analysis is being done, and that --  
3 when you start out with small numbers you  
4 shoot yourself in the foot.

5 SESSION CHAIR PORTIER: Dr.  
6 Krishnan?

7 DR. KRISHNAN: I'm going to agree  
8 with the statisticians. I'm not going to  
9 argue. I just want to get back to your  
10 comment.

11 Given the experimental design and  
12 the animals models and the lack of dose  
13 response, that's what really stuck me. And I  
14 see your point. I don't think I mentioned my  
15 reading -- it was not a question of dismissing  
16 an evidence, you know, that clearly indicates  
17 that something is a carcinogen, because I  
18 don't see these studies showing that the  
19 atrazine in itself is a carcinogen.

20 But there's some questionable  
21 evidence of it being a promoter. So what I  
22 would suggest is that essentially in the

1 weight of evidence -- in the overall weight of  
2 evidence, they do park these animal studies  
3 and do reconsider in rating the overall weight  
4 of evidence when they develop the narrative.

5 Whether it fits a specific mode of  
6 action -- whether it fits this house or not I  
7 think, as you alluded to, I think sometimes  
8 that the incidence itself sometimes just  
9 catches the eyes, rather than whether you can  
10 explain it by an MOA or not. I don't think  
11 that's -- at least for me that's not a major  
12 consideration.

13 So how about recommending that  
14 these studies be considered in developing an  
15 overall weight of evidence narrative as the  
16 other human data and so on come in? All I was  
17 saying -- that I would agree, but all I'm not  
18 agreeing to is that these studies in itself,  
19 you know, take them from the current class and  
20 make them a likely carcinogen, which is not  
21 the case.

22 DR. REED: Well, that was --

1 DR. KRISHNAN: We are on the same  
2 side, maybe not on the same page.

3 DR. REED: Right. Same side of  
4 the table? No, that's what I'm saying. I  
5 mean, I would recommend that we park this  
6 rather than coming with an affirmative as, you  
7 know, what I thought what we're saying.

8 Rather than coming with  
9 affirmatives, saying, yes, we do not see any  
10 evidence. I'm saying -- and that's what I was  
11 reading before -- that we park this issue  
12 because of this. And I think it's a -- you  
13 know, I guess you and I now agree. But that  
14 was my recommendation. Let's park it.

15  
16 SESSION CHAIR PORTIER: I think we  
17 have a good sense of what we're going to do in  
18 writing this up. So I think it's kind of --  
19 I'm reading general agreement with the EPA  
20 statement and with a caveat -- kind of a  
21 minority report that we're going -- that when  
22 we write up the report we'll make sure that's

1 in there. Yes. Dr. Reed?

2 DR. REED: Can I make just a very  
3 brief comment? I don't think it's reasonable  
4 to separate out a chemical whether it is an  
5 initiator or, you know, being a promoter would  
6 be of less important or less relevant to  
7 humans because there's all kinds of initiators  
8 out there already.

9 And so if a chemical is a promoter  
10 it is a cause for concern in that it could be  
11 enhancing or increasing or shortening the  
12 latency or whatever of something that is  
13 already out there that if initiated that  
14 possibly be a tumor.

15 So that's why I'm putting a lot  
16 of, you know, credence to also a promoter.  
17 And I don't think, in cancer risk assessment  
18 guideline, the promoter/initiator has been  
19 parted out in a way that promoter is not  
20 important.

21 DR. KRISHNAN: No, I guess. But  
22 the way you would do an assessment would be

1 different, because in one case you might end  
2 up having -- identifying a threshold for  
3 promotion, but as for initiation you'd rather  
4 to go with a unit risk kind an approach or  
5 something. But we're not getting into any of  
6 the -- those response modeling.

7 SESSION CHAIR PORTIER: I think at  
8 this point I'm going to close this question  
9 and close today's session. I want to thank  
10 the panel for sitting through all these  
11 presentations and being patient, and let you  
12 know that 8:30 tomorrow morning we're going to  
13 start on question 1.2, and we're going to run  
14 through these questions.

15 Thank you very much.

16 (Whereupon, at 5:48 p.m., the  
17 above-entitled matter was concluded.)  
18  
19  
20  
21  
22

A	
<b>abandon</b> 256:7	230:4 251:10
<b>ability</b> 50:21 57:3	320:18 344:17
85:2 103:4 172:2	<b>accounted</b> 156:12
174:17,20 197:20	<b>accumulated</b> 264:7
198:18 200:4	<b>accumulation</b>
204:6 213:16	263:7
217:14 219:19	<b>accuracy</b> 17:14,16
399:8	21:7,12
<b>able</b> 30:7,13 58:5	<b>accurate</b> 288:10
64:10 66:15 75:15	330:22
101:11 105:3	<b>achieve</b> 49:15
112:12 135:10	<b>achieved</b> 100:10
158:21 175:20,21	212:20 311:22
202:20 219:20	<b>acknowledged</b>
233:21 245:16	360:8
285:8 295:15	<b>acquired</b> 240:21
297:11 304:4	<b>acre</b> 112:2
342:22 400:7	<b>acreage</b> 107:6
417:9	<b>acres</b> 102:22 126:9
<b>abnormal</b> 350:7	<b>acronyms</b> 262:12
395:19	<b>act</b> 1:4 90:10
<b>above-entitled</b>	262:14 355:12
96:14 323:20	376:4,5 399:8
425:17	<b>acted</b> 205:2
<b>absence</b> 118:6	<b>ACTH</b> 203:15,16
199:17 219:8	208:8 392:12
<b>absolute</b> 207:3	<b>acting</b> 356:6
<b>absolutely</b> 126:18	<b>action</b> 46:19 107:9
250:5 260:22	107:13 114:2
286:9 320:5	135:15 136:13
321:19	141:19,22 142:2
<b>absorb</b> 380:10	148:18,20 150:8
<b>absorbing</b> 102:5	150:19,20 152:2,3
<b>absorption</b> 181:20	152:7,14 158:1,16
<b>abundant</b> 379:7	174:3 251:19
<b>accelerated</b> 350:6	317:6 318:15
<b>accept</b> 44:21	350:14 360:4
<b>acceptable</b> 48:20	364:4 384:14
371:20	385:3,17 388:22
<b>acceptance</b> 370:18	389:3,7,13 391:10
<b>access</b> 393:21	391:21 393:5,12
<b>accidental</b> 359:5	398:15 400:18
<b>account</b> 30:10 34:3	403:13 404:4,22
34:4,12 35:2 43:4	405:22 406:1,12
43:5 60:6 64:21	407:8,17 408:3
70:13 71:11 77:16	412:6 413:11,14
	414:7 422:6
	<b>actions</b> 137:10
	256:3 265:21
	<b>activate</b> 217:15,20
	<b>activated</b> 328:16
	328:17
	<b>activation</b> 197:13
	230:3 391:21
	393:6
	<b>active</b> 106:12
	108:13 109:14
	111:18 167:2
	175:12 196:20
	197:11
	<b>activist</b> 120:20
	<b>activists</b> 113:21
	120:2
	<b>activities</b> 121:7
	179:20 220:14
	266:2 268:8
	<b>activity</b> 163:8
	164:22 167:3,13
	167:18 168:1
	171:20 172:13
	173:3,7,11 196:20
	197:15 199:4,10
	217:5 376:2
	<b>acts</b> 129:6 376:17
	391:5
	<b>actual</b> 26:1,7,12,14
	68:9 269:2 279:2
	340:18
	<b>actuality</b> 309:12
	<b>acute</b> 32:21 33:1
	203:7 205:1 211:4
	255:17 334:15
	<b>adapted</b> 101:3
	114:9
	<b>add</b> 29:10 31:19
	45:11,15 51:15
	81:15 89:14 94:6
	98:17 126:17
	221:22 266:15
	291:6 296:4
	300:16 327:12
	404:10 406:8
	413:3 418:18
	<b>added</b> 10:4,13 40:7
	43:15 121:15
	310:18
	<b>adding</b> 45:18
	100:20 137:5
	157:9 411:3,4
	<b>addition</b> 84:19
	138:22 189:11
	238:14 262:5
	264:4 266:3
	268:10 271:3
	276:14 292:17
	381:10
	<b>additional</b> 31:1
	33:8 35:3 43:17
	43:18 51:12 53:10
	72:3 101:9 103:15
	168:7 182:20
	188:2 189:9 250:9
	260:16 283:6
	310:16 328:10,15
	329:6 331:1,3
	333:20 334:6
	379:9 383:9
	388:21 393:8
	<b>additionally</b> 270:16
	281:21 380:4
	<b>address</b> 122:5
	134:19 136:4
	196:12 210:19
	212:11 219:16
	248:21 249:7
	280:19 302:3
	329:1 375:14
	383:6 400:7
	<b>addressed</b> 221:6
	348:5 371:5
	<b>addresses</b> 294:7
	<b>addressing</b> 192:19
	194:12,17
	<b>adenomas</b> 388:15
	388:16,20
	<b>adequate</b> 382:15
	<b>adequately</b> 21:10
	77:21 344:17,20
	349:9 351:2
	<b>adjourned</b> 183:15
	<b>adjust</b> 251:8
	<b>adjusted</b> 40:6
	<b>adjusting</b> 58:4
	<b>adjustment</b> 251:9
	<b>administered</b>
	195:11 212:14,15
	250:20
	<b>administration</b>
	122:16 123:15,20
	167:9 170:18
	195:1 199:18
	208:8,17 211:6
	374:19
	<b>administrations</b>
	122:11
	<b>admittedly</b> 246:12
	296:7
	<b>adolescence</b> 345:13
	<b>adopters</b> 103:9
	<b>adoption</b> 102:9
	<b>adrenal</b> 164:19
	206:21 207:2,3,4
	208:6 215:10
	217:20 387:1,3,5
	396:17
	<b>adrenalectomize</b>
	213:20,20
	<b>adrenalectomized</b>
	213:15 215:8
	254:9 255:1
	395:13
	<b>adrenalectomy</b>
	214:21 216:11
	217:5 231:12
	232:4
	<b>adrenals</b> 214:15
	392:15
	<b>adrenocorticotro...</b>
	392:11
	<b>adult</b> 127:5 195:7
	246:16 312:9
	322:19,20 347:21
	<b>adulthood</b> 347:14
	<b>adults</b> 308:21
	<b>advance</b> 382:22
	<b>advantage</b> 51:6
	235:21 361:6
	<b>advantages</b> 51:2

79:14	378:10 385:7	411:8	<b>alternations</b> 348:2	<b>ample</b> 220:3
<b>adverse</b> 236:4	386:4,11 388:8	<b>agriculture</b> 28:15	<b>alternative</b> 106:20	<b>amplitude</b> 153:17
385:19	397:22 401:1,8,13	29:21 30:1 99:19	107:12 126:1	153:18 166:5
<b>advice</b> 345:7	403:10,22 410:17	99:21 100:4 101:2	131:18 152:16	201:17,21 214:8
369:18 377:12	410:18 414:13	102:8 103:14	260:15 336:10	214:14 215:6
378:9	415:14 418:7	104:4 106:4	389:12	230:13 254:1
<b>advises</b> 343:5	419:7	112:20 114:8	<b>alternatives</b> 106:9	<b>analogous</b> 244:5
<b>advising</b> 139:1	<b>agency's</b> 119:15	122:9 352:4 353:8	106:10 108:8	<b>analyses</b> 107:15,19
<b>advisories</b> 322:12	158:5 348:9	379:6	109:3	109:18 159:6
<b>advisors</b> 376:21	385:13 387:12	<b>ah</b> 413:21	<b>alters</b> 194:19	221:18 234:21
<b>advisory</b> 1:4 9:22	398:9 399:14	<b>ahead</b> 90:19	206:13	260:10 261:13,15
100:3 308:19	410:12	<b>air</b> 100:21 396:13	<b>amassed</b> 265:7	262:6 273:12
309:3 312:9 345:7	<b>agenda</b> 10:8 11:1	<b>Akana</b> 2:2 7:15,15	<b>ambient</b> 39:13 56:8	282:1 295:19
357:2 363:11	<b>agents</b> 170:16	33:13,14 34:8	300:20	<b>analysis</b> 26:8,13
364:9 384:10	171:3 342:17	232:11,13,18,22	<b>amenorrhea</b>	29:11 34:12 80:20
<b>advocate</b> 373:21	<b>age-adjusted</b>	250:11,12 251:5	161:16 162:4,8	81:17 108:15,21
<b>aerates</b> 100:18	351:18	254:7,8	<b>America</b> 368:15	110:2 111:6
<b>AFC</b> 245:12	<b>aggregated</b> 285:11	<b>al</b> 137:4 138:4	373:8	113:18 135:19
<b>affect</b> 115:14,15	288:22 289:5	192:5,6 401:4,4	<b>American</b> 5:15	148:18 150:1
149:2 213:16	290:7	<b>Alan</b> 324:11 364:6	100:4,5 106:4	155:22 236:13
393:19	<b>aggregates</b> 169:7,7	<b>alarmed</b> 415:6	225:9 324:12	282:2 285:7,10,12
<b>affirmative</b> 423:6	169:17	<b>albeit</b> 207:15	325:4 373:11	288:10 289:20
<b>affirmatives</b> 423:9	<b>aggregation</b> 290:21	331:18	374:2,9 379:4	291:8 292:10,21
<b>afford</b> 49:21,22	296:19	<b>alcohol</b> 373:20	<b>America's</b> 102:22	293:5 297:4
<b>afforded</b> 49:20	<b>aging</b> 148:14 385:4	<b>aldosterone</b> 204:2	<b>amino</b> 89:1 330:18	299:15 330:15
<b>afraid</b> 112:14	386:2	205:13 206:1	<b>ammeline</b> 164:3	355:11 361:10
267:14	<b>ago</b> 43:14 70:17	<b>algorithm</b> 34:1,9	166:9	388:8,18 400:2,7
<b>afternoon</b> 32:11	115:3 116:15	<b>algorithms</b> 39:3	<b>amount</b> 102:6	421:2
193:18 195:10	125:13 126:5,6,10	40:15	116:22 128:10	<b>analyte</b> 178:14
323:14 324:15	126:15 129:13	<b>allegedly</b> 371:16	130:12,13 146:14	<b>analytical</b> 70:7
338:20 384:7,17	136:18 274:22	<b>allocating</b> 21:15	266:15 346:15	330:18 370:15
<b>age</b> 146:15 161:7,8	340:1 369:12	<b>allocation</b> 24:3	360:1,3	<b>analyze</b> 89:2
188:11,16 189:7	<b>agonist</b> 196:3	<b>allow</b> 194:14	<b>amounts</b> 82:14	<b>analyzed</b> 109:8
189:16 190:7	<b>agree</b> 23:18 165:9	<b>allowed</b> 375:10	120:7 121:11,21	110:18 111:14
191:3 192:19	219:1,5 220:9	381:19	318:6	202:22 340:2
216:17	364:6 399:14	<b>allowing</b> 118:13	<b>AMP</b> 13:4 20:13	349:15 357:14
<b>agencies</b> 122:10	416:22 420:14	381:14	171:9,13 172:1,8	362:12
336:5	421:7 422:17	<b>allows</b> 102:3	172:14 262:19	<b>analyzes</b> 261:17
<b>agency</b> 1:1 8:21	423:13	196:16 360:15	266:5,9,15 269:12	<b>Anatomy</b> 6:18 7:22
23:7 87:13 123:5	<b>agreed</b> 123:10	<b>allude</b> 158:7	269:16 270:8	<b>Andrew</b> 149:21
123:11,14 139:6,7	138:16	<b>alluded</b> 422:7	271:14 272:3	<b>androgen</b> 154:3
155:10 188:21	<b>agreeing</b> 422:18	<b>alterations</b> 198:3	279:8 280:11	217:10
342:6 343:9	<b>agreement</b> 353:7	347:6	283:3 287:18	<b>androgens</b> 203:21
350:16 371:20	394:12 423:19	<b>altered</b> 197:20	289:16 290:20	204:6 205:15,17
372:6 374:22	<b>agricultural</b> 30:17	198:12,13 350:4	<b>amphibians</b> 151:12	205:18 209:1
375:5 376:20,22	86:16 94:11	<b>altering</b> 220:4	347:18 349:18	210:14 216:4
377:13,20 378:1	133:16 275:21	387:1	350:3	<b>androstenedione</b>

203:22 205:15 206:2 209:6,10 <b>and/or</b> 388:14 <b>anecdotal</b> 328:20 <b>animal</b> 1:7 5:8 136:9 137:16 144:1,8 152:1 182:15 186:17,18 188:11 222:4 236:2 347:12 368:2 387:14 397:19 398:9 406:12 409:20,22 410:2 413:1 422:2 <b>animals</b> 144:2,19 145:21 146:3,4 156:18 158:21 159:1,16 186:12 186:21 188:1,16 189:3,5,8,15 190:5,18 191:7,20 197:17 198:18 200:10 201:4,10 201:13 202:14,17 202:20 203:1,4 206:8 207:19,22 212:1,6,13 213:16 213:21 214:1,10 215:8 216:16 222:1 226:20 228:19 232:15 235:2 245:19,21 246:16,20 247:1 249:21 254:9,13 254:17 255:2 257:11 343:16,22 344:2 347:18 349:1 395:13 396:8,10,11,14 398:15 412:4,7,16 420:19 421:12 <b>ANN</b> 57:15 65:20 336:14 <b>Anna</b> 69:14 304:12 <b>Anna's</b> 93:10 <b>announce</b> 5:2 <b>announced</b> 94:3	<b>announcement</b> 97:17 <b>annual</b> 21:21 57:18 108:3 259:16,19 264:13 267:17,19 268:10 310:4 326:22 330:13 335:4 337:3 <b>annualized</b> 56:2 <b>annually</b> 103:17 <b>ANOVA</b> 242:5 <b>anovulatory</b> 161:13 <b>answer</b> 32:1 48:15 69:22 77:19 91:6 92:12,13 133:8 163:9 194:7 219:20 247:15 255:4 272:8,20 276:22 279:16 296:22 304:12,18 321:1 325:11 334:22 340:21 341:9,21 372:3,17 387:22 393:16 400:13 417:9 <b>answered</b> 334:21 <b>answering</b> 261:3 310:22 420:10 <b>answers</b> 297:1,3 298:19 340:20,22 355:6 372:14 <b>answer's</b> 81:4 <b>antagonist</b> 255:4 <b>antibodies</b> 225:16 225:22 226:1 227:20 238:22 <b>antibody</b> 203:12 204:7 218:5 225:12,18,20 226:10 240:20 <b>antigens</b> 240:19 <b>anti-asialo</b> 245:11 <b>anybody</b> 4:11,14 404:9 <b>anybody's</b> 392:21 <b>anymore</b> 130:22	<b>anyway</b> 305:16 308:5 309:10 325:2 403:16 <b>apologize</b> 18:17 285:9 <b>apparent</b> 401:21 <b>apparently</b> 265:22 416:8 <b>appear</b> 21:16 41:21 166:18 176:13 179:21 <b>appearance</b> 41:13 <b>appeared</b> 184:17 263:13 <b>appearing</b> 105:14 181:22 <b>appears</b> 17:14 21:10 48:19 167:5 218:16 220:5,20 344:12 409:22 <b>application</b> 11:17 84:1 104:15 128:13 221:14 265:19 329:21 331:15 336:11 <b>applications</b> 78:11 <b>applicators</b> 353:10 354:19 359:9 360:13 <b>applied</b> 8:19 11:19 63:6 102:20 273:6 274:8 311:12 321:16 353:13 359:7 360:2 <b>applies</b> 31:8 369:19 <b>apply</b> 63:21 74:6 74:10 75:10,19 92:6 359:1,15 360:13,16,20 <b>applying</b> 73:8 78:3 129:21 353:19,20 380:13 <b>appointees</b> 116:6 <b>appreciate</b> 105:21 133:13 144:19 157:2 323:14 325:16	<b>approach</b> 12:13 24:6 55:13 64:21 72:5,19 75:9,19 87:14 89:5 141:16 203:11,18 226:11 239:7 271:12 272:4,21 274:7 279:5 291:4 294:6 294:16 336:3,14 336:15,20 337:11 337:14 373:16 376:14 425:4 <b>approached</b> 382:5 <b>approaches</b> 76:11 76:17 79:8,13 92:8,14 203:13 204:7 271:3 272:15,17 281:2 283:6 289:9 290:12 325:17 <b>approaching</b> 217:13 <b>appropriate</b> 156:20 181:12 187:5 190:12 320:7 325:22 333:17 334:8 335:14,18 335:20 336:1 372:1 398:14 405:1 <b>approved</b> 122:9 330:16,19 <b>approximately</b> 135:4 177:16 190:6 192:4 284:5 352:19 <b>April</b> 1:13 13:22 183:16 266:5,13 270:18 326:15 357:17 <b>aquatic</b> 6:2 361:22 <b>aquifers</b> 284:2 <b>AR</b> 43:6 <b>arbitrary</b> 22:5 131:8 <b>archive</b> 134:8 <b>arduous</b> 254:12	<b>area</b> 9:4,17 31:10 31:12 32:2,16 34:20 86:13 138:19 161:4 163:16 190:16 191:4 201:19 215:7 235:21 239:12 240:8 241:6,12 242:20 243:2 244:6,8 248:11 253:2 275:16,18,20 297:13 365:7 <b>areas</b> 24:2 31:4 56:4 57:3 70:22 71:5 246:2 332:4 <b>area-under-the-c...</b> 31:7 <b>argue</b> 73:5 117:12 122:21 125:9 421:9 <b>argument</b> 294:15 <b>arguments</b> 27:20 84:3 155:9 <b>Arizona</b> 193:21 <b>aromatase</b> 136:5,7 136:9 149:2 151:10 156:11,17 163:7,7 164:22 165:10,16,22 167:6,10,18 168:9 168:15 172:3,8,15 173:21 174:17,18 174:21 175:9,15 175:22 216:8 348:10 350:15 <b>arose</b> 389:1 <b>arrive</b> 50:2 296:1 <b>article</b> 349:13 <b>articles</b> 120:16 <b>articulate</b> 374:4 <b>articulated</b> 316:19 <b>artificial</b> 3:13 11:17 36:1,4,15 37:15 42:18 50:4 50:5 51:2 222:18 223:4 336:2
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<b>AR1</b> 53:15	<b>assessment</b> 8:11,22	131:22 132:3	163:6,10,13,17	265:17 267:18
<b>AR2</b> 42:11 43:7	9:1,5,13 71:3	240:6 330:8,11	164:10,10,12,17	268:4,9,17 269:21
<b>ascertain</b> 180:12	73:17 74:8,10	331:1 385:18	164:21 165:7,15	272:13 282:7
<b>Ashby</b> 192:5	82:7,16 89:22	<b>assumed</b> 98:11	165:20 166:3,4,21	304:19 306:4,20
<b>aside</b> 25:13 413:20	94:21 95:2,5,6,9	<b>assuming</b> 90:18	167:1,1,3,4,9	308:8 309:13
414:8 420:4,7	95:20 134:12	161:8	168:3,6,10,20,22	316:8 317:13,16
<b>asked</b> 10:12 83:10	141:11 151:22	<b>assumption</b> 173:22	169:4,9,13,14	317:21 318:5,7,14
118:22 164:8	153:9 155:10	<b>as-requested</b> 366:5	170:2,11,15,20,22	320:14,15 326:18
168:7 182:19	164:17 186:3	<b>Atlanta</b> 5:16	171:8,13,16,20	326:21 327:13,19
195:17 206:20	255:15 258:5,8,9	<b>atrazine</b> 1:7 4:8 5:7	172:4,11 173:1,2	328:13,22 329:5,7
213:13 214:20	281:19 283:11	36:6,10 38:3,11	173:6,21 174:4,18	329:15 330:3
267:4 270:1	305:3,5 321:17	38:15 39:10 40:11	174:20 175:9,10	331:16,21 332:12
282:19 301:2	360:17 369:22	41:7 51:9 56:2,4	175:13 179:2,7,15	333:2,12 335:2,6
304:15 317:14	370:4,11 371:14	71:3 76:20 78:4	179:18 181:22	342:10,12 343:11
345:16 368:1	372:7 384:13	78:10,11,13,18	184:10 187:2	344:9,20 345:11
369:9,20	387:16 388:5	86:17 87:1,16,19	190:2,8,15,21	347:9,17 348:16
<b>asking</b> 18:18 23:6	393:13 394:15	88:5,7,7,15,16	191:3,18 193:2	349:17 350:1,10
49:18 81:17	398:11 404:2	89:3,11,18,19	194:4,9,18 195:1	350:13,18,22
157:19 172:11	408:10 410:11	90:13 98:11,20	195:4,11 196:6	351:15 352:9
221:7	419:17 424:17,22	99:1 100:2 102:20	197:6,11,17	353:3,4 354:1,13
<b>asks</b> 206:12	<b>assessments</b> 23:2	103:2,4,8 104:8,9	198:13,16,20	355:2,12,18,19
<b>aspect</b> 180:8	23:13 176:19	104:12,17,19	199:1,14 200:10	356:1,12,20 357:6
391:19 393:18	257:10 319:19	105:22 106:3,15	201:5,14,22 202:4	358:18,21 359:1,2
399:18	321:9 369:14	106:17,18 107:2	202:15 203:4,7,8	359:15,18,20
<b>aspects</b> 256:3	<b>assessor</b> 418:10	107:11,17 108:8,8	206:9,13,21 207:1	360:1,10 361:11
283:10 300:6	<b>assessors</b> 417:19	108:22 109:1,2,4	207:8,18 208:1,12	361:18 362:15
<b>assay</b> 83:19 84:5	<b>assist</b> 134:15	109:11 111:20	208:14,16,19	363:2 366:8
170:5 173:11	<b>assistance</b> 84:6	112:1,13,19 113:4	209:4 210:16	369:11,22 370:4
209:16,19,20	<b>associate</b> 5:20	113:7,22 114:5,17	211:6 212:2,14,17	370:11 371:14,18
210:8,11 218:6	394:10	114:20 117:4,10	213:1,3,17,22	372:6 374:20
226:5 245:11,12	<b>associated</b> 153:15	118:15 120:1,3,12	214:6,12,16,22	375:21 378:11
247:18 330:18	154:6,9,21 155:2	121:3,9 122:2,8	215:1,6,9,12,14	381:15 382:11
<b>assays</b> 89:1 149:9	160:18 162:3,4	122:14,14 125:6	215:19 216:3,11	383:7 384:14
170:6 204:9 218:5	238:4 248:6	125:13 126:3	216:13,20 217:3,6	385:14,18 386:18
225:12 227:19	261:12 272:16	127:8 130:18	217:9,15,20 218:1	386:22 387:5,16
389:16	348:16,20,21,21	131:6,20 134:17	221:12,14 222:9	388:9 389:7 390:3
<b>assay's</b> 245:15	353:11 356:20	136:6 137:12,20	223:7,18 232:14	391:16 393:19
<b>asserted</b> 355:4	357:16 358:12	138:21 139:3	237:6,14 238:11	394:16 397:11,15
<b>assess</b> 36:10,21	359:20 377:14	140:1,7 141:13,22	241:14 244:13	398:11 399:5,13
50:20 151:17	386:2 403:19	142:9,14 143:11	246:5 248:3,6,9	401:3,22 406:9
187:17 188:3	<b>Associates</b> 272:20	144:16,18 149:8	248:19 253:8	407:18 408:1
417:13	<b>association</b> 97:7	149:18 150:7,10	254:20 255:17	410:11,14 411:11
<b>assessed</b> 170:14	143:1 154:7,11	150:16 152:19	256:3,15 258:15	414:20 421:19
173:10 179:7	324:12 325:4,7	153:9,14,14,16	259:14,17 260:3,7	<b>atrazine's</b> 106:22
378:9	350:17,22 355:4	154:1,4,7,9,12,14	261:14 262:18	126:9 172:1
<b>assessing</b> 37:12	373:8	154:18 155:6,19	263:1,5,18 264:9	184:16 186:19
187:8	<b>assume</b> 54:2 125:5	156:3,13 162:14	264:13,20,20	385:2 399:8

<b>atrazine-treated</b> 361:1	38:19 52:13 53:5 53:6 55:21 67:13	<b>B</b>	<b>Bailey</b> 2:22 4:3,4 96:9 236:9 324:9	344:13 366:5 419:12
<b>atrial</b> 214:3	76:19 87:10 88:14	<b>B</b> 189:7 232:22	365:12 366:4	<b>baton</b> 99:8
<b>ATS</b> 1:22	88:16,22 96:1	<b>babies</b> 357:8 358:12	367:5,8	<b>batting</b> 303:12
<b>attacked</b> 40:5	111:10 119:4,6	<b>back</b> 10:20 40:12	<b>balance</b> 7:19 82:6	<b>BDL</b> 59:8 60:6
<b>attempt</b> 334:10	209:18 259:16,19	49:17 50:2 56:21	<b>Ballroom</b> 1:16	<b>bear</b> 259:8
<b>attempted</b> 157:22	259:20 264:13	57:1,15 69:8,12	<b>banished</b> 8:4	<b>beat</b> 419:3
<b>attention</b> 137:18	288:12 306:8	74:21 84:13 94:1	<b>banned</b> 120:3	<b>beautiful</b> 416:3
138:11 171:4	312:12 315:12	94:15 109:7	131:6,10	<b>beg</b> 369:6
306:21	326:22 330:11	112:22 116:7	<b>banning</b> 383:7	<b>began</b> 138:18
<b>attentive</b> 375:6	335:4 337:3	124:4 125:12	<b>bar</b> 37:10 349:12	200:22 204:18
<b>attribute</b> 396:1	361:18 363:6	127:14 128:1	<b>barring</b> 279:1	232:20
<b>attributed</b> 185:9	<b>averaged</b> 362:22	130:18,19 141:15	<b>Barry</b> 2:3 7:6	<b>beginning</b> 14:2
191:21	<b>averages</b> 13:12,16	152:4 154:21	<b>basal</b> 227:6 247:21	15:9 81:16 113:4
<b>AUC</b> 31:15	14:19,20,21,21	160:5 171:11	<b>base</b> 370:3	137:3 369:1
<b>audience</b> 302:20	17:17,19 19:15,16	178:11 180:3	<b>based</b> 29:12 30:8	<b>beginnings</b> 96:22
324:16	20:10 21:11 22:5	225:7 229:2,6	34:12 36:13 72:11	<b>begins</b> 165:17
<b>audio</b> 4:22	31:5 32:13,13	232:6 238:15	89:22 118:20	199:7
<b>augment</b> 12:17	271:21 272:2	249:6,18 254:17	152:4 197:18	<b>begs</b> 213:6
<b>augmented</b> 12:22	307:19	258:15 261:21	203:12 204:7	<b>behalf</b> 97:12
<b>August</b> 14:1 340:1	<b>averaging</b> 280:12	264:16,17 282:9	218:5 225:12	105:14 237:16
340:10	308:7	291:21 292:3	226:11 272:12	368:21 373:22
<b>Australia</b> 119:21	<b>avoid</b> 118:6 299:13	296:8 298:7 301:5	283:7 285:11	<b>behave</b> 44:21 45:4
152:21	299:21	303:13 305:10	292:18 309:5	280:7
<b>author</b> 158:13	<b>aware</b> 78:12 156:3	307:11 309:3,9	310:7 311:9 316:4	<b>behaved</b> 66:7
<b>authority</b> 333:8	256:20 257:17,18	317:17 320:7	320:9 321:9,16	<b>behaves</b> 45:1
<b>authors</b> 354:9	275:1 287:1 400:3	332:8 337:13	326:22 335:3	<b>behavior</b> 347:21
<b>autocorrelation</b>	411:7	341:19 366:15	343:14 345:22	348:2
42:6,7,12 43:1,18	<b>awful</b> 29:18	368:10 377:5,13	352:6 365:4	<b>behavioral</b> 257:9
51:21 52:3 67:18	<b>awfully</b> 40:4	383:19 392:18	384:13 389:5,14	<b>beings</b> 378:11
<b>automatically</b>	<b>axes</b> 233:13 394:14	396:4 417:11	400:1	<b>belief</b> 294:16 296:2
365:1	<b>axis</b> 7:18 46:9 95:6	418:6 420:15	<b>baseline</b> 37:20	346:4
<b>auto-samplers</b>	138:14 178:9	421:9	<b>basic</b> 94:19 193:20	<b>believable</b> 407:13
85:15	194:8,21,22 195:2	<b>backed</b> 117:17	334:12	<b>believe</b> 70:9 114:17
<b>available</b> 55:18	196:9 200:18	<b>background</b>	<b>basically</b> 63:8,11	114:20 115:21
112:13 121:14	202:5 211:5 213:8	105:15 143:9	81:14 227:16	116:2 123:9
155:22 179:11	213:9,12,14,18	146:6 259:13	231:9 332:10	127:19 139:11
247:22 274:16	216:15,21 217:1,3	260:4 285:9	399:3	157:12 163:10
280:18 281:8	217:4,17 218:19	338:21 339:18	<b>basin</b> 28:14,15,20	175:9,17 185:8
283:12,13 291:9	238:13,15,16	395:10 414:16,19	29:13,22 30:3	225:6 247:10
338:3 366:22	302:14,18 306:1	415:21	33:21 72:14,15	280:5 304:7
368:4 387:7	311:17 386:8,12	<b>backslide</b> 112:14	275:17,20	310:10 316:12
406:13	387:1,3 389:8	<b>backup</b> 380:2	<b>basins</b> 28:20 29:6	318:16 366:2
<b>average</b> 11:15 14:8	391:22 394:4	<b>backwards</b> 41:17	75:15	374:21 375:8
16:11,12,19,20	395:5,8 400:20	62:9	<b>basis</b> 31:12 237:21	378:3 386:11
17:2,2,9,10 18:20	<b>a.m</b> 1:15 4:2 96:15	<b>bad</b> 20:4 292:14	251:4 306:11	407:6 411:1
19:3 26:3 37:18	96:16	383:17,18	311:1 334:1	<b>believed</b> 115:18,20

<b>bell</b> 324:2,3	144:15 259:12,17	330:5 334:1	<b>bothering</b> 65:15,16	261:22 274:18
<b>belt</b> 35:2 110:7,13 125:7	260:1 264:14	355:10 379:12	<b>bottom</b> 19:6 77:20	281:22 369:7
<b>benchmark</b> 321:13	269:10,18 278:2,5	395:15 402:1	93:13 129:19	<b>bright</b> 335:5,14
<b>bend</b> 72:10	278:6 309:1,17	407:11 415:13,17	313:18 393:3	<b>bring</b> 69:12 86:6
<b>benefit</b> 107:16	311:3 313:13,21	415:22 416:6	398:2	119:14 140:1
109:6,13,15	314:4 315:7 318:1	<b>biweekly</b> 12:22	<b>bought</b> 130:4	151:16,19 303:13
110:20 111:12,20	326:22 332:2,21	14:1 21:9	<b>bounds</b> 77:13	305:1,10 366:7
112:1,4 130:16	332:22 333:1	<b>black</b> 122:22	78:20	382:18
333:16	335:3,8 337:3	<b>blanks</b> 51:10,14	<b>bovine</b> 172:5	<b>bringing</b> 40:11
<b>benefits</b> 100:9	355:19,20 361:19	65:9	<b>box</b> 122:22 307:10	410:2
104:18 106:22	361:19 362:5,6,8	<b>bleeding</b> 243:20	311:14,18	<b>brings</b> 107:10
112:5,21 113:15	362:9,19	<b>blend</b> 82:15	<b>boxes</b> 152:4	<b>broad</b> 18:12 19:6,6
113:18	<b>bioassay</b> 143:6	<b>blending</b> 300:6,9	<b>Bradbury</b> 91:13,15	19:10 93:3
<b>best</b> 16:15 17:15	145:20,20 157:7	<b>block</b> 214:21	<b>brain</b> 168:14 198:9	<b>broadened</b> 363:22
26:20 39:5 43:7	157:14 388:10	216:12 217:5	251:16 347:4,6	<b>broadening</b> 81:7
55:9 57:17 78:20	<b>bioassays</b> 140:9,12	231:13	<b>branching</b> 403:17	<b>broader</b> 18:12
105:17 129:4,5	145:19 159:19	<b>blocked</b> 174:16	<b>break</b> 4:17 10:10	110:11
261:16 287:11	344:11	<b>blocks</b> 216:11	10:11,15 96:8	<b>broadleaves</b> 108:12
300:14	<b>bioconcentration</b>	<b>blood</b> 190:12 203:1	182:22 183:13,13	<b>broken</b> 270:4
<b>best-fitting</b> 57:15	180:16	239:18 243:21	302:21 323:4,18	<b>brought</b> 27:6
<b>better</b> 16:22 19:10	<b>biological</b> 27:20	247:6 353:1	369:2	141:17 151:7
19:19 21:14 28:8	86:9 143:1 180:17	<b>blue</b> 33:17,17 34:2	<b>breakdown</b> 171:9	257:14 304:13
29:5 52:15 53:9	183:12 371:3	143:7 295:10,12	<b>breaking</b> 100:16	<b>Brusick</b> 149:19
55:12 57:22 58:1	395:7	362:8	274:20	<b>brutally</b> 257:18
58:7 63:15 65:4,7	<b>biologist</b> 7:5	<b>blush</b> 122:20	<b>breaks</b> 84:8	<b>Bucher</b> 1:21 5:19
65:7 84:11 101:11	<b>biologists</b> 419:1	<b>BMPs</b> 104:7,11,18	<b>breast</b> 154:11	5:19 256:12,18
106:8,9,10 127:22	<b>biology</b> 89:10	104:21 128:17	159:10	257:6 394:10,11
133:8 245:16	127:1	<b>board</b> 2:1 146:17	<b>Breckenridge</b>	<b>Bucher's</b> 256:10
318:12,12,18	<b>biosynthesis</b>	<b>Bob</b> 8:8 89:14	134:9,10 135:12	<b>budgetary</b> 109:22
367:15 414:4	204:17	193:19 237:3	156:6,7 165:4	<b>buffer</b> 104:13
<b>beyond</b> 68:19	<b>biotransformation</b>	291:7 304:7	177:10 180:7	<b>build</b> 42:11 102:4
78:11,13 89:2	182:10	<b>bodies</b> 119:18	182:4 183:5 184:4	288:5
341:13	<b>biotransformatio...</b>	261:11 270:6,13	184:7 193:14	<b>buildup</b> 188:13
<b>bias</b> 27:7 111:1	178:13 180:13	285:15 356:11	194:5 228:20	<b>built</b> 174:9 273:12
349:11 351:5	<b>bio-statistician</b>	<b>body</b> 72:12 121:13	234:22 236:18	310:14,15 312:3
<b>big</b> 40:1 72:13,14	5:16	121:22 206:11,13	249:7,8,17 250:1	322:5
252:6 275:10	<b>birth</b> 115:8,10	206:16 207:4	250:3,7,16 254:11	<b>built-in</b> 321:21
314:20 362:8	115:8,10	233:1 235:7,12	255:9 256:16,22	<b>bulk</b> 194:16
367:13 387:19	348:20 349:2	313:18 322:19	257:12 274:20	<b>bullets</b> 141:12
417:1	357:4,7,7,15	342:9 357:7	310:9 323:8,11	<b>bumping</b> 343:7
<b>bigger</b> 53:7 302:12	358:11	<b>bootstrap</b> 301:13	<b>bridge</b> 137:13	<b>bunch</b> 59:13
<b>biggest</b> 23:12 112:9	<b>births</b> 357:14	336:13	<b>brief</b> 194:12 252:8	<b>burden</b> 328:11
<b>bill</b> 330:12	<b>bit</b> 11:3,4 17:8 18:5	<b>bootstrapping</b> 3:8	253:20,22 271:8	342:21
<b>billion</b> 18:6,8 22:6	32:10 41:18	11:13 12:13	397:5 424:3	<b>buried</b> 115:2
22:6 61:13 103:17	107:18 202:2,9	<b>border</b> 98:1,2	<b>briefe</b> 211:17	<b>bushels</b> 109:2,12
120:8,9 133:1	203:11 206:7	<b>boring</b> 303:3	<b>briefly</b> 68:6 107:17	111:10 124:20,20
	210:19 243:5	<b>born</b> 115:8 357:9	199:17 204:16	124:22
	291:7 296:12,13			

<b>business</b> 418:8	399:21 404:1	<b>careful</b> 108:9 165:1	<b>caught</b> 25:2 286:21	260:14 296:3
<b>busy</b> 18:16	405:4 406:10	376:11,13 377:1	<b>cause</b> 62:5 64:22	<b>central</b> 97:5 107:21
<b>byproducts</b> 121:16	408:10 411:6	380:3	147:2 254:2 343:3	108:1 109:20
<b>by-period</b> 421:2	424:17	<b>carefully</b> 106:2	345:1 346:19	233:15 387:1
<b>b0</b> 37:19 39:20	<b>cancers</b> 407:21	236:19 280:2	347:3 385:19	<b>certain</b> 61:2 62:2
57:21 58:22	<b>cancer/non</b> 94:9	282:15 393:15	408:1 424:10	79:3 116:5,22
<hr/>	<b>candidate</b> 50:20	<b>Carlo</b> 45:8	<b>caused</b> 248:8 344:2	163:5 189:6
<b>C</b>	<b>candy</b> 315:21	<b>Carmen</b> 2:17 7:1	<b>causes</b> 41:2,3,4	253:13 254:4
<b>C</b> 189:7	<b>cannula</b> 214:3	<b>Carolina</b> 6:13	66:4 103:15	261:1 295:1 381:2
<b>cages</b> 396:15	<b>capabilities</b> 119:12	135:18	141:22 165:15	404:17
<b>calculate</b> 38:19	<b>capability</b> 103:2	<b>carried</b> 12:12	211:20 334:13	<b>certainly</b> 23:7
43:22 44:1 173:12	<b>capacity</b> 147:14	13:17 138:2 254:8	<b>causing</b> 243:17	68:16 93:3 98:7
<b>calculated</b> 31:4	<b>capture</b> 11:4 17:6	<b>carry</b> 100:19	343:15,22	113:20 115:6
207:3 271:20	20:7,22 21:6	<b>carrying</b> 249:9	<b>caution</b> 168:20	116:22 117:5,9,14
322:10	32:17 37:5 70:20	<b>cars</b> 130:7	395:3	119:14 124:3,4
<b>calculating</b> 31:10	264:12 294:14	<b>cascade</b> 393:20	<b>caveat</b> 229:12	125:9 127:19
<b>calculation</b> 313:11	<b>captured</b> 15:20	<b>case</b> 29:3 46:11	326:9 387:10	128:16 157:14
322:11	17:6 89:3 291:20	52:11,17 66:6	423:20	163:11 182:17
<b>calculations</b> 31:7	292:1	77:17 78:18 86:20	<b>CDC</b> 359:16	252:1 276:8
314:12 322:13	<b>capturing</b> 269:20	115:12 117:4	<b>CDI</b> 388:12	395:14
<b>California</b> 6:4 7:16	<b>carbon</b> 102:5	133:7 156:4	<b>cell</b> 163:5 164:7,9	<b>certainty</b> 282:21
8:18,21 98:5	327:11 328:16,17	167:14 170:1,16	164:18,19 165:1,6	294:13 316:13
352:2	328:21 329:6	174:1 186:13	165:20 167:10	343:1 349:11
<b>calisthenics</b> 303:8	333:4	223:6 224:10	170:5 171:1	351:5
<b>call</b> 20:18 129:17	<b>carcinogen</b> 122:15	242:11 243:16	173:19 174:1,6	<b>cessation</b> 198:16,20
226:3 273:21	341:16,18 342:2	274:13 290:21	175:17 176:11	199:8 217:2
340:6 383:9	387:17 394:17	292:8 313:21	238:22 240:21	<b>cetera</b> 272:14
<b>called</b> 12:9 38:1	398:12,13 408:13	314:16 337:2	247:17,17	372:1
42:5,8 186:21	409:4 413:5	412:8,18 418:5	<b>cells</b> 159:2 165:11	<b>cFos</b> 196:18,19,21
196:18 278:21	421:17,19 422:20	422:21 425:1	168:14 169:11	197:2,5,7,10
310:1 408:12	<b>carcinogenic</b> 140:3	<b>cases</b> 174:15 271:7	170:1,8,21 172:19	<b>CFR</b> 217:15
<b>calling</b> 262:15,18	152:11,19 343:19	292:3,18 302:11	172:20 173:17,18	<b>chain</b> 45:7 205:4
<b>Canada</b> 9:12	385:14 388:9	351:17 354:13,14	175:2,4 176:12,22	<b>Chair</b> 1:18,18,20
119:20	389:4 399:17	<b>casually</b> 113:21	180:9,12 198:6	1:21 5:4 8:6 9:18
<b>cancer</b> 5:15 94:10	404:21 409:1	<b>catalysis</b> 350:15	240:17,19 242:16	9:21 10:1 24:8
94:13 115:2,4,5	412:2	<b>catch</b> 16:1 25:2	251:18 347:4	25:20 26:22 30:4
127:5 135:15	<b>carcinogenicity</b>	285:8	<b>cellular</b> 238:18	32:6,8 33:7,10
137:10 140:8,12	140:7 143:16	<b>catches</b> 422:9	<b>center</b> 7:7 9:11	35:4,14,18 51:16
141:10 143:5	160:3 344:10	<b>catecholamine</b>	110:7 163:2	53:17,19 55:16
145:15,22 146:6	345:12 412:16,17	251:19 252:7,11	368:13,22	57:13 58:20 59:5
151:22 154:6,8,11	<b>carcinogens</b> 406:22	<b>catecholamines</b>	<b>centered</b> 291:2	59:20 60:3,10,21
154:19 155:5	388:20	251:16 252:1,15	<b>centers</b> 217:16	61:7,14,20 62:16
159:10 183:4	<b>carcinomas</b> 388:15	<b>categories</b> 286:1	<b>centile</b> 268:12,17	62:20 63:1,4 65:8
184:5 342:3,7,8	388:20	<b>categorized</b> 342:19	268:21 269:10,13	67:9 69:5 79:22
343:3,15 344:2	<b>care</b> 44:2,22 66:11	<b>category</b> 343:8	269:17 270:9,11	83:8,10 84:16
345:2,14 347:13	158:8 360:15	382:11 408:12	270:19 282:21,22	85:1 86:3 90:22
385:3,8,16 395:22	380:7	<b>catheters</b> 254:14	<b>centiles</b> 259:7	93:18 96:6,17
	<b>career</b> 99:20 114:4			

124:7 125:2	6:6 180:2,3 193:9	391:17	76:6	398:21
126:19 128:4	193:10,15 223:4	<b>characterize</b> 50:9	<b>chemographs</b>	<b>circumstances</b> 64:9
131:1 133:10	396:12	71:16 72:1 73:15	12:16 18:1	87:12 281:5 299:2
135:9 155:13	<b>chance</b> 42:2 178:17	77:21 143:21	<b>Chen</b> 287:6,9 304:6	<b>citations</b> 365:13
157:3 160:9,13	349:11 351:5	297:2 300:19	<b>chief</b> 344:7	<b>cited</b> 359:16
162:20 176:5	380:15 419:6	336:21	<b>child</b> 312:10	<b>citizens</b> 378:20
178:19 180:1	<b>chances</b> 130:15	<b>characterized</b>	322:20,22	<b>claims</b> 113:21
182:18 183:10	<b>change</b> 45:21 57:4	142:13 152:10	<b>childhood</b> 345:13	<b>clarification</b>
184:3 193:8,16	68:19 87:3,4	261:22 280:13	<b>children</b> 116:12	297:10,17 321:4
218:8 221:3	88:11 150:6	<b>characterizing</b>	308:22 310:21	<b>clarify</b> 30:6 160:12
223:12 226:12	153:18 188:16,18	391:20	360:22	250:9 297:18
229:4 232:9 234:3	201:18 202:1,10	<b>charge</b> 3:22 87:6	<b>chloryrifos</b> 352:15	<b>class</b> 240:17 254:22
249:1 250:11	219:14 329:11	87:11 118:11	<b>chlorals</b> 177:18	422:19
251:13 252:21	331:9 385:13	135:14 340:18,20	<b>chlorinated</b> 86:22	<b>classical</b> 203:12
254:7 255:6 256:9	387:15 394:14	341:2 384:9,12	166:1	412:2
283:17 285:4	398:4 399:4,13	<b>charged</b> 343:10	<b>chlorination</b>	<b>classification</b>
290:1 297:14	409:14	345:17	121:16	154:19 342:8
301:1,3 302:13,19	<b>changed</b> 125:10	<b>Charles</b> 134:10	<b>chlorometabolites</b>	343:18 385:8
319:5 323:3,7,17	152:5 196:8 268:5	139:18 156:7	167:17	399:5,13 406:22
324:1,10,21 338:8	341:22 413:1	249:8	<b>chlorotriazines</b>	412:20 413:2
338:11,16 339:2,6	<b>changes</b> 89:4 114:6	<b>Charlottesville</b> 9:3	89:17,21 90:5	<b>classified</b> 343:13
364:18 366:10	121:5 161:7,8	<b>chart</b> 247:5	163:15,17 175:12	345:3 360:9
367:12,20 368:5	194:22 195:2,19	<b>charts</b> 37:10	260:2	<b>classify</b> 341:17
372:19 373:2	196:10 197:14	<b>cheap</b> 89:1	<b>chlorpyrifos</b>	342:12 344:9
379:8 383:3	198:8 200:21	<b>check</b> 96:11 246:18	355:20 356:1	<b>classifying</b> 282:13
387:18 394:9	202:11 206:11,17	<b>checks</b> 152:3	<b>choice</b> 103:9	342:1,15
398:6 400:14	208:16 210:10,16	<b>chemical</b> 86:17	<b>cholesterol</b> 204:20	<b>clause</b> 412:1
404:7 405:6,10	211:2 214:16,18	140:22 168:13	<b>choose</b> 104:5 134:3	<b>clean</b> 124:22
406:16 407:14	216:6,9 217:4	185:18 299:15	135:7,13	<b>cleaner</b> 298:17
408:5,18 410:6,15	218:7 243:11,16	346:5 360:16	<b>chose</b> 12:18,20 13:2	<b>cleanup</b> 303:12
411:19 413:7	248:17 392:5	413:5 424:4,9	<b>Christmas</b> 266:1	<b>clear</b> 30:5,6 92:9
416:16 418:15	399:7 409:17	<b>chemicals</b> 121:10	<b>chromatid</b> 149:22	168:13 246:9
419:19 421:5	<b>changing</b> 29:7	121:14 171:15	<b>chromatograms</b>	338:12,17 377:16
423:16 425:7	45:14 46:3 87:2	180:9 238:1 252:3	204:15 210:5	380:22 413:9
<b>chairman</b> 97:4,14	243:5 295:3	252:9,12 254:19	<b>chromatography</b>	<b>clearly</b> 16:14 30:21
99:11 134:9 135:1	<b>channel</b> 278:21	299:12 346:11	203:18	32:12 144:21
184:8 228:20	298:17	347:9 355:13	<b>chromocytomas</b>	235:10 312:1
235:16 258:2	<b>Chapel</b> 135:18	356:6 376:8	396:17	395:9 421:16
323:12 373:6	<b>characteristic</b>	380:10,12,14	<b>chromosome</b> 150:1	<b>clear-cut</b> 414:15
<b>chairs</b> 134:1	42:10	382:12	<b>chronic</b> 33:2	<b>cleavage</b> 205:4
<b>challenge</b> 49:22	<b>characteristics</b>	<b>chemical's</b> 389:4	142:13 145:6	<b>clever</b> 299:22
57:2 187:11	299:6	<b>chemist</b> 317:15	221:11 334:15,17	<b>climate</b> 30:17
258:10	<b>characterization</b>	<b>chemistries</b> 125:18	395:22	<b>Clinton</b> 122:16
<b>challenged</b> 261:4	178:6 182:9,16	125:20	<b>chronically</b> 221:12	<b>Cloath</b> 156:9,15
<b>challenges</b> 129:15	185:22 235:20	<b>chemograph</b> 12:9	<b>circling</b> 392:18	<b>cloned</b> 179:10
<b>chamber</b> 201:7	305:4 393:11	14:12,22 15:17	<b>circulating</b> 217:10	<b>close</b> 18:7 52:4
<b>chambers</b> 1:22 6:6	<b>characterizations</b>	16:21 21:18 72:9	227:2 248:3 391:5	59:15 60:18

314:17 383:14 425:8,9 <b>closely</b> 225:3 369:17 <b>closer</b> 160:14 181:17 252:13 292:22 <b>closest</b> 82:16 <b>closing</b> 113:1 183:1 183:6 <b>closure</b> 27:21 <b>clothing</b> 359:6,11 <b>cloud</b> 401:18 <b>clusters</b> 286:6 <b>coated</b> 170:2 <b>cocaine</b> 253:21 <b>code</b> 278:16 309:14 <b>coherence</b> 143:2 <b>cohort</b> 186:21,21 189:5 190:5 191:1 191:10,15 192:11 247:1 <b>cohorts</b> 186:20 187:6 <b>coincides</b> 250:19 <b>Coli</b> 121:19 <b>colleagues</b> 92:19 94:10 134:15 256:6 398:19 411:6 <b>collect</b> 91:9 214:3 <b>collected</b> 250:17 294:9 363:18 <b>collection</b> 84:7 91:7 247:6 250:13,14 251:1 331:2 <b>collectively</b> 123:12 304:11 <b>College</b> 6:7,17 7:21 9:15 193:21 225:8 261:21 275:13 276:2 279:21 <b>column</b> 15:19 157:10 245:6 <b>columns</b> 19:11 <b>combination</b> 106:15,17 191:15	291:14 355:22 381:17 <b>combinations</b> 36:12 126:12 <b>combined</b> 273:10 329:6 <b>combining</b> 86:21 <b>come</b> 10:20 28:9 31:22 77:9 82:16 83:13 87:3,13 88:3,18 92:11 94:4 96:11 110:2 130:20 134:20 138:9,16 141:9 169:4,15 178:11 216:15 224:4 229:2 236:20 256:6 261:21 270:18 274:8,21 277:21 280:16 297:18 301:4 341:10 368:10 398:4 399:22 402:15 404:5 415:4 422:16 <b>comes</b> 57:8 79:18 82:6 116:22 277:20 309:11 314:3 318:14 377:19 417:11 <b>comfortable</b> 89:10 418:3 <b>coming</b> 67:8 69:18 79:6 87:8 187:21 263:8 276:16 277:7 281:17 304:16 381:18 401:19 423:6,8 <b>commend</b> 286:16 <b>comment</b> 4:13 10:18 27:15 127:9 158:8 168:18 180:8 226:15 236:17 325:16 327:2 333:22 341:14 350:20,21 372:13 374:4	379:11 383:5,11 383:14 387:12 405:7 418:18 421:10 424:3 <b>commented</b> 127:7 <b>commenter</b> 368:12 373:3 <b>commenters</b> 10:12 10:16 383:10 <b>commenting</b> 69:16 348:9 368:21 <b>commentor</b> 324:11 <b>commentors</b> 133:12 323:10 324:4 <b>comments</b> 3:20 4:10,15,21 10:3 10:21 53:10 93:10 93:10 96:10 99:5 113:1 156:9 182:20 255:13 324:7,13 326:4,5 326:13,14,16 327:18 328:8 338:6 340:14,15 351:21 371:13,18 404:8 412:13 416:11 <b>commission</b> 404:16 <b>commissioned</b> 245:6 <b>commitment</b> 128:9 <b>committed</b> 139:6 188:21 256:1 378:21 <b>committee</b> 97:4 98:4 366:2 370:15 374:16 <b>commodities</b> 97:19 <b>common</b> 79:9 101:19 129:12 204:19 <b>commonly</b> 154:2 196:19 356:9 <b>communicate</b> 377:1 378:2 <b>communication</b>	376:1,20 378:5 <b>communities</b> 285:17 298:9,15 299:7 <b>community</b> 12:19 54:2 55:19 56:3,7 56:9,15 67:3 71:4 71:15 72:11 74:5 75:7,10,20 78:4 89:15 97:16 262:10 263:2,9,15 263:19 264:12,18 265:2 269:11,15 269:20 270:2,5 271:13 272:11,22 273:9,14 275:1,9 276:20 277:1,18 278:9 279:19 280:13 282:9,11 284:8 285:16 286:5 288:19 298:5,19 299:3 301:6,8,12,14,17 301:19,22 302:16 311:8 329:8 340:4 364:15 378:15 382:8 <b>companies</b> 225:11 225:13,15 <b>company</b> 373:22 <b>company-sponso...</b> 110:16 <b>comparable</b> 174:2 247:14 294:17,20 <b>compare</b> 226:9 227:12 241:18 306:12 308:14 311:7 314:16 315:1 318:19 319:21 320:8 <b>compared</b> 117:11 124:20 146:13,17 156:5 221:18 241:21 244:8 271:21 273:8 279:8 314:14 324:6 353:17	<b>compares</b> 321:8 <b>comparing</b> 108:7 242:5 321:10 322:1 397:7 <b>comparison</b> 145:18 153:13 260:1 281:16 287:14 310:2 311:6 312:11,14,15 <b>comparisons</b> 108:10,10 229:1 273:11 <b>compelling</b> 399:4 <b>compiled</b> 14:8 <b>complete</b> 145:13 161:22 162:8,9 229:22 333:11 <b>completely</b> 119:1 161:6 167:19 169:10 219:5 220:10 255:1 382:4 393:16 <b>complex</b> 73:11,22 79:20 158:19 240:17 265:19 336:4 <b>complexities</b> 51:4 <b>complexity</b> 72:19 <b>compliance</b> 262:22 263:4 326:20 329:11 330:7,16 330:20,22 331:3,9 333:20 334:3 335:3 336:6 337:1 <b>compliment</b> 258:13 <b>complimentary</b> 281:1 <b>comply</b> 327:12 328:13,18,22 333:5 370:5 <b>component</b> 95:2,17 125:14,17 133:17 180:15 200:17 220:7 240:20 393:7,8 406:4 411:5 <b>components</b> 82:12
-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

185:20 211:4 218:18,20,21 237:11 389:8 <b>composite</b> 88:22 276:13 <b>compost</b> 102:7 <b>compound</b> 90:13 132:18 140:4 148:22 163:14 235:11 375:21 377:15 <b>compounds</b> 177:13 179:22 261:18 263:1 381:13,15 <b>comprehensive</b> 117:5 140:6 164:15 <b>compromised</b> 356:4 <b>compromises</b> 354:16 <b>computer</b> 236:10 <b>computing</b> 13:15 <b>concentrate</b> 284:20 <b>concentrating</b> 379:18 <b>concentration</b> 11:18 13:6,9 14:15 22:11 24:1 37:18 38:3 41:8 42:14 44:15,16 45:19 56:3 57:18 61:17 62:1 85:3 133:5 164:16 165:19 174:8 241:13 242:20 248:12 300:14 306:8 319:22 334:8 335:15,19 <b>concentrations</b> 11:15 12:3 16:19 16:20 18:20 42:20 44:10,13 58:15 65:6 70:2 75:5 77:18 79:15 167:15 169:9,22 170:11 172:2	176:4 264:13 267:17 268:18 300:18 306:4 307:6,15,22 322:2 329:15 331:18 361:18 <b>conception</b> 186:22 190:20 <b>conceptual</b> 90:19 <b>conceptualized</b> 139:10 <b>concern</b> 23:12 25:21 26:18 50:11 50:13,14,19 58:6 66:4 71:13 76:22 77:10 88:6 89:6 117:16 132:5 259:22 328:10 334:19 337:2,6 360:20,22 375:20 386:9 399:19 400:8 424:10 <b>concerned</b> 13:9 42:1 44:4 46:18 48:17 59:19,20 66:3,8 112:6 114:12 136:14 327:20 402:2,4 420:21 <b>concerning</b> 113:3 394:16 395:12 <b>concerns</b> 71:1 104:20 116:18 120:4 131:7 178:7 360:8 <b>conclude</b> 175:7 240:1 280:9 <b>concluded</b> 152:18 284:15 350:17 402:16 412:8 425:17 <b>conclusion</b> 93:20 152:6 153:3 155:4 246:5 348:10 385:6,13 387:13 398:5,10 399:15 399:16 401:19	402:16 <b>conclusions</b> 135:22 152:22 155:10 267:9 272:1 273:13 274:5 290:9 387:15 389:2 393:9 394:15 399:7 409:15,17 410:4 <b>conclusive</b> 357:21 <b>concordance</b> 167:21 177:15 224:16 410:3 <b>concur</b> 27:2 <b>condition</b> 155:2 405:2 <b>conditions</b> 105:1 180:18 <b>conduct</b> 256:1 328:2 371:8 379:5 <b>conducted</b> 135:20 138:7 149:7 151:13 153:1 157:13 167:13 351:11 371:9 388:18 391:13 <b>conducting</b> 257:2 <b>confidence</b> 77:13 77:22 78:20 79:5 82:2 117:20 119:11 153:2 260:13 268:22 269:3 271:1 272:16 280:10 283:5 292:6 303:21 308:4 314:9 336:16 343:2 349:6 351:7 351:22 354:5,7 355:5 <b>confident</b> 123:1 273:17 274:2 282:1 298:22 <b>confirmation</b> 192:8 <b>confirms</b> 361:14 <b>conformance</b> 371:9 <b>confounding</b>	349:11 351:5 <b>confused</b> 289:4 <b>Congress</b> 376:6 <b>Congressional</b> 377:17 <b>conifer</b> 360:15 <b>conjecture</b> 118:4 <b>conjugate</b> 176:9,12 176:15 <b>conjugated</b> 163:18 164:2 167:3,5 177:4 <b>conjugates</b> 166:21 175:13 176:10,22 177:20 180:5 <b>connect</b> 66:21 <b>connecting</b> 63:16 <b>connection</b> 64:12 236:7 <b>connections</b> 330:10 347:4 <b>cons</b> 36:15,22 51:13 82:13 <b>consecutive</b> 62:15 <b>consensus</b> 409:16 <b>consequence</b> 386:7 398:20 <b>consequences</b> 48:16 100:18 138:12 151:14 184:9 344:14 409:8 <b>conservation</b> 100:1 101:6,17 102:3,10 102:11,14,21 103:2,10,12 104:13 107:1 112:5,8,15 126:17 <b>conservative</b> 117:20 379:21 <b>conservatively</b> 122:8 <b>conserved</b> 155:7 <b>conserves</b> 101:12 <b>consider</b> 47:2 91:21 92:8 93:17 111:22 117:15	148:19 218:14 233:9 345:10 348:7 356:17 361:3 369:9 378:1 407:8 <b>considerable</b> 193:1 240:13 267:1 <b>considerably</b> 252:4 270:19 <b>consideration</b> 159:21 182:17 377:19 378:4 400:5 422:12 <b>considerations</b> 218:4 382:1,19 397:14 <b>considered</b> 31:20 280:3 320:13 332:3 357:12 358:3 369:14 377:12 399:16 401:13 407:12,13 408:4 420:6 422:14 <b>considering</b> 21:20 90:5 112:8,17 115:20 127:1 233:3,12 282:11 369:21 377:2 398:8 407:16 <b>considers</b> 371:20 412:22 <b>consistency</b> 142:22 <b>consistent</b> 17:12 30:15 152:13 165:15,22 167:12 168:1 261:16 281:14 349:9 351:2 385:6 408:3 412:5,5,21 <b>consistently</b> 22:16 234:19 236:14 <b>constant</b> 45:11,15 109:16 125:7 142:13 146:12 200:3 291:1 298:21 300:13
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<b>constantly</b> 410:13	<b>continued</b> 85:22 125:5 323:13	<b>convene</b> 374:19	154:2	<b>country</b> 120:3 129:17
<b>constrain</b> 91:16 92:3 93:14	<b>continues</b> 124:6 382:22 386:11	<b>convened</b> 1:15	<b>correlation</b> 171:22 244:10 352:3	<b>counts</b> 68:1
<b>constraints</b> 49:8	<b>continuing</b> 5:10 77:4 105:3 256:1	<b>convenient</b> 135:6 275:19	353:1 357:5 360:4 365:6 366:14	<b>Coupe</b> 2:2 8:12,12 28:11,11,18 29:4
<b>construct</b> 38:14	<b>continuous</b> 120:19 187:18 188:10	<b>converged</b> 281:9	<b>correlogram</b> 42:8	29:17 91:1,2 379:10,11
<b>constructs</b> 174:10	277:2 285:19,21	<b>convergence</b> 393:4	<b>correspond</b> 216:8	<b>couple</b> 4:9 28:7 41:19 57:16 79:6
<b>consultant</b> 9:3 99:21	<b>continuously</b> 299:2	<b>conversation</b> 81:10 301:5 368:6	<b>corresponding</b> 21:6 162:6 269:15	79:10 129:13 155:14 196:17
<b>consumers</b> 116:13 117:22	<b>contour</b> 104:15	<b>converse</b> 79:1 177:9	<b>correspondingly</b> 270:10	221:8,8 225:8 238:19 319:7
<b>consumption</b> 323:1 377:9	<b>contrary</b> 118:19 120:3	<b>conversion</b> 136:10 313:17 314:3	<b>cort</b> 221:13 236:7	<b>coupled</b> 199:3,19 214:14
<b>contacting</b> 110:4	<b>contrast</b> 144:12 166:8 175:16	<b>convert</b> 313:16	<b>cortex</b> 387:5	<b>course</b> 15:5 18:4 22:8,10 59:18
<b>contain</b> 110:15 362:15	<b>contribute</b> 92:21 93:3 294:22	<b>converted</b> 163:14	<b>cortical</b> 164:19	87:16 114:4 173:20 214:19
<b>containing</b> 109:2 223:5 355:18,18	<b>contributed</b> 329:7	<b>converts</b> 313:20	<b>corticosteroid</b> 223:18,19	219:7 230:9 259:22 265:13
<b>contaminant</b> 117:12 309:2,15 309:16	<b>contributing</b> 238:16	<b>convince</b> 52:6,8	<b>corticosterone</b> 138:20 203:14	276:14 288:10 289:15 292:12
<b>contaminants</b> 86:14 121:22 358:4 382:9	<b>contribution</b> 232:21 238:5 309:8,9 319:18	<b>convincing</b> 413:1	206:2 207:7,10,14 207:19 208:10,19	306:10 307:17 308:22 312:8,10
<b>contaminate</b> 103:20 327:16 328:7	320:12,20,21 321:5,12 322:12	<b>Cooper</b> 142:8 143:18 145:10 149:4 151:5 184:19 194:13 199:16 233:20	211:5,10,12,15,21 212:5,18 213:4,8 213:10 214:18 215:15,20 216:14	375:2 396:21 415:10
<b>contaminated</b> 352:4 361:14,15 362:2 373:19	<b>control</b> 98:21 100:17 101:5 103:8,11 108:11 112:10,12 125:14	<b>coordinated</b> 128:14	220:21,22 228:17 232:15,21 238:14 239:11,18 240:1 241:6,9,13,20 242:20,22 243:1	<b>cover</b> 101:9,21 149:9
<b>contamination</b> 333:11 352:7,13	130:20 144:8 146:3 189:12 201:10 203:5 221:19 233:6 234:19 242:7 245:13 327:10 387:2 396:8,17 397:8 401:17 414:17	<b>coordinating</b> 370:14	243:21 244:3,20 245:22 246:19 248:4,5,8,10,12 248:16 252:5,6,14 253:4 303:18 312:19 392:14	<b>coverage</b> 282:20
<b>contemplating</b> 373:18	<b>controlling</b> 48:3 147:9 238:15 329:4	<b>copyright</b> 365:22	<b>copy</b> 4:15 255:11 338:1 408:10,14	<b>covered</b> 149:3
<b>context</b> 281:18 303:14 308:12,16 312:7 314:6 317:8 382:20 403:13	201:10 203:5 221:19 233:6 234:19 242:7 245:13 327:10 387:2 396:8,17 397:8 401:17 414:17	<b>core</b> 377:6	<b>copyright</b> 365:22	<b>covering</b> 101:20 169:11 263:21 344:21 351:3
<b>contexts</b> 382:5	<b>control</b> 98:21 100:17 101:5 103:8,11 108:11 112:10,12 125:14	<b>corn</b> 35:2 97:6,11 99:7,13 102:22 106:12 107:12 110:7,13 111:7,10 124:10,11 125:7	<b>copy</b> 4:15 255:11 338:1 408:10,14	<b>co-occurrence</b> 86:13 88:4
<b>contextual</b> 305:4 318:22	130:20 144:8 146:3 189:12 201:10 203:5 221:19 233:6 234:19 242:7 245:13 327:10 387:2 396:8,17 397:8 401:17 414:17	<b>corner</b> 8:4 267:11	<b>copy</b> 4:15 255:11 338:1 408:10,14	<b>craft</b> 49:7
<b>continually</b> 148:21	<b>controlling</b> 48:3 147:9 238:15 329:4	<b>correct</b> 84:22 85:12 90:21 193:14 255:9 272:10,10 287:15,20 319:16 320:6 322:3 366:3 407:3	<b>copy</b> 4:15 255:11 338:1 408:10,14	<b>Crawford</b> 12:5,13 12:20 23:18 29:1
<b>continue</b> 11:7 100:11 184:4 189:9 208:4 328:12 333:13 361:15 380:19 409:20	201:10 203:5 221:19 233:6 234:19 242:7 245:13 327:10 387:2 396:8,17 397:8 401:17 414:17	<b>correction</b> 322:4	<b>cost</b> 82:8 84:4,8,12 84:14 91:7 111:21 111:22 331:2,6 333:16	<b>Crawford's</b> 12:15 29:19
	<b>controls</b> 106:19 124:18 143:8 145:3 211:19 226:18,22 227:1 233:2 372:1 397:9	<b>correctly</b> 290:3 320:4	<b>costs</b> 83:12,15 85:10 330:17	<b>create</b> 291:12
	<b>controversy</b> 204:5	<b>correlated</b> 153:22	<b>Council</b> 339:8,16	<b>created</b> 12:15 18:3
			<b>counted</b> 198:5	<b>creating</b> 64:15
			<b>counter-intuitive</b> 290:10	<b>creatinine</b> 251:9
				<b>CREB</b> 172:15
				<b>credence</b> 424:16

<b>credible</b> 44:12,14 60:22 61:1	176:14 403:5	<b>cytotoxic</b> 168:10 170:16 171:1	77:6 78:4,21 83:10 95:5,8,11 109:9 110:12 111:5 117:10,19 137:6 139:13 141:2,2 144:1 149:14 158:11 159:12 165:2,4,5 165:8,9 167:21 169:16,21 172:6 172:18 174:11 176:9 177:6,11,17 178:11,18 179:12 179:13 181:19 184:20 189:6 195:3,6,21 199:11 200:6 202:2,21 203:15 204:2 229:16 233:20 234:1 236:20 238:21 241:5 244:6 247:21 252:2 266:15,21 268:19 269:9,15 271:18 274:8,15 274:21 275:13 276:4,5,12,16 279:4,9,10 280:10 280:20 281:3,6,8 282:1,2 283:12,13 284:14,19 285:11 285:15,19,21 286:6,14 287:18 288:1,4,8 289:8 290:15 291:10,15 291:16 292:18,20 294:7,9 296:6,16 297:20 301:14 305:12,19,21 307:1 315:21 316:20 319:11,13 327:21 329:10,10 332:6,11,16 337:7 337:15 340:2,6,11 345:16,18 346:9 348:1,4,11,12 357:11 359:14,16	362:11 363:4,18 364:10,13 370:22 371:7,15,20 372:2 372:9,11,13 375:15 377:10 381:7 385:9,10 386:21 387:8,13 388:21 396:4 402:17 403:12 404:1,3,3,6 406:10,12 407:20 409:4 411:13 413:1,12 415:10 418:21 422:16
<b>creek</b> 277:8,11,22 278:3,12 300:20	<b>current</b> 13:12 20:13 21:9 122:17 258:17 259:18 280:11,19 283:2 293:6 328:13 335:2,22 392:3,9 397:20 416:3 422:19	<b>C-O-N-T-E-N-T-S</b> 3:4	<b>database</b> 109:18 110:14,22 111:2 117:5,13 140:7 260:9,11,19,21 261:15 262:6 264:7 265:3,15,16 266:12,16,18 267:6,21 268:16 270:4 274:15 278:15 280:19 282:7,17 284:7 292:22 316:11,15 316:17 397:4	
<b>creeks</b> 277:9	<b>currently</b> 9:21 120:11	<b>D</b>	<b>databases</b> 107:15 258:16 261:16	
<b>creeps</b> 230:18	<b>currents</b> 78:19	<b>D 2:8</b>	<b>datasets</b> 403:11	
<b>CRE's</b> 371:13,18	<b>curve</b> 31:4,10,13 32:2,17 41:22 42:3,19,22 48:9 61:3 138:20 143:12 190:17 191:5 201:19 207:12 215:7 239:12 240:9 241:6,13 242:21 243:2 244:6,9 248:12 253:3	<b>DABT</b> 1:21,22 2:4 2:14	<b>date</b> 140:2 151:8,16 164:16 167:21 179:8 329:21	
<b>CRH</b> 213:11 392:6	<b>customer</b> 374:9	<b>daily</b> 12:17 13:21 14:18 15:14 19:16 23:16 27:22 32:12 39:14 80:15 81:19 91:4,9 199:1 207:18,21 212:2,4 212:22 262:1 274:8,15,16 276:13,16 279:4 279:10,18 280:20 281:6,8,11 293:1 294:7 296:10	<b>dates</b> 191:12	
<b>cringe</b> 63:3	<b>customers</b> 277:3 328:12	<b>dampened</b> 42:9	<b>Dating</b> 171:11	
<b>Crisp</b> 9:3	<b>cut-offs</b> 22:5	<b>dams</b> 186:22 187:16 193:11	<b>David</b> 149:19	
<b>criteria</b> 108:18 316:4 334:10 335:17 342:6 370:18 412:21	<b>cut-down</b> 189:1	<b>Dan</b> 6:1 8:2 180:22 233:10	<b>Dawley</b> 140:12,17 142:10,11,16 143:8 144:7 145:19 146:18 147:3,14,18,22 148:6 150:21 152:9 155:8 157:6 157:17 185:14 186:13 202:12 207:22 215:18 243:6 384:19	
<b>criterion</b> 377:22 419:13,17	<b>CWS</b> 12:21 278:16 296:22 302:18 305:15 306:5	<b>dangerous</b> 121:19 342:11		
<b>critical</b> 47:11,17,19 48:2,6,13 93:12 126:18 172:8 231:20 240:19 346:12,17 347:10 386:9,13 390:19 394:18	<b>CWSes</b> 22:7 23:21 30:8 291:8,13 292:4 296:20 306:17,19 316:2	<b>DANIEL</b> 1:23 2:16		
<b>criticized</b> 72:22	<b>CWS/year</b> 291:14	<b>dark</b> 169:7		
<b>crop</b> 97:1,10 101:8 101:15,16,20 102:12 103:5 110:14 275:22 368:15 373:7,10 373:21 374:12 376:8 381:2 382:10	<b>cycle</b> 130:9 143:21 218:12,18 250:15 384:20	<b>data</b> 12:20,21 26:1 26:12 28:12 29:4 36:6,13 37:8 38:21 39:1,10,12 40:2,13,20 43:19 44:11 53:4,13 54:8,21 55:17,20 56:4,14,18 57:8 57:10 58:10 59:16 63:13,14,21 64:5 64:7 65:18 66:1 66:12 67:13,13,16 67:22 68:1,3,11 68:14,17 71:14,21 72:21 73:6,9 74:12,17,18,20,22 75:12,20 76:1,7		
<b>cropping</b> 87:2	<b>cycles</b> 190:11	<b>daniel</b> 1:23 2:16		
<b>crops</b> 87:3 100:13 107:5 109:15 111:19	<b>cyclic</b> 147:20 171:9 171:13 172:1,8,14	<b>data</b> 12:20,21 26:1 26:12 28:12 29:4 36:6,13 37:8 38:21 39:1,10,12 40:2,13,20 43:19 44:11 53:4,13 54:8,21 55:17,20 56:4,14,18 57:8 57:10 58:10 59:16 63:13,14,21 64:5 64:7 65:18 66:1 66:12 67:13,13,16 67:22 68:1,3,11 68:14,17 71:14,21 72:21 73:6,9 74:12,17,18,20,22 75:12,20 76:1,7		
<b>cross</b> 176:11	<b>cyclicality</b> 210:20 216:16 386:5,13	<b>data</b> 12:20,21 26:1 26:12 28:12 29:4 36:6,13 37:8 38:21 39:1,10,12 40:2,13,20 43:19 44:11 53:4,13 54:8,21 55:17,20 56:4,14,18 57:8 57:10 58:10 59:16 63:13,14,21 64:5 64:7 65:18 66:1 66:12 67:13,13,16 67:22 68:1,3,11 68:14,17 71:14,21 72:21 73:6,9 74:12,17,18,20,22 75:12,20 76:1,7		
<b>Crowne</b> 1:16	<b>cycling</b> 394:19	<b>data</b> 12:20,21 26:1 26:12 28:12 29:4 36:6,13 37:8 38:21 39:1,10,12 40:2,13,20 43:19 44:11 53:4,13 54:8,21 55:17,20 56:4,14,18 57:8 57:10 58:10 59:16 63:13,14,21 64:5 64:7 65:18 66:1 66:12 67:13,13,16 67:22 68:1,3,11 68:14,17 71:14,21 72:21 73:6,9 74:12,17,18,20,22 75:12,20 76:1,7		
<b>crunched</b> 340:2	<b>cyclophosphamide</b> 245:12	<b>data</b> 12:20,21 26:1 26:12 28:12 29:4 36:6,13 37:8 38:21 39:1,10,12 40:2,13,20 43:19 44:11 53:4,13 54:8,21 55:17,20 56:4,14,18 57:8 57:10 58:10 59:16 63:13,14,21 64:5 64:7 65:18 66:1 66:12 67:13,13,16 67:22 68:1,3,11 68:14,17 71:14,21 72:21 73:6,9 74:12,17,18,20,22 75:12,20 76:1,7		
<b>Cruz</b> 8:18		<b>data</b> 12:20,21 26:1 26:12 28:12 29:4 36:6,13 37:8 38:21 39:1,10,12 40:2,13,20 43:19 44:11 53:4,13 54:8,21 55:17,20 56:4,14,18 57:8 57:10 58:10 59:16 63:13,14,21 64:5 64:7 65:18 66:1 66:12 67:13,13,16 67:22 68:1,3,11 68:14,17 71:14,21 72:21 73:6,9 74:12,17,18,20,22 75:12,20 76:1,7		
<b>CSF</b> 222:18 223:4 223:7		<b>data</b> 12:20,21 26:1 26:12 28:12 29:4 36:6,13 37:8 38:21 39:1,10,12 40:2,13,20 43:19 44:11 53:4,13 54:8,21 55:17,20 56:4,14,18 57:8 57:10 58:10 59:16 63:13,14,21 64:5 64:7 65:18 66:1 66:12 67:13,13,16 67:22 68:1,3,11 68:14,17 71:14,21 72:21 73:6,9 74:12,17,18,20,22 75:12,20 76:1,7		
<b>cultivating</b> 100:22		<b>data</b> 12:20,21 26:1 26:12 28:12 29:4 36:6,13 37:8 38:21 39:1,10,12 40:2,13,20 43:19 44:11 53:4,13 54:8,21 55:17,20 56:4,14,18 57:8 57:10 58:10 59:16 63:13,14,21 64:5 64:7 65:18 66:1 66:12 67:13,13,16 67:22 68:1,3,11 68:14,17 71:14,21 72:21 73:6,9 74:12,17,18,20,22 75:12,20 76:1,7		
<b>culture</b> 169:1 247:16		<b>data</b> 12:20,21 26:1 26:12 28:12 29:4 36:6,13 37:8 38:21 39:1,10,12 40:2,13,20 43:19 44:11 53:4,13 54:8,21 55:17,20 56:4,14,18 57:8 57:10 58:10 59:16 63:13,14,21 64:5 64:7 65:18 66:1 66:12 67:13,13,16 67:22 68:1,3,11 68:14,17 71:14,21 72:21 73:6,9 74:12,17,18,20,22 75:12,20 76:1,7		
<b>cumulative</b> 353:12		<b>data</b> 12:20,21 26:1 26:12 28:12 29:4 36:6,13 37:8 38:21 39:1,10,12 40:2,13,20 43:19 44:11 53:4,13 54:8,21 55:17,20 56:4,14,18 57:8 57:10 58:10 59:16 63:13,14,21 64:5 64:7 65:18 66:1 66:12 67:13,13,16 67:22 68:1,3,11 68:14,17 71:14,21 72:21 73:6,9 74:12,17,18,20,22 75:12,20 76:1,7		
<b>curious</b> 91:3		<b>data</b> 12:20,21 26:1 26:12 28:12 29:4 36:6,13 37:8 38:21 39:1,10,12 40:2,13,20 43:19 44:11 53:4,13 54:8,21 55:17,20 56:4,14,18 57:8 57:10 58:10 59:16 63:13,14,21 64:5 64:7 65:18 66:1 66:12 67:13,13,16 67:22 68:1,3,11 68:14,17 71:14,21 72:21 73:6,9 74:12,17,18,20,22 75:12,20 76:1,7		

385:1,4 388:11	212:14,22 215:18	327:22 334:12	82:10,17 99:19	<b>depends</b> 63:10
397:17 413:12	229:14 233:3	410:18	207:15 308:2,4	124:15 125:1
<b>Dawleys</b> 140:13	236:21 241:21	<b>declared</b> 120:21,22	371:3 410:3	298:19 329:20
146:1,12 388:17	245:7 257:15	<b>declined</b> 18:4	<b>dehydrogenase</b>	<b>depletion</b> 147:10
<b>day</b> 5:5,11,12 13:8	265:14 277:17	102:12,16,18	170:17	<b>deprivation</b> 148:15
13:11,22 14:7,21	279:7 295:1	<b>declines</b> 15:5	<b>delay</b> 231:2	<b>derive</b> 78:1
15:14,16,17 16:18	296:15 306:9,9,10	<b>declining</b> 283:1	<b>delayed</b> 166:4	<b>derived</b> 149:19
17:10 29:19 33:2	335:11 339:12	<b>decrease</b> 38:3,6	231:7 350:5	204:19
43:2,2,11 58:11	353:12,13,16	40:11 41:4 161:9	386:14	<b>describe</b> 36:3 38:2
63:13 80:5,8	367:9 390:16	162:4 199:2,3	<b>delays</b> 386:5	38:5,7,9 53:13
83:17 87:11 105:2	<b>day's</b> 42:2,13,15,15	206:16 214:13	<b>Delclos</b> 2:3 7:6,6	92:7 204:16
116:20,21 183:16	42:17 43:9 120:22	232:1,3 244:15	181:11 182:19	388:22
184:19,20,20	<b>deal</b> 83:4 87:15	251:11 268:7	<b>deliberate</b> 376:13	<b>described</b> 37:3
202:16 206:15	135:14 172:6	392:15	<b>deliberations</b> 105:6	40:11 76:11
207:20 208:2	184:8 261:9	<b>decreased</b> 153:16	105:10 118:9	177:17 178:3
241:20 250:14	272:15 275:6	154:4 242:19	<b>delineated</b> 218:16	190:14 392:2
265:14 266:1,2	284:12 364:1	390:5,10,11,14,15	<b>Democratic</b> 122:11	<b>describes</b> 37:17
273:5,5,6 274:16	<b>dealing</b> 23:3	390:20	<b>demonstrate</b>	38:6,18 391:1
274:17,17 278:3	135:19 314:17	<b>decreases</b> 146:15	165:21 196:19	<b>describing</b> 41:7
279:18 280:12	<b>deals</b> 265:10 271:5	214:6 243:10	211:1	42:20 235:19
292:9,15 293:6,11	274:11	<b>decreasing</b> 48:8	<b>demonstrated</b>	371:1
296:9,12 304:13	<b>dealt</b> 391:8 406:9	121:4 143:11	347:17 370:22	<b>description</b> 85:9
307:19,20,20	<b>dear</b> 182:12	329:9	<b>demonstrating</b>	178:12 248:15
309:6 310:8	<b>death</b> 355:21 356:2	<b>dedicated</b> 123:22	372:5,8	412:3
311:20 313:7,16	<b>decadal</b> 268:14	325:15	<b>demonstration</b>	<b>descriptive</b> 25:18
313:19 314:2,17	<b>decades</b> 117:18	<b>deep</b> 123:13	395:4	137:17 398:12
314:20,21 317:11	122:14 129:13	<b>deeper</b> 284:2	<b>dense</b> 63:12 64:4	<b>deserve</b> 159:20
320:10,20 323:1	<b>December</b> 35:6	<b>defect</b> 358:11	65:18 68:14	413:20
338:15 373:20	122:3 139:10	<b>defects</b> 115:8,10	<b>density</b> 265:12	<b>desethyl</b> 166:2
378:7	<b>decent</b> 39:8 60:2	348:20 349:2	<b>depart</b> 38:18 252:4	<b>design</b> 27:22 50:2
<b>days</b> 13:1,20 14:6	<b>decide</b> 37:8 91:22	357:16	<b>department</b> 6:2,12	65:7 86:12,19
14:18 16:1,2,3,9	334:10	<b>defending</b> 65:4	6:18 7:10,21 8:15	87:21 88:10,19
16:10 17:18,18,18	<b>decided</b> 374:19	<b>Defense</b> 339:8,15	8:18 193:20 258:4	89:8 90:8 91:17
17:19,19 19:15,17	<b>decision</b> 37:7 44:5	<b>defer</b> 28:10 157:1	<b>departure</b> 42:16,17	91:19 92:6 158:10
20:11,11 26:4	46:17,18 47:1,12	287:8	43:9,12,13,14,16	182:6 202:13
33:2,6 42:21	47:12 48:17 49:2	<b>deficits</b> 197:16	95:22	203:3 213:19
43:11,14 44:10	49:8,11,18 50:11	<b>define</b> 334:11	<b>departures</b> 42:22	371:10,21 421:1
58:15 60:13,20	50:19 58:7 66:5	<b>defined</b> 76:8	<b>depend</b> 30:16	421:11
61:9,19 62:1,11	82:9 87:8 89:12	<b>defining</b> 409:1	47:12 54:15 72:20	<b>designated</b> 2:22 4:5
62:15 96:3 118:13	297:21 298:16	<b>definitely</b> 245:14	104:22	<b>designations</b>
145:2 146:9,12,15	334:6 335:13	<b>definition</b> 119:15	<b>dependence</b> 148:5	404:16
185:1 187:9 188:2	344:8 358:16,17	404:17,20 405:11	<b>dependent</b> 42:14	<b>designed</b> 118:6
189:17 190:7	360:8 411:5	406:21 407:1,2,4	54:4 100:5 152:12	173:15 186:15
198:19,19,21	<b>decisions</b> 36:13	<b>definitions</b> 407:10	192:19 225:19	238:8 243:2
199:5,8 201:5	73:16 93:5,8	<b>degradants</b> 86:17	240:11 310:3	249:10 335:21
202:17,17 203:2	122:18,22 123:7	<b>degrades</b> 133:4	<b>depending</b> 31:16	337:17
206:10 209:4,8	141:18 298:6	<b>degree</b> 73:13 82:3	205:6	<b>designing</b> 79:2 80:2

83:11 172:20	333:17 422:4	12:3,7 13:10,14	206:3 209:7	394:10
<b>designs</b> 139:6	<b>developed</b> 210:12	22:15 29:20 36:8	<b>dihydrotestotero...</b>	<b>discussed</b> 55:14
260:16	308:18 335:1	36:9,9 37:13	204:1	279:6 291:17
<b>desisopropyl</b> 166:2	336:3,15	38:13 42:21 44:20	<b>diligently</b> 123:3	386:14 391:11
<b>despite</b> 109:13	<b>developing</b> 25:22	45:3 46:7 47:10	<b>diminish</b> 395:6	<b>discussing</b> 178:16
111:12,17 120:2	105:17 257:10	52:22 76:1,16	<b>diminished</b> 397:16	181:14 189:4
169:17	282:5 283:14	78:22 87:1 88:6	<b>diminishes</b> 393:9	<b>discussion</b> 65:14
<b>detail</b> 212:12 259:3	336:5,16 346:18	91:17,19 92:7,13	<b>dioxide</b> 102:5	80:8 81:6 82:12
267:13,14 269:6	422:14	97:12 110:3	<b>direct</b> 282:2 360:4	83:3,6 96:3
317:5 326:16	<b>development</b> 7:13	123:20 126:4,6,11	360:5 387:4	137:10,11 157:2
405:4	127:3,11 246:6,21	127:2,3 130:21	<b>directed</b> 226:1	237:12 257:13
<b>detailed</b> 157:1	336:10 346:12	140:8 141:12	<b>direction</b> 52:8	338:19 368:8,9
269:3	347:10,19 350:8	159:1,2 178:22	64:18 65:3 328:1	379:15 383:15,22
<b>details</b> 271:9 400:3	350:18 388:21	187:6 195:12	329:22	384:1 394:6
<b>detect</b> 189:14	389:9 402:22	196:6 202:15	<b>directly</b> 110:8,9	403:10 416:1
225:20 226:17,21	<b>developmental</b>	203:8,17 204:9	217:21 226:9	<b>discussions</b> 76:4
227:10,22 347:2	115:9 246:7	205:6,7 210:22	257:1 265:11	117:7 155:12
<b>detectability</b>	248:18 339:19	211:7,22 212:15	319:22 356:18	<b>disease</b> 350:19
226:20	391:15	220:13 224:11	359:7 387:7 390:4	351:1,13,18 352:8
<b>detectable</b> 228:18	<b>deviation</b> 337:7,17	225:11,15 227:18	393:19 403:18	352:20 353:3
361:17	<b>DHT</b> 205:16	227:19,19 229:13	<b>director</b> 5:14,20	355:3 356:3
<b>detected</b> 132:4	<b>diabetes</b> 154:3	233:6 239:8	8:9 9:10 97:6	<b>dish</b> 169:11
331:21 332:12	<b>diagram</b> 238:12	240:12 241:16	99:7,13 344:6	<b>disinfect</b> 380:11
<b>detecting</b> 315:6	277:6 307:10	244:19 247:18	<b>disadvantage</b> 51:4	<b>dismiss</b> 113:21
<b>detection</b> 59:15,16	311:15,18	278:16 287:1	55:2	418:3
131:16 235:5	<b>dial</b> 88:17	290:12 295:16	<b>disadvantages</b> 51:2	<b>dismissed</b> 419:11
332:2	<b>diaminochlorotri...</b>	334:16 335:17	79:14	419:12
<b>detections</b> 131:15	166:10	340:3 349:21,22	<b>disagree</b> 401:6	<b>dismissing</b> 421:15
263:18	<b>dichotomy</b> 175:8	350:11 373:16	<b>disappears</b> 215:17	<b>displaced</b> 381:13
<b>deterioration</b>	<b>Dick</b> 113:2	379:13 382:4	255:1	<b>disprove</b> 406:5
188:14	<b>dieldrin</b> 353:2	394:5 396:6,7,10	<b>disciplines</b> 119:1	<b>disregarded</b> 344:12
<b>determinations</b>	<b>diet</b> 320:13	396:21 401:9	<b>disconnect</b> 293:10	<b>disregulation</b>
117:9 122:13	<b>dietary</b> 309:9	402:15,16 406:22	<b>discontinued</b>	161:21
<b>determine</b> 197:5	<b>differ</b> 36:17 397:1	407:11 414:11	131:11	<b>disrupt</b> 213:17
217:22 327:11	<b>difference</b> 32:14	416:5,10 425:1	<b>discount</b> 405:18	<b>disrupted</b> 213:14
334:7 343:14	46:14 53:8 146:10	<b>differential</b> 30:20	<b>discounted</b> 152:17	<b>disrupting</b> 347:9
344:9 349:6 394:4	192:13,14 196:5	30:21 244:16	<b>discounting</b> 235:3	<b>disruption</b> 200:15
<b>determined</b> 116:10	228:10 241:19	396:2	<b>discourages</b> 420:8	233:14 348:18
152:15 282:22	242:7 289:10	<b>differently</b> 21:17	<b>discovery</b> 373:9	350:10 376:15
358:18 361:20,21	291:11 300:17,22	179:2	393:7	386:5,12 395:8
385:2	314:18 315:3,10	<b>difficult</b> 51:5 54:17	<b>discrepancy</b> 177:22	<b>disruptions</b> 386:7
<b>determining</b> 47:17	<b>differences</b> 18:9	55:6,12 62:12,21	227:14,17	<b>disruptive</b> 101:5
242:17 371:19	34:18 155:18	159:5,13 227:10	<b>discrete</b> 200:8	<b>disruptor</b> 348:19
<b>deterministic</b> 73:1	218:2 224:2,6	365:9 396:1	<b>discriminate</b>	<b>disruptors</b> 358:7
<b>deuterated</b> 204:13	225:4 251:10	<b>difficulties</b> 300:2	235:13	<b>disrupts</b> 386:22
<b>develop</b> 78:20	286:22	<b>digging</b> 358:15	<b>discuss</b> 366:13	387:3
118:13 326:4	<b>different</b> 11:14	<b>dihydrotestoster...</b>	<b>discussant</b> 387:20	<b>disservice</b> 123:21

130:14	395:9 397:20	<b>dose-related</b> 145:4	105:11,12 124:8,9	230:5,9,10 231:2
<b>dissolved</b> 222:9	410:16 420:9	<b>dosing</b> 163:14	124:13 125:2,4,18	231:5,11,16,19,21
<b>distorting</b> 63:19	<b>dominant</b> 164:2	193:11 244:2	126:7,19,21 128:4	232:8,11,13,16,18
<b>distribution</b> 30:2	<b>dosage</b> 241:8	252:8	128:6 131:1,5,12	232:19,22 233:8
46:2 266:4 273:13	313:15	<b>dots</b> 33:17 63:16	131:16,22 132:10	233:10,18,19
297:2,6 301:16	<b>dosages</b> 225:3	66:21 295:10,12	132:13,20 133:3	234:4,9,15,17,22
302:15 307:5	239:21 253:2,5	<b>dotted</b> 241:10	134:4,9 135:12,17	236:5,9,11,18
327:5	312:20	<b>double</b> 38:10 90:20	136:3,17 137:15	237:1,3 249:1,2,5
<b>distributions</b> 65:1	<b>dose</b> 50:1 95:15	181:20	137:22 138:15,22	249:7,13,16,17,19
286:13 287:17	96:2 142:20 143:5	<b>doubling</b> 167:11	139:16,17 141:5	250:1,2,3,6,7,11
<b>distributors</b> 373:10	143:15 145:16	331:4	142:8 143:17	250:12,16,21
<b>disturbance</b> 101:7	146:1,7,11 152:12	<b>doubt</b> 10:15 117:19	145:10 149:3,20	251:5,7,13,15,21
<b>disturbing</b> 100:14	159:14 171:12	<b>downgraded</b>	151:2,5,15 153:9	252:21 253:1,10
<b>diverse</b> 32:5 98:7	182:2,14 184:14	343:17	155:15,16 156:6	254:7,8,11,15,18
135:2 348:16	187:5 188:15	<b>downhill</b> 205:5	157:3,4,12,18,21	255:9,13 256:10
349:5 350:9,10,13	189:21 190:22	<b>download</b> 367:16	158:1,2,4,17	256:12,16,18,22
<b>divided</b> 320:10	206:14,18 207:11	<b>downloaded</b>	160:9,11,15 161:2	257:6,12 258:1,5
322:17,20,21	209:9 211:12	366:21	161:3,5,10,15,17	258:20 259:12
323:1 353:14	212:3 215:20	<b>downstream</b> 75:7	162:2,7,19,22	261:18 265:11
<b>DMBA</b> 159:9	230:1 233:7 238:3	<b>downturn</b> 40:7	165:4 167:13	266:21 267:4
<b>DMSO</b> 169:12	239:16 240:3,5,11	<b>downward</b> 267:16	176:6,8,17 177:2	269:4,6 272:19
176:20 180:16	241:17 242:3,8	<b>downwards</b> 260:12	177:10,14 178:19	274:20 279:5,14
<b>doable</b> 179:11	245:7,17 248:15	267:22 268:7	178:21 179:6	281:19 283:16,18
<b>docket</b> 1:10 4:11	248:19 250:19	294:8	180:1,3,3,7,22	283:19 284:4
10:14 267:12	257:19 318:8	<b>Dr</b> 5:19 6:1,6,11,15	181:7,11 182:4,12	285:4,6,14 286:7
326:15 365:21	346:1,19,22	6:20 7:1,6,9,15,20	182:19 183:5	286:9,20 287:4,6
366:12,20 367:3	396:19 397:9	8:2,6,8,12,14,17	184:3,7,18 185:12	287:7,8,8,9,12,20
367:10,11,16	401:14 402:5,6,8	8:20 9:2,6,9,14	188:7 192:22	287:21 288:9,13
<b>document</b> 320:17	402:10 414:16,20	10:2 24:9,10 25:6	193:8,10,14,15,16	288:18,21 289:1,3
389:18 390:1	414:21 415:12,16	25:10,16,19,20,21	193:18 194:5	289:7,8,14,18,19
392:4,7,10 395:10	415:18,20,20	26:11,17,22 27:2	199:16 212:11	289:22 290:1,2,11
<b>documents</b> 10:13	421:12	28:5,11,18 29:4	218:8,10 219:2,3	291:6 293:8 294:4
169:2 239:4 243:8	<b>dosed</b> 189:9,16	29:17 31:1,3 32:6	219:4,9,10,12,13	294:11,12 295:2
285:9 388:4	239:15	33:13,14 34:8	219:17,18,22	295:13,14,18
<b>dogma</b> 346:1	<b>doses</b> 145:14,14	51:16,18 52:1,2	220:9,11,12,15,16	296:4 297:9 298:2
<b>doing</b> 23:13 26:8	163:6 165:13	53:12,17 54:10	220:19,20 221:2,3	298:4,18 301:1
31:6 40:2 46:3	166:11 182:11,12	55:6,8 58:3 59:3	221:5,15,16,17,20	302:2,2,4,5,5,17
69:2 70:18 71:19	193:12,13 195:12	59:18,22 60:7,12	221:22 222:2,3,5	303:2,7,15 304:4
72:21 76:14 82:1	196:6 197:11,12	61:6,10,15 62:10	222:6,7,14,15,17	304:5,6,6,13,15
84:4,15 94:4,22	202:15 206:9	62:18,22 63:2,4,6	222:20,21 223:1,2	305:12 310:9,10
112:16 129:21	207:2,18,21	65:12,13,21 66:14	223:10,11,12,14	313:8 315:14
143:11 144:16	208:17 209:5	67:6,7,10 68:4,5	223:22 224:14	316:18 317:11
172:10 175:3	211:7,16 212:2,4	68:21 74:3 79:22	225:6 226:12,13	319:6,7,16,17
257:3 267:7 297:8	214:13 216:20	80:1 81:3,14 83:8	226:14,19,22	320:2,3,5 321:3
300:1 308:2 314:5	240:3 242:5	85:7,7 86:3,5 90:6	227:1,11,16,21,22	321:18 322:7,9,14
327:9 364:11	244:14 248:2,6	91:1,2,13 92:3	228:4,6,8,13,20	322:16 323:6,7,11
376:12,18 377:2	346:2,3,5,7,10	93:20,21 99:8	229:4,5,6,11,19	339:7,8,10 344:3

364:19,20,22	281:16 283:10	189:10 191:13	<b>ECHO</b> 290:17	134:16 137:12
365:18 366:6,18	284:9 300:19,21	225:5 254:6,13	<b>eco</b> 276:2,5 277:9	138:12 151:19
366:19 367:1,7,18	307:7 310:1,19	258:19 273:1	280:4	155:7 156:10
367:22 369:1	311:5 312:10	308:20 309:21	<b>ecological</b> 34:16	164:17 168:10
374:13 375:7	313:14,19 315:19	310:2,5 334:17	35:7 39:12 70:18	171:5 172:1,22
379:10,11 384:7	317:2 325:8,9,17	400:6	74:22 75:17 78:9	175:8 176:2
387:19,21 392:7,9	326:5 328:7	<b>durations</b> 12:3	84:18 85:22 326:7	184:10,16 185:1
394:9,11 395:11	330:19 331:10,22	13:10 14:16 77:22	331:11 335:16	186:9,19,19 193:2
398:6,8 400:14,16	332:7,9 333:3,3	187:7 292:15	357:19 382:2	195:16,18 196:9
404:11,12,20	333:18 334:1	293:5	<b>ecologist</b> 419:3	202:3 206:21
405:6,8,21 406:7	337:5 340:5 358:7	<b>dust</b> 123:2	<b>ecomonitoring</b>	208:19 214:16,22
406:16,18 407:5	361:10 362:4,11	<b>dwell</b> 274:19	262:3	215:9 216:11,13
407:14,16 408:8,9	362:14,17 375:16	276:17	<b>economic</b> 112:3,20	216:14 217:1,3,6
408:16,18,20	376:4,16 377:15	<b>dwelling</b> 214:3	330:6	217:9 218:1
409:11 410:5,6,8	378:12,14 380:20	<b>DWLOC</b> 310:3	<b>economies</b> 130:1	231:14 233:17
410:9 411:3,19,21	381:2 382:21	<b>dynamic</b> 410:12	<b>ecotoxicology</b> 6:2	235:4 237:6,13
413:7,8 416:10	<b>drive</b> 43:21 129:10	<b>dynamics</b> 201:20	<b>education</b> 381:14	238:16 240:5
417:18 418:15,17	147:11 200:4	<b>D-ALA-6</b> 196:4	<b>educational</b> 105:19	241:1,8,11,11
420:14 421:5,7	338:2 366:7	<b>D.C</b> 1:17 339:18	<b>effect</b> 37:22 62:5	242:22 243:18
422:22 423:1,3	<b>driven</b> 122:17		64:22 146:13	245:9,20 246:5,13
424:1,2,21	161:7 214:17	<b>E</b>	159:14 184:21	248:7,7,9,13,19
<b>draft</b> 155:10	<b>drives</b> 148:12	<b>E</b> 1:22 2:22 121:19	185:3,9 186:4,6	249:15 251:22
366:16 385:12	<b>driving</b> 34:14	184:1,1	186:12 188:13	252:3 253:17
386:10,16 388:5	142:6 216:19	<b>earlier</b> 13:7,13 70:1	189:19 190:2,20	257:7 325:21
<b>drag</b> 298:1	220:14 252:16	83:11 156:15	191:18,19 207:1	345:13 346:10
<b>drains</b> 279:1	<b>droplets</b> 359:7	185:13 223:8	207:13 209:3	347:3,11,12,21
<b>dramatic</b> 202:3	<b>dropped</b> 402:6	232:20 270:2	213:1 216:1,3	349:17 350:3,10
207:9 208:12	415:16	275:18 291:17	222:13 232:1	371:17 375:20
212:18 228:11	<b>drops</b> 41:7 211:18	325:10 343:18	235:11 236:4	376:7 382:2
<b>dramatically</b>	308:6	345:7,19 391:19	244:17,21 245:14	385:19 386:1,20
200:13 201:15,17	<b>drying</b> 277:4	393:10 407:2	252:4,17 254:22	389:7 391:16,18
<b>drastically</b> 246:15	<b>due</b> 92:18 121:4	<b>earliest</b> 187:10	387:4 395:18	393:20 402:12
<b>draw</b> 290:9 295:15	180:16 188:10,10	<b>early</b> 121:6 142:14	402:8	415:18
297:12 376:2,11	195:16 196:10	144:8,10 178:12	<b>effective</b> 68:7	<b>efficacious</b> 130:22
412:10	218:3 243:12	186:11 246:21	103:11 104:11	<b>efficacy</b> 108:5
<b>drawn</b> 46:9	252:1 265:18	265:11 284:13	111:21 192:2	<b>efficiencies</b> 100:10
<b>drinking</b> 1:8 5:8	282:19 327:15	326:20 344:22	272:7 282:18	<b>efficiency</b> 130:10
35:22 62:3,3 71:2	331:14 333:4	346:18 347:19	336:13 338:5	<b>efficient</b> 88:18
74:8 78:8 89:22	334:2	358:13 361:3	378:7	130:11 299:1
90:4,9 94:17	<b>Duluth</b> 6:21	388:14 399:20	<b>effectively</b> 133:5	<b>effort</b> 124:1
95:17 119:2	<b>dumped</b> 372:10	<b>early-life</b> 400:8	191:10,11 207:14	<b>efforts</b> 97:18
121:11,15,17	<b>duration</b> 21:4,5	<b>easier</b> 265:10	217:20 379:5	104:22 105:19
131:7,14 258:15	71:13,21 77:1,5	282:12 300:12	381:16	129:5 151:17
259:9,10,20 261:8	77:10 79:4,16	<b>easily</b> 38:9 145:1	<b>Effectiveness</b>	<b>EGFP</b> 196:13
261:12 262:10,13	164:16 184:14,18	145:11	368:14,22	<b>eggs</b> 348:22
268:17 275:5,7	185:2,17 186:1,2	<b>east</b> 97:5	<b>effects</b> 1:6 4:7 5:7	<b>EHP</b> 155:20
276:3,20 280:1,8	186:11 188:15	<b>easy</b> 62:11 243:19	88:4 127:2,10,12	<b>eight</b> 285:7 331:5

331:20	<b>encourage</b> 51:15 128:17	<b>environmental</b> 1:1 6:3,12 7:2 8:21 99:20 100:11 106:22 112:4,21 126:13 155:20 333:9 339:16	358:17 360:17,19 361:11 369:8 370:2,8 371:6,18 372:8,14 382:20 395:9,14 406:21 407:2	226:7 236:5
<b>either</b> 15:15 20:18 38:2,21 41:22 44:6 66:8 79:15 108:8 132:11 175:18 181:20 190:19 202:16 223:5 242:6 250:4 271:19 297:1 322:19 328:15 356:7 388:13 390:4	<b>encouraging</b> 268:2 <b>ended</b> 137:16 204:15 <b>endocrine</b> 7:3 134:16 137:12 138:12 156:22 184:10 202:11 237:13 245:20 256:4 347:8 348:17,18 350:9 358:7 371:17 376:7,15 385:21	<b>enzyme</b> 136:10 205:4 <b>enzymes</b> 205:3,7 <b>EPA</b> 1:1 3:8,13,18 5:5 10:10 86:11 97:17 98:9 113:16 113:16 116:1,6,8 116:9 118:5 119:7 122:9,18 123:11 141:1,11 149:22 152:18 239:3 260:17 271:4 275:14 278:10,16 284:14 285:2 288:1 297:15 308:13,17 311:6 312:16 320:17 325:2 326:14 327:18 333:7,7,11 333:15 334:7,21 335:13 336:3 338:2 340:6 341:19 342:2,13 343:6 345:6,10 349:6 356:17 358:17 359:8 360:8,9,21 361:20 363:12,12,19,19 364:1,10 369:20 369:21 370:3,9,13 371:7,16 372:3,10 376:3,11 383:19 384:8 385:2 388:18 391:12 397:20 402:16 405:16 411:22 412:21 417:12 420:2,17 423:19	<b>EPA-HQ-OPP-2...</b> 1:10 <b>epi</b> 352:2 369:19 400:1 404:5 406:12 <b>epidemiologic</b> 369:16 <b>epidemiological</b> 87:22 333:16 365:5 380:17 387:11 407:20 <b>epidemiology</b> 354:15 357:19 366:13 368:3,10 385:10 406:8,10 410:2 <b>episodes</b> 147:22 <b>episodically</b> 148:3 <b>equal</b> 273:19 <b>equally</b> 21:15 <b>equation</b> 37:17 43:10 <b>equipment</b> 359:11 380:7 <b>equipped</b> 127:22 <b>equivalent</b> 32:2 192:4 241:12 <b>erosion</b> 101:12 102:11,15,18 103:16,18 104:3 <b>error</b> 19:13 20:7 31:12 42:3 43:15 45:22 47:9 48:5 48:18 49:5 50:22 65:6 251:3 <b>errors</b> 44:5 47:12 48:13,17 49:12 369:4 <b>especially</b> 23:11 138:13 178:8 184:10 225:22	<b>essentially</b> 165:5 166:14 173:19 174:16 175:11 261:7 287:17 290:15 388:3 390:22 412:10 421:22 <b>establish</b> 61:1 305:18 <b>established</b> 118:19 309:3 312:14,16 336:18 370:17 <b>establishing</b> 318:4 <b>estimate</b> 11:15 44:10 46:22 47:5 52:21 58:8,14 60:8 61:8 63:9 76:17 258:18 268:20 274:3,3 352:7 379:21 <b>estimated</b> 19:12 103:16 230:11 279:10 <b>estimates</b> 13:15 27:16 45:7 47:8 56:2 63:10 66:1 77:12 78:21 79:3 270:19 296:1 316:11 351:6 <b>estimating</b> 12:2,7 21:11 58:1 62:10 62:13 73:13 79:15 279:17 281:10 283:3 297:21 <b>estimation</b> 85:6 281:2 <b>estradiol</b> 203:20 205:19 206:3 209:13,22 224:20 227:7 228:18 <b>estriol</b> 203:21 205:19 206:4 209:13 210:1 <b>estrocycle</b> 218:12 <b>estrogen</b> 136:11,14
<b>elaborate</b> 190:2 <b>elaborated</b> 192:21 <b>electronic</b> 4:15 110:14 <b>electronically</b> 383:4 <b>electronics</b> 338:1 <b>elevated</b> 147:17 148:2,4 153:16 155:3,6 160:19 201:17 211:13 215:21 248:4,8 330:4 398:21 <b>elevations</b> 241:15 <b>eleven</b> 118:13 273:1 <b>Eligibility</b> 358:16 <b>eliminating</b> 101:9 <b>elimination</b> 163:19 178:3 <b>Elizabeth</b> 384:8 <b>elucidate</b> 228:22 256:2 <b>elucidated</b> 152:12 <b>embarked</b> 197:4 202:8 <b>embedded</b> 91:18 163:10 <b>emergence</b> 126:12 <b>emphasize</b> 74:2 377:7 <b>emphasizes</b> 398:18 <b>employ</b> 17:15 <b>enclosed</b> 396:15 <b>encompasses</b> 98:1	<b>endocrinological</b> 235:20 <b>endogenous</b> 142:4 142:17 145:6 196:1 395:1 403:19 <b>endometrial</b> 154:6 154:8 <b>ends</b> 14:2 <b>energy</b> 7:19 <b>engaged</b> 98:19 <b>engineer</b> 326:11 <b>engineered</b> 196:14 <b>enhance</b> 169:12 <b>enhanced</b> 163:7 196:15 253:20 397:18 <b>enhances</b> 254:3 <b>enhancing</b> 170:21 176:21 424:11 <b>enormous</b> 266:19 <b>enrollment</b> 353:13 <b>ensure</b> 92:15 98:9 370:9 <b>ensuring</b> 122:5 <b>enter</b> 83:16 103:19 <b>entire</b> 110:22 111:2 265:15 273:3,9 281:4 289:20 <b>entirely</b> 190:19 <b>entry</b> 191:10 327:4 <b>environment</b> 9:8 99:3,3 103:1	<b>EPA's</b> 4:10 119:11 312:13 329:10 332:5,8 342:3		

142:4,17 145:7	247:12 250:21,22	400:10 412:5,6,15	259:11,20 301:20	<b>expecting</b> 358:8
146:15 147:16	342:17 406:1	413:4,6 421:16,21	302:1 362:7,19,20	<b>experience</b> 49:10
148:11,15,16	407:7 409:3	422:1,2,4,15	<b>exceeding</b> 284:22	70:12 114:17
150:15 155:6	<b>evaluating</b> 12:1	423:10	286:3	115:7
160:16 161:1,7	63:7 64:7 127:12	<b>evolved</b> 141:7	<b>excellent</b> 233:8	<b>experiment</b> 197:4
162:1,6,17 190:10	141:1 142:21	<b>ex</b> 201:1 222:8	<b>exception</b> 115:6	202:13 203:3
195:22 198:15	239:5,10 336:8	<b>exact</b> 94:14 226:6	360:14,18	210:18 234:15
212:7,8 214:22	385:8	238:4 250:4	<b>exceptional</b> 260:21	243:4 244:11
215:5 217:10	<b>evaluation</b> 76:15	411:10	282:17	274:10 371:8
219:15,19 224:9	86:12 245:7 376:7	<b>exactly</b> 28:3 136:19	<b>exceptions</b> 70:10	417:14
225:11 226:17	389:14	137:19 177:8	<b>excess</b> 132:2 244:3	<b>experimental</b> 1:7
227:2,22 228:12	<b>Evanston</b> 7:11	204:14 229:11	264:14	5:7 108:15 160:20
228:14,18 384:21	<b>evening</b> 118:12	236:21 247:11	<b>excessive</b> 318:6	228:21 343:15
391:5 398:21	373:15	297:20 317:8	<b>exchange</b> 149:22	344:11 349:4
402:17 403:19	<b>event</b> 145:17 390:3	408:22	<b>excited</b> 303:17,20	385:9,11 387:13
<b>estrogenic</b> 149:1	390:7,12,17,22	<b>exam</b> 107:15	<b>exclude</b> 349:10	398:15 412:4,7,16
150:10,16 395:2	391:4 392:10,12	<b>examination</b> 194:3	351:4	421:11
<b>estrogens</b> 203:20	392:15 393:6	202:18 223:8	<b>excuse</b> 174:17	<b>experimentally</b>
204:6 205:18,20	395:17	352:11	<b>executive</b> 97:6 98:3	152:17 344:16
209:13 210:11,13	<b>events</b> 64:2,14,16	<b>examine</b> 21:20	99:6,13 340:12	<b>experimentations</b>
216:5 395:1	95:12 142:6,19	142:6 201:1 203:6	<b>exemplary</b> 33:3	257:20
<b>estrone</b> 167:14	152:10 178:8,13	204:18 227:18	<b>exercise</b> 18:15	<b>experiments</b> 64:20
203:20 205:19	277:12 288:16	<b>examined</b> 197:21	23:10,18	237:19 238:8
206:3 209:13,22	299:10,21 389:19	198:17 199:15	<b>exhibit</b> 184:17	244:13 254:16,19
<b>estrous</b> 384:20	390:1 392:1,4,17	201:8 209:1,8	<b>exist</b> 255:15 344:19	288:2
386:5,13 394:19	392:21 393:2,4	211:3 214:1,19	355:2	<b>expert</b> 54:11,17,18
397:2	<b>eventually</b> 31:15	236:22 282:14	<b>existing</b> 77:6 78:2	153:11 161:3
<b>estrus</b> 142:13	263:20	353:6 374:21	281:18 322:2	300:7 325:20
143:21 144:6,9,21	<b>event's</b> 128:19	377:11	333:4 413:3	341:6 348:5
145:2 146:9,12	<b>Everybody</b> 303:8	<b>examining</b> 141:2	<b>exogenous</b> 170:18	<b>expertise</b> 9:12
147:21	<b>everybody's</b> 337:13	148:20 379:20	241:9 242:22	119:4 132:15
<b>et</b> 137:4 138:4	<b>everyone's</b> 130:10	<b>example</b> 15:3 74:19	252:5,5	233:13 326:3
192:5,5 272:14	<b>evidence</b> 94:9	126:8 162:3	<b>expand</b> 142:8	333:16 378:22
372:1 401:3,4	114:1 115:19	171:11 207:6	403:10	<b>experts</b> 271:10
<b>EU</b> 120:5,11	122:6 136:6 145:6	253:21 273:15	<b>expanded</b> 386:18	325:22 341:7
152:21	149:17 150:7	302:6 305:13	<b>expect</b> 15:22 17:14	344:5
<b>European</b> 120:5	151:13 152:1,1	320:8,9 330:8,11	19:19 24:15 25:3	<b>explain</b> 34:18 43:2
127:7,10	156:16,17 160:20	347:1 348:18	30:18 54:5,13,13	43:18 225:4
<b>evaluate</b> 11:14 45:3	161:19 162:18	351:16 358:5	54:14 56:5 61:17	233:16 286:15
75:19 76:16 77:7	171:18 179:1	370:8,13 371:6,13	65:2 75:5 115:15	376:12 396:1
142:18 245:19,21	198:2 204:8 220:3	371:21 412:2	306:19	422:10
247:8,10,13 297:5	229:13 231:3	<b>examples</b> 11:10	<b>expected</b> 21:3 30:8	<b>explained</b> 90:15
371:7	243:14 328:20	18:14	42:16,17,20 43:9	143:20 251:19
<b>evaluated</b> 12:6	343:15,16 344:10	<b>exceed</b> 309:20	43:16 176:10	<b>explaining</b> 66:12
127:10 140:16	349:4 355:1	336:17 360:19	232:2 302:9,10	<b>exploratory</b> 366:14
148:22 150:12	389:14 398:14	362:22 363:3,8	319:20 321:8,14	<b>explore</b> 151:18
240:15 244:12	399:4,6,9,12	<b>exceeded</b> 131:8	358:4 397:1	232:20

<b>explored</b> 224:3 336:12	<b>exposures</b> 32:22 33:1 34:14,19 73:2 76:17,18 78:8,9 169:3 212:22 241:18 258:22 271:6,6 272:18 283:4 287:15 335:6 344:22 345:1 346:19 347:19 351:4 358:13 359:5,12 360:5,9 360:19 361:2,3 400:8	<b>eye</b> 40:3 <b>eyeball</b> 40:3,13 <b>eyeballing</b> 68:16 <b>eyes</b> 49:4 395:6 422:9 <b>e-mail</b> 4:16,17 366:1 367:9,9 <b>e-mailing</b> 367:14	<b>factored</b> 322:1 <b>factors</b> 34:5,13,17 35:3 95:22 117:17 117:17,20 121:5 188:12 265:20 279:14,17 281:10 321:17,22 329:20 330:1 371:21 377:11,14	105:4 121:7 <b>farmer</b> 130:5 374:10 379:4 <b>farmers</b> 97:13,22 98:18 100:5 101:3 101:10,14 103:9 104:5,6,22 107:8 112:7,15,16 117:21 120:11 128:15,17 129:7 129:10,20 358:22 359:14 373:11 374:2
<b>exploring</b> 34:21	<b>express</b> 196:15 197:2,10	<b>eye</b> 40:3	<b>facts</b> 122:5	<b>farmer's</b> 100:15
<b>expose</b> 144:14	<b>expressed</b> 196:21 197:5 360:21	<b>eyeball</b> 40:3,13	<b>fact's</b> 294:3	<b>farms</b> 105:1 114:14 129:14,17 130:10
<b>exposed</b> 62:2 155:19 187:16 191:1 212:1 224:17 246:20 247:1 317:8 318:5 320:22 355:22 358:20 376:9	<b>expression</b> 163:7 164:21 165:16 168:9,15 172:3,9 174:18,21 175:15 175:21 181:3,8 197:7 198:4,8 199:5 230:7,16,20 240:16	<b>eyeballing</b> 68:16	<b>fail</b> 380:1	<b>farther</b> 75:4
<b>exposing</b> 373:19	<b>extended</b> 18:13 211:15	<b>eyes</b> 49:4 395:6 422:9	<b>failed</b> 356:17	<b>fascinated</b> 231:13
<b>exposure</b> 32:1,2 33:3 34:16 70:19 71:1,6,13,17,21 72:9 73:14 74:8 74:10,22 75:17 76:21,22 77:1,10 77:12,22 78:21 79:3,17 81:10 86:18 90:4 115:12 138:20 142:3,14 142:17 143:10 145:6 148:11,15 154:1 156:3,13 160:17 161:1 162:17 163:5,11 168:6 181:17 194:10 199:14 208:14 212:17 213:3 214:11,12 223:7 225:5 248:19 255:15 256:15,19 258:5,8 258:18 274:12 283:11 284:16 305:8,9,14,18 314:1 317:3 319:10 320:15 321:15 346:16,21 347:1,8,14 351:13 355:2 357:6 359:9 359:20 371:17 375:19 378:10,12 381:20 384:14 390:4 396:6 399:20 400:5,6	<b>extensive</b> 121:2,13 165:9 210:18 315:18 316:3,14 329:18	<b>face</b> 224:14 234:5	<b>failure</b> 147:5,6,8 161:20,22 162:9	<b>fascinating</b> 118:3
<b>exposure</b> 32:1,2 33:3 34:16 70:19 71:1,6,13,17,21 72:9 73:14 74:8 74:10,22 75:17 76:21,22 77:1,10 77:12,22 78:21 79:3,17 81:10 86:18 90:4 115:12 138:20 142:3,14 142:17 143:10 145:6 148:11,15 154:1 156:3,13 160:17 161:1 162:17 163:5,11 168:6 181:17 194:10 199:14 208:14 212:17 213:3 214:11,12 223:7 225:5 248:19 255:15 256:15,19 258:5,8 258:18 274:12 283:11 284:16 305:8,9,14,18 314:1 317:3 319:10 320:15 321:15 346:16,21 347:1,8,14 351:13 355:2 357:6 359:9 359:20 371:17 375:19 378:10,12 381:20 384:14 390:4 396:6 399:20 400:5,6	<b>extensively</b> 262:13	<b>fact</b> 87:2 98:2,20 118:5,5,7 120:21 120:22 132:8 134:19 146:14 156:14 177:11 188:10,11 189:5 189:13 190:1,13 195:8,15,21 196:4 197:15 198:12,15 200:7 207:7,17 210:15 211:1,8 212:3 217:8 218:20 219:14 231:5 239:1 242:8 243:17 267:10 278:13 286:22 290:6 293:13,17 293:22 294:3 299:14 300:3 318:4 320:6 328:19 374:16 375:7 391:9 396:4 415:21 417:1 419:15 420:5	<b>fair</b> 108:10	<b>fashion</b> 126:4 199:19 200:3 213:4
<b>exposure</b> 32:1,2 33:3 34:16 70:19 71:1,6,13,17,21 72:9 73:14 74:8 74:10,22 75:17 76:21,22 77:1,10 77:12,22 78:21 79:3,17 81:10 86:18 90:4 115:12 138:20 142:3,14 142:17 143:10 145:6 148:11,15 154:1 156:3,13 160:17 161:1 162:17 163:5,11 168:6 181:17 194:10 199:14 208:14 212:17 213:3 214:11,12 223:7 225:5 248:19 255:15 256:15,19 258:5,8 258:18 274:12 283:11 284:16 305:8,9,14,18 314:1 317:3 319:10 320:15 321:15 346:16,21 347:1,8,14 351:13 355:2 357:6 359:9 359:20 371:17 375:19 378:10,12 381:20 384:14 390:4 396:6 399:20 400:5,6	<b>extent</b> 73:14 80:19 168:8 178:10 294:9 370:19 389:9	<b>factor</b> 33:22 45:21 46:13 54:8 59:4 86:12 273:21 281:15 283:7 302:20 309:7 310:14,15,17,17 311:2,11 312:3 313:17 319:14 320:11 321:11 322:18 338:12,13 351:20 365:9	<b>fairly</b> 17:7 48:4 60:2 68:13 73:10 139:12 159:9 177:17	<b>fast</b> 40:1 139:12 221:9 224:8 325:2
<b>exposure</b> 32:1,2 33:3 34:16 70:19 71:1,6,13,17,21 72:9 73:14 74:8 74:10,22 75:17 76:21,22 77:1,10 77:12,22 78:21 79:3,17 81:10 86:18 90:4 115:12 138:20 142:3,14 142:17 143:10 145:6 148:11,15 154:1 156:3,13 160:17 161:1 162:17 163:5,11 168:6 181:17 194:10 199:14 208:14 212:17 213:3 214:11,12 223:7 225:5 248:19 255:15 256:15,19 258:5,8 258:18 274:12 283:11 284:16 305:8,9,14,18 314:1 317:3 319:10 320:15 321:15 346:16,21 347:1,8,14 351:13 355:2 357:6 359:9 359:20 371:17 375:19 378:10,12 381:20 384:14 390:4 396:6 399:20 400:5,6	<b>extra</b> 361:7 377:1	<b>factor</b> 33:22 45:21 46:13 54:8 59:4 86:12 273:21 281:15 283:7 302:20 309:7 310:14,15,17,17 311:2,11 312:3 313:17 319:14 320:11 321:11 322:18 338:12,13 351:20 365:9	<b>fall</b> 28:19 94:2,15 101:17 129:6	<b>father</b> 115:2
<b>exposure</b> 32:1,2 33:3 34:16 70:19 71:1,6,13,17,21 72:9 73:14 74:8 74:10,22 75:17 76:21,22 77:1,10 77:12,22 78:21 79:3,17 81:10 86:18 90:4 115:12 138:20 142:3,14 142:17 143:10 145:6 148:11,15 154:1 156:3,13 160:17 161:1 162:17 163:5,11 168:6 181:17 194:10 199:14 208:14 212:17 213:3 214:11,12 223:7 225:5 248:19 255:15 256:15,19 258:5,8 258:18 274:12 283:11 284:16 305:8,9,14,18 314:1 317:3 319:10 320:15 321:15 346:16,21 347:1,8,14 351:13 355:2 357:6 359:9 359:20 371:17 375:19 378:10,12 381:20 384:14 390:4 396:6 399:20 400:5,6	<b>extract</b> 54:17	<b>factor</b> 33:22 45:21 46:13 54:8 59:4 86:12 273:21 281:15 283:7 302:20 309:7 310:14,15,17,17 311:2,11 312:3 313:17 319:14 320:11 321:11 322:18 338:12,13 351:20 365:9	<b>falling</b> 312:13	<b>favorite</b> 120:1 393:1
<b>exposure</b> 32:1,2 33:3 34:16 70:19 71:1,6,13,17,21 72:9 73:14 74:8 74:10,22 75:17 76:21,22 77:1,10 77:12,22 78:21 79:3,17 81:10 86:18 90:4 115:12 138:20 142:3,14 142:17 143:10 145:6 148:11,15 154:1 156:3,13 160:17 161:1 162:17 163:5,11 168:6 181:17 194:10 199:14 208:14 212:17 213:3 214:11,12 223:7 225:5 248:19 255:15 256:15,19 258:5,8 258:18 274:12 283:11 284:16 305:8,9,14,18 314:1 317:3 319:10 320:15 321:15 346:16,21 347:1,8,14 351:13 355:2 357:6 359:9 359:20 371:17 375:19 378:10,12 381:20 384:14 390:4 396:6 399:20 400:5,6	<b>extraordinary</b> 169:22 170:10	<b>factor</b> 33:22 45:21 46:13 54:8 59:4 86:12 273:21 281:15 283:7 302:20 309:7 310:14,15,17,17 311:2,11 312:3 313:17 319:14 320:11 321:11 322:18 338:12,13 351:20 365:9	<b>false</b> 37:12,13 46:22 47:5,15,15 48:3,5,7,8,12,12 49:9,9,14,14 50:13,15,22,22 66:8,9	<b>Fawcett</b> 96:21 99:8 105:11,12,13 124:13 125:19 126:7
<b>exposure</b> 32:1,2 33:3 34:16 70:19 71:1,6,13,17,21 72:9 73:14 74:8 74:10,22 75:17 76:21,22 77:1,10 77:12,22 78:21 79:3,17 81:10 86:18 90:4 115:12 138:20 142:3,14 142:17 143:10 145:6 148:11,15 154:1 156:3,13 160:17 161:1 162:17 163:5,11 168:6 181:17 194:10 199:14 208:14 212:17 213:3 214:11,12 223:7 225:5 248:19 255:15 256:15,19 258:5,8 258:18 274:12 283:11 284:16 305:8,9,14,18 314:1 317:3 319:10 320:15 321:15 346:16,21 347:1,8,14 351:13 355:2 357:6 359:9 359:20 371:17 375:19 378:10,12 381:20 384:14 390:4 396:6 399:20 400:5,6	<b>extraordinary</b> 315:17	<b>factor</b> 33:22 45:21 46:13 54:8 59:4 86:12 273:21 281:15 283:7 302:20 309:7 310:14,15,17,17 311:2,11 312:3 313:17 319:14 320:11 321:11 322:18 338:12,13 351:20 365:9	<b>family</b> 129:17 284:11 304:19	<b>FDA</b> 7:7 239:3 243:9
<b>exposure</b> 32:1,2 33:3 34:16 70:19 71:1,6,13,17,21 72:9 73:14 74:8 74:10,22 75:17 76:21,22 77:1,10 77:12,22 78:21 79:3,17 81:10 86:18 90:4 115:12 138:20 142:3,14 142:17 143:10 145:6 148:11,15 154:1 156:3,13 160:17 161:1 162:17 163:5,11 168:6 181:17 194:10 199:14 208:14 212:17 213:3 214:11,12 223:7 225:5 248:19 255:15 256:15,19 258:5,8 258:18 274:12 283:11 284:16 305:8,9,14,18 314:1 317:3 319:10 320:15 321:15 346:16,21 347:1,8,14 351:13 355:2 357:6 359:9 359:20 371:17 375:19 378:10,12 381:20 384:14 390:4 396:6 399:20 400:5,6	<b>extreme</b> 24:17 64:15 268:22	<b>factor</b> 33:22 45:21 46:13 54:8 59:4 86:12 273:21 281:15 283:7 302:20 309:7 310:14,15,17,17 311:2,11 312:3 313:17 319:14 320:11 321:11 322:18 338:12,13 351:20 365:9	<b>families</b> 115:16 358:20	<b>feature</b> 43:19
<b>exposure</b> 32:1,2 33:3 34:16 70:19 71:1,6,13,17,21 72:9 73:14 74:8 74:10,22 75:17 76:21,22 77:1,10 77:12,22 78:21 79:3,17 81:10 86:18 90:4 115:12 138:20 142:3,14 142:17 143:10 145:6 148:11,15 154:1 156:3,13 160:17 161:1 162:17 163:5,11 168:6 181:17 194:10 199:14 208:14 212:17 213:3 214:11,12 223:7 225:5 248:19 255:15 256:15,19 258:5,8 258:18 274:12 283:11 284:16 305:8,9,14,18 314:1 317:3 319:10 320:15 321:15 346:16,21 347:1,8,14 351:13 355:2 357:6 359:9 359:20 371:17 375:19 378:10,12 381:20 384:14 390:4 396:6 399:20 400:5,6	<b>extremely</b> 258:22 280:6	<b>factor</b> 33:22 45:21 46:13 54:8 59:4 86:12 273:21 281:15 283:7 302:20 309:7 310:14,15,17,17 311:2,11 312:3 313:17 319:14 320:11 321:11 322:18 338:12,13 351:20 365:9	<b>far</b> 82:22 83:1,4 108:4 162:19 182:9 253:13,15 256:21 394:8 403:7	<b>February</b> 139:11 357:3 366:12,12 366:15,20 369:10 369:10,11
<b>exposure</b> 32:1,2 33:3 34:16 70:19 71:1,6,13,17,21 72:9 73:14 74:8 74:10,22 75:17 76:21,22 77:1,10 77:12,22 78:21 79:3,17 81:10 86:18 90:4 115:12 138:20 142:3,14 142:17 143:10 145:6 148:11,15 154:1 156:3,13 160:17 161:1 162:17 163:5,11 168:6 181:17 194:10 199:14 208:14 212:17 213:3 214:11,12 223:7 225:5 248:19 255:15 256:15,19 258:5,8 258:18 274:12 283:11 284:16 305:8,9,14,18 314:1 317:3 319:10 320:15 321:15 346:16,21 347:1,8,14 351:13 355:2 357:6 359:9 359:20 371:17 375:19 378:10,12 381:20 384:14 390:4 396:6 399:20 400:5,6		<b>factor</b> 33:22 45:21 46:13 54:8 59:4 86:12 273:21 281:15 283:7 302:20 309:7 310:14,15,17,17 311:2,11 312:3 313:17 319:14 320:11 321:11 322:18 338:12,13 351:20 365:9	<b>farm</b> 98:1 99:4,16	<b>feedback</b> 23:7 24:4

83:2,5 218:15,15 218:21 219:8,15 220:2 391:1,3 <b>feeding</b> 238:15 278:9,19 <b>feeds</b> 277:20 <b>feel</b> 30:6 340:22 405:1 411:14 414:15 417:19,20 418:3,5,10 <b>feeling</b> 30:12 55:6 70:4 <b>feet</b> 276:8 <b>fellow</b> 134:11 258:3 <b>felt</b> 343:21 401:15 401:20 414:10 418:19 419:9 <b>female</b> 140:13 142:9,15 143:8 145:21 152:9 157:17 185:13 186:13 195:5 196:1 212:12 218:12 229:8 242:1 249:3 384:19,22 389:11 396:20 398:20 401:22 <b>females</b> 140:9,15 140:19 150:21 195:7,7 210:18,20 211:2,9,9 213:2 215:19,22 223:17 224:7,13 227:4 228:15 249:9 386:6 388:16 397:8 <b>Fenner</b> 9:2 <b>Fenner-Crisp</b> 2:4 9:2 141:5 366:18 366:19 367:18,22 387:19,21 392:9 <b>fertility</b> 7:4 102:1 <b>fetal</b> 7:13 127:4 347:15 <b>fetus</b> 347:5 <b>fewer</b> 22:12 41:12	53:16 280:14 <b>fibroadenomas</b> 388:15 <b>fickle</b> 128:21 <b>fidelity</b> 204:8 <b>field</b> 64:13 101:9 101:10 102:2 124:15,21 128:20 <b>fields</b> 100:20 124:16 <b>FIFRA</b> 1:4,19 9:22 90:15 118:20 333:8 371:7 384:10 <b>Fifteen</b> 308:6 <b>fifteen-minute</b> 10:20 <b>fifth</b> 390:22 <b>fight</b> 115:3 <b>figure</b> 42:6 46:5 47:14 232:6 386:15 389:17,19 389:22 392:19 <b>figured</b> 293:21 <b>figures</b> 89:17 177:3 <b>files</b> 96:12 <b>fill</b> 64:11 69:21 <b>filling</b> 65:9 <b>filter</b> 104:14 382:9 <b>final</b> 4:19 20:9 317:1 323:8 345:9 358:17 360:8 371:13 410:18 <b>finalized</b> 328:18 342:5 388:7 <b>finally</b> 36:14 40:10 137:8 138:9 176:1 316:22 333:22 <b>find</b> 18:18 39:5 48:7 49:7,11,15 55:12 75:6 158:22 187:11 207:5,7 209:3 211:9 212:4 212:7 213:1 216:3 217:9 242:6 265:9 295:6 304:20 306:19 311:8	316:7 352:11 392:20 397:11 <b>finding</b> 39:10 66:11 314:8 319:1,2 364:3 406:11 <b>findings</b> 141:20 197:18 349:15 353:7 394:12 395:11 <b>finds</b> 356:9 <b>fine</b> 53:5 135:8 293:19,20 405:9 <b>finish</b> 116:20 133:22 172:17 175:7 <b>finished</b> 121:3 259:10,16 260:2 261:12 263:10 264:4,6,8 265:7,8 272:22 278:5 283:10 300:18 306:16 307:7 315:18 327:5 332:5 333:3 362:15,21 363:9 375:16 377:15 378:12 379:18 381:2 <b>finite</b> 291:3 295:21 <b>firm</b> 124:14 <b>firms</b> 373:10 <b>first</b> 6:19 10:9 16:17 34:6 37:19 38:4 39:8,19 41:2 51:17 52:5 54:11 72:21 74:16 81:22 94:17 96:19 100:3 105:7 106:13 108:21 115:8 134:4,5 135:13,17 136:6 140:1 141:14,15 156:8 158:20 184:12 186:21 187:7 190:4,5 194:12 206:6 208:2,11 239:7 258:14	261:9 267:5 270:5 271:5 272:18 282:9 303:4 305:7 305:17 306:20 324:11 334:7 361:8 372:4 383:20 400:5 417:10,17 <b>Fischer</b> 140:18 145:20 146:5,13 146:18,22 147:3,7 147:15,19 148:1,4 148:6 157:6 388:12 396:18,20 <b>fish</b> 151:12 155:18 156:2 349:17 350:2 <b>fit</b> 36:6 40:2,4,7,13 41:11 51:22 52:18 53:1,4,15 57:17 59:17 65:19 67:17 68:15,18,19 120:18 158:15 313:2,3 414:5 416:3,14,14 <b>fits</b> 59:6 133:16 422:5,6 <b>fitting</b> 39:6,18 43:8 59:8 404:4 <b>fit's</b> 69:2 <b>five</b> 13:4 15:10 41:20,21 56:18 62:8 185:1 187:8 189:16 190:7 212:1,4 214:4 229:14 271:16 275:3 285:20 301:21 319:9 321:12 324:22 415:8 <b>five-day</b> 87:10 <b>fix</b> 64:2 <b>fixed</b> 273:4 <b>flashy</b> 280:6 <b>flat</b> 181:21 <b>flattening</b> 154:22 <b>flavor</b> 37:15	<b>flexible</b> 51:7 <b>flies</b> 35:19 <b>flipped</b> 177:6 <b>Florida</b> 8:16 98:5 349:14 <b>flowing</b> 56:10 72:12 270:11 271:18 280:15 <b>flows</b> 205:5 272:14 396:13 <b>fluctuate</b> 358:2,4 <b>fluorescent</b> 196:15 <b>fluoride</b> 121:15 <b>flush</b> 329:19 330:2 336:22 <b>focus</b> 37:7,11 56:8 70:22 77:15 92:22 93:4 153:8 218:17 237:9 260:8 285:3 306:21 326:5 368:2 375:8 <b>focused</b> 56:7,10 98:8 151:4 266:19 284:8 316:1 328:9 381:10 <b>focuses</b> 336:16 <b>focusing</b> 78:10 92:16 156:22 189:2 264:22 375:15 <b>fold</b> 165:16 314:18 315:10 <b>folks</b> 32:1 69:16 70:11 76:13 81:11 127:21 169:2 388:2 389:22 <b>follicles</b> 147:11 <b>follow</b> 14:13 65:14 87:13 90:7 226:14 239:17 290:2 292:16 344:15 345:6 359:10 <b>following</b> 10:11 14:5 40:20 96:21 194:22 196:5 198:7,15 199:8,14 207:8,15 208:22
-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

211:6 214:11,12 215:20 217:2 228:15,16 232:4 313:3 326:17 354:16,18 368:14 <b>follow-up</b> 403:7 <b>food</b> 100:12 233:6 320:16,18,20 376:5,16 379:7 <b>foodborne</b> 320:14 <b>foot</b> 421:4 <b>Foradori</b> 138:3 <b>forcing</b> 53:3 <b>forecasts</b> 128:14 <b>foreign</b> 240:18 <b>forewarn</b> 234:4 <b>forget</b> 418:14 <b>forgive</b> 221:10 <b>form</b> 164:2 166:22 167:8 328:22 <b>formally</b> 406:21 <b>format</b> 265:9 <b>formation</b> 175:11 <b>formed</b> 97:15 98:4 <b>former</b> 139:19 344:6 <b>forming</b> 347:5 <b>forms</b> 166:3 175:2 <b>formula</b> 36:3 38:8 38:14 <b>formulators</b> 373:10 <b>forth</b> 49:17 50:2 288:16 310:5 312:21 315:16 341:19 418:13 <b>fortunate</b> 138:15 <b>forward</b> 96:2 124:5 195:14 257:14 258:11 341:10 376:22 400:11 410:20 <b>Fos</b> 199:5 229:21 230:3,6,7,16,20 <b>found</b> 22:8 29:1,11 43:6 53:14 125:21 132:1 155:18 156:4 198:2,7	205:17,20 207:12 225:14 243:22 292:20 315:5,11 333:2 336:20 349:18 353:5 356:9 357:5 358:11 359:4 413:10 <b>foundation</b> 65:4 98:21 <b>four</b> 13:20 16:1,2,9 19:3,15 38:8 41:20,21 52:14 59:14 62:4 78:14 140:12 165:13 174:4 198:19,21 199:1,8 201:5 212:21 213:5 263:6 271:15 273:6 275:15 279:21 323:19 324:4 331:5 332:22 333:6 392:4,15 393:2,6 <b>fourteenth</b> 208:14 <b>fourth</b> 40:10 104:1 293:11 390:17 <b>four-day</b> 15:15 18:21 <b>four-node</b> 40:18 41:12,15 51:21 52:5,16 53:9 <b>four-page</b> 373:12 <b>FQPA</b> 2:1 <b>fraction</b> 38:1,4,6 61:11 <b>fractions</b> 37:21 38:9 <b>frame</b> 102:19 119:13 178:8 334:8 335:15,19 <b>frames</b> 27:11 335:10 <b>framework</b> 135:19 141:1,16 142:19 148:18 150:19 335:22 400:19	407:10 <b>France</b> 342:9 <b>Francisco</b> 7:16 <b>Frankenberry</b> 3:11 11:12,21 24:20 25:14,17 26:9,15 26:19 28:16,22 29:8 279:6 <b>Frankenberry's</b> 72:7 <b>frankly</b> 23:12 63:15 114:8 116:1 402:4 403:5 <b>free</b> 340:22 <b>free-standing</b> 413:6 <b>frequencies</b> 78:22 271:15 280:11,17 <b>frequency</b> 1:8 5:9 11:14 71:10 73:7 75:2 88:13 91:17 94:18 95:18 201:16 214:7,13 258:17 259:15 260:8 262:2 265:4 266:20 271:1 272:6,11 273:16 274:13 280:10,22 301:16 325:18 326:6 334:2 <b>frequent</b> 16:16,16 17:16 21:4 72:4 76:6 78:2 80:17 82:5 282:6 288:6 316:6 <b>frequently</b> 77:20 79:4 333:2 337:20 337:22 <b>freshwater</b> 156:2 349:17 350:2 <b>friendliness</b> 372:16 <b>friends</b> 304:18 <b>Frigid</b> 302:19 <b>frogs</b> 348:22 349:1 <b>front</b> 94:3 105:8 118:9 139:14 375:12,18 377:4	383:20 <b>fronts</b> 95:1 119:2 <b>frustrated</b> 420:12 <b>frustrating</b> 420:2 <b>fuel</b> 101:15 <b>Fukamachi</b> 158:6 401:3,10 414:14 <b>full</b> 82:12 188:22 265:6 271:18 279:10 283:13 344:21 345:17 351:3 <b>fully</b> 82:11 160:7 <b>fun</b> 55:5 69:6,11 <b>function</b> 42:6,7 179:4 188:14,14 196:11 202:12,19 238:22 347:7 356:7 385:20 <b>functional</b> 151:14 155:18 238:18 239:4 <b>functioning</b> 170:7 <b>functions</b> 256:4 <b>fundamental</b> 334:20 399:1 <b>fundamentally</b> 394:14 <b>funded</b> 138:17 <b>FUNGICIDE</b> 1:3 <b>fungicides</b> 88:8 <b>funny</b> 41:14 <b>further</b> 26:14 31:17 75:7 114:2 117:15 154:19 159:20 180:8 314:13 385:8 <b>Furthermore</b> 151:9 151:15 387:4 <b>future</b> 127:17 354:20,20 400:12 <b>F.L</b> 2:15 <hr/> <b>G</b> <hr/> <b>G</b> 1:17,20 <b>gain</b> 235:1 <b>gallon</b> 277:14,16	<b>gallons</b> 277:15 <b>gap</b> 314:8,14,19 <b>gardens</b> 102:7 <b>garnish</b> 233:21 <b>gas</b> 102:6 <b>gavage</b> 195:11 203:6 207:11 211:20 <b>gavages</b> 199:1 <b>gavaging</b> 187:4 <b>GCMS</b> 330:16 <b>gears</b> 202:1 243:5 <b>gene</b> 172:8 <b>general</b> 29:13,21 70:9,11 78:19 85:14 116:11 225:1 244:16,17 255:22 333:6 379:3 394:11 395:20 396:9 418:17 423:19 <b>generalization</b> 286:8,10 <b>generalized</b> 208:20 <b>generally</b> 17:16 21:14 242:11 333:2 345:22 351:14 419:3 <b>generate</b> 32:18 73:2 76:18 <b>generated</b> 195:16 279:6 301:22 <b>generation</b> 202:6 215:10 <b>generator</b> 137:19 200:16 <b>generously</b> 119:7 <b>genotoxic</b> 149:1,8 149:18 150:7 389:12 391:9 <b>genotoxicity</b> 159:22 389:15 399:10 <b>Geological</b> 8:9,13 <b>Georgetown</b> 210:12 <b>Georgia</b> 6:16
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<b>GERALD</b> 1:22	193:11,12 257:7,9	<b>go</b> 5:12 11:10 16:22	88:2 94:6,11,12	384:15
<b>germane</b> 293:4	282:6 294:13	18:5 19:7 22:10	96:18,21 99:5	<b>gonadotropin-rel...</b>
<b>Germany</b> 141:4	338:1 340:19	24:13,19 29:1	113:11 115:14	390:9
<b>germinate</b> 103:6	378:9 420:22	32:15 41:17 44:18	126:22 132:14	<b>gonads</b> 387:6
<b>Gerry</b> 6:11	421:11	69:18 72:4 73:22	133:20 134:2,17	<b>good</b> 5:4 21:12 24:2
<b>gestation</b> 246:21	<b>gives</b> 75:8 85:5	83:1,4,7 88:20	134:19 135:3	25:4 40:4 47:8
<b>getting</b> 57:4 65:18	140:5 178:12	89:10 93:15 94:1	137:8 138:5,10	64:6 65:19 66:1
67:19 68:1 78:15	244:2 251:2,6	96:13 110:11	145:5 156:21	69:2 73:20 79:19
81:8,8 110:3	266:18 282:20	112:8 116:7	160:5 161:2	80:5 90:22 92:4
233:5 282:18	307:3 331:2	125:12 127:14	178:10 180:10	92:13 102:8 105:9
289:3 300:9 301:5	379:21 380:2	128:1,19 130:18	182:5,7 183:12	133:15,21 158:2
306:2 318:5 425:5	<b>giving</b> 27:14 191:4	130:18 141:15	188:4 189:3,4,6	164:9 167:20
<b>Gilliom</b> 2:5 8:7,8,8	258:12 267:8	151:22 157:15	189:18 216:21	171:18 182:21
27:1,2 28:5 63:5,6	305:6 311:7 349:4	159:8 186:10	218:5 226:8 227:8	193:18 248:13
86:4,5 90:6 125:3	<b>glad</b> 248:21	194:15 225:7	230:22 231:15	269:20 284:4
125:4 261:19	<b>gland</b> 157:8 390:13	232:6 238:13,21	233:11,16 234:5	292:4 300:1
265:11 285:5,6	391:6 401:5	249:5,18 259:1,13	237:8 255:7,12,14	308:10 317:4
286:7,20 287:7,12	402:18 403:1	267:13 300:5	256:14,19 258:13	324:14,15 330:20
287:21 288:13,21	<b>global</b> 289:13	318:13 320:7	258:14 259:6	333:14 369:18
289:3,8,18,22	<b>globally</b> 128:10,11	326:12 332:8	260:4,19,20 262:9	371:10 372:22
364:19,20 367:1,7	<b>glucocorticoid</b>	348:12 367:16	262:12 264:16	373:15 384:7
<b>GIS</b> 352:5	240:6 255:2,3	377:5 389:21	271:2,7 274:11	404:14 408:8
<b>give</b> 4:17 10:4,7	<b>glucocorticoids</b>	418:6 419:8	277:5 278:4,13	413:11 423:17
11:12 65:4,5 79:5	205:14 241:2	420:15 425:4	283:20 292:3	<b>gotten</b> 19:19 24:21
80:15 84:10 85:4	244:9,17	<b>goal</b> 309:16	293:12 294:2,13	337:13
87:7 89:7 112:10	<b>glutamate</b> 170:17	<b>goals</b> 94:15	294:22 297:10	<b>govern</b> 370:2
118:21 124:13	<b>glutathione</b> 166:22	<b>goes</b> 82:8 89:2	298:7 299:18	<b>government</b> 119:18
126:8 128:1	176:12,15 177:4	129:9 368:7	300:11,12 302:20	<b>GPS</b> 130:1
134:21 149:6	<b>glyphosate</b> 125:21	<b>going</b> 5:12 10:3,8	305:9,9 306:13	<b>graciously</b> 305:12
178:17 189:6	<b>GMO</b> 87:3	11:6,10,12,16,20	311:19 317:18	<b>grades</b> 125:14
205:11,18 235:17	<b>GM1</b> 245:11	14:17 17:21 27:20	320:21,22 323:4,5	<b>Graduated</b> 99:18
243:2 246:17	<b>GNR</b> 392:15	30:16,16 31:17,21	323:9,17 332:14	<b>grain</b> 97:7,9,10
247:14,16 248:17	<b>GnRH</b> 137:19	32:11 35:22 36:2	338:22 339:12	99:14
255:10 271:7	184:16 185:10	36:5,7,17 37:2,7	340:16 341:19	<b>grand</b> 289:8
273:15 308:15	195:16,20 196:2,3	39:19 41:14 43:1	343:2 345:5 355:8	<b>grandchild</b> 115:8
312:7,11,15	196:4,8,13,14	44:8,18,18 45:2,2	368:8,10,18	<b>grandkids</b> 114:13
313:14 314:6	197:1,5,9,13,14	45:9,21 52:7,9,18	376:22 383:8,11	<b>grant</b> 237:18
318:22 332:14	197:15,19,21,21	53:7 57:1,11 62:7	383:11,13,15,19	<b>granular</b> 328:16
340:21 387:21	198:1,3,8,11,12	64:13 67:2,4	383:21,22 384:1,3	<b>graph</b> 15:7 16:17
388:2 408:15	198:14 199:4,10	69:12,13,15 70:4	384:9 405:3,8	18:11 20:9 240:10
412:3	199:12,18,20	70:12 71:1 72:16	408:1,20 409:2,5	285:7 286:8
<b>given</b> 38:21 39:1	200:2,2,16,22	72:18,20 73:10,12	414:16 416:2,3,4	337:12
43:20 44:6 46:10	201:1,8,11,15,19	73:18 75:3,6,11	418:8 421:7,8	<b>graphed</b> 240:11
46:19 78:17 80:22	220:14 222:8	75:16,22 76:8,10	423:17,21 425:8	<b>graphics</b> 286:11
87:9,12 119:13,22	230:16,21 384:16	76:15 78:13 80:11	425:12,13	<b>graphs</b> 239:14
125:5 158:12	390:11,12,14	80:14,16 81:15,21	<b>gonadal</b> 8:3 350:7	241:3
178:7 190:7 192:8	<b>GNRP</b> 153:19	84:12 86:19 87:21	<b>gonadotropin</b>	<b>grass</b> 108:12

<b>gray</b> 365:7	<b>grower</b> 97:16	<b>habituation</b> 213:3	166:16 176:3	339:17 342:12
<b>great</b> 72:14 172:6	<b>growers</b> 97:7 99:7	224:6 229:7	265:22 397:21	343:4,9,10 344:5
284:12 290:6	99:14,14 103:1	241:22	409:6	344:14 348:17
314:9 315:22	117:2,3 268:8	<b>HAL</b> 259:12	<b>happened</b> 231:17	349:19 353:5,8
317:5 419:9	329:3 381:16	308:21,21	<b>happening</b> 59:7	356:19 375:20
<b>greater</b> 101:1	<b>growing</b> 111:8	<b>half</b> 20:19,20 46:14	162:15 168:2	384:13 393:12
120:7 212:19	264:3 266:6	46:15 264:14	175:17 293:22	397:15 411:8
259:16 267:20	<b>growth</b> 233:5	316:5 353:21	420:19	<b>hear</b> 25:5 28:9
273:18 391:11	<b>guess</b> 27:9 28:6	<b>half-a-million</b>	<b>happens</b> 49:6,10	84:17 120:14
396:10 405:4	38:20 58:20 59:10	307:3	95:7 106:14	188:6 327:6
<b>greatest</b> 344:5	64:17 82:18 89:6	<b>half-hour</b> 324:5	163:21 208:9	416:11
<b>greatly</b> 300:21	90:6 96:4 109:9	<b>hall</b> 24:11 369:1	311:13 363:4	<b>heard</b> 61:21 72:7
323:14 372:15	126:16 134:4	<b>hallmarks</b> 143:15	<b>happy</b> 25:9 127:22	79:10,21 91:3
<b>green</b> 163:16	176:10 184:4	<b>Hamilton</b> 1:16,16	231:22 294:5	95:1 106:21 112:4
196:15 205:10	224:22 234:1	<b>hand</b> 39:2 63:20	325:11	121:7 133:14
<b>greenhouse</b> 102:6	287:21 324:10	64:8 66:2 146:5	<b>hard</b> 343:4	142:7 154:10
<b>Greenwood</b> 2:6 9:6	365:19 383:16	238:10 343:6	<b>harder</b> 40:22	261:20 275:14
9:6 177:2,2	400:21 402:1	<b>Handa</b> 137:16,22	210:19	283:22 308:22
<b>grew</b> 99:16	413:20 414:3	161:5,15 162:2,19	<b>harm</b> 113:21	315:14,15 324:7
<b>ground</b> 100:15	423:13 424:21	188:7 192:22	116:11 127:8	325:10 341:7
101:21 284:6	<b>guessing</b> 68:16	193:17,18,19	346:20 356:6	350:19 379:15
360:12	122:18	219:2,4,10,13,18	<b>harmful</b> 361:21	400:17 409:12,15
<b>groundwater</b> 35:22	<b>guidance</b> 89:7	220:9,12,16,20	<b>harmonized</b> 94:8	409:16
120:7 131:15,17	239:3 243:8 295:5	221:15,17,22	<b>hasten</b> 280:1	<b>hearing</b> 77:3
132:2,4 284:16	365:10	222:3,6,14,17,21	<b>Hawaii</b> 98:6	312:18 340:8
285:1 327:16	<b>guideline</b> 408:11	223:2,11,22 225:6	<b>Hayton</b> 2:7 9:14,14	363:17 390:15
<b>groundwaters</b>	424:18	226:19 227:1,16	304:15	409:12
331:18	<b>guidelines</b> 141:11	227:22 228:6,13	<b>hazard</b> 82:7,15	<b>heart</b> 182:13
<b>group</b> 15:3 19:1,1,5	151:22 342:4,15	229:11 230:5,10	95:2,4,20 149:10	<b>heaven</b> 304:2
19:22 20:1 32:5	370:2,6,6,9	231:5,16,21	<b>hazardous</b> 345:21	<b>heavily</b> 65:17 104:7
45:6 86:22 94:2	399:21 408:15,22	232:16,19 233:8	346:9	275:21
98:8 133:18	411:22	233:18 234:15	<b>hazards</b> 360:11	<b>heeded</b> 345:20
139:14 145:12	<b>gut</b> 182:1 349:3	236:9 254:15	<b>HCTH</b> 217:18,18	<b>Heeringa</b> 1:17,20
187:13 189:7,12	358:12	304:5 395:11	<b>head</b> 6:12,17 128:3	9:18,18 32:7,8
209:17 218:13	<b>guys</b> 24:19 25:12	<b>Handa's</b> 151:2	419:4	53:18,19 55:16
222:1 226:17	27:3,12 73:1 87:7	<b>handle</b> 82:5	<b>heading</b> 101:17	83:9,10 84:16
235:2 242:3 276:4	156:4 286:21	<b>handlers</b> 114:12	<b>heads</b> 232:5	85:1 266:21 301:2
302:9 342:16,20	299:22 341:10	<b>handling</b> 252:8	<b>health</b> 1:6 4:7 5:6	301:3 302:5,13
343:13,19,21	357:2	<b>handout</b> 271:9	7:2 62:5 91:8	<b>Heidelberg</b> 12:20
344:10 382:18	<hr/>	274:6 278:7	94:11,21 120:4	39:13 57:10 63:14
412:11 420:19	<b>H</b>	<b>handouts</b> 184:17	127:2,10,11 131:6	75:12 261:20
<b>groupies</b> 370:16	<b>H</b> 2:2,9 153:19	339:9,20	155:20 163:1	275:13 276:2
<b>grouping</b> 29:15	<b>habitat</b> 101:13	<b>hands</b> 184:22	170:7 284:22	279:20 290:17
<b>groups</b> 10:12 98:1	<b>habituate</b> 216:1	<b>handy</b> 341:3	304:17 308:19	292:19
152:20 209:15	223:17 224:8,12	<b>Hanover</b> 141:4	309:2 312:9	<b>height</b> 190:16
234:14 245:10,13	229:8	<b>happen</b> 71:4 73:3	322:12 325:20	191:5
251:3 396:3	<b>habituated</b> 208:1	81:21 146:14	334:9,18 335:15	<b>held</b> 396:15

<b>help</b> 87:7 130:2 181:2 251:11 280:20 294:1 368:7 408:9	257:19 259:7,15 260:14 266:20 268:12,16,21 270:11 278:7	230:22 304:14	218:10,11 219:3,9 219:12,17,22 220:11,15,19 221:2 283:18,19 298:4 408:16,19 408:20 418:16,17	147:15,19 148:1,9 148:14 152:1,2 155:5 181:17 182:16 236:3 283:11 341:18 342:1 343:3 344:19,22 349:3 351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
<b>helpful</b> 83:14 155:11 274:9 408:17,21	282:21,22 283:5 286:4 336:16 337:19,19 352:12 363:2,14,20 401:17 402:5,6,8 415:18,20,21	<b>hits</b> 69:15 106:13 166:17	<b>Horton's</b> 298:2	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
<b>helping</b> 34:18 72:17 93:10	<b>higher</b> 20:8,20 22:11,17 24:1 44:6 48:5 75:5 109:3,12 111:11 113:8 119:8 145:22 169:8 182:2 186:4 265:4 266:8,8 269:21 270:9,13,19 286:4 304:2 396:16	<b>hold</b> 333:13	<b>host</b> 24:17	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
<b>helps</b> 73:16 100:17	<b>Hendley</b> 258:1,2 284:4 285:14 286:9 287:4,8,20 288:9,18 289:1,7 289:14,19 292:5 294:4 298:18 302:2 304:6 315:14 316:18	<b>holds</b> 410:22	<b>Hotel</b> 1:17	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
<b>Herbert</b> 2:12 8:17	<b>highest</b> 21:22 25:2 47:22 206:14 209:9 211:11 225:17 227:4 288:6 316:12 332:19 353:15 357:18 358:3	<b>holes</b> 69:22	<b>hour</b> 10:19 165:12 239:20	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
<b>herbicide</b> 87:4 103:13 106:12,20 107:3,4,9,11 108:5 109:14,15 111:18,19 120:13 124:11,12,18,21 129:9 130:11 132:1	<b>highlighted</b> 403:3	<b>home</b> 5:15 99:21 216:19,22	<b>hours</b> 10:17,18 165:13,17,18 169:20,21 211:14 212:21 228:16 230:10 239:17 244:1 248:11 250:18 251:1 276:6 383:16	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
<b>herbicides</b> 116:10 128:8,13 129:21 327:14 351:14,20	<b>highlighting</b> 402:21	<b>homeowners</b> 358:19 360:16,20	<b>hour-and</b> 10:19	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
<b>Herschel</b> 287:9	<b>highly</b> 165:21	<b>homogenate</b> 179:14	<b>house</b> 403:14 416:3 422:6	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
<b>Hey</b> 91:2	<b>Hill</b> 135:18	<b>homogenous</b> 300:10	<b>housed</b> 396:11	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
<b>hierarchal</b> 55:4	<b>hinted</b> 83:21	<b>honest</b> 78:7 83:5 210:17	<b>HPA</b> 95:6,10 138:13 151:4 178:9 195:2 211:4 213:7 217:4,17 218:19 233:13 238:12 387:1 391:21 392:22 393:6,21 394:4,13 395:4 400:20	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
<b>high</b> 13:5 46:15 47:18,19 48:2,3 50:14,16 59:22 71:5 82:4 84:1 102:18 125:16 143:5,9 145:13,14 148:5 159:14 162:14 163:6 165:19 169:22 171:12 176:3 189:21 197:11 216:20 227:3 233:7 244:14 248:2 253:4,22	<b>hints</b> 171:7	<b>honestly</b> 82:21	<b>hour-and</b> 10:19	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
	<b>histocompatibility</b> 240:16	<b>hope</b> 94:7 113:9 155:11 260:22 318:21 400:1,4	<b>house</b> 403:14 416:3 422:6	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
	<b>historical</b> 101:4 267:21 282:3 337:7,15	<b>hopefully</b> 69:21 84:16 175:5 194:17 233:11	<b>housed</b> 396:11	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
	<b>historically</b> 56:21	<b>hoping</b> 69:18	<b>HPG</b> 151:4 194:22 196:9 213:9 216:15,21 217:1,3 220:8 233:13 238:16 386:8,12 387:3 389:8 394:4 394:14 395:8 400:20	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
	<b>history</b> 57:9 71:6 92:18 263:18 264:19 268:1 269:21 272:12 274:14 281:4 286:3	<b>horizon</b> 128:19	<b>HPG/HPA</b> 404:4	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
	<b>hit</b> 166:11,15	<b>hormonal</b> 149:3 195:5,9 214:16,20 345:12	<b>Huffington</b> 116:3	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
		<b>hormone</b> 199:15,17 202:5 208:6,6 214:2 216:9 217:6 218:2 221:1 347:8 350:2 384:16,18 390:9 392:12	<b>huge</b> 111:5 280:18	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
		<b>hormones</b> 8:4 194:19 203:9,12 203:13 204:4,10 204:15,17,18,19 205:9,12 207:6 210:6 402:22	<b>human</b> 1:6 4:7 5:6 7:22 91:8 94:20 127:9 136:21 146:18,22 147:10	351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16
		<b>Horton</b> 2:9 7:9,9 126:20,21 218:9		351:3 356:19 360:9 375:20 377:9 378:11 384:13 387:17 388:8 389:4 393:12 394:17 398:12,13 399:2 404:22 405:1 422:16

161:15 162:3,8 194:20 196:10 200:17 201:2 213:17 217:16 385:19 390:6,7 392:5	<b>Idaho</b> 8:2 <b>idea</b> 10:7 49:12 75:8,18 80:22 97:9 225:17 227:2 230:6 231:18 233:9 243:7 245:16 247:17 306:3 307:21 308:8 312:12 313:12 318:18 361:2	<b>immunocytoche...</b> 196:18 198:7 <b>immunological</b> 202:11,19 237:6 238:6 239:4 240:5 242:12,13 243:15 243:18 245:9 246:10 247:4,8,20 248:6,17 253:16 254:3	376:15 <b>implicated</b> 334:18 <b>implication</b> 27:11 27:13,19 329:12 <b>implications</b> 115:2 115:11 136:1 275:20 330:6 334:3 405:13 <b>importance</b> 200:2 374:9 375:14 402:21 <b>important</b> 18:9 27:21 28:2 33:5 98:14,15 105:3 106:1,2,3 107:1,4 114:22 121:18 126:14,15 140:4 185:5 200:17 242:17 259:8 276:1 278:20 280:20 325:5 328:3 334:9 346:21,22 356:18 357:1 374:6,17 376:11 383:17 406:2 407:5 410:10 424:6,20 <b>importantly</b> 138:5 141:9 377:3 <b>impossible</b> 103:14 <b>improper</b> 347:4 <b>improve</b> 17:17 82:6 100:8 130:15 171:19 372:15 <b>improved</b> 292:13 <b>improvement</b> 382:16 <b>improvements</b> 100:10 268:9 <b>improves</b> 101:13 101:22 106:18 <b>improving</b> 85:13 391:14 <b>inactive</b> 166:19 168:4 175:12 <b>inadequate</b> 343:16 <b>incapacitate</b> 394:3	<b>inception</b> 192:12 <b>incidence</b> 143:9,14 145:22 146:3 152:8 384:22 401:17 402:5 414:17 422:8 <b>incidences</b> 396:2 <b>incident</b> 353:11 354:1,10 388:14 <b>incidentally</b> 139:9 <b>include</b> 27:22 127:16 370:7 403:10 <b>included</b> 13:5 63:17 127:20 351:20 358:22 365:1,10 388:20 399:3 <b>includes</b> 97:21 <b>including</b> 101:18 104:8,12,20 116:13 119:19 120:4 121:5 152:21 160:6 182:11 279:7 344:22 345:12 347:22 350:3,13 350:15 351:14 356:12 371:22 382:2,10 <b>inconsistencies</b> 225:2 <b>inconsistent</b> 229:16 342:3 <b>incorporate</b> 53:22 55:10 65:6 <b>incorporated</b> 113:17 114:7 406:11 <b>incorporates</b> 410:19 <b>incorporation</b> 104:16 <b>incorrect</b> 344:17 <b>increase</b> 38:2,5 39:21 40:1,9 41:2 41:3 45:18 48:7
<b>I</b>	<b>ideal</b> 82:16 <b>identical</b> 46:8 165:5 187:15 189:8 215:9 <b>identified</b> 103:21 168:3 239:3 356:21 363:13 386:4 391:19 <b>identify</b> 174:3 200:8 204:14 <b>identifying</b> 172:18 217:13 425:2 <b>ideology</b> 122:7 <b>ignorance</b> 342:11 <b>ignore</b> 418:11 <b>ignored</b> 364:6 <b>Illinois</b> 7:11 <b>illustrate</b> 74:15 75:2 <b>illustrated</b> 239:14 <b>illustrates</b> 300:22 <b>imagine</b> 33:15 54:15 98:12 <b>immediately</b> 198:22 205:8 247:4 <b>immune</b> 138:21 156:1 236:8 238:17 240:21 246:6,13 248:7,9 248:13 346:13 348:1,19 355:7,14 356:4,6 <b>immunization</b> 196:2 <b>immuno</b> 254:2	<b>immunoneutralize</b> 217:18 <b>immunosuppress...</b> 407:22 <b>immunosuppress...</b> 408:2 <b>immunotox</b> 235:18 235:21 <b>immunotoxicity</b> 156:18 239:6 242:18 <b>immunotoxicolo...</b> 139:3 <b>immunotoxicolo...</b> 6:19 <b>immunotoxicology</b> 6:22 <b>impact</b> 213:11 249:11 256:4 331:8 345:14 374:8 387:6 <b>impacted</b> 394:5 <b>impacting</b> 218:20 <b>impacts</b> 100:12 101:1 220:7 236:3 337:1 <b>impair</b> 176:13 <b>impaired</b> 348:22 350:7 <b>impairing</b> 176:16 355:14 <b>impairs</b> 348:19 <b>implantation</b> 190:10 <b>implement</b> 92:1 <b>implemented</b> 14:4 <b>implementing</b>		
<b>IARC</b> 152:21 342:7 342:14,16,17 343:5,12 344:6,7 407:1,4,7,13 412:11 <b>IARC's</b> 407:1 412:14 <b>IBMX</b> 173:4,8 179:18 <b>ICCVAM</b> 370:16 370:17 <b>icon</b> 263:13 264:21 <b>ICV</b> 222:11 <b>IC50</b> 173:5 <b>IC50s</b> 173:11				

112:1 141:17	238:19 241:9	<b>industry</b> 374:2,7	<b>inhibited</b> 172:4	170:22
142:1 143:14	243:8,13 247:5	379:3 380:22	<b>inhibiting</b> 171:19	<b>intake</b> 29:14 54:4
144:20 145:15	259:10 260:11	<b>ineffective</b> 173:14	<b>inhibition</b> 145:9,13	<b>integral</b> 32:19
146:2,11 148:11	413:16	<b>infant</b> 349:3	173:3 175:21	<b>integrate</b> 85:3
160:16,22 162:17	<b>indicates</b> 235:11	<b>infants</b> 116:12	199:12 215:12	<b>integrated</b> 84:20
165:16 167:14,18	236:15 386:17	310:4	232:3	85:16 385:10
167:22 168:1	421:16	<b>infection</b> 348:1	<b>inhibitor</b> 170:17	<b>integrating</b> 60:11
171:13 172:14	<b>indicating</b> 172:7	356:3	173:5 255:3	60:12,19
175:21 195:9	197:10	<b>inference</b> 297:12	394:18	<b>integrity</b> 100:6
207:9,19 211:10	<b>indication</b> 244:2	<b>inferences</b> 295:15	<b>inhibitors</b> 171:17	<b>intend</b> 178:5
211:20 212:5	317:4	<b>inferred</b> 116:15	173:14	<b>intense</b> 23:22 28:21
214:14 248:3	<b>indicator</b> 395:7	<b>infertility</b> 347:13	<b>inhibitory</b> 172:21	80:15
330:7 331:5 353:9	<b>indirectly</b> 390:4	<b>influence</b> 203:7	<b>inhibits</b> 142:9	<b>intensity</b> 28:15
355:14,21 356:2	393:21	213:9 220:17,18	215:2	308:2 329:21
388:10 391:6	<b>indistinguishable</b>	<b>influenced</b> 104:3	<b>initial</b> 39:8,10	382:3
392:6 401:21	272:5	<b>influences</b> 72:9	40:14 94:7 207:8	<b>intensive</b> 75:13,18
415:7 416:22	<b>individual</b> 22:4	<b>influencing</b> 218:22	398:18 399:15	83:22 101:4 141:8
<b>increased</b> 47:18	23:1,14 144:1	<b>influential</b> 370:10	<b>initially</b> 49:13	306:18
59:4 103:16	273:11 284:11	370:11	214:1	<b>intent</b> 188:11
144:21 148:15	289:13 306:5,22	<b>inform</b> 182:9	<b>initiated</b> 125:11	377:17
152:7 153:17,20	340:4 351:6	<b>information</b> 25:11	136:16 139:10	<b>intentionally</b>
154:5,7 164:21	373:22	30:7 54:1 105:22	424:13	378:13
192:16 201:21	<b>individually</b> 296:21	177:22 186:6	<b>initiates</b> 199:21	<b>inter</b> 371:1
347:22 356:3	297:6	188:20 192:18	<b>initiating</b> 403:4	<b>interact</b> 88:6 226:2
357:15 384:21,21	<b>individuals</b> 97:22	239:22 246:11,18	<b>initiation</b> 160:6	<b>interacting</b> 171:8
388:14 391:5	299:5 407:22	248:18 258:12	408:7 413:14	<b>interaction</b> 7:18
392:11,13	<b>induce</b> 163:6	262:1 266:16,22	414:1 425:3	170:15 179:7
<b>increases</b> 162:6	165:21 172:2	267:1 298:14	<b>initiator</b> 399:8	185:17
200:8 207:14	174:17,18,20	299:17 306:15	424:5	<b>interactions</b> 7:13
208:12 214:7	175:14 198:18	311:21 318:13	<b>initiators</b> 424:7	<b>intercept</b> 37:20
215:15,19 216:7	215:4 252:10	323:15 328:4	<b>injection</b> 208:11	39:20 45:12 46:7
228:16 303:18	385:21 402:18	369:8,14,15 370:8	<b>innovating</b> 381:12	58:5
352:19 394:22,22	<b>induced</b> 138:20	370:10,12 377:18	<b>input</b> 365:4 374:22	<b>interest</b> 9:4 44:2,17
<b>increasing</b> 102:9	190:9 195:5	383:6 386:16	<b>inquire</b> 135:1	45:20 207:17
146:15 407:17	214:20 215:1	398:3 413:6 414:6	<b>INSECTICIDE</b> 1:3	245:1 257:13
415:16 424:11	<b>inducer</b> 402:20	417:12,22,22	<b>insecticides</b> 351:21	265:1 266:20
<b>independent</b>	<b>induces</b> 136:7	418:11 419:11	<b>insights</b> 93:15	272:18 310:12
350:11	154:12 253:22	<b>informative</b> 253:3	<b>insist</b> 113:22	379:3
<b>independently</b>	<b>inducing</b> 167:10	253:9,9	<b>insoluble</b> 168:20	<b>interested</b> 29:18
218:19 220:6	390:13	<b>informed</b> 93:8	<b>install</b> 380:6	57:17 58:19 86:9
348:14 349:16	<b>induction</b> 151:10	<b>ingredient</b> 106:12	<b>installed</b> 328:15	180:17 187:8
<b>Indiana</b> 357:9	159:10 165:22	<b>ingredients</b> 108:13	<b>instance</b> 17:20	189:12
<b>indicate</b> 21:3 202:3	166:7 168:8	109:14 111:18	122:12	<b>interesting</b> 106:11
258:16 386:21	173:21 230:16	<b>inhalation</b> 359:7	<b>instances</b> 208:21	143:19 160:2
<b>indicated</b> 149:17	<b>indulgence</b> 339:11	396:11,18 397:5,6	<b>Institute</b> 7:2 9:20	235:12 240:14
155:17 157:7	369:6	<b>inhibit</b> 197:12	<b>insufficient</b> 390:20	264:20 299:16
205:10 209:2	<b>industries</b> 104:6	216:20 219:19	<b>insults</b> 168:14	357:22 402:12

<b>interestingly</b> 53:14 208:15 269:14	44:12,14 45:6 60:22 76:2 271:2 273:5,5,6,6 274:6 351:8 354:8	331:13	<b>January</b> 341:20	262:15 298:17 323:5 364:11 405:2,5 406:3 410:14
<b>interests</b> 258:4	<b>interview</b> 54:12,17	<b>involvement</b> 395:4	<b>Jason</b> 355:10	<b>keeping</b> 167:1
<b>interfere</b> 172:12 346:12	<b>intra</b> 371:1	<b>involving</b> 365:6	<b>Jay</b> 368:14 373:3,7	<b>Ken</b> 5:3,14 30:5 57:14 65:8 67:9 405:11 416:16
<b>intermediate</b> 283:4 313:6	<b>intracellularly</b> 180:11	<b>in-depth</b> 388:18	<b>Jean</b> 2:15 6:20	<b>Kenneth</b> 1:18,21 2:3
<b>intermittent</b> 162:12,14	<b>intraperitoneally</b> 212:16	<b>in-dwelling</b> 254:14	<b>JEG3</b> 172:20 173:18	<b>Kentucky</b> 99:7,13 99:14,15,16,18
<b>intermittently</b> 294:15 362:2	<b>introduce</b> 5:13 212:10	<b>Iowa</b> 126:8,8	<b>Jennifer</b> 339:14 341:3 365:14,16	<b>kept</b> 206:9 234:7,7 393:17
<b>intermixed</b> 365:3	<b>intrigued</b> 176:9	<b>IRED</b> 327:22 388:7	<b>Jere</b> 97:5 99:11,12 112:22	<b>Kevin</b> 2:13 7:20 128:6
<b>internal</b> 204:13	<b>introduce</b> 5:13 212:10	<b>ironically</b> 64:4	<b>Jerry's</b> 226:15	<b>key</b> 51:6 66:14 95:12 133:17 142:6,18 145:17 152:10 216:18 275:14 389:18 390:1,3,7,12,17 390:22 391:4 392:1,4,10,12,15 392:17,21 393:2,4 393:5
<b>international</b> 140:22 152:20 269:4 325:6 342:6 370:14	<b>introducing</b> 11:8 194:14	<b>irrelevant</b> 416:14	<b>Jim</b> 135:17 162:22	<b>keynote</b> 260:18
<b>interpolate</b> 282:5	<b>introduction</b> 109:13 111:17 255:13 267:9	<b>irreparable</b> 346:20	<b>job</b> 40:20 51:7 57:22 58:1 129:8 129:21 269:20 277:2 300:1 303:22 304:22 341:20 364:16	<b>kg</b> 185:2 189:17,20 190:15,22 192:3 235:14 255:17,18
<b>interpolated</b> 13:18 14:6 26:2 31:11 74:17 273:3 291:10 321:16	<b>Introductions</b> 3:6	<b>irreversible</b> 347:21	<b>jobs</b> 121:18 171:10	<b>kick</b> 182:7
<b>interpolating</b> 65:11	<b>introductory</b> 183:7	<b>isolate</b> 86:16	<b>Joe</b> 4:4 134:1 324:7 408:15	<b>kids</b> 114:13 315:20
<b>interpolation</b> 12:16 63:8 290:13,14,18 290:22 305:14,19 306:2 307:2	<b>intuitive</b> 84:2	<b>isolated</b> 296:16	<b>John</b> 1:21 5:18,19 153:9	<b>kill</b> 121:19
<b>interpolations</b> 290:4	<b>inventory</b> 102:13	<b>issue</b> 32:12 86:8 125:19 158:5 159:3 181:15 325:5 327:14 338:21 341:16 375:13 385:12 386:10,16 404:11 405:4 408:6,7 417:12 423:11	<b>Joseph</b> 2:22 236:9	<b>killer</b> 238:22 242:16
<b>interpret</b> 73:7,8 74:10 91:14 159:13 160:7 413:12	<b>inverse</b> 62:9	<b>issues</b> 9:1 78:16 88:3 92:16,20 93:1 113:20 114:11 115:19 116:21 129:3,11 149:2 158:10 259:2 325:21,21 326:8 328:9 329:1 329:2 335:16 371:15 374:14,17 374:20 375:6,11 375:17 379:2 404:1	<b>journal</b> 352:22 365:22	<b>kills</b> 368:19
<b>interpretation</b> 93:12 134:16 158:11 416:21	<b>invested</b> 104:7	<b>item</b> 274:20	<b>judged</b> 285:3	<b>kilogram</b> 195:13 201:5,14 202:16 206:15,18 207:14 207:16 209:10 211:8 212:3 213:22 239:16 241:5,7 242:4,10 253:15 309:6 310:8 311:10 312:21 313:7,15 313:18 314:2
<b>interpreting</b> 169:16 395:22	<b>investigate</b> 136:18 257:21	<b>iterations</b> 354:20	<b>judgment</b> 369:5	
<b>interrelated</b> 265:19	<b>investigated</b> 220:6 238:7 255:21	<b>I.D</b> 149:10	<b>July</b> 116:8 139:8 188:22 246:1 248:1 266:6 270:18 357:17	
<b>interrelationships</b> 394:13	<b>investigating</b> 27:12 257:16	<b>i.e</b> 143:12 144:9 385:3	<b>jump</b> 356:16 404:10 417:1	
<b>interrupted</b> 391:2	<b>investigations</b> 139:5 180:21 239:9 247:19		<b>Jumping</b> 348:8	
<b>interval</b> 61:1 78:1 250:17 291:2 351:22	<b>investigators</b> 243:9		<b>June</b> 187:22	
<b>intervals</b> 14:17 15:15,16,16 18:21	<b>investment</b> 118:5		<b>jurisdictions</b> 299:8	
	<b>invite</b> 383:19		<b>K</b>	
	<b>invited</b> 134:14		<b>K</b> 45:17	
	<b>inviting</b> 119:16		<b>Kannan</b> 2:10 9:9	
	<b>involve</b> 244:13		<b>Kansas</b> 97:5,6,7,12 98:5	
	<b>involved</b> 22:12 84:14 86:2 105:18 107:14 114:5 117:8 119:13 123:18 129:2 194:20 217:16 224:9 240:18 246:8 257:1		<b>keep</b> 23:5 32:21 33:5 71:12 169:15 176:17 183:12	
		<b>J</b>		
		<b>J</b> 2:5,16,17,18 383:5		
		<b>James</b> 136:3		
		<b>Jan</b> 6:6		
		<b>JANICE</b> 1:22		

320:10,19 402:3 402:13 415:9,10 <b>kilograms</b> 322:21 322:22 <b>kilometer</b> 402:7 414:21 <b>kind</b> 10:4 11:4 15:22 19:20 24:11 26:20 27:5,10 28:13 30:2 36:4 36:18,22 40:7,13 42:12 46:19 48:18 50:5 64:2 65:9,10 65:13,16 69:17 86:15 89:8 90:20 129:18 140:2 157:1 185:22 230:19 233:5 234:12,13 235:7 235:17 254:16 257:19 277:14 280:21 286:8 289:5 295:9 296:2 307:11 308:8,12 314:15 318:8 365:7,8 378:4 379:12 380:1 381:9 382:17 402:8 403:5 405:5 406:18 415:4,13 418:11 420:4 423:18,20 425:4 <b>kinds</b> 48:22,22 89:12 180:19 257:21 358:6 375:3 378:8 379:2 381:19 416:20 420:1 424:7 <b>kinetics</b> 178:3 <b>King's</b> 7:21 <b>Kligerman</b> 149:21 <b>knew</b> 191:12 337:4 <b>knobs</b> 88:12 <b>knock</b> 172:21 174:10 <b>Knoth</b> 96:20 99:6 99:10,12	<b>know</b> 19:21 24:12 25:11 28:2,7 29:10,19 30:15 31:5,9,17 43:3 53:22 55:18 57:1 59:14 61:3,11 62:6 63:2 68:19 69:17,20 70:1 71:9 72:13 73:21 74:11 75:2 77:2 80:1,13,13,16 83:6,21 84:6,11 85:13 88:15 91:8 93:7,9 98:22 99:1 103:15 113:14 114:18 115:10 116:14 117:4 120:17 121:12 125:8,9,12 126:2 127:15 128:2,21 128:22 129:5,7,9 129:11,13,18 130:17 131:3 132:5,6 136:9 141:20 158:10,22 161:18 162:1,9,11 162:19 167:2 177:1,21 179:10 180:14 181:2,7,9 183:2 213:9 215:14 216:21 219:14 221:13 222:3,10,12 229:7 229:9,14 230:5 231:17 256:15 257:2,4 262:4 266:7 267:3 289:19 292:4,6 293:14 294:3 295:5,21 298:9 299:19,20,20 300:11 303:20 304:9,9,10 308:3 316:13 317:5,12 318:3 324:2 326:20 332:17 339:11,12 341:6	342:22 343:2 346:8 347:7 348:6 348:14 357:19 359:4,13,17,22 360:3 364:5 370:16 379:22 380:9,15 382:4,11 382:14 401:15 403:7,15,17,18,22 404:15 405:14 408:21 410:10 411:10 413:21 414:18 415:3,4,12 415:14,21 416:1,8 416:12 417:1,19 417:20 418:2,4,7 418:13 420:2,7 421:16 422:19 423:7,13 424:5,16 425:12 <b>knowledge</b> 54:18 65:10 93:4 272:13 280:15,16 <b>known</b> 42:10 68:6 142:12 151:1 170:16,22 196:22 292:1 327:4 344:19 <b>known/unknown</b> 27:5 <b>knows</b> 90:3 <b>kriging-type</b> 55:13 <b>Krishnan</b> 2:10 9:9 9:9 31:2,3 319:6,7 319:17 320:3 321:3 322:7,14 392:7 398:7,8 405:7,8 410:5,7,8 411:20,21 421:6,7 423:1 424:21 <b>Krishnan's</b> 416:10 <b>K.H</b> 2:12 <b>k0</b> 57:21 <hr/> <b>L</b> <hr/> <b>L</b> 2:7 <b>lab</b> 190:1 194:2	398:9 <b>label</b> 104:9 121:5 125:14 130:21 359:10 <b>labeled</b> 89:18 106:16 114:6 130:19 244:13 <b>labels</b> 114:8 <b>labor</b> 83:17 84:6 101:14 <b>laboratories</b> 370:21 <b>laboratory</b> 151:3 189:13 347:11,17 371:2,10 387:14 <b>laboratory's</b> 151:16 <b>labs</b> 218:3 <b>lack</b> 147:4,4 224:15 327:21 355:4 412:15,17 415:19 415:19 421:12 <b>lacking</b> 123:21 <b>lactation</b> 187:1 191:2 <b>lactational</b> 256:19 <b>lactationally</b> 187:4 <b>laid</b> 420:4,6 <b>lakes</b> 104:2 261:11 <b>land</b> 57:4 100:8 102:12 105:20 114:15 <b>laptop</b> 96:12 <b>large</b> 21:1 107:5,15 109:18 111:5 134:6 149:6 258:22 268:20 287:2 290:16 291:14 308:1 316:17 317:3 372:10 411:8,13 411:14,15 <b>largely</b> 104:2 208:7 268:8 <b>larger</b> 29:6,22 169:8 200:14 311:17 314:20	346:2 <b>largest</b> 103:19 108:4 <b>larvae</b> 355:17,22 <b>larval</b> 356:2 <b>lastly</b> 212:9 216:10 382:7 <b>latch</b> 406:4 <b>late</b> 187:21 274:19 383:16 <b>latency</b> 143:12 424:12 <b>latest</b> 151:20 <b>Laughter</b> 324:18 <b>Laura</b> 96:20 99:6,6 99:9,12 105:12 <b>law</b> 377:22 <b>lawn</b> 358:21 360:14 360:21 <b>lawns</b> 102:7 361:1 <b>Laws</b> 192:5 <b>layered</b> 90:14 <b>lays</b> 398:17 <b>LCMS</b> 204:4 209:2 217:11 218:6 226:10 227:15 <b>lead</b> 83:2 134:5 136:13 360:18 387:20 416:2 <b>leading</b> 103:22 104:1 152:11 258:8 386:19 390:5 <b>leads</b> 184:21 346:4 384:15,20 <b>learn</b> 92:21 339:3 354:20 <b>learned</b> 34:14 304:8 339:4 <b>leave</b> 51:14 256:10 309:18 316:22 317:18 318:10 325:21 405:8 <b>leaving</b> 101:8 <b>LeBLANC</b> 1:22 6:11,11 131:2,5 131:12,16,22
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

132:10,13,20	281:16 292:12	<b>LH</b> 142:9 145:9,13	41:10,16 394:16	381:19
133:3 223:13,14	309:7,19 311:5,7	147:4,8,13 148:10	<b>likelihoods</b> 60:1	<b>link</b> 95:13 351:12
224:14 252:22	311:10 312:11	153:15,16,17,17	<b>likewise</b> 102:17	353:22 354:9
253:1 407:15,16	315:4,11 318:15	154:22,22 155:3	188:8 190:22	355:2
<b>led</b> 263:6 270:21	318:16 337:1,5	160:15,19,20,22	313:22 315:8	<b>linking</b> 95:12
273:13 394:7	352:12 361:20	161:7,21 162:5,13	<b>limit</b> 47:20 59:15	<b>links</b> 359:18
<b>Lee</b> 2:12 8:17,17	371:1 381:4 382:2	184:21 185:6,13	59:16 131:8 132:2	<b>liquid</b> 203:18
25:20,21 26:11,17	390:19	186:5,10,19	132:22 292:7	<b>list</b> 113:12 128:1
51:17,18 52:2	<b>levels</b> 36:9 47:10	187:11 188:3	309:2,13,15,16	267:2 335:9 341:3
55:7,8 68:4,5 74:3	50:12,14,18 58:6	189:14,19 190:3,9	312:22 317:16,20	<b>listed</b> 51:1,4
85:7	59:8,14 61:12	190:13,15,20	317:22 332:2	<b>listening</b> 257:12
<b>left</b> 14:16 22:20	117:16 121:3	191:17,18,20	<b>limitations</b> 257:18	307:12 380:4
24:12 46:12,14	122:19 127:3	192:21,22 194:4,7	401:7	393:14
51:10 101:20	130:17 131:7,14	195:5,9,13 197:1	<b>limited</b> 284:16	<b>lists</b> 51:15
143:13 162:1	132:1,21 154:3	197:2,3,8,12,16	288:7 369:19	<b>liter</b> 323:1
195:8 225:13	155:6 160:19	198:18 199:2,7,12	<b>limiting</b> 89:11	<b>literally</b> 98:1 170:2
241:5 324:2 384:4	162:14 165:11	199:18,22 200:1,4	205:3	<b>literature</b> 24:17
<b>left-hand</b> 267:11	171:13 172:22	200:8,20 202:7	<b>limits</b> 101:14 269:3	25:9 79:9 95:4
<b>legislations</b> 300:8	174:13,14,15	212:7,8 214:17,20	308:13,14,19	141:20 155:22
<b>legitimate</b> 116:18	181:3,8,17 182:3	215:1,2,4,7,10	312:9 313:10	171:7 224:5
<b>lending</b> 114:3	184:21 185:3	216:12,13 217:7	318:20	249:14 329:18
354:10	186:4,12 201:19	219:6 220:1,14	<b>Linda</b> 2:18 8:14	387:11 394:21
<b>length</b> 103:7 233:4	204:2,11,11	230:1,12,12 231:6	65:12 234:6	395:16 397:7
273:3 391:12	205:22 209:5,10	232:2,4 249:11	297:14 420:13	409:21,22 410:13
<b>lengthens</b> 384:20	210:13 211:12,18	384:18 390:14,15	<b>lindane</b> 354:14	420:3
<b>leptin</b> 233:4	212:19 214:18	390:17,20 394:19	<b>Linda's</b> 301:6	<b>liters</b> 313:19
<b>Leroux</b> 171:14	215:21 216:9	395:13	302:14	322:21,22
<b>lessen</b> 100:11	217:10 221:13	<b>lies</b> 120:2	<b>line</b> 46:10 60:5	<b>little</b> 10:4,7 11:3,4
<b>lessening</b> 384:17	223:19 224:18,20	<b>life</b> 115:14 118:1	93:13 129:19	12:10 16:22 17:8
<b>lesser</b> 133:5 247:2	226:6,7,20 227:3	120:20 144:10	157:5,9,19 164:19	17:9 18:5 20:3
<b>letter</b> 373:12	227:5,6 228:1,14	146:21 186:11	165:1,6 167:10	32:10 40:22 41:13
<b>let's</b> 4:3 60:17	228:18 235:8	222:6 345:1	170:10 241:10	41:18 42:1 85:9
69:20 74:9,14	238:18 248:3,5,8	346:18 347:15	268:4 269:8 335:5	107:18 117:19
96:18 160:5	248:16 253:4,6,11	358:13 361:3	335:14 379:14	164:12 173:10
188:13 232:11	306:12 309:20	368:15 373:7,21	393:3 397:22	194:1,15 202:2,9
261:9 264:5	310:1 312:2,14,16	374:12 399:20	398:2 403:8	203:10 206:7
290:15,19 320:18	312:20 313:5	<b>lifelong</b> 347:6	<b>linear</b> 12:16 242:19	210:19 213:2
330:11 405:2,5	314:10,15 315:2	<b>lifetime</b> 309:2	273:2 290:4,13,14	230:2 237:10
418:13 423:14	317:6 318:11,18	344:6	305:13,19 306:1	239:8 259:5
<b>level</b> 23:14 35:9	319:2 322:1 330:4	<b>light</b> 190:11 250:13	307:2	263:13 267:13
40:12 45:17 46:4	332:15 334:17	372:2 394:7	<b>linearly</b> 13:1	280:7 289:4 291:7
47:3 59:1 61:18	347:2 352:7 353:1	399:21 414:11	291:10	296:12,13 300:16
62:11,15 79:5	358:21 359:18	<b>lightly</b> 115:4,17	<b>lines</b> 28:18 144:1,5	324:5 326:15
132:5,14 181:21	360:19 361:17	123:15,17	144:5 163:5 164:7	330:5 334:1
207:13 227:4	363:3,6 384:21	<b>lights</b> 250:18	164:9 171:2 174:1	337:21 355:9
239:11 251:19	390:20 396:9	<b>likelihood</b> 38:20,21	234:18 241:15	357:11 372:12
259:21 264:15	398:21	38:22 39:5 40:17	267:18 286:7	379:12 402:1

403:14 407:11 415:13,17,22 416:6 <b>live</b> 49:19 50:3 73:21 97:5 99:4 <b>lived</b> 163:14 <b>livelihood</b> 100:7 <b>liver</b> 172:5 179:13 <b>livers</b> 171:14 <b>lives</b> 114:15 <b>Liz's</b> 392:19 <b>load</b> 126:13 358:22 <b>loaded</b> 96:12 <b>local</b> 35:3 <b>localized</b> 34:17 357:9 <b>located</b> 1:17 339:17 342:9 <b>locations</b> 295:16 297:11,12 <b>locked</b> 230:17 <b>LOEL</b> 253:7 <b>log</b> 37:18 38:20 39:5 41:10 42:20 61:4 <b>logical</b> 108:10 293:10 <b>logistic</b> 351:19 <b>logistically</b> 23:11 <b>London</b> 7:21 <b>long</b> 79:16 90:3 98:13 130:8 175:14 211:16 215:22 233:1 255:18 324:21 338:14 339:12 340:1 <b>longer</b> 17:9 21:5 32:15 33:1 53:5 56:21 185:2 243:9 250:22 271:6 280:12 298:2 312:6 313:1,6 314:1 315:8 <b>longer-term</b> 17:17 <b>longest</b> 209:8 <b>longevity</b> 347:22	<b>long-lasting</b> 347:20 <b>long-term</b> 33:3 283:4 348:3 <b>look</b> 10:15 15:6 16:6 18:9 19:4,7 19:10 20:15,18 23:14 25:9 29:2 33:11 35:7 51:20 52:12,16 56:22 57:7,12 59:7,12 67:4 72:16 73:21 74:6,9 75:11,15 75:22 76:8,14 78:17 79:11,12,20 85:11 87:6 88:10 88:11,15 110:1,12 116:16 117:10,11 120:15 124:4 127:14,18 147:13 148:9 165:1 166:1 169:18 170:6,8 207:5 224:4 225:3 236:19 239:20 241:17 249:10 265:10 268:16 270:17 277:8 286:17 297:4,22 305:8,9,11 306:10 306:15 307:9,14 307:15,17,18 309:13 312:5 313:4,22 314:18 317:20 332:9 341:10 345:16 364:13,14 379:17 380:19 401:20 403:12 405:13 406:3 414:4,14 417:13 418:1 420:3,18 <b>looked</b> 12:20 13:7 13:13 14:16,20 18:2,14 25:12 29:5 35:5 37:11 42:4,5 74:16 79:11 84:18 157:15 160:17	166:20 179:3 183:2 229:17 253:18 264:17 267:6 271:15,17 276:12 285:17,22 286:6 292:19 302:8 369:2 401:14 405:12,14 405:16,17,22 413:11 414:11,12 416:12 417:8 <b>looking</b> 11:22 12:1 17:1 19:20 22:2 23:8 27:17 29:15 34:21 37:14,16 53:6 56:18 64:18 71:6,10 72:10 74:5 75:16 77:1 86:18 89:9,15 96:2 124:14 127:4 127:21 138:18 142:20 143:13 187:14 191:8 201:11 202:10 219:18 220:12 226:7 239:11 243:5 249:3 258:11 279:4 281:3 288:11 291:8 292:14 295:12 297:11 302:6,13,14,17,21 315:9 334:21 337:16 358:10 379:1 380:9,18 400:11 402:14 405:3 413:10 417:7 418:20 <b>looks</b> 15:2 20:10 22:4 40:4 117:13 128:18 146:8 200:11 202:13 263:10 <b>loop</b> 391:1 <b>loosened</b> 100:19 <b>Lorenzo</b> 344:3 <b>lose</b> 90:7 167:3	<b>loses</b> 147:14 200:4 <b>losing</b> 290:8 <b>loss</b> 154:1 186:7 199:14 216:16 <b>lost</b> 11:5 115:3 208:13 <b>lot</b> 29:18 35:6 39:14 52:14 55:3 57:9 58:21 65:22 67:22 70:12,18 75:13 80:13 82:13 84:2 88:2 94:22 95:1,18 105:17 108:17 113:17 123:22 124:16 129:9 158:9 178:18 221:6 234:5 235:19 297:22 312:19 318:14 325:22 329:20 339:4 341:5,8 363:5 366:13 388:1 411:16 413:21 414:9 415:18 417:20 419:20 420:1,9 421:1 424:15 <b>Louis</b> 290:18 <b>love</b> 67:21 <b>low</b> 13:5 47:2 50:12 50:12,17 60:4 68:1 101:18 106:18 182:12 185:1 204:8,11,11 209:21 210:3,13 226:7 242:2,7 277:5 286:2 331:18 332:1 337:21 346:7,10 346:19 347:2 354:12 363:6 418:13 <b>lower</b> 16:8,11,12 22:11 44:6 45:16 48:6 111:22 126:11 132:21	146:6 182:11 185:3,4 194:17 211:16 253:11 270:12 272:6 280:11 285:2 313:22 346:5 <b>lowest</b> 16:13 20:2 59:1 225:16 253:14 332:18 353:17 414:21 <b>Lowit</b> 69:14 81:14 92:3 93:20,21 304:12,13 406:7 409:11 410:9 411:3 <b>luck</b> 105:9 <b>lucky</b> 378:20 <b>Luebke</b> 237:3 <b>lunch</b> 10:19,20 96:18 133:21,22 182:22 <b>luteinizing</b> 384:18 <b>luxury</b> 103:12 <b>lymphocyte</b> 244:15 247:16
<b>M</b>				
<b>M</b> 1:18,21 383:5 <b>machinery</b> 101:15 <b>magnitude</b> 173:20 260:8 261:5 266:19 381:5 <b>main</b> 78:16 125:13 328:10 <b>maintain</b> 254:13 <b>maintained</b> 114:9 207:20 211:13 212:21 <b>maintaining</b> 102:1 <b>maintains</b> 147:15 147:16 <b>maintenance</b> 395:12 <b>major</b> 94:22 99:19 111:7 153:8 240:16 246:4 252:11 327:14				

391:19 411:5 422:11 <b>majority</b> 226:19 <b>maker</b> 66:5 <b>makers</b> 46:17 47:1 49:11,18 50:11,19 58:7 <b>making</b> 4:20 37:7 44:5 46:18 66:13 73:16 87:8 89:12 93:5 96:10 134:17 137:9 229:1 255:13 281:17 298:6 316:11 410:17 <b>male</b> 140:18 202:12 207:22 208:7 210:17 215:18 217:11 229:8,17 243:5 249:3 348:21 388:11 396:17 401:22 <b>males</b> 140:9,17 216:2 223:17 224:8,12 227:3,8 249:15 386:6 <b>mammals</b> 163:11 <b>mammary</b> 142:1 143:10 145:15,22 146:6 152:8 154:10 157:8 384:22 388:15,19 389:9 391:6,6,20 393:5,11 394:22 395:5 396:20 397:7 398:19 401:5 402:18,20 403:1 <b>manage</b> 107:13 <b>managed</b> 262:14 262:16,18 <b>management</b> 105:18 107:3 333:17 <b>managers</b> 81:12 82:8 <b>managing</b> 274:3	<b>mandated</b> 264:10 <b>manner</b> 18:22 145:4 242:19 294:17 394:5 <b>manufacturers</b> 373:9 <b>manuscripts</b> 165:3 365:21 <b>map</b> 33:16,17,19 33:20,21 34:1,6 <b>margin</b> 255:14 319:10,20 321:6,8 321:15 <b>margins</b> 258:21 317:2 <b>Mark</b> 118:1 <b>markedly</b> 144:12 154:5 <b>market</b> 106:13 <b>marketed</b> 106:14 <b>Markov</b> 45:7 <b>marks</b> 414:9 <b>Marshall</b> 153:9 <b>Mary</b> 3:11 11:11 11:20 37:3 72:7 <b>Mary's</b> 36:18 <b>mass</b> 85:5 203:18 <b>massive</b> 34:8 121:22 260:9 262:6 <b>match</b> 393:1 <b>material</b> 134:7 183:12 271:9 <b>materials</b> 345:22 <b>maternal</b> 7:12 <b>mathematical</b> 36:3 <b>mathematically</b> 67:20 <b>Mathematics</b> 8:19 <b>matrix</b> 14:14 226:3 <b>matter</b> 96:15 100:21 102:2,4 236:2 293:18 297:20 299:11 304:18 318:4 323:21 376:1 377:8 425:17	<b>maturation</b> 191:2,9 191:22 <b>maturity</b> 191:7 <b>Maumee</b> 39:11 <b>max</b> 292:7,8 302:11 <b>maxima</b> 259:7 260:5 272:2 273:7 273:8 274:4 <b>maximize</b> 39:5 <b>maximum</b> 12:2 13:10,16 14:6,7,9 14:10 16:20 17:6 19:12 20:7 21:1 24:16 28:1 40:17 41:15 47:21 57:18 58:1,8 61:22 64:21 80:7 177:19 179:17 238:2 271:21 273:17,19 279:17 281:10 291:20 295:1 301:8,11,21 309:1 309:15,15 332:15 333:1 <b>maximums</b> 63:17 362:7 <b>McCoy</b> 349:15 <b>MCL</b> 259:18 264:15 316:5 322:10 326:21 327:12 328:17 329:1 333:5 335:2 362:22 363:3,8 <b>MCLG</b> 259:18 <b>MCLs</b> 326:19 <b>mean</b> 15:21 16:6,7 19:4,7 20:2,15,16 29:17 32:3 38:13 43:22 44:15 45:19 47:22 59:12 61:21 63:14 66:20 68:13 70:8 81:4,12 84:5 117:6 129:8 158:9 159:16 161:8 190:16 201:19 204:11 227:12,12 227:16 228:11	231:13 234:17 235:3 262:20 267:17,19 268:11 286:21 288:22,22 295:3,4,11,11,19 296:7 304:17,21 307:16 308:11 314:22 315:4 321:13 337:6,16 368:8 400:19 404:13,18 409:5 410:9,22 415:17 416:21 417:18,19 423:5 <b>meaning</b> 158:13 <b>meaningful</b> 139:13 182:14 <b>means</b> 74:15 173:13 227:8 303:14 313:12 337:19,21 360:12 405:11 <b>meant</b> 80:12 380:10,11 <b>measure</b> 58:11 89:16 185:6 190:13 203:13,19 204:4,6,9 205:22 208:4 210:13 218:5,6 221:1,13 221:21 225:18 232:14 233:4,4 239:18 240:8 243:19 247:3,20 300:21 <b>measured</b> 38:18 47:21 58:15 185:7 185:13 190:16 199:4 209:12 212:6 216:4,5 219:6,7 228:14 231:6 242:12,14 247:21 271:22 281:6 336:17 <b>measurement</b> 39:15 85:10 236:1 291:3	<b>measurements</b> 58:12 89:19,20 167:12 218:3 226:10 265:16 268:21 269:2 275:7 311:8 <b>measuring</b> 203:11 210:8,10 225:7,11 <b>mechanical</b> 104:16 <b>mechanism</b> 136:15 145:8 156:11,22 159:15,17 168:16 192:21,22 220:1,2 220:4 223:21 224:1 343:21 348:10 349:7 401:2 405:19 <b>mechanisms</b> 137:11,20 151:17 151:18 155:7 194:3 220:8,13 249:11 256:2 350:12,14 391:17 <b>mechanistic</b> 141:2 318:16 344:13 <b>media</b> 167:15 180:11 201:3 222:9,15 <b>median</b> 20:17 44:1 44:15 45:19 332:14,20 <b>mediated</b> 195:19 240:21 <b>mediating</b> 174:20 <b>mediator</b> 252:16 <b>Medical</b> 6:21 193:20 <b>Medicine</b> 6:8,17 193:21 <b>medium</b> 13:5 19:5 28:13 148:6 329:13 <b>medium-term</b> 32:22 <b>meet</b> 108:19 263:3 335:1 343:4 370:5 372:8
---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<b>meeting</b> 4:6 5:3,6 141:3,6 154:19 182:6 183:15 257:15 324:3 357:3 366:12,20 383:17 419:13	166:22 <b>mercury</b> 347:2 <b>mere</b> 118:13 <b>merely</b> 280:5 <b>merit</b> 158:13 <b>message</b> 48:21 166:7 167:6,12,22 172:21 317:1	<b>methodologies</b> 229:2 <b>methodology</b> 236:16 <b>methods</b> 3:10 9:13 11:13 12:12 13:13 74:9 79:20 109:8 169:18 236:12 255:5 295:22 336:12 349:22 370:16 420:22	276:10 <b>milieu</b> 149:3 <b>milk</b> 187:2 <b>milligram</b> 206:18 209:21 212:2 230:1 241:7 253:15 309:6 310:7 311:10 312:20 313:7,15 415:8,10	169:19 200:9 201:12 203:6 207:10 208:11 211:11 214:4 215:16 258:7 324:22 366:11 369:7,10,11,13 384:2,6
<b>meets</b> 81:17,18 <b>mega</b> 277:14,16 <b>member</b> 5:17,21 6:4,9,14 139:19 276:19 325:12,19 370:14 373:22	<b>messages</b> 223:16 <b>messenger</b> 165:11 165:17 <b>Messner</b> 3:15 11:16 35:20,21 52:1 53:12 54:10 58:3 59:3,18,22 60:7,12 61:6,10 61:15 62:10,18,22 63:2 65:21 67:6	<b>methomyl</b> 352:13 <b>metric</b> 96:2 <b>metrics</b> 189:6 <b>mgs</b> 189:17,20 190:15,22 192:3 235:14 255:17,18 <b>MHC</b> 254:22 <b>mice</b> 157:7,9,10 212:13,19 229:8 239:15 242:1 388:12	<b>milligrams</b> 185:2 195:12 201:4,14 202:16 206:15 207:13,16 209:9 211:7 213:22 239:16 241:4 242:4,10 314:1 320:10,19 402:3,7 402:13 414:21 <b>millimolar</b> 173:12 <b>million</b> 277:15 357:14 <b>millionfold</b> 315:3 <b>millions</b> 49:16,16 268:5	<b>mirror</b> 326:13 <b>misinterpret</b> 233:22 <b>missed</b> 106:19 113:5 221:10 290:5,5 <b>missing</b> 23:15 26:7 26:12 58:13,14 64:1 67:19 68:1 <b>mission</b> 62:5 <b>Mississippi</b> 6:8 118:2 298:21 <b>Missouri</b> 98:5 275:1,10 292:19 298:20
<b>membership</b> 97:22 <b>membrane</b> 176:11 176:21 <b>memories</b> 135:21 <b>men</b> 359:19 <b>Mendez</b> 310:11 313:8 384:7,8 404:20 405:21 407:5	<b>met</b> 349:12 369:1 <b>meta</b> 155:21 355:10 <b>metabolism</b> 163:10 164:13 177:13 178:2 <b>metabolite</b> 167:16 180:10 <b>metabolites</b> 163:20 164:3,4,18 166:2 166:6,13,18 167:8 168:4,5,11 170:13 171:1 172:12 173:9 178:15	<b>microbiologists</b> 419:21 <b>micromolar</b> 165:14 165:14 168:2,22 169:1,6,14 170:1 173:6 <b>micromolars</b> 169:10 <b>mid</b> 95:3 284:12 342:18 <b>middle</b> 15:3 19:5,5 20:1,19 39:15 48:10,14,20 187:21	<b>mind</b> 23:5 32:21 33:5,15 57:9 71:12 167:1 169:15 176:17 259:8 405:3,5 406:3 413:19 <b>minds</b> 70:19 <b>mineralocorticoids</b> 205:13 <b>minimize</b> 300:2 <b>minimizes</b> 101:7 <b>minimum</b> 101:19 <b>Minnesota</b> 6:21 119:22 <b>minor</b> 25:21 33:14 <b>minority</b> 423:21 <b>minute</b> 274:22 296:8 318:3 369:12 <b>minutes</b> 35:8 53:11 135:4 163:3	<b>mistake</b> 123:8 <b>mitigated</b> 334:14 <b>mitochondria</b> 170:7 205:1 <b>mix</b> 106:16 358:22 412:12 <b>mixed</b> 247:16 <b>mixture</b> 125:18 289:9 <b>mixtures</b> 86:14 356:13 365:7 <b>ml</b> 209:22 210:1,2 227:6,13 <b>MOA</b> 388:5 407:12 422:10 <b>MOAs</b> 406:6 <b>mode</b> 92:20 107:9 107:12 135:15 136:13 137:10 141:19,21 142:2 148:18 150:8,19 150:19 152:2,3,7 152:14 158:1,15 317:6 318:15
<b>mentioned</b> 34:15 131:5,18 177:14 181:13,14 199:16 241:22 242:16 245:18 274:21 275:17 292:5 312:22 319:13 332:11 335:7 348:4 357:1 369:12 374:14 421:14	<b>metabolize</b> 165:20 <b>metabolized</b> 175:10,19,19 <b>metabolizing</b> 164:10 <b>metal</b> 396:12 <b>metamorphosis</b> 350:4 <b>meta-analysis</b> 349:18 <b>method</b> 63:21 64:5 112:11 227:15 330:17,18 <b>methodological</b> 218:4	<b>Midwest</b> 81:20 97:9 266:1 306:17 307:6 312:1 329:14 330:9 <b>Midwestern</b> 330:2 <b>mike</b> 3:15 11:16 24:5 160:14 287:13 <b>miles</b> 275:17	<b>minutes</b> 35:8 53:11 135:4 163:3	
<b>mentioning</b> 303:16 <b>mercapturate</b>				

384:14 385:3,17 389:6,13 391:10 391:17,20 393:5 393:11 398:15 400:18 403:13 404:4,22 405:22 406:12 407:7,17 408:3 412:6 413:11,14 414:7 422:5	<b>modes</b> 148:19 152:16 388:22 389:3 406:1 <b>modest</b> 166:3 <b>modification</b> 156:17 194:9 220:8 <b>modified</b> 197:6 <b>modulates</b> 390:8 <b>moisture</b> 101:12 <b>molar</b> 173:13 <b>moldboard</b> 100:22 <b>molecular</b> 6:13 339:19 419:1 <b>molecule</b> 226:2 <b>moment</b> 274:9 <b>money</b> 130:16 <b>monitor</b> 363:16 409:21 <b>monitored</b> 56:12 56:21 362:1,18 <b>monitoring</b> 1:8 5:9 21:6,10 34:15,16 36:12,13 44:20 45:3 50:20 70:19 71:14 72:4,21 73:6,9 74:22 75:12,17 76:6,7 77:6 78:21 79:2 82:14,14 85:22 87:9,21 89:4,8,16 90:8,10,20 94:18 119:3 121:2 258:15,17 259:14 260:3,7 262:17,19 263:12,21,22 264:10 266:20 280:18 282:17 306:18 311:22 315:17 316:3 318:20 319:3 325:18 326:6,7 328:2,5 329:12 330:7,20,22 331:6 331:9 332:6 333:9 333:20 334:2,3,6 335:20 336:6	337:9 340:7 361:9 361:11 363:15,22 364:10 410:13 <b>monograph</b> 344:7 <b>Monte</b> 45:8 <b>month</b> 118:10 330:12 <b>monthly</b> 330:12 <b>months</b> 93:2,2 144:16 185:15 <b>Montreal</b> 9:11 <b>morning</b> 4:4,14 5:2 5:5 10:9 12:1 95:19 117:7 324:14 339:1,9 366:6 425:12 <b>Morseth</b> 185:11 310:9 <b>Mosquin</b> 269:4,7 279:14 290:11,11 294:11,12 295:13 295:18 <b>mother</b> 128:21 187:3 347:3 <b>mothers</b> 357:16 <b>mouse</b> 140:8 157:15 159:3,4 181:21 229:20 <b>move</b> 10:3 33:11 103:4 162:21 232:10 234:4 255:7 258:20 263:15 384:5 406:5,13 <b>moved</b> 263:16 284:18 <b>movement</b> 176:22 <b>moves</b> 103:6 269:17 410:20 <b>moving</b> 37:17 38:19 58:22 87:10 88:13,16,22 90:19 258:7 <b>mRNA</b> 197:22 <b>mulch</b> 101:20 102:7 <b>multi</b> 134:17	<b>multiple</b> 117:16 261:17 349:9 351:2 <b>multiplied</b> 320:11 <b>multiplier</b> 68:10 <b>multiply</b> 273:22 <b>multi-year</b> 273:4 <b>mutagenic</b> 389:13 <b>mutagenicity</b> 399:9 <b>mutually</b> 349:9 351:2 <b>M.D</b> 2:17	<b>Nebraska</b> 362:9 <b>necessarily</b> 68:10 162:16 220:17 224:7 226:6 231:1 291:19 410:22 <b>necessary</b> 101:3 250:8 334:7 <b>necessity</b> 103:12 <b>need</b> 4:18 23:1,14 27:21 68:10,14 72:4 73:22 76:14 77:11,13,20 79:20 80:6,16 83:3 86:11,20 87:10 88:12,16 91:8 92:16 93:14 94:20 114:11,16 125:5 126:3 127:14 130:12,14 148:20 183:6,11 218:17 236:9 243:14 257:21 282:14 293:8 295:5 316:21 317:7 327:11 334:13,20 380:2 414:8 417:22 418:20 <b>needed</b> 283:7 333:20 334:5 336:21 417:7 <b>needing</b> 361:3 <b>needs</b> 71:12 88:10 130:2 220:5 334:7 369:16 377:20 <b>negates</b> 393:9 <b>negative</b> 37:9,13 45:16 46:18,22 48:5,8,12 50:15 50:22 140:10,16 140:17,19 149:11 150:2,15 157:8,14 166:10 167:4,20 218:15,21 219:8 219:15 <b>negatively</b> 213:11 <b>negatives</b> 47:16 49:9,14 66:9
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<b>negotiated</b> 363:14	<b>neurons</b> 196:15,17 196:20 197:1,6,9 197:13,14,19 199:4,10 217:15 217:16 230:17,18 230:19,21	<b>node</b> 38:1,2 40:6,8 40:10 41:2,3,4,6 52:15	<b>noting</b> 335:16,21	251:12 278:8
<b>neither</b> 170:20 393:9	<b>neurotoxicity</b> 127:5	<b>nodes</b> 38:9 52:7,9 52:21 53:2,16	<b>notion</b> 129:16,19 346:2 373:17	281:17 299:7 322:15 335:7 359:2 364:16 393:1 421:3
<b>Nelson</b> 3:18 11:22 11:22 22:3 29:9 31:18 53:21 55:17 83:11	<b>never</b> 93:7 122:6 286:3	<b>NOEL</b> 253:7 255:17 313:1	<b>November</b> 184:13	<b>numerous</b> 348:16
<b>Nelson's</b> 93:9	<b>nevertheless</b> 189:22 403:9	<b>NOELs</b> 255:15 313:1	<b>no-detect</b> 67:14	<b>nutrient</b> 102:1
<b>neonatal</b> 347:15	<b>new</b> 95:5 106:11 109:13,14 111:12 111:18,18 116:2 116:16,16 125:18 125:20 130:7 136:1 137:5 138:6 151:7 152:22 243:8 255:19 266:1 323:15 328:18 369:22 385:10 386:16,21 387:13 398:9 399:3,6,10 400:18 409:14,21	<b>noise</b> 251:2 396:14	<b>no-effect</b> 192:2 306:12 309:6 311:10 312:20 315:1,3,10 318:11 318:18	<b>nutrients</b> 104:20
<b>nervous</b> 168:12 257:11 346:14 387:2	<b>newborn</b> 358:12	<b>non</b> 183:3	<b>no-level</b> 313:5	<b>Nu-may</b> 2:14 8:20
<b>nervousness</b> 100:2	<b>newer</b> 127:16	<b>non-cancer</b> 137:13 184:6,11	<b>NPA</b> 170:18	<b>N.W</b> 1:17
<b>nested</b> 22:9	<b>news</b> 120:15	<b>non-detects</b> 331:20 363:5	<b>NRDC</b> 116:4 404:15	<hr/> <b>O</b> <hr/>
<b>network</b> 36:2,4,15 36:19 37:16 42:19 50:5,6 51:3,22 53:9 96:19 97:15 97:15,22 105:14 133:13 336:3	<b>nice</b> 40:20 41:15 51:7,19 67:20,22 155:16 221:6 223:14 237:5 244:2,10	<b>non-drinking</b> 261:8,9 262:7	<b>NTP</b> 396:18 397:4	<b>O</b> 184:1,1,1
<b>networks</b> 3:14 11:18 51:19 55:8 68:6	<b>nicely</b> 240:11 253:2	<b>non-existent</b> 148:7	<b>nuance</b> 192:10	<b>Obama</b> 122:4
<b>neuradrenergic</b> 233:15,15	<b>nicer</b> 41:13	<b>non-genotoxic</b> 389:6	<b>nucleus</b> 196:21	<b>obesity</b> 154:3
<b>neural</b> 3:13 11:17 36:2,4,15,19 37:16 42:19 50:4 50:6 51:3,19 55:8 220:14 257:9,13 336:3	<b>night</b> 366:21	<b>non-profit</b> 325:6 339:16	<b>number</b> 14:22 18:2 18:13 26:6,6 34:5 39:3,3 46:6 68:8,9 75:14 85:19,20 119:5,8 121:4 124:10,14 141:8 149:6 150:3,11 169:8 171:7 179:15 186:8 194:6 198:5 200:12 201:21 203:8 205:3 209:15 213:10 221:22 225:10 229:13 240:12 253:12 254:20 278:16 281:13 290:16 295:1 303:22 305:22 309:10 320:19 336:21 351:10 354:13 356:17 371:21 372:10 374:14 377:21 381:6,12,13 411:10 412:14	<b>objective</b> 98:9
<b>neurobiologists</b> 304:4 315:15	<b>nighttime</b> 250:13	<b>non-specific</b> 238:3 243:12 397:19	<b>numbered</b> 392:21	<b>objectives</b> 335:1
<b>neurobiology</b> 7:10 304:10 305:1	<b>NIH</b> 237:17 353:8	<b>norepinephrine</b> 390:6,8,10	<b>numbers</b> 15:1,12 119:6 158:22 163:22 234:13	<b>obligation</b> 378:5
<b>neuroendocrinol...</b> 283:20	<b>nine</b> 271:17 276:9 285:19 362:5	<b>normal</b> 50:1 64:9 118:17 199:8 201:11 391:2		<b>obliterate</b> 195:13 196:1
<b>neuroendocrinol...</b> 7:12 154:14	<b>ninety</b> 121:6	<b>normally</b> 5:11 12:21 149:10 214:6 390:8,17		<b>obliterated</b> 231:9
<b>neuroendrocine</b> 7:14	<b>nineties</b> 121:6 130:20 284:13 326:20	<b>north</b> 6:13 107:21 108:1 109:20 110:7 135:18 136:4 163:1		<b>obliteration</b> 229:22 232:1
<b>neurological</b> 257:7	<b>nitrate</b> 88:5	<b>Northwestern</b> 7:11 218:11		<b>obscured</b> 122:6
<b>Neurology</b> 352:22	<b>NK</b> 245:11 251:18	<b>notably</b> 194:20		<b>obscuring</b> 122:19
<b>neuron</b> 195:17 197:15		<b>notches</b> 15:6		<b>observation</b> 163:4 163:8
<b>neuronal</b> 196:20 198:11		<b>note</b> 179:17 268:3 276:1		<b>observations</b> 26:2 26:4 136:8,20 290:16

<b>occasional</b> 166:15 166:17	298:11	<b>oncogenic</b> 413:15	161:21 228:9	<b>ovarian</b> 147:6,11
<b>occasionally</b> 166:16	<b>Oh</b> 355:8 372:22	<b>ones</b> 22:15,17	326:6 333:3	161:22 402:21
<b>occur</b> 30:16 39:22 42:2 54:5 75:4	<b>Ohio</b> 9:15	30:14 31:11 88:5	379:17 381:1	<b>ovariectomized</b> 140:15 159:17
120:7 127:2 129:1	<b>okay</b> 11:9 14:22	129:20 138:4	<b>optimistic</b> 373:17	190:9 195:22
200:21 201:12	18:16 19:14 25:16	239:2 252:18	<b>optimize</b> 39:4	211:9 402:19
211:2 293:12	25:19 28:5 33:13	286:3,4 288:14	<b>option</b> 333:17	<b>ovariectomy</b> 246:12,16,19
305:15 317:7	33:18,19 39:13,19	364:2 408:8 420:6	<b>options</b> 93:16	<b>ovaries</b> 390:18
359:5,9 381:21	40:3 41:17 43:20	<b>one's</b> 409:16	<b>ORD</b> 389:6	<b>ovary</b> 148:12 153:7
391:18	45:4 67:7 69:10	<b>one-day</b> 80:7	<b>order</b> 15:10 77:21	<b>overall</b> 45:16 46:3
<b>occurred</b> 121:5	80:4 83:3 93:18	241:18 259:12	110:1 222:4	58:1 93:19 242:18
122:16 155:1	96:17 131:12	307:14 308:21	268:19 287:18	305:15 315:13
188:18 198:20	158:4 162:20	311:5	298:16 305:11	400:10 414:6
347:15	177:10 182:4	<b>one-page</b> 267:8	324:8 328:12	422:1,3,15
<b>occurrence</b> 36:6,10	192:18 193:15,16	<b>one-week</b> 28:1	352:7	<b>overestimate</b> 17:8
37:20 38:7,11,15	193:18 202:1	<b>ongoing</b> 138:8	<b>organ</b> 238:18	<b>overlaps</b> 129:12
44:5 45:1,13,17	213:6 215:13	139:1 175:1	346:13	<b>overlay</b> 33:20
46:1,4,20,22 47:2	219:12,13,22	187:20 194:2	<b>organic</b> 102:2,4	<b>overview</b> 140:6
47:4 50:9,10,12	220:11,15,19	276:15 387:11	299:11,11	155:16 237:5
51:8 58:6 269:22	221:16,20 222:5	394:6 400:2	<b>organization</b> 139:20 343:5	<b>over-applying</b> 129:11
345:14	223:9,11 226:3	<b>online</b> 134:7	<b>organizations</b> 97:21 119:19	<b>ovulate</b> 161:20
<b>occurrences</b> 288:3	227:11,18 230:8	<b>onset</b> 191:2,9 231:7	<b>organized</b> 28:19	162:11
<b>occurring</b> 40:9	230:15 232:18	386:6,14 388:14	<b>organizes</b> 28:14	<b>ovulation</b> 390:19
164:13 180:13	233:2 234:22	<b>onward</b> 192:12	<b>organochlorine</b> 353:2 354:10	390:21
230:20 266:8	237:1 250:2,6	<b>open</b> 49:3 119:15	<b>organochlorines</b> 351:15	<b>ovulatory</b> 161:18
298:13 386:6	255:6 258:1,11	155:14 176:6	<b>orientation</b> 134:21	<b>O'Byrne</b> 2:13 7:20
<b>occurs</b> 105:2 168:6	270:21 284:4	341:2 404:8	<b>origin</b> 208:6	7:20 128:5,6,6
195:10 199:9	287:12 303:3,9	<b>opening</b> 3:6 185:8	<b>original</b> 102:22	229:5,19 230:9
208:10 346:16	311:13 319:3	187:9 191:8,12,22	286:10 288:4,7	231:2,11,19 232:8
<b>October</b> 35:5	324:1 338:15,18	<b>operate</b> 99:17	393:5 398:5	<b>o'clock</b> 323:19
<b>odd</b> 41:18	344:3 363:21	398:16 412:7	<b>originally</b> 210:11	
<b>odds</b> 155:9 351:21	366:9 367:7 393:2	<b>operating</b> 70:3,14	249:9	<b>P</b>
352:13,15,17	394:9 400:14	<b>operation</b> 190:1	<b>ought</b> 93:4 166:16	<b>package</b> 150:5
353:4,17,21 354:4	415:15	<b>operative</b> 136:15	267:2 382:5	367:2
<b>odor</b> 329:2	<b>old</b> 100:22 130:6	385:5,17	<b>outcome</b> 98:8	<b>packaged</b> 356:13
<b>offense</b> 91:10	249:20	<b>opinion</b> 316:18	236:4	<b>packet</b> 134:6 137:1
<b>offer</b> 92:2 93:15	<b>older</b> 186:12,18	399:11 401:9	<b>outcomes</b> 257:22	138:4
<b>office</b> 5:16 35:21	381:13,14	<b>OPP</b> 12:11,18 13:9	349:5,20 353:5	<b>page</b> 319:9 337:12
308:18 309:22	<b>oligo</b> 161:17	13:13	357:4	359:2 389:20,21
322:13 382:21	<b>oligomenorrhea</b> 162:10	<b>opportunities</b> 374:3	<b>outlet</b> 108:3	392:3 423:2
<b>official</b> 2:22 4:6	<b>Ominous</b> 344:14	<b>opportunity</b> 30:20	<b>output</b> 101:14	<b>pages</b> 340:17
309:19	<b>onboard</b> 224:10	105:21 164:7	251:10	367:19,19
<b>offspring</b> 249:4	<b>once</b> 16:2 66:20	237:2 259:5	<b>outside</b> 110:13	<b>paid</b> 364:7
<b>off-patent</b> 98:17	72:17 74:7 90:7	323:15 325:3,16	<b>outweigh</b> 70:5	<b>pairs</b> 173:15 174:6
<b>oftentimes</b> 230:15	335:18 344:15	339:3 356:16		<b>panel</b> 1:4,15 5:12
	378:16 382:17	378:17		
	383:11	<b>opposed</b> 116:17		

5:13,17,22 6:5,10 6:14,19 9:22 35:5 83:15 86:10 87:20 94:3 99:11 100:3 105:5 106:1 113:9 113:14 119:12 124:8 127:1,17 134:7 141:5 156:14 168:19 197:8 206:12 258:12 261:3 270:1 271:1 272:9 276:19 282:10 283:17 297:16 338:9 339:9 345:15 357:2 363:11 364:9,19 365:8 366:15,17 367:2,15 368:2 372:19 373:6 375:4 383:11,15 383:21 384:11 387:22 404:9 408:14 425:10	38:22,22 40:5,8 41:1,12 43:8,17 43:21 51:5 55:3 65:22 66:2 67:12 67:12 68:8,9,11 129:7 237:7 238:20 239:5 240:15 241:1 242:12 245:1,3 246:14,14 247:4,8 247:11,13 252:12 252:20 253:19 254:21 255:20	66:13 68:7 71:2 75:6 77:17 138:10 185:7 189:2 192:20 230:8 234:16 242:1 244:11 252:17 291:2 305:15 309:5 310:6 313:16,20 349:7 350:1 357:10 374:1,20 375:19 376:18 389:21 395:17 412:1	<b>passively</b> 217:17 <b>Pastoor</b> 255:14 258:5,20 259:13 281:19 283:16 303:2,7,10 319:16 320:2,5 321:18 322:9,16 323:6 <b>patents</b> 270:14 <b>path</b> 44:18 <b>pathogens</b> 121:19 <b>Pathologists</b> 225:9 <b>pathway</b> 95:13 172:16 386:19 393:6,8 394:4 <b>patience</b> 256:8 323:13 <b>patient</b> 425:11 <b>patiently</b> 298:3 <b>pattern</b> 45:13 46:20 47:2 71:7,8 71:12 147:20 200:1 240:4 245:17 252:19 306:3 <b>patterns</b> 11:19 23:21 36:9 50:10 50:10,12,17,17,18 51:8 57:4 64:14 78:18 87:1,3,4 194:5 <b>Paul</b> 258:2 290:11 292:5 302:4 <b>pause</b> 44:8 303:6 <b>pay</b> 48:5 333:19 <b>pbbs</b> 322:15 <b>PBS</b> 169:4 <b>PCOS</b> 153:11,14 153:15,17,20 154:2,5,7,10,13 154:16 155:2,12 160:18 161:13 <b>PDE</b> 173:14 175:21 <b>PDEs</b> 179:2 181:1 <b>PDE3</b> 179:3 <b>PDE4</b> 174:12 <b>PDE4D</b> 174:9,12 <b>PDE4s</b> 174:19	<b>PDE8</b> 174:9,14 <b>peak</b> 15:4,7,9 17:1 18:3 24:13 26:8 26:12 30:14 38:7 38:10 52:12,20 53:3,7 54:13 80:16,22 181:20 190:16 191:5 199:2,6 201:21 211:18 215:6 230:12,22 260:14 264:2 268:12,16 273:8 282:13 288:6 294:18 295:6 296:8 299:21 <b>peaks</b> 17:22 18:13 19:2,6,6,10 21:22 22:4,7 26:5 28:13 28:13,20 53:1 54:5,14,14 68:22 201:22 204:14 211:11 253:8 259:7 260:5 290:5 293:12 294:14,21 300:12 306:11 362:5,18,20 363:7 <b>peak's</b> 30:16 <b>peer</b> 116:4 <b>pellet</b> 190:10 <b>PENELOPE</b> 2:4 <b>Penny</b> 9:2 <b>people</b> 90:10 96:10 98:14,16 117:8 123:22 133:7 253:19 265:9 299:7 300:7 317:8 330:10 380:5 410:10 411:9,10 416:12 419:8 <b>percent</b> 16:2,3,5,8 16:11,12,14 17:3 17:3,4 19:8,8,9,21 19:22 20:1,6,6,8 20:21 43:12 48:11 48:12 61:16,19 62:11 102:16,18
270:1 271:1 272:9 276:19 282:10 283:17 297:16 338:9 339:9 345:15 357:2 363:11 364:9,19 365:8 366:15,17 367:2,15 368:2 372:19 373:6 375:4 383:11,15 383:21 384:11 387:22 404:9 408:14 425:10	<b>pardon</b> 100:2 <b>park</b> 149:22 404:1 422:2 423:5,11,14 <b>Parkinson's</b> 350:18 351:1,13,18 352:8 352:20 353:3,10 353:11 354:1,11 355:3	<b>particularly</b> 52:11 70:15,21 74:4 176:15 186:14 204:10 211:5 212:6 213:15 228:11 237:11 254:22 261:17 329:13 376:17 381:7 388:19 401:16	<b>passively</b> 217:17 <b>Pastoor</b> 255:14 258:5,20 259:13 281:19 283:16 303:2,7,10 319:16 320:2,5 321:18 322:9,16 323:6 <b>patents</b> 270:14 <b>path</b> 44:18 <b>pathogens</b> 121:19 <b>Pathologists</b> 225:9 <b>pathway</b> 95:13 172:16 386:19 393:6,8 394:4 <b>patience</b> 256:8 323:13 <b>patient</b> 425:11 <b>patiently</b> 298:3 <b>pattern</b> 45:13 46:20 47:2 71:7,8 71:12 147:20 200:1 240:4 245:17 252:19 306:3 <b>patterns</b> 11:19 23:21 36:9 50:10 50:10,12,17,17,18 51:8 57:4 64:14 78:18 87:1,3,4 194:5 <b>Paul</b> 258:2 290:11 292:5 302:4 <b>pause</b> 44:8 303:6 <b>pay</b> 48:5 333:19 <b>pbbs</b> 322:15 <b>PBS</b> 169:4 <b>PCOS</b> 153:11,14 153:15,17,20 154:2,5,7,10,13 154:16 155:2,12 160:18 161:13 <b>PDE</b> 173:14 175:21 <b>PDEs</b> 179:2 181:1 <b>PDE3</b> 179:3 <b>PDE4</b> 174:12 <b>PDE4D</b> 174:9,12 <b>PDE4s</b> 174:19	<b>part</b> 11:8 27:9 39:15 57:2 75:3 77:2 80:8,15 83:11 86:21 95:20 105:3 114:14,14 114:15 120:8,8 123:4 134:18 141:10 148:17 163:18 165:8 168:16 220:1,7 232:22 258:9,14 263:11,20 309:1 315:7 327:8,9,18 332:6,21 355:19 355:20 361:19,19 362:5,6,7,9,19 365:2 413:15
<b>panelists</b> 379:9 <b>panels</b> 127:17 345:8,9,20 <b>panel's</b> 183:11 <b>paper</b> 11:11 12:11 26:7 53:12 74:4 76:12 158:5,20 159:9 255:11 278:10,17 385:12 386:10,16 392:8 392:10 398:17 <b>papers</b> 137:2,3 158:18 160:2,2 366:8 395:15 419:10 <b>parallel</b> 376:2,10 412:11 <b>parallels</b> 332:10 <b>parameter</b> 37:6 38:13,17 39:6 44:9 45:7,11 67:16 242:14,17 <b>parameters</b> 38:16	<b>part</b> 11:8 27:9 39:15 57:2 75:3 77:2 80:8,15 83:11 86:21 95:20 105:3 114:14,14 114:15 120:8,8 123:4 134:18 141:10 148:17 163:18 165:8 168:16 220:1,7 232:22 258:9,14 263:11,20 309:1 315:7 327:8,9,18 332:6,21 355:19 355:20 361:19,19 362:5,6,7,9,19 365:2 413:15	<b>particulate</b> 100:21 <b>parties</b> 124:5 390:16 <b>partitioning</b> 292:20 <b>partly</b> 364:20 403:18 <b>parts</b> 18:6,7 22:6,6 61:12 62:4 132:22 133:2 144:15 183:8 259:11,17 260:1 264:14 269:10,18 278:2,4 278:6 309:16 311:2 313:12,21 314:3 318:1 326:21 332:2,22 333:1 335:3,8 337:2 <b>pass</b> 28:10 99:8 338:22 363:12 <b>passed</b> 109:5 340:16 376:6 419:14 <b>passive</b> 196:2	<b>parted</b> 424:19 <b>participated</b> 113:3 <b>participation</b> 114:19 119:17 327:8 <b>particular</b> 31:6 36:4 38:8,16 44:7 44:19 53:3 54:22 56:14 60:14 66:12	

102:21 109:3,12 111:8,11 145:2,4 145:5 146:3,9,21 147:1 163:20 174:13,14 176:20 177:4,5,19 179:19 181:5 197:9 209:17 235:1,9 273:16,19 274:1 275:21 292:6,9 301:10,20,21 302:10,12 309:8 319:18 320:12,13 320:22 322:4,7,10 325:13 331:7,21 332:13 352:19 354:7,13 362:13 362:16 363:19 401:18 414:19,22 415:1,1,7,7,9,11 416:22	281:10 283:8 291:18 292:5,13 293:2 297:4 <b>performances</b> 297:7 <b>performed</b> 212:11 295:20 302:7 <b>performing</b> 19:22 <b>perinatal</b> 127:4 <b>period</b> 10:9 31:6 61:8 76:21,22 85:3,17 88:18 107:20 108:20 109:1,11 111:10 144:3 194:12 200:9 211:16 214:5 215:22 218:14 239:17 240:13 244:4 247:2 266:10 267:16 268:6 270:18 374:4 383:14 421:1 <b>periodic</b> 56:2 <b>periodically</b> 162:10 <b>periods</b> 32:15 41:19 59:11 76:19 83:22 85:19 127:4 182:10 208:18 274:7,12 280:13 <b>peri-fused</b> 201:2 <b>permanent</b> 5:17,22 6:5,10,14 94:3 347:11,20 <b>permit</b> 254:15 282:1 <b>peroxide</b> 170:19 <b>persistence</b> 147:21 <b>persistency</b> 148:2 <b>persistent</b> 144:6,9 144:21 397:2 <b>persists</b> 165:18 <b>person</b> 62:2 128:7 404:15 <b>personally</b> 66:3 115:1 416:6 <b>persons</b> 353:19,20	<b>perspective</b> 325:3 378:17 <b>perspectives</b> 91:21 92:1,12 93:16 155:21 <b>pertain</b> 141:13 <b>pertaining</b> 156:10 401:4 <b>pertains</b> 135:16 138:13 <b>pertinent</b> 178:15 <b>perturb</b> 386:19 <b>perturbations</b> 385:21 <b>per-fed</b> 233:2 <b>pesticide</b> 6:9 8:10 8:22 11:18 70:1 77:18 78:19 79:15 115:11 117:6 118:17 120:6 309:22 328:6 333:10 352:6 353:12 356:12 360:11 381:17 <b>pesticides</b> 9:8 78:6 104:8,11,21 351:13,20 352:5 352:10 353:19,20 356:8,14 357:17 358:2,9 359:1 <b>Pfizer</b> 237:20 243:7 <b>pharmaceuticals</b> 358:5 <b>pharmacokinetic</b> 178:11 181:13,16 181:19 <b>pharmacokinetics</b> 9:12,17 <b>pharmacy</b> 9:15,16 <b>phenomenon</b> 142:7 184:15 235:5 347:16 392:1 <b>philosophy</b> 66:15 <b>phosphodiesterase</b> 171:17 172:5,13 173:3,4,7,17 179:14,19	<b>phosphodiesterase...</b> 171:6,10 172:19 174:2,5,16 179:9 179:16,21 <b>phosphodiesterase...</b> 171:19 <b>phosphodiesterases</b> 179:1 <b>phosphorylation</b> 172:16 <b>photomicrograms</b> 168:21 <b>phrase</b> 266:21 <b>physical</b> 84:5 168:14 254:4 <b>physically</b> 83:17 84:12 <b>physiological</b> 180:18 200:2 210:3 216:9 227:5 <b>physiologist</b> 7:17 8:1 <b>Physiology</b> 7:10 <b>Ph.D</b> 1:17,18,20,21 1:21,22,22,23 2:2 2:2,3,4,5,6,7,8,9 2:10,12,13,14,15 2:16,17,18 <b>Pia</b> 348:13 <b>pick</b> 27:22 61:3 83:18 134:2 236:15 <b>picked</b> 174:5 <b>picking</b> 234:20 <b>picogram</b> 227:6,7,9 227:13 <b>picograms</b> 204:12 209:21 210:1,2 <b>picture</b> 57:16 217:19 <b>piece</b> 82:7 192:17 193:6 210:21 269:6 406:7 411:4 <b>piecemealed</b> 229:12 <b>pieces</b> 414:5 <b>pituitary</b> 153:19,21	181:3,5,10 195:17 195:19 196:8 384:18 385:20 387:2 388:16 389:10 390:13 392:12 <b>pituitary-adrenal</b> 194:21 <b>pituitary-gonadal</b> 200:18 213:18 <b>PKA</b> 172:15 <b>place</b> 34:6 77:13 113:6 131:19 181:12 304:2 306:20 381:9 <b>placed</b> 223:3 <b>placental</b> 165:6 <b>places</b> 56:11 227:18 <b>plan</b> 74:1 90:20 180:21 245:22 293:7 334:22 364:1 <b>planned</b> 246:7 <b>planning</b> 104:15 249:3 <b>plans</b> 36:12 <b>plant</b> 164:4 277:20 278:4,13,19 300:12 <b>planted</b> 107:5 <b>planting</b> 100:16 316:7 <b>plants</b> 361:21,22 380:1,6 <b>plant's</b> 300:11 <b>plasma</b> 205:22 209:5 248:11 <b>plausibility</b> 143:2 <b>plausible</b> 152:16 <b>play</b> 31:22 47:16 83:13 216:15 326:11 360:22 385:22 393:8 404:5 411:16 415:4 <b>Plaza</b> 1:16
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<b>please</b> 4:20 96:11 100:2 140:20 141:14,15 142:5 143:3,17 144:14 144:22 145:8,18 146:8,16 148:8,17 149:5,16 150:9 151:21 152:6 154:17 256:17 350:20 385:16 387:12	383:8,13 397:13 403:20 404:8 407:6 409:10 421:14 425:8 <b>pointed</b> 74:3 284:21 <b>pointing</b> 23:19 <b>points</b> 31:9 67:13 68:11,17 76:18 90:2,16 95:21 98:19 137:13 156:2 184:11 186:2 216:18 236:14 238:6 239:10 254:4 258:18 259:1 268:20 288:12 289:4,15 300:17 301:10 305:12,19 305:21 307:1,3,3 310:11 348:17 386:9 404:14	230:21 268:21 269:18 270:8,10 270:20 285:18,20 291:3 295:7,22 408:2 <b>populations</b> 344:19 <b>Portier</b> 1:18,21 5:3 5:4,14 8:6 10:1 24:8 25:20 26:22 30:4,5 32:6 33:7 33:10 35:4,14,18 51:16 53:17 57:13 57:14 58:20 59:5 59:20 60:3,10,21 61:7,14,20 62:16 62:20 63:1,4 65:8 65:9 67:9,10 69:5 79:22 83:8 86:3 90:22 93:18 96:6 96:17 124:7 125:2 126:19 128:4 131:1 133:10 135:9 155:13 157:3 160:9,13 162:20 176:5 178:19 180:1 182:18 183:10 184:3 193:8,16 218:8 221:3 223:12 226:12 229:4 232:9 234:3 249:1 250:11 251:13 252:21 254:7 255:6 256:9 283:17 285:4 290:1 297:14 301:1 302:19 303:15 319:5 323:3,7,17 324:1 324:10,21 338:8 338:11,16 339:2,6 364:18 366:10 367:12,20 368:5 369:1 372:19 373:2 379:8 383:3 387:18 394:9 398:6 400:14	404:7 405:6,10,11 406:16 407:14 408:5,18 410:6,15 411:19 413:7 416:16,17 418:15 419:19 421:5 423:16 425:7 <b>portion</b> 251:21 <b>Portsmouth</b> 9:7 <b>Portuguese</b> 351:16 <b>positive</b> 37:9 45:17 47:6,17 48:4,7,12 50:13,22 140:15 149:12 218:15 220:2,4 245:13 412:4 <b>positives</b> 37:12 47:15 49:9,14 66:9 <b>possibilities</b> 235:15 <b>possibility</b> 158:7,14 233:18 403:3,16 413:13 414:8 416:5 <b>possible</b> 27:15,19 60:22 82:11 180:4 253:10 265:21 333:12,18 335:13 336:9 352:12 355:1 388:22 389:12 394:3 401:2 403:22 <b>possibly</b> 52:4 82:17 343:19 350:15 352:4,5 394:7 424:14 <b>post</b> 116:3,10 126:11 187:3 <b>posting</b> 116:8 <b>postulate</b> 141:18 185:19 <b>postulated</b> 141:21 184:14 389:7,19 <b>post-emergence</b> 104:15 <b>post-lactationally</b> 187:17	<b>potent</b> 173:8 <b>potential</b> 88:4 120:6 137:11 139:3 140:3 148:19 149:8 150:10 155:5 158:8,15 171:5 202:10 220:5 327:16 328:7 329:11 331:22 333:10 334:2 336:22 337:9 341:17 345:1 346:9 350:22 351:19 388:9 389:4 397:15 403:4 406:1,6 413:16,22 <b>potentially</b> 52:12 161:20 162:12 218:17 350:14 361:2 <b>potentiate</b> 171:2 <b>potently</b> 215:2 <b>pounds</b> 103:17 268:5 <b>powdered</b> 328:16 <b>power</b> 267:1 274:14 354:17 416:19 417:15 <b>powered</b> 234:12 349:10 351:3 418:13 <b>powerful</b> 229:21 <b>ppb</b> 269:12 278:14 286:4,5 <b>PPM</b> 144:18 <b>practical</b> 21:19 23:11 94:16 346:7 383:1 <b>practice</b> 30:17 133:16 <b>practices</b> 101:4,6 102:11 103:10 104:5,13 105:18 371:10 <b>practicing</b> 418:21
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<b>precedent</b> 374:6	174:7 213:1	125:7 221:9 228:8	13:11 29:2 55:11	98:18 99:1 106:5
<b>precipitating</b> 317:14	255:14,16 325:3 354:6 389:18	228:10 288:15,20 298:22 338:4,22 367:13,21	55:12 56:17 57:5 63:14,15 68:22 77:3 97:9 120:21 126:4 127:13,21 130:3 133:7 145:11 168:15 176:20 182:21 222:12 235:4 246:10 251:5 252:15 261:15 287:5 296:9 342:8 344:4 354:3 384:1	106:16,19 113:18 114:9,13 130:2 132:6 133:16 134:13 213:7 258:3 374:1
<b>precipitation</b> 64:14	<b>presentation</b> 3:8,13	<b>prevail</b> 114:2	<b>problem</b> 27:5	<b>production</b> 100:12
<b>precise</b> 129:8 150:22	5:10 10:10 11:12 31:8 33:12 53:20 72:8 74:13 96:22 133:20 134:18 135:5 153:12 162:21 223:15 235:18 237:4 260:19 262:9 286:15 302:22 335:10 341:1 374:13 377:6 389:1 392:22 400:17	<b>prevailing</b> 396:22 <b>prevalent</b> 179:4 <b>prevention</b> 232:3 <b>previous</b> 42:14,17 43:11,11 57:6 92:18 122:18 123:17 154:21 170:13 214:5 335:9 374:22 385:13	63:22 64:10 87:21 89:2 103:22 104:1 299:16 363:10 367:14 413:21	101:16 104:5 136:14 170:9 241:20 349:1 350:7 392:13
<b>precision</b> 38:17		<b>previously</b> 192:5 238:7 332:11	287:5 296:9 342:8 344:4 354:3 384:1	<b>products</b> 356:12 360:20 373:11 376:8 381:3,12 382:10
<b>precursor</b> 204:20 204:20		<b>pre-birth</b> 344:22 347:1	<b>problems</b> 86:19 125:21 413:19	<b>professor</b> 6:2,7,16 9:10,16 193:19
<b>predecessor</b> 122:10	<b>presentations</b> 4:10	<b>pre-ovulatory</b> 202:7	<b>procedure</b> 296:21 297:5	<b>profile</b> 30:9,9 32:15 32:16,17 54:3,6 59:2 85:4 120:13 273:4,9,12,18 291:12 292:8 296:5,11 306:4 308:7
<b>predict</b> 52:10	96:19 262:4 350:19 393:15 425:11	<b>price</b> 48:4	<b>proceed</b> 31:17 135:2 383:15	<b>profiles</b> 12:9,18 21:21 32:18 66:17 258:18 272:22 281:4 291:21
<b>predictable</b> 242:19	<b>presentation's</b> 36:17	<b>primacy</b> 336:5	<b>proceeding</b> 372:16	<b>profiling</b> 180:10
<b>predictions</b> 66:13 271:22	<b>presented</b> 11:10	<b>primarily</b> 110:7 151:4 306:17 325:8 328:9 389:5	<b>process</b> 82:9 83:12 85:11 87:8,12 89:7 98:13 116:14 116:22 118:6,7,17 118:19 123:14,20 124:6 163:18 189:14 246:9 281:19 318:11 326:18 327:10,19 334:5 406:15	<b>profound</b> 126:5
<b>predictive</b> 244:21	14:11 26:6 28:12 76:12 79:8 135:20 165:3 322:15 340:9 388:8 401:3 401:7,14 420:17	<b>primary</b> 114:12 198:1 249:15	<b>processes</b> 180:18 193:2	<b>progesterone</b> 147:16 203:14 206:1 208:5,5,7 208:10,13,20 215:5,15 392:14
<b>predictor</b> 64:12	<b>presenters</b> 133:19 134:19 381:6	<b>primate</b> 178:4	<b>produce</b> 43:16 56:1 101:15 197:21	<b>progestins</b> 205:11
<b>predictors</b> 248:13	<b>presenting</b> 12:14 240:18	<b>primates</b> 160:21 164:1 177:15	<b>produced</b> 100:13 179:17 225:15 244:3 260:9 381:8	<b>program</b> 5:21 8:11 20:13 90:14 136:17 138:1 140:22 259:14 260:3 261:18,21 262:3,14,14,17,19 262:21,22 263:9 263:11,12,16,21 263:22 264:9,10 265:5 271:14 276:5 284:7
<b>predominant</b> 147:20 167:8 168:5 205:17,20	<b>presentation's</b> 36:17	<b>prime</b> 414:18	<b>Producers</b> 97:8	
<b>predominantly</b> 149:11 164:12	<b>presented</b> 11:10	<b>primer</b> 173:15 174:6	<b>producing</b> 63:9 64:6 98:16 112:20 171:17	
<b>prefer</b> 373:14	14:11 26:6 28:12 76:12 79:8 135:20 165:3 322:15 340:9 388:8 401:3 401:7,14 420:17	<b>principal</b> 147:2 303:11	<b>product</b> 98:15,17	
<b>preferable</b> 283:14	<b>presenters</b> 133:19 134:19 381:6	<b>principles</b> 333:13		
<b>preference</b> 375:2	<b>presenting</b> 12:14 240:18	<b>prior</b> 53:22 54:1,18 198:21 221:14 266:21,22 280:16 296:2		
<b>pregnancy</b> 186:7	<b>preserve</b> 45:12	<b>private</b> 9:3		
<b>pregnant</b> 347:3 357:17	<b>president</b> 373:7	<b>probabilities</b> 37:12 47:11,15 49:5,13		
<b>preliminary</b> 23:18 25:15 139:4 348:9 387:12 398:10 399:15	<b>President-elect</b> 122:4	<b>probability</b> 24:12 37:4 47:5 62:7		
<b>premature</b> 385:3	<b>presiding</b> 1:18	<b>probably</b> 11:2		
<b>premier</b> 342:8	<b>presumably</b> 132:21 186:9 356:4 396:13			
<b>prenatal</b> 357:6	<b>presumed</b> 185:9 191:20			
<b>prep</b> 182:6	<b>presumption</b> 346:4			
<b>prepackaged</b> 106:15	<b>pretty</b> 20:12 58:17 58:17 64:6 67:21 68:18 71:18 94:16			
<b>preparation</b> 172:6 179:14				
<b>preparing</b> 100:15				
<b>presence</b> 122:1 205:6 231:6 377:14				
<b>present</b> 1:19 2:1,21 15:1 121:10,20,20 150:5 163:21				

310:20 312:1 316:4,6 319:3 327:9 339:17 344:7 361:11 363:15,22 <b>programming</b> 63:3 <b>programs</b> 39:3 56:1 98:22 257:3 260:7 261:6 276:2 276:15 279:19 280:4,12 284:18 289:16 306:18 309:22 315:17 340:7 361:9 382:22 <b>progress</b> 108:4 245:5 248:14 329:4 <b>progression</b> 399:11 <b>progressively</b> 185:3 <b>project</b> 124:1 237:19 243:6 <b>prolactin</b> 147:9 148:2,5 203:14 208:16,21 216:4 398:22 <b>prolonged</b> 142:3,16 147:17 <b>prominent</b> 407:22 <b>promise</b> 303:2 <b>promoter</b> 404:11 413:2 421:21 424:5,9,16,19 <b>promoter/initiator</b> 424:18 <b>promotes</b> 142:14 <b>promoting</b> 403:4 <b>promotion</b> 160:1,6 160:7 399:11 403:8,12 408:6 413:15 414:2 425:3 <b>promotional</b> 158:7 158:14 401:2,2 403:3 413:17,18 416:9,9	<b>prompting</b> 390:18 <b>prone</b> 277:4 <b>proof</b> 342:21 346:16 <b>propaganda</b> 120:20 <b>propargite</b> 352:17 <b>proper</b> 178:12 <b>properly</b> 245:15 353:6 <b>properties</b> 21:21 104:4 <b>proposes</b> 342:13 <b>proposing</b> 342:2 <b>pros</b> 36:14,22 51:12 82:13 <b>prospective</b> 354:15 <b>prostate</b> 115:4 <b>protect</b> 100:8 101:11 121:15 360:5 <b>protecting</b> 170:20 343:10 <b>protection</b> 1:1 8:21 97:1 110:15 335:16 359:11 373:11 376:5,8,17 381:3 382:10 <b>protective</b> 101:21 168:16 <b>protects</b> 334:9 <b>protein</b> 196:16,18 205:2 240:17,18 <b>proteins</b> 179:10 <b>protocol</b> 254:10 364:21 <b>prove</b> 189:22 <b>provide</b> 25:8 36:14 44:12,14 58:7 77:12 79:3 101:21 104:18 117:20 188:21 248:14 254:16 271:9 277:2 351:6 354:22 365:19 366:2,4 379:6 383:10 399:4,12	408:13 <b>provided</b> 39:12 41:10,11 55:20,21 119:7 134:6 339:8 344:10 361:13 362:12 365:14 366:17 369:16 370:22 372:12 374:1 378:14 <b>provides</b> 99:2 261:2 282:18 390:18 <b>providing</b> 188:20 377:12 419:11 <b>provisions</b> 376:16 <b>provocative</b> 160:2 <b>Pruett</b> 138:16,22 202:19 212:11 234:5 236:5 237:1 249:5,16 250:21 251:7,21 253:10 254:18 <b>pseudopregnancy</b> 147:22 <b>pubertal</b> 127:5 <b>puberty</b> 386:6,14 <b>public</b> 3:20 4:13 10:2,12,16,18,21 96:10 323:10 324:4,7 334:9 335:15 342:11 343:9,10 344:5,14 364:13 368:12 372:11,12 373:3 374:4 378:2 379:3 383:9,14 <b>publication</b> 109:20 109:21 137:5 <b>publications</b> 138:3 141:8 <b>publicly</b> 366:21 <b>publish</b> 364:10,12 <b>published</b> 102:13 108:2,5 159:22 342:5 349:13,16 352:22 365:21 386:17	<b>publishing</b> 137:6 <b>pull</b> 160:13 264:18 367:13 <b>pulled</b> 389:19 <b>pulling</b> 148:8 <b>pulls</b> 307:11 <b>pulsatile</b> 185:10 186:10 191:20 192:22 199:15,19 200:1 201:8 202:5 214:2,17 217:6 218:22 219:6 221:1 <b>pulse</b> 137:19 153:17,18 199:22 200:9,16 214:13 214:14 <b>pulses</b> 200:12,14,20 201:11,15 214:7,8 216:12 219:5,20 223:8 232:2 <b>pump</b> 277:10,13,15 279:2 298:6,7,16 299:1,10 <b>pumping</b> 298:10,12 <b>pups</b> 187:2,4,16 193:12 <b>purpose</b> 64:19 90:8 171:16 186:3 <b>purposes</b> 73:4 180:20 <b>Pursuit</b> 391:16 <b>purview</b> 412:14 <b>push</b> 11:2 <b>put</b> 13:20 14:18 37:10 53:10 58:4 59:9 75:9 105:8 114:18,18 130:2 150:8 153:11 160:5 164:10 175:18 193:5 201:7 277:12 297:1 308:12,16 311:16,19 317:7 342:21 363:4 365:20 373:13 381:11 413:20	<b>putting</b> 189:12 415:18 424:15 <b>put-together</b> 414:7 <b>pyramid</b> 263:14 264:22 <b>P-R-O-C-E-E-D-...</b> 4:1 <b>p.m</b> 183:17 184:2 323:21,22 425:16 <b>P450</b> 205:4 <hr/> <b>Q</b> <hr/> <b>qualifying</b> 111:4 <b>qualities</b> 282:7 <b>quality</b> 8:11 41:11 56:1 72:20 105:16 359:19 369:8,15 370:9 372:3,9 376:5,17 418:21 <b>quanta</b> 199:20 <b>quantitative</b> 64:6 238:5 <b>quarter</b> 11:3 68:17 165:12 <b>quarterlies</b> 363:8 <b>quarterly</b> 13:19 14:18 90:12 327:1 335:4 <b>quartile</b> 353:16 <b>quartiles</b> 353:15 <b>question</b> 27:10 33:15 51:17,20 53:20 55:16 57:14 72:5 73:18 78:5 79:19 80:9 81:18 81:22 89:9 91:6 92:10 94:20 117:1 119:15 126:22 128:12 136:5 137:18 138:11 139:2 153:6 158:4 161:6 168:7 172:11 178:22 180:4 181:1,12 182:20 186:16 192:19 195:18 213:6,13 214:21
---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

222:8 228:21	334:20,22 338:7,9	355:17 371:14	130:19 205:3	120:15 169:2
229:21 231:12	340:19,20 341:2	404:14	<b>rates</b> 47:9 50:22	340:16,20 342:14
233:11 234:7	344:1 364:19	<b>raises</b> 420:11	108:17 126:11	345:5 355:8,9
236:12,16 256:11	372:4,14,18,20	<b>raising</b> 393:22	178:2 396:7,17	383:7,20 388:2
256:13 267:3	379:9 384:10	<b>Ralph</b> 143:4	397:7,8,11	407:2
270:1,21 272:16	386:15 420:11,11	194:13	<b>rating</b> 422:3	<b>readily</b> 144:19
274:12 276:19	425:14	<b>rambled</b> 131:4	<b>ratio</b> 207:4 278:18	<b>reading</b> 293:9
283:19,21 284:5	<b>question's</b> 224:22	<b>ran</b> 15:13 18:15	292:7 351:22	384:9 421:15
293:4 294:8 295:4	409:13	223:4 263:17	352:13,15,17	423:11,19
297:15,16 298:3,5	<b>quick</b> 4:10 193:4	<b>random</b> 14:5 42:3	353:17,21 354:4	<b>readjusted</b> 10:8
301:2,6 304:12	193:10 234:6	43:15 46:6	<b>ratios</b> 147:17	<b>reads</b> 297:16
310:22 314:6	256:10,13	<b>range</b> 14:9,10	273:10 279:11	<b>ready</b> 93:19 96:13
321:2 341:15	<b>quickly</b> 125:21	27:11 56:16 66:17	353:4	237:1 400:21
345:9,18 348:8	126:7 200:4,7	67:4,15 93:16	<b>rats</b> 49:22 142:10	404:2
350:16 356:15,16	215:14 249:8	147:1 169:3	142:16 143:9	<b>real</b> 73:2 81:19
361:6 364:21	301:4	170:11 173:13	144:15 155:9	93:5,6 193:10
365:3 368:17,18	<b>Quinn</b> 383:5	227:6,7,9,13	171:14 185:14	201:18 291:15
383:21 384:12	<b>quite</b> 43:4 53:4,15	279:19 280:8	196:1 202:12	292:18 299:18,19
387:9,19 394:2	68:10 114:8 116:1	281:12 332:17,20	208:1 212:13,20	306:14 324:20
399:1 404:10	159:8 177:7 186:8	332:21 333:1	215:18 217:11	361:4
414:9 417:10	231:19 238:1	344:18,21 351:3	227:4 229:8,15	<b>realistic</b> 51:8 66:5
421:15 425:8,13	241:11 242:21	352:1 375:11	243:6 384:19	66:10 291:10,16
<b>questionable</b>	244:14,18,21	382:9 402:2	385:1,22 388:11	<b>reality</b> 64:19 65:2,5
421:20	246:4 262:4	<b>ranged</b> 13:19	388:12 389:11	81:18 126:1
<b>questioning</b> 234:11	266:17 293:21,21	<b>ranges</b> 182:15	396:18,20 397:5	<b>realize</b> 90:11
<b>questions</b> 3:22	305:22 314:19	279:7 332:14	398:20 401:12	260:22 278:20
10:22 24:7,8 28:8	382:15	<b>ranging</b> 13:11	402:1,19,19	<b>realized</b> 26:16
31:1 32:1 33:8	<b>quote</b> 25:22 154:18	169:19 279:8	413:12	<b>realizing</b> 27:4
57:16 69:17,22	369:13 370:19	<b>rank</b> 111:16	<b>raw</b> 121:3 264:5	67:11
77:19 78:14 79:6	371:19	<b>rapid</b> 211:10	265:7 267:19	<b>really</b> 17:12 27:7
79:12 94:16	<b>quote-unquote</b>	<b>rapidly</b> 133:4	271:12 275:21	32:21 49:19,19
118:11 124:8	396:2 415:19	175:10 199:13	276:3 277:19	54:10,13 55:4,9
134:20 135:6,10		211:18	278:3,8,18 285:15	55:11 56:7 63:12
135:14 139:14	<b>R</b>	<b>rarely</b> 346:8	292:22 327:7	64:13,15 65:11,19
155:15 157:4	<b>R</b> 1:21 184:1	<b>rat</b> 140:18 142:11	362:15,18 377:9	66:7 69:1 72:22
164:8 173:16	<b>radar</b> 27:13,14	143:21 144:7	378:14	73:3 80:6 81:16
176:6 193:4 194:6	<b>radiolabeled</b>	146:5,13,18,18,22	<b>reach</b> 191:11	82:18 87:7 88:12
194:13,18 218:7	177:12	147:3,7,15,22	206:18 209:11	88:18 96:2 109:16
221:6,9 232:10	<b>Radiology</b> 6:18	148:1 152:9 154:2	246:4	125:12,19 133:11
234:6 238:10	<b>Rain</b> 100:19	181:21 186:13	<b>reached</b> 135:22	159:12,16 160:18
248:22 261:3	<b>rainfall</b> 33:20 34:3	195:5 196:13,14	152:22 326:2	173:10 176:8
269:5 270:22	54:16 102:16	198:8 205:17,21	393:10	182:5 201:20
272:21 279:16	128:18 265:19	229:20 249:20	<b>reaches</b> 235:8	219:14 224:12
280:19 281:22	279:2 329:22	385:4 394:20,21	<b>reaction</b> 374:18	225:19 226:4
282:19 283:15,18	<b>raise</b> 92:2 276:18	395:6,18 397:6,17	<b>reactive-oxygen</b>	234:10 236:1
289:11 295:17	277:22	<b>rate</b> 47:1 48:4,6,7,8	170:9	237:21 238:7
319:4,5,8 325:10	<b>raised</b> 153:6	106:18 114:6	<b>read</b> 51:11 113:10	240:3 241:19

266:16 275:5	335:12 364:9	<b>reducing</b> 102:5	<b>regarding</b> 113:7	<b>related</b> 28:6,8
280:7 286:14	410:21 423:5	104:11 174:15	122:14 194:2,7	42:16 43:10 64:11
292:2,4,14 293:3	<b>recommendation</b>	<b>reduction</b> 167:6	204:5 283:21	87:17 146:2
293:7 296:19	385:7 407:18	179:19 235:1,9	284:1 334:13	159:22 161:13
304:20 308:11	409:7 417:16	381:20,20	348:10 399:7	162:13 220:13
316:19 325:1	423:14	<b>Reed</b> 2:14 8:20,20	404:15	240:7 296:6,12,13
337:16 338:3	<b>recommendations</b>	157:3,4,18 158:1	<b>regardless</b> 113:13	296:16 348:17
339:11 341:6	333:7 361:5,8	158:4 400:15,16	<b>regards</b> 296:18	405:19
343:8 356:22	363:11 409:9	408:8,9 413:7,8	<b>regime</b> 283:2	<b>relates</b> 100:1 178:8
375:18,22,22	410:19 416:17	417:18 422:22	<b>regimes</b> 281:11	184:11
404:13,18 406:9	<b>recommended</b>	423:3 424:1,2	<b>regions</b> 110:13	<b>relating</b> 186:5,9
409:17 411:16,16	345:10	<b>reevaluate</b> 407:19	111:8	231:12 345:11
412:22 417:7	<b>recommending</b>	<b>reevaluated</b> 409:6	<b>register</b> 358:17	<b>relation</b> 296:14
420:8 421:13	383:6 410:17	<b>reevaluation</b> 1:6	<b>registered</b> 106:13	<b>relations</b> 288:5
<b>realm</b> 65:17	422:13	4:7 5:6 94:4	108:14,17 132:8	<b>relationship</b> 95:15
<b>reason</b> 24:18 25:13	<b>reconsider</b> 384:4	333:12	<b>registrant</b> 328:5	138:19 145:16
58:4 83:20 106:7	422:3	<b>refer</b> 258:14	329:3 331:12	146:7,11 244:18
223:21 237:22	<b>reconsideration</b>	<b>reference</b> 267:10	363:15 364:7	245:8 248:15
263:14 277:22	94:12	271:8 318:22	<b>registrants</b> 98:12	399:20 400:9
299:9 346:6	<b>reconvene</b> 183:14	<b>referenced</b> 364:22	328:2 333:19	<b>relationships</b>
<b>reasonable</b> 21:11	183:16 323:18	375:7	<b>registrant's</b> 55:20	142:20,21 245:3
66:21 125:4 231:3	<b>record</b> 96:15	<b>references</b> 359:3	<b>registration</b> 118:17	<b>relative</b> 137:12
349:10 351:4	182:19 323:21	<b>referencing</b> 392:8	118:18 358:16	139:2 166:4 174:8
424:3	365:2 372:4,7	<b>referred</b> 184:19	<b>regression</b> 34:11	181:8 182:14
<b>reasoning</b> 398:1,18	373:13 377:16	310:9,11 398:19	68:12 351:19	184:15 186:18
<b>reasons</b> 32:4 57:20	<b>recorded</b> 4:21	<b>referring</b> 234:16	<b>regular</b> 90:9	290:16 308:12,16
109:22 161:14,18	<b>records</b> 264:17	313:8 344:8	<b>regulated</b> 90:13	312:13 319:17
257:17 268:3	<b>recover</b> 199:7	<b>refers</b> 165:4	121:10 122:8	322:11 352:20
310:18 346:8	247:7	<b>refining</b> 318:11	263:1	<b>relatively</b> 106:18
381:22	<b>recovered</b> 199:13	<b>reflected</b> 125:15	<b>regulating</b> 98:14	124:22 163:6,13
<b>reassessing</b> 321:4	<b>recovery</b> 188:4	<b>reflects</b> 268:8	191:21 217:17	288:15 324:6
<b>recall</b> 184:13	198:15	<b>refreshing</b> 135:21	<b>regulation</b> 194:9	332:1
<b>recapitulation</b>	<b>red</b> 46:10 144:5,5	<b>Regal</b> 2:15 6:20,20	255:16 336:18	<b>release</b> 147:9
185:21	358:15 359:2	124:8,9 226:13	345:21	162:13 185:10
<b>recaptured</b> 20:2	360:7,18 388:7	229:4,6 249:1,2	<b>regulations</b> 120:5	186:10 191:21
<b>receive</b> 383:4	<b>reduce</b> 128:9 173:7	249:13,19 250:2,6	332:8	201:1,8 332:5
<b>received</b> 365:4	195:4 209:10	<b>regard</b> 32:3 72:6	<b>regulators</b> 117:21	384:15 390:8,11
<b>receiving</b> 187:2	231:7 360:1,2	84:15 114:2	119:18	390:14 392:6,11
<b>Recio</b> 286:19	<b>reduced</b> 130:19	156:18 177:13	<b>regulatory</b> 114:2	392:16
<b>reciprocal</b> 274:1	147:18,19 148:4	200:22 238:11	123:7 177:12	<b>released</b> 118:12
<b>recognize</b> 185:16	153:14 166:5	283:22 310:21	205:2 220:8	199:18,21 200:3
326:8	174:12,14 197:13	315:16 374:5	262:22 326:18	<b>releasing</b> 384:16
<b>recognized</b> 153:11	200:13 201:15,22	375:18,20 376:3	327:21 368:13,22	<b>relevance</b> 136:8
395:2	230:13 348:3	376:13,20 377:16	370:1 372:2	148:9 152:2 280:2
<b>recognizes</b> 363:20	357:6,7 384:15	377:22 378:4,8,10	<b>reinforced</b> 374:18	280:7 282:3 389:2
<b>recommend</b> 25:8	<b>reduces</b> 85:20	378:11 381:19	<b>reiterate</b> 95:19	393:12 399:2
107:7 283:9	101:12 215:6	389:3 393:10	237:8	400:22

<b>relevancy</b> 136:20	417:12,14	<b>represented</b> 16:18	9:11,21 92:20,22	223:17,19 253:3
<b>relevant</b> 31:16 82:2	<b>repeated</b> 418:12	133:14 375:4	104:7 107:20	374:11
87:20 152:15	<b>repeatedly</b> 173:6	<b>representing</b> 51:8	108:2 109:7,22	<b>respectfully</b> 92:9
262:1 275:11	<b>replacement</b> 14:4	325:8 381:7	110:6 119:4	<b>respond</b> 68:6 80:11
278:12 282:2	<b>replica</b> 250:4	<b>represents</b> 18:2	121:13 124:17	156:8 196:3
283:13 286:18	<b>replicate</b> 64:1	143:22 373:8	136:1,17,22 138:1	340:18
288:3 319:2 344:1	<b>replication</b> 371:22	<b>reproducibility</b>	138:6,17,18	<b>respondents</b>
345:11 349:8	<b>report</b> 25:7 102:13	370:7,10,20 371:2	149:21 151:7,11	409:13
356:19 361:4	107:20 108:2,4	371:4 372:5	153:1 160:4	<b>responds</b> 165:7
386:3 407:9 415:5	109:7,22 110:6	<b>reproducible</b>	235:22 255:19	213:4
424:6	113:10 116:4,5	371:12	256:2 342:7	<b>response</b> 33:9 50:1
<b>reliability</b> 369:15	170:7 171:12	<b>reproductive</b> 7:3,4	349:16,22 391:12	54:3 97:16 108:22
<b>reliable</b> 165:22	188:22 202:22	7:12,14 8:1	420:10	118:14 142:20
346:9	203:15 206:22	142:12,15 144:20	<b>researchers</b> 349:14	143:15 145:16
<b>relied</b> 154:20	209:14,18 246:1	147:11 148:13,14	359:16 389:6	146:7,11 150:20
<b>relies</b> 294:16	267:12 269:3	150:14 154:12	<b>resemble</b> 154:13	152:11 154:22
<b>reluctant</b> 257:19	286:17 297:6	156:10 157:16	<b>resembles</b> 305:2	157:8 166:3
<b>relying</b> 65:18	339:21,22 340:9	346:14 385:4	<b>reservoir</b> 29:13	167:16 173:21
<b>remain</b> 125:6	345:10 361:13	386:2,19 391:15	33:21 72:12	196:5 198:14
215:21 330:3,4	364:11 366:8,16	<b>reproductive/dev...</b>	277:14,16,21	199:22 207:12,21
<b>remainder</b> 20:12	366:19 367:14,15	386:1	300:4 330:3	208:8,16,21
<b>remained</b> 109:6	423:21,22	<b>Republication</b>	<b>reservoirs</b> 278:22	210:16 211:4,15
<b>remaining</b> 10:10	<b>reported</b> 14:10	122:11	298:17 330:2	211:17 212:8
324:4	113:8 171:14,21	<b>request</b> 92:9	<b>residuals</b> 42:4	229:15 236:8
<b>remains</b> 45:22 46:2	172:4 175:6 192:5	<b>require</b> 21:4 170:6	<b>residue</b> 101:8	238:4,5 240:4,5
106:3 111:12,20	216:6 248:5	280:14 333:9	103:5 270:13	240:20,21 243:13
112:1,19 393:18	253:19 268:13	335:17 370:9,18	278:2	243:15,17,20
398:22 399:2	278:2,14 349:19	<b>required</b> 49:18	<b>residues</b> 264:20	245:8,17 247:18
<b>remarkable</b> 266:17	351:11,17 352:3	90:15 94:18 330:6	266:8 285:1,2	248:15,20 252:7
<b>remarks</b> 3:6 183:1	352:22 353:9,22	332:8 342:21	<b>resist</b> 397:22	252:11 253:21
377:7	354:9 357:15	<b>requirement</b> 128:8	<b>resistance</b> 107:3,13	254:1 291:7
<b>remember</b> 159:2	395:11 397:9	328:6 376:4	125:22 130:15	371:18 372:21
214:5 215:1	<b>reporters</b> 120:16	<b>requirements</b>	<b>resistant</b> 107:11	395:5,20 401:14
216:19 276:5	<b>reports</b> 116:16	50:21 104:9 328:5	179:21	402:10 414:16
279:22 317:13	120:15 225:8,21	337:10 359:10	<b>resolution</b> 92:17	415:12,20 421:13
362:4	350:9 352:6	370:2,5,7 372:3,9	293:19,20	425:6
<b>remind</b> 389:22	354:21 364:21	<b>requires</b> 39:7 62:12	<b>resolve</b> 286:22	<b>responses</b> 138:21
<b>reminded</b> 133:15	<b>represent</b> 15:7	<b>requiring</b> 119:3	<b>resolved</b> 92:17	186:5 212:7 224:2
<b>reminder</b> 4:19	97:19 111:7 130:5	328:1	<b>resource</b> 261:2	243:12 397:17
<b>removal</b> 232:14	144:6 177:18	<b>reregistration</b>	275:4 375:9	<b>responsible</b> 134:12
<b>remove</b> 214:15	296:1 379:1	97:18 116:9	381:10 382:3	215:11 390:13
<b>removed</b> 201:6	<b>representative</b> 13:3	<b>resample</b> 14:5	<b>resources</b> 24:3	<b>responsive</b> 164:20
<b>reopen</b> 94:20	17:22 169:21	301:15	99:19 100:7	<b>responsiveness</b>
<b>repeat</b> 22:15 47:9	253:7 278:17	<b>resamples</b> 16:7	102:13,14 339:8	184:15
145:12 256:17	280:5	<b>resampling</b> 287:17	339:15 375:3	<b>rest</b> 19:17 89:9
419:6,8	<b>representatives</b>	<b>rescale</b> 311:15	381:11,18 417:9	177:19 262:8
<b>repeatability</b>	292:17	<b>research</b> 7:8,17	<b>respect</b> 92:18 156:8	323:4,10

<b>restatement</b> 120:19	<b>revealed</b> 388:10	57:18 58:2 59:9	393:12 394:15	<b>rollings</b> 292:10
<b>restating</b> 329:17	391:18	59:11,15,18 61:6	404:2 408:10	<b>romantic</b> 129:18
<b>restraint</b> 241:10	<b>revenue</b> 330:13	61:14 65:19,20	410:11 417:18	<b>room</b> 10:4 80:4
243:1 252:3,10,13	331:7	67:5,15 69:11,13	418:10 419:17	81:6 92:19 123:4
254:5	<b>reversability</b> 188:6	70:14 74:18 76:20	424:17 425:4	123:5 133:8
<b>restrict</b> 120:5	<b>reversal</b> 156:12	77:11 82:1 88:13	<b>risks</b> 334:14,14	286:12 287:10
<b>restricted</b> 233:7	232:13	88:13,17 91:20	356:20 378:8	324:3 382:16
360:10	<b>reversed</b> 217:1	151:7 157:18	<b>River</b> 39:11 275:10	<b>rooms</b> 304:1
<b>restricting</b> 53:2	<b>review</b> 1:7 2:1 5:7	197:8 214:3 219:9	362:8	<b>Rooney</b> 247:12
<b>result</b> 23:6,15	95:4 97:17 108:22	222:14,20 223:1	<b>rivers</b> 103:22	<b>roughly</b> 178:1
40:16 45:16 100:8	113:5,6 114:20	226:6,15 229:10	261:11 287:3	263:1 284:15
102:9 104:3	116:4,20 117:18	249:16,22 251:8	<b>Riverside</b> 6:4	<b>round</b> 137:8 330:4
116:11 142:3	118:10,18,22	261:1 289:7,18,22	<b>RNA</b> 165:11,17	<b>route</b> 212:15 321:1
145:15 155:1	119:5 125:11	295:13,18 302:6	<b>RNAs</b> 172:21	375:19
162:5 168:14	127:8 141:19	302:22 303:3,7	<b>road</b> 69:15 81:17	<b>routes</b> 396:6
192:7 197:21	151:2 155:20	307:16 308:6	81:18 304:14	<b>routinely</b> 107:7
198:10,14 201:18	268:14 332:7	319:12 320:7	375:12	356:10
205:5 206:10	345:18 369:21	321:19 322:6,9	<b>roadmap</b> 87:7	<b>routines</b> 39:7
209:17 226:5	372:13 387:10	323:6 328:1	<b>Roberge</b> 172:4	<b>row</b> 41:21
287:2 347:6	397:6,20 401:8	366:17,18 381:9	<b>Roberson</b> 324:11	<b>Rowe</b> 247:12
384:19 390:10	415:15 419:9,14	414:12 416:19,19	324:13,19 325:1	<b>RTI</b> 269:4 290:11
392:16 396:7	<b>reviewed</b> 128:2	417:16,17 423:3	338:10,14,18	304:7
<b>resulted</b> 172:18	156:15 284:14	<b>right-hand</b> 15:19	339:4 364:6	<b>rubber</b> 69:15 81:16
<b>resulting</b> 102:15	342:9 343:12	19:11	<b>Robert</b> 2:5 137:15	81:18 304:14
352:18 392:5	345:8 357:8	<b>right-of-ways</b>	<b>robot's</b> 417:21	<b>Ruby</b> 2:14 8:20
<b>results</b> 17:11,13	366:15 367:21	331:15	<b>robust</b> 75:1,12	<b>Ruby's</b> 418:19
18:19 23:17 52:16	381:5 401:1	<b>rigor</b> 416:1,7	117:14,19 231:1	<b>rule</b> 47:13 49:2,8
53:9 139:4 142:16	<b>reviewing</b> 419:22	<b>rise</b> 205:11,18	411:9,14,18	400:22
143:2 148:14	<b>reviews</b> 120:1	212:18	<b>robustness</b> 382:17	<b>ruled</b> 406:2
173:2 190:4 196:7	123:9 127:15	<b>rises</b> 15:4 208:22	<b>rodent</b> 178:4 195:6	<b>rules</b> 336:10
201:3 206:5,7,11	149:19 414:13	<b>risk</b> 8:22,22 9:5,13	210:2 388:9	365:20 371:7
209:3 210:22	<b>revised</b> 399:21	23:2 81:11 82:7	395:22	<b>ruling</b> 368:6
211:22 214:6,9	411:22	94:21 95:6,9	<b>RODENTICIDE</b>	413:13
215:3 234:10	<b>re-registration</b>	141:10 151:22	1:4	<b>Rumsfeld</b> 27:6
245:22 251:17	327:19	152:8 182:9,16	<b>rodents</b> 164:1	<b>run</b> 14:8 16:13
281:7 316:9	<b>re-review</b> 118:15	186:3 258:9	177:7,13,15 248:4	20:13 187:6
337:14 344:11	<b>RfD</b> 319:14	281:18 305:3,3,5	254:1	210:18 286:11
371:11 388:10	<b>RIA</b> 227:15	319:19 333:17	<b>Rohr</b> 349:14	418:22 425:13
395:19 411:17	<b>RIAs</b> 227:17	351:7,19 352:20	355:10	<b>running</b> 13:16
412:4	<b>rich</b> 102:2	353:10,14 355:3	<b>role</b> 98:11 297:21	33:22 145:3 233:2
<b>resumed</b> 96:16	<b>Richard</b> 2:2,6 8:12	357:15 361:1	385:22 394:18	249:12 259:19
323:22	9:6 28:11 96:20	363:14,20 369:14	<b>roll</b> 55:1 124:3	262:21
<b>rethink</b> 95:21	105:13 177:2	369:22 370:4,11	<b>rolling</b> 31:5 76:19	<b>runoff</b> 84:1 101:13
406:14	<b>ridge</b> 101:18	371:14 372:7	96:1 259:20	102:16 104:11
<b>return</b> 96:8 183:8	<b>right</b> 22:7 29:8	377:11,13 381:20	271:21 272:2	264:3 265:17
<b>returns</b> 16:6 19:4,7	30:11,19 37:19	384:13 387:16	288:12 307:19	266:8 271:16
20:2,3,16 118:4	44:8 46:11,16	388:5 391:6	312:12 315:12	277:11 284:1

288:16 299:10,20 329:20 <b>runs</b> 16:7,13 17:6 20:6 25:2 <b>RUP</b> 360:10 <b>rural</b> 260:2 284:9 359:19 <b>R2D2</b> 417:21	401:16 415:1,5 417:15 <b>sampled</b> 12:21 13:22 15:15 16:10 18:20 19:15,16 265:21 273:7,17 273:22 288:20 291:21 <b>samplers</b> 84:21 <b>samples</b> 15:8,21 21:15 23:4 45:8 49:16,21 71:16 83:16 85:19 166:14 214:4 225:10 231:8 243:22 245:21 259:11 263:6,7 264:1,2,5,6,8 265:7,8 266:10,14 266:14,15 271:16 271:20 272:3,4 273:7 274:17 275:3,10 276:13 280:14 282:6 284:6,22 287:19 298:12 301:22 302:16 315:19 316:2 327:1,7 331:4,19,22 332:3 332:13 335:4 336:21 362:14,16 <b>sampling</b> 11:14 12:2,7,17 13:14 13:17,19,20 14:3 14:15,17 16:1,3,4 16:9,15 17:16 18:10 19:20 20:10 21:5,9,13,16 23:16,19,22 24:3 30:21,21 49:20 64:20 65:7 70:6 71:10 74:13,19 75:1,13,18 76:1,3 76:17 77:20 78:2 78:22 80:14,17 81:19 82:6 83:18 83:22 84:19,20	85:14 86:12,19 88:10,20,22,22 91:4,16,18,19 92:6 167:7 200:12 260:15,16 263:5 265:4,12 266:1 269:19 271:1,15 272:6,17 273:4,18 274:13 279:7,13 279:18 280:10,17 280:22 281:1,4,9 281:11,14 282:1 283:7 284:2 288:6 293:1,6 296:6,10 298:11,15 308:1 327:3 334:11,22 336:9,13 337:17 379:19 382:3 <b>San</b> 7:16 <b>Sanderson</b> 164:20 167:13 171:21 <b>sane</b> 128:7 <b>Santa</b> 8:18 <b>SAP</b> 1:4,19 5:5 35:8 70:16 77:3 94:5 105:7 106:1 113:3 119:1,5 122:18 123:19 135:20 137:18 139:19 140:1 153:8 154:18 156:20 280:19 325:2 333:7 369:9 369:11,20 374:12 374:19 375:18 376:21 377:8,12 378:5 379:1 382:18 385:6 388:6 406:8 409:3 <b>SAPs</b> 113:7,11 123:4,6,12,17,17 375:1 <b>Sass</b> 339:7,8,10,14 364:22 365:18 366:6 375:7 <b>Sass's</b> 374:13 <b>sat</b> 94:2 318:2	<b>satellites</b> 129:10 <b>satisfied</b> 393:16 <b>satisfies</b> 49:8 <b>satisfy</b> 50:21 <b>satisfying</b> 415:13 <b>save</b> 222:4 297:15 <b>savings</b> 86:2 <b>saw</b> 18:1 24:10 29:5 33:17 34:3 69:3 130:20 167:11 224:16 231:22 240:4 249:14 286:10 317:13 390:10 <b>saying</b> 74:14 81:5 89:14 158:13 160:18 226:16 227:14 259:9 298:9 301:18 306:7 321:14,20 324:14 373:15 388:4 405:17 414:3 415:15 417:5 422:17 423:4,7,9,10 <b>says</b> 11:2 91:8 393:17 <b>scaffold</b> 171:16 <b>scale</b> 34:13 35:2 45:14 60:4 61:5 95:8 110:12 130:1 178:7 210:4 317:21 <b>scales</b> 293:15,16 <b>scaling</b> 46:9 <b>scenarios</b> 91:17 <b>schedule</b> 272:3 <b>scheduled</b> 118:18 <b>schedules</b> 13:18 <b>schema</b> 189:2 <b>schematic</b> 157:10 <b>scheme</b> 21:9 158:16 291:22 <b>Schlenk</b> 1:23 6:1,1 176:7,8 226:12,14 226:22 227:11,21 228:4,8	<b>Schlenk's</b> 180:4 <b>school</b> 6:21 100:22 <b>science</b> 2:1 9:22 105:8 107:21 108:1 109:20 116:16 117:8 118:3,20 122:1 163:2 333:14 345:11 383:1 <b>Sciences</b> 6:3 7:3,22 193:20 <b>science-based</b> 376:14 377:20,21 <b>scientific</b> 1:4 91:20 92:1 93:4 114:1 114:20 117:18 119:11 120:10 121:13 325:7 342:11 343:1,1 345:7 346:1,16 355:5 357:2 363:11 364:9 377:18 378:22 382:17 384:10 419:14 <b>scientifically</b> 82:22 115:19 <b>scientist</b> 105:16 303:11 339:15 418:22 420:8 <b>scientists</b> 107:7 123:2 <b>scope</b> 89:11 365:8 <b>Scott</b> 368:12,20 373:3 <b>scrambled</b> 175:2 <b>scratching</b> 232:5 <b>screamed</b> 286:11 <b>screen</b> 89:1 143:13 <b>screening</b> 73:3 150:11 330:21 <b>scrutinized</b> 369:17 <b>SD</b> 394:20,21 395:5 397:5,6 398:20 <b>SDWA</b> 262:16,21 263:9 265:15 266:3 269:9,15,19
<b>S</b>				
<b>S</b> 184:1,1,1 <b>sacrifice</b> 203:5 <b>sacrifices</b> 187:21 <b>safe</b> 90:9 114:16 121:10,11,12,21 122:1 259:10 262:13 317:2 325:15 376:4,16 379:6 382:21 <b>safer</b> 346:5 <b>safest</b> 114:21 <b>safety</b> 99:2 117:16 117:17,20 120:13 127:7 134:12 140:22 238:2 258:3,21 259:6 310:14,15,17,17 311:11 312:3 319:20 383:1 <b>sagittal</b> 223:2 <b>salamander</b> 355:17 <b>sale</b> 130:4 <b>saline</b> 254:17 <b>sample</b> 22:20 23:4 47:22 63:7 64:7 73:6 79:4 83:18 84:13 85:16 145:12 190:12 200:7 228:3 244:1 262:1 268:19 292:7 293:11,15 293:20 294:14,18 294:21 301:13,14 301:20 302:11 330:16 331:1,3 337:20,22 362:3 371:22 382:1				

284:6 309:14	15:13 16:7,21	386:15 395:15	142:15 144:9,20	328:14,20 329:19
<b>se</b> 407:4	19:18 22:11 24:22	396:16 398:3	146:19 147:2,12	330:8 334:4
<b>sea</b> 98:2,2	25:18 31:5 35:8	399:6 405:12,17	148:13 154:12	378:21
<b>seas</b> 98:3	40:19 41:5 45:6,9	408:8 409:21	157:16	<b>servicing</b> 4:5 379:2
<b>season</b> 13:22 19:17	46:8 47:11 56:9	413:4,22 414:5	<b>senior</b> 134:10	<b>session</b> 1:18,21
20:11 71:16 264:3	58:21 64:17 69:3	415:22 416:6	258:3	4:14 5:4 8:6 10:1
266:7 271:17	69:4 70:5,6 73:18	421:14,18 423:9	<b>sense</b> 45:5 84:7	24:8 25:20 26:22
279:18 316:7	76:15 77:19 78:12	<b>seed</b> 46:7	94:1 128:9 281:18	30:4 32:6 33:7,10
<b>seasonal</b> 13:21	109:5,9 113:14	<b>seeing</b> 34:19	291:5 305:6 418:9	35:4,14,18 51:16
23:22 87:1 358:9	134:1 144:4 145:2	144:12 151:19	423:17	53:17 57:13 58:20
<b>Seasonally</b> 21:13	145:11,21 146:9	159:18 169:14	<b>sensitive</b> 186:14,18	59:5,20 60:3,10
<b>seasons</b> 101:22	146:19,20 149:13	228:12 234:7	210:9 220:22	60:21 61:7,14,20
<b>second</b> 5:12 32:9	152:3 153:13	341:10 392:18	241:1 242:13	62:16,20 63:1,4
38:6 40:6 41:4	162:15 165:2,3,5	414:22	330:21 407:21	65:8 67:9 69:5
47:22 55:16 94:19	165:7,14 166:3,16	<b>seeking</b> 24:4	<b>sensitivity</b> 153:19	79:22 83:8 86:3
122:17 145:19	167:17 169:4,10	<b>seen</b> 22:13 89:18	153:21 185:18	90:22 93:18 96:6
150:9 159:8	170:4,5,8,12,15	114:6 145:11	192:20 195:19	96:17 119:6 124:7
219:22 229:7	187:20 188:5	195:3 207:15	196:8 209:16,19	125:2 126:19
264:9 268:15	190:13 191:16	215:12 216:16	209:20 219:15	128:4 131:1
274:10 296:18	194:22 195:8	238:12 245:4	225:20 394:21	133:10 135:9
303:5 343:21	196:9 197:7,13,16	251:17 252:20	395:19	155:13 157:3
372:7 390:7	198:21 199:2	257:8 258:13	<b>sensitized</b> 60:2	160:9,13 162:20
<b>secondary</b> 168:9	200:6,11,14 201:9	260:17 267:21	<b>sensor</b> 354:5	176:5 178:19
195:1 217:4	201:14,18 205:5,8	271:4 315:4	<b>sentence</b> 154:21	180:1 182:18
<b>secondly</b> 180:14	206:14,17 207:9	329:18 335:6	<b>separate</b> 34:15	183:10 184:3
<b>secreted</b> 208:7	207:11,18 208:9	395:21 397:17	88:3 94:13 119:1	193:8,16 200:13
<b>secretion</b> 148:2	208:12 210:7	412:22 420:16	185:19 188:12	218:8 221:3
153:15,16 194:19	211:8,19 212:16	<b>segue</b> 235:17	218:18 291:4	223:12 226:12
197:16 199:16	214:11,13,15	<b>select</b> 55:18	292:21 326:7	229:4 232:9 234:3
200:5,8,22 202:6	218:1 219:11	<b>selected</b> 49:3	411:5 424:4	249:1 250:11
214:2 215:7,16	225:2 228:1,2,17	189:17 239:1	<b>separately</b> 34:22	251:13 252:21
218:2,22 219:7	230:15,19 232:2	352:10	110:19	254:7 255:6 256:9
221:1 390:6	233:5 236:6	<b>selection</b> 53:11	<b>September</b> 77:4	283:17 285:4
<b>secretions</b> 215:11	239:14,19 240:9	<b>selective</b> 210:7	94:8 124:4	287:10 290:1
217:7	241:3,8,12,14,19	<b>selectively</b> 266:9	<b>sequence</b> 134:22	297:14 301:1
<b>secretory</b> 194:4	244:14,18 245:14	<b>Selvage</b> 2:16 8:2,2	<b>series</b> 18:12,12	302:19 319:5
<b>section</b> 76:11 135:4	252:12,19 253:16	10:2 180:22,22	50:8 66:16 140:11	323:3,7,17 324:1
137:9,14 138:10	265:20,22 266:4,5	221:4,5,16,20	168:11 171:14	324:10,21 338:8
183:1 385:11	266:9 267:10,15	222:2,5,7,15,20	202:8 206:8 212:9	338:11,16 339:2,6
<b>sections</b> 184:8	268:4 269:8,16	223:1,10 233:10	242:14 286:3,12	364:18 366:10
257:14 386:9	277:6 291:18	233:10 251:14,15	<b>seriously</b> 378:6	367:12,20 368:5
<b>sediment</b> 103:19	293:11 302:8	<b>semi</b> 32:22	<b>serum</b> 203:19	372:19 373:2
104:2 277:12	305:22 308:3,20	<b>semi-chronic</b>	353:1 390:20	379:8 383:3
299:10 380:11	309:14 311:21	334:15	<b>serve</b> 97:14 325:13	387:18 394:9
<b>sedimentation</b>	313:4 320:18	<b>send</b> 69:8	376:21	398:6 400:14
300:3	332:17 338:11	<b>senesce</b> 397:1	<b>serves</b> 330:9	404:7 405:6,10
<b>see</b> 4:12 14:17 15:8	341:3 364:15	<b>senescence</b> 142:12	<b>service</b> 102:14	406:16 407:14

408:5,18 410:6,15 411:19 413:7 416:16 418:15 419:19 421:5 423:16 425:7,9 <b>set</b> 39:12 47:19 53:13 55:18 56:14 57:8,10 58:10 63:13 65:18 66:12 67:13 68:14 71:14 74:12,18,20 75:1 165:9 172:10 175:1 186:2 190:11 264:11 265:6 271:18,20 275:13,19 279:4 279:10,21 288:4 289:8 291:15,16 300:13 308:13 319:11,13 332:16 335:17,19 337:4 340:11 409:4 411:13 414:8 <b>sets</b> 26:1 37:20 64:5 64:7 75:12 76:1 167:21 262:12 274:8,16 280:20 281:6,8 282:3 286:6 290:15 292:20 308:17 324:6 402:17 <b>setting</b> 237:4 393:20 <b>settles</b> 123:2 <b>settling</b> 277:14 <b>seven</b> 15:15 16:3,10 17:18 20:11 26:4 76:3 80:8 133:19 134:1 207:18 229:18 279:7,18 326:15 335:11 356:10 <b>seventh</b> 208:2,13 <b>seven-day</b> 16:19,20 17:1 26:3 88:16 273:15,18 281:11 283:2 292:11	308:21 <b>seven-year</b> 312:8,9 <b>severe</b> 63:22 115:9 <b>severely</b> 362:2 <b>sex</b> 140:14 142:2 156:12 224:1,5 225:4 351:18 388:13 <b>sexual</b> 191:2,7,9,21 <b>sham</b> 213:20 214:10 <b>shape</b> 21:17,21 42:9 45:12 46:1 52:20 53:1,3 72:8 76:7 282:13 <b>share</b> 105:22 107:17 138:6 139:4 323:15 378:17,18 <b>shared</b> 113:16 <b>sharp</b> 26:5 28:13 <b>sharper</b> 28:20 <b>shed</b> 403:14 <b>she'll</b> 99:8 <b>shift</b> 57:21,21 59:1 112:17,18,22 <b>shifted</b> 230:14,15 <b>shifts</b> 143:12 <b>shoot</b> 222:11 421:4 <b>short</b> 27:20 79:16 119:13 137:14 163:13 165:12 166:11 178:7,21 182:10 184:18 186:2 254:6 255:18 267:8 283:4 292:15 293:4,15,16 312:22 313:5 324:6,20 347:18 387:22 <b>shortening</b> 424:11 <b>shorter</b> 17:18 21:4 71:20 77:1,5 95:7 178:6 186:1,11 272:17 274:12 311:20 335:5	339:13 <b>shorter-term</b> 288:3 <b>shortly</b> 137:7 212:12 246:19 <b>short-term</b> 27:16 52:13 53:6 187:19 288:15 389:15 <b>shoulder</b> 328:12 <b>show</b> 15:2,20 16:12 17:21 36:5,7 74:18 121:2 151:13 164:14 167:18 168:6 174:1 189:13 195:21 200:19,21 201:16 206:5 210:5 212:3 216:10 229:15 230:2 232:5 237:19 252:2 258:16 271:2 283:6 284:19 292:12 293:5 361:20 <b>showed</b> 142:10 143:4,18 170:13 171:18 172:12 173:20 179:13 194:5 200:20 228:15 229:17,22 231:8 252:19 253:1,14 311:14 319:10 321:7 351:19 361:17 371:17 <b>showing</b> 50:6 146:4 172:17 195:4 206:11 216:7 298:8 316:10 359:14 395:16 421:18 <b>shown</b> 22:3 144:22 148:22 163:15,19 164:4,20 165:10 168:21 169:6,20 184:22 191:4 197:22 201:3	209:3 245:2 254:21 312:1 337:11 344:16 347:11 348:3 355:12 <b>shows</b> 21:8 39:9 46:5 47:14 48:9 145:16 198:2 265:13,14 287:2 307:9 379:22 392:21 <b>side</b> 84:18 86:10 195:8 205:4 255:8 256:6 278:21 298:17 301:5 303:16,19 327:2 331:10 423:2,3 <b>Sielken</b> 272:19,19 291:6,7 296:4 302:2,4,5,17 304:7 305:12 <b>sign</b> 119:11 241:22 272:12 <b>signal</b> 172:14 390:18 <b>signaling</b> 173:1 <b>signed</b> 111:15 <b>significance</b> 151:9 206:19 209:11 234:20 235:7 395:7 403:11 415:3 <b>significant</b> 100:9 102:6 111:15 114:6 122:13 128:18 136:10 166:18 192:13,16 206:16 230:3 234:11 242:8,9 263:18 308:4 331:8 351:12 352:14,16,18 353:18 354:2,3,11 356:2,8 357:5 358:11 359:21 396:13 417:2 <b>significantly</b>	241:16 268:6 <b>silt</b> 100:20 <b>simazine</b> 86:21 89:19 326:18 <b>similar</b> 13:13 20:17 21:7 56:9 97:11 109:12 110:2 111:11 120:12 132:6,18 152:22 155:8 159:18 163:22 167:16 185:22 211:2 213:4 241:11 243:2 244:19 245:3 247:14 257:4 265:6 268:11,13 274:5 281:7 319:9 353:5 397:12 <b>similarly</b> 47:1 209:12 240:2 242:21 246:2 254:4 <b>Simpkins</b> 134:4 136:3,17 151:15 161:3 162:22,22 176:17 177:14 179:6 181:7 304:5 317:11 <b>simple</b> 27:18 73:19 73:20 79:19 88:4 128:12 188:15 242:5 <b>simpler</b> 101:5 336:14 <b>simplest</b> 86:20 <b>simplify</b> 78:16 300:15 <b>simplistic</b> 73:10 <b>simply</b> 18:11 45:11 45:14 114:18,18 116:7 130:21 161:17 164:8 318:7 338:4 396:15 397:22 <b>simulate</b> 11:18 36:8 46:20,21
---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

47:3 50:10,11,14 50:16,18 58:5 60:16 64:19 65:1 <b>simulated</b> 271:20 279:6,9,11 288:1 302:7 <b>simulation</b> 30:11 60:17 62:13 279:5 302:16 <b>simulations</b> 46:6 49:1 <b>single</b> 13:8,11 14:7 14:18 15:14,14,17 16:18 17:9,19 18:3 98:8 140:14 140:14,14 171:12 184:20 212:17 215:16,20 239:10 239:16 330:15 <b>single-day</b> 17:1 306:11 <b>sips</b> 85:15 <b>sir</b> 156:6 157:2 182:17 183:9 <b>siRNA</b> 174:10 175:3 <b>siRNAs</b> 174:12,13 <b>sister</b> 149:22 <b>sit</b> 134:3 304:4,5 <b>site</b> 62:6 83:17 84:13 104:22 140:14 174:3 290:20 294:13 295:8,9 337:8 <b>sites</b> 75:6,17 140:10 140:16,18,19 265:1 266:19 267:19 276:14,16 288:21 289:5 294:10,17,18,19 294:20 296:2 396:8 <b>site's</b> 294:22 <b>site-by-site</b> 285:12 <b>sitting</b> 425:10 <b>situ</b> 196:17 198:6 <b>situation</b> 81:19	178:2 <b>six</b> 10:11 15:10 93:2 144:16 185:15 194:13 244:1 248:11 250:18 264:18 271:17 276:7 332:9 363:2 391:4 <b>six-hour</b> 244:1 <b>six-month</b> 144:3 185:12 <b>six-year</b> 332:7 <b>size</b> 28:14,20 29:13 33:22 34:4 72:14 72:15 169:8 231:7 371:22 401:16 411:15 415:1,5 417:15 <b>sizes</b> 22:20 23:4 29:20 268:19 <b>skin</b> 359:6,8 <b>skinny</b> 19:2 <b>Slaughter</b> 368:13 368:20,21 372:22 <b>sleep</b> 340:22 <b>sleeves</b> 124:3 <b>slices</b> 201:2 223:3 306:7 <b>slide</b> 19:14 57:15 93:21 140:5 143:4 143:19,22 149:13 149:14 150:17 153:6,12 154:17 157:5 163:16,20 185:21 186:5,15 188:19 189:1 190:4,18 191:6 192:10,18 197:22 198:2 200:20 226:16 227:12 244:7 285:7 287:13 298:7 317:12,18,19 319:8,9 320:7 <b>slides</b> 143:18 149:6 155:17 169:6 170:14 183:3	212:10 267:4 302:22 303:4 324:16 <b>slight</b> 161:21 <b>slightly</b> 119:8 249:21 401:8 402:15 414:11 416:4 <b>slopes</b> 241:15 <b>slotted</b> 340:19 <b>slower</b> 29:7 <b>slowly</b> 15:5 175:19 230:18 <b>small</b> 49:13 60:4 99:14 129:16 166:17 172:21 199:22 226:2 228:9 229:20 276:7,9,9,21 277:4 329:13 330:8 401:16 415:1 421:3 <b>smaller</b> 28:20 30:3 68:8 82:14 284:10 299:3 346:3 <b>smallest</b> 129:20 <b>smart</b> 23:19 <b>smarter</b> 72:17 <b>smearing</b> 191:8 <b>smears</b> 143:20 <b>smooth</b> 42:19 300:13 <b>smoothing</b> 52:14 63:19 65:11 100:16 290:6 <b>snapshot</b> 95:3 230:7 <b>Social</b> 9:20 <b>society</b> 5:15 100:9 107:21 108:2 109:21 129:16 <b>soil</b> 100:6,14,18,19 101:1,5,7,11,22 102:1,4,10,11,15 102:17 103:5,7,17 103:18 104:3,4 <b>sold</b> 356:13	<b>Soldin</b> 210:12 <b>solid</b> 123:13 294:1 <b>solubility</b> 169:13 169:18 176:21 181:15 182:1 317:15,20,22 <b>solubilize</b> 169:12 <b>soluble</b> 380:14 382:12 <b>solution</b> 169:15 317:14 <b>solutions</b> 169:5 <b>somebody</b> 275:17 313:19 <b>something's</b> 187:18 420:19 <b>somewhat</b> 15:5 113:8 128:21 129:14 131:8 159:7 235:21 268:11 396:16 <b>soon</b> 69:1 167:9 328:17 333:12,18 335:13 <b>sorghum</b> 97:8,10 <b>sorry</b> 12:19 28:17 45:8 160:15 177:21 256:12 278:10 310:7 323:2 349:2 384:5 <b>sort</b> 26:13 32:22 37:9 40:2 41:6,11 42:3,9 48:9 49:12 52:19 53:5 54:11 55:1 63:2 68:15 84:1 85:2 95:3 163:4 177:6 259:5 264:5 272:10 274:18,20 279:5 293:2 300:9 327:2 328:19 340:3 356:15 413:16 416:15 <b>sorts</b> 55:15 382:19 <b>sound</b> 114:1 118:20 <b>sounds</b> 27:3 <b>source</b> 38:10 54:22	107:22 108:5 177:5 270:6 271:19 272:13 280:14 282:11 286:1 299:4 319:18 320:20 321:5,12 322:11 328:2 329:5,16 <b>sources</b> 26:5 54:5 55:22 56:5 172:7 177:11 262:11 298:10 331:22 333:4 375:15 <b>sourcing</b> 270:2 <b>South</b> 349:14 <b>space</b> 290:8 293:19 361:7 <b>span</b> 119:3 146:21 <b>spanned</b> 354:5 <b>spanning</b> 41:5 <b>parser</b> 63:21 <b>spatial</b> 23:20 70:20 77:16 282:20 <b>spatially</b> 70:2,5 71:5 <b>speak</b> 36:1 138:16 151:6 237:2 406:5 <b>speaker</b> 135:17 339:7 <b>speakers</b> 11:8 134:22 348:5 <b>speaking</b> 91:15 185:12 <b>speaks</b> 55:1 <b>special</b> 90:14 97:17 108:22 113:4,6 118:21 125:11 187:18 <b>specialist</b> 7:4 <b>specialty</b> 7:17 <b>species</b> 142:1 156:19 163:12 170:9 172:22 173:16 174:10 218:13 229:10 349:21 350:11 <b>specific</b> 84:20 87:9
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

87:17,19 105:1 127:9 142:2 178:14 179:7,8 210:9 224:9 247:17 308:20 309:21 310:5 336:6,17 337:1 374:4 375:13,16 377:22 395:18 404:16 422:5 <b>specifically</b> 128:1 156:11 185:6 234:2 352:8 <b>specificity</b> 142:22 225:19 <b>specified</b> 77:22 <b>spectrometry</b> 203:19 <b>spend</b> 10:9,13 193:22 194:11 384:2 <b>spending</b> 235:19 375:10 <b>spent</b> 130:16 194:17 276:6 304:1 323:13 419:20 <b>sperm</b> 349:1 350:7 359:19 <b>spikes</b> 358:9 <b>spiking</b> 363:1 <b>spills</b> 359:5 <b>spite</b> 129:4,4 <b>splashes</b> 359:6 <b>spleen</b> 240:17 251:18,20 <b>spoke</b> 145:10 146:19 287:11 <b>sponsored</b> 237:18 <b>sporadic</b> 166:11 <b>spot</b> 48:10,19 49:7 <b>Sprague</b> 140:11,13 140:17 142:10,11 142:15 143:8 144:7 145:19 146:1,12,17,20 147:3,14,18,21	148:3,6 150:21 152:9 155:8 157:6 157:17 185:14 186:13 202:12 207:22 215:18 243:6 384:19,22 385:4 388:11,17 397:17 413:12 <b>spray</b> 128:20 <b>sprayer</b> 129:10 130:3 <b>spreadsheet</b> 338:1 <b>spring</b> 330:2 336:22 358:1,5 <b>square</b> 275:16 276:10 <b>St</b> 290:18 <b>stack</b> 111:5 <b>staff</b> 297:18 325:19 338:2 373:13 <b>stage</b> 237:4 368:16 <b>stages</b> 127:3,11 346:18 347:19 376:18 411:1 <b>staggering</b> 105:9 <b>stakeholder</b> 119:16 <b>stakeholders</b> 118:11 <b>stance</b> 395:14 <b>stand</b> 303:8 <b>standard</b> 68:12 120:10 159:9 285:1 328:13,19 337:7,17 <b>standards</b> 204:13 210:6 332:9 <b>standpoint</b> 85:2 307:4 374:8 <b>standpoints</b> 117:2 <b>stands</b> 146:20 <b>star</b> 37:10 <b>start</b> 5:18 10:21 14:5 24:11 34:17 51:19 56:13,18 57:7 67:18 68:1 69:2,20 71:9 74:6 97:1 112:16	144:11 169:14 232:11 235:3,8 261:6 301:7 306:7 308:7 316:11 324:14,17 338:20 384:9 387:18 388:4 421:3 425:13 <b>started</b> 4:3 72:21 74:5,14 94:1 99:20 110:4 141:3 151:3 187:4 233:3 341:20 <b>starting</b> 17:7 68:2 74:12 144:4 <b>starts</b> 144:9 146:20 <b>state</b> 4:20 6:8,13 8:3 9:15 119:22 129:3 332:16,18 336:4 343:1 352:6 369:13 371:7 397:2 <b>stated</b> 118:16 <b>statement</b> 127:6 183:6,7 288:10 309:17 393:17 423:20 <b>statements</b> 156:8 <b>states</b> 33:16 97:20 98:4 102:15 103:21 110:5 111:7 132:9 262:15 263:21 265:3 332:6 378:20 <b>static</b> 270:6,12 272:5 280:14 <b>statistic</b> 37:5 48:1 <b>statistical</b> 83:12 84:3 85:2 159:6 235:5,6 236:16 297:3 325:17 326:3 354:17 415:2 420:22 <b>statistically</b> 166:15 192:13 351:12 352:14,16,18	353:18 354:11 359:21 417:2 <b>statistician</b> 9:20 35:21 326:10 <b>statisticians</b> 45:5 69:6 91:10 315:20 416:18 421:8 <b>statistics</b> 5:14 8:15 8:19 25:18 29:6 37:4 43:22 111:14 191:4 304:8 305:1 415:3 419:2,22 <b>status</b> 149:14 <b>statutory</b> 309:13 309:17 <b>stay</b> 175:14,20 <b>steadily</b> 102:12 121:4 <b>steeper</b> 268:11 <b>step</b> 25:4 150:18 195:14 314:13 328:1 391:8 <b>stepwise</b> 291:11 376:14 <b>steroid</b> 204:4,17,19 204:21 205:12 208:6 225:22 <b>steroidogenesis</b> 387:6 <b>steroidogenic</b> 205:1 <b>steroids</b> 204:13 205:10 <b>Steve</b> 6:15 9:18 90:15 91:15 138:15 202:19 210:12 <b>Steven</b> 1:17,20 2:8 <b>steward</b> 99:1 <b>stewards</b> 103:1 <b>stewardship</b> 100:1 104:8,18,21 105:2 114:7 121:6 268:9 329:5 <b>stick</b> 338:2 <b>stimulate</b> 390:21 <b>stimulation</b> 195:9	<b>stochastic</b> 28:9 265:18 <b>Stoker</b> 185:5 <b>stop</b> 11:2 51:14 133:11,21 193:3 <b>storage</b> 277:16,21 <b>store</b> 315:21 <b>stored</b> 85:19 <b>story</b> 120:18 <b>straight</b> 170:10 236:14 <b>straightforward</b> 58:17 <b>strain</b> 142:2 389:10 395:18 <b>strains</b> 144:13 388:12 <b>strange</b> 397:21 <b>strategies</b> 12:2,7 13:15 14:15 17:15 21:14,16 23:20 36:11 44:21 45:3 50:20 63:7 64:8 336:6 <b>strategy</b> 13:21 14:3 49:2,3 83:21 334:11 335:20 <b>stratified</b> 264:2 271:16 <b>stratify</b> 30:8 <b>stream</b> 29:14 66:13 277:4 298:21 <b>streams</b> 56:11 75:14 104:1 261:11 276:7 <b>Street</b> 1:17 <b>strength</b> 142:22 399:12 413:3 <b>strengthened</b> 153:2 <b>stress</b> 7:18 8:3 208:20 224:2 238:3 241:10 243:12,13,14,17 243:20 252:3,7,16 253:20 254:1,5 395:20 396:3,9 397:19
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<b>stressor</b> 208:22 224:6,8	210:22 212:10 213:10 216:7	246:11 249:10,12 250:9 256:13,18	288:11	269:2 373:14 388:3	
<b>stressors</b> 240:13 244:12,16,19 251:22 254:5	221:11 222:8 224:17 229:14 233:1 237:16,17	310:8,9,10 331:19 332:1 352:2,11,21 353:8,22 354:15	<b>succinate</b> 170:17 <b>succinctly</b> 337:10 <b>sucking</b> 183:11 <b>sudden</b> 294:2 <b>suffered</b> 115:9 <b>suffice</b> 238:13 310:22	<b>summarized</b> 337:11 <b>summarizing</b> 136:21 137:22 285:13,14	
<b>stretched</b> 341:11 341:13	237:22,22 242:6 242:15 246:4 247:12,22 248:14	354:17 355:10,16 356:5 357:5,13 371:9,21 401:10 401:14,19 402:11	<b>sufficient</b> 258:17 283:3 316:10 343:14 399:12 417:9	<b>summary</b> 3:18 23:17 43:21 50:4 69:9 93:19 255:10 267:8 271:8 340:12,13,13	
<b>strike</b> 181:18	249:14,21 250:5 253:11,12 257:8 257:10 284:8	417:4,6 418:7,8 419:6,8 420:5 421:1	<b>suggest</b> 48:14 91:15 122:19 123:19 196:7 199:11 219:3 281:9 282:4,8 283:12 337:15 345:19 385:12 402:17 403:9,21 412:12 413:5 419:15 421:22	<b>summed</b> 348:13 357:10 <b>summer</b> 116:4 175:6	
<b>strikes</b> 115:5	319:1 344:21 347:12 349:10,16 349:19,20 350:3 350:11 351:3,11 354:22 356:18	<b>studying</b> 168:12 <b>stuff</b> 59:6 69:14 127:16 183:4 222:11 277:13 307:11	<b>suggested</b> 156:1 233:19 344:13 356:5 <b>suggesting</b> 156:5 174:19 197:14 207:21 213:2 214:17 215:9 252:14 408:1 412:15	<b>summing</b> 60:13,19 <b>superb</b> 261:22 <b>superfusion</b> 201:7 223:4 <b>supervises</b> 261:19 <b>supplement</b> 90:9 <b>supplemental</b> 80:21 342:4 <b>supplied</b> 116:3 <b>supplies</b> 284:2 308:1 314:9 315:5 <b>supply</b> 259:9 277:3 277:17 299:7 300:10 379:7 383:2	
<b>striking</b> 146:10	357:19 359:17 365:5,13 366:14 366:14 368:2 369:16,19,20 370:3,4 372:6,8 372:11,13 385:11 387:14 394:6,13 395:22 396:11,14	<b>subgroup</b> 187:13 187:14 188:4 189:5 <b>subgroups</b> 191:14 191:16 <b>subject</b> 255:19 329:14 <b>submit</b> 139:7 228:21 282:10 <b>submitted</b> 110:5 119:5 137:2 225:10 326:14 373:12 <b>subsection</b> 135:7 <b>subset</b> 21:22 270:11 <b>subsets</b> 270:4 271:19,19 <b>subside</b> 54:6 <b>substances</b> 395:2 <b>substantial</b> 84:11 84:14 117:10 209:15 317:3 346:15 <b>substitute</b> 131:19 <b>subtypes</b> 181:9 <b>sub-chronic</b> 334:15 <b>success</b> 55:13	<b>sum</b> 260:20 266:11 355:9,11 <b>summarize</b> 17:11 215:13 248:2	<b>supported</b> 95:8 387:7 389:13 394:20 <b>supporting</b> 122:1 <b>supports</b> 395:14 <b>suppose</b> 54:20 365:14 <b>suppress</b> 160:20 <b>suppressed</b> 156:2 187:12 <b>suppressing</b> 394:19 <b>suppression</b> 148:10 160:16,22 162:13	
<b>string</b> 41:20	395:22 396:11,14 396:18,19,19 397:4,5,6,10 398:9 399:3,10 400:1,3 401:1,9 402:15 403:6,8 413:3,17,18 414:4 414:10 416:10,13 420:1,4,16 421:18 422:2,14,18	<b>subgroup</b> 187:13 187:14 188:4 189:5 <b>subgroups</b> 191:14 191:16 <b>subject</b> 255:19 329:14 <b>submit</b> 139:7 228:21 282:10 <b>submitted</b> 110:5 119:5 137:2 225:10 326:14 373:12 <b>subsection</b> 135:7 <b>subset</b> 21:22 270:11 <b>subsets</b> 270:4 271:19,19 <b>subside</b> 54:6 <b>substances</b> 395:2 <b>substantial</b> 84:11 84:14 117:10 209:15 317:3 346:15 <b>substitute</b> 131:19 <b>subtypes</b> 181:9 <b>sub-chronic</b> 334:15 <b>success</b> 55:13	<b>sum</b> 260:20 266:11 355:9,11 <b>summarize</b> 17:11 215:13 248:2	<b>study</b> 8:3 34:15,16 44:20 50:1 79:2 80:2 94:11 108:16 139:5 141:8 144:3 144:11,17 158:10 176:18 182:6 185:6,7,11,12 186:16,20 187:20 189:21 192:3 198:17 211:3 212:1 213:19 214:10 215:4 229:12 234:13 242:1 245:5 246:7	
<b>strips</b> 104:14,14	210:22 212:10 213:10 216:7 221:11 222:8 224:17 229:14 233:1 237:16,17 237:22,22 242:6 242:15 246:4 247:12,22 248:14 249:14,21 250:5 253:11,12 257:8 257:10 284:8 319:1 344:21 347:12 349:10,16 349:19,20 350:3 350:11 351:3,11 354:22 356:18 357:19 359:17 365:5,13 366:14 366:14 368:2 369:16,19,20 370:3,4 372:6,8 372:11,13 385:11 387:14 394:6,13 395:22 396:11,14 396:18,19,19 397:4,5,6,10 398:9 399:3,10 400:1,3 401:1,9 402:15 403:6,8 413:3,17,18 414:4 414:10 416:10,13 420:1,4,16 421:18 422:2,14,18	<b>studying</b> 168:12 <b>stuff</b> 59:6 69:14 127:16 183:4 222:11 277:13 307:11 <b>subgroup</b> 187:13 187:14 188:4 189:5 <b>subgroups</b> 191:14 191:16 <b>subject</b> 255:19 329:14 <b>submit</b> 139:7 228:21 282:10 <b>submitted</b> 110:5 119:5 137:2 225:10 326:14 373:12 <b>subsection</b> 135:7 <b>subset</b> 21:22 270:11 <b>subsets</b> 270:4 271:19,19 <b>subside</b> 54:6 <b>substances</b> 395:2 <b>substantial</b> 84:11 84:14 117:10 209:15 317:3 346:15 <b>substitute</b> 131:19 <b>subtypes</b> 181:9 <b>sub-chronic</b> 334:15 <b>success</b> 55:13	<b>sum</b> 260:20 266:11 355:9,11 <b>summarize</b> 17:11 215:13 248:2		
<b>strong</b> 171:22 395:21 411:18 412:6	210:22 212:10 213:10 216:7 221:11 222:8 224:17 229:14 233:1 237:16,17 237:22,22 242:6 242:15 246:4 247:12,22 248:14 249:14,21 250:5 253:11,12 257:8 257:10 284:8 319:1 344:21 347:12 349:10,16 349:19,20 350:3 350:11 351:3,11 354:22 356:18 357:19 359:17 365:5,13 366:14 366:14 368:2 369:16,19,20 370:3,4 372:6,8 372:11,13 385:11 387:14 394:6,13 395:22 396:11,14 396:18,19,19 397:4,5,6,10 398:9 399:3,10 400:1,3 401:1,9 402:15 403:6,8 413:3,17,18 414:4 414:10 416:10,13 420:1,4,16 421:18 422:2,14,18	<b>studying</b> 168:12 <b>stuff</b> 59:6 69:14 127:16 183:4 222:11 277:13 307:11 <b>subgroup</b> 187:13 187:14 188:4 189:5 <b>subgroups</b> 191:14 191:16 <b>subject</b> 255:19 329:14 <b>submit</b> 139:7 228:21 282:10 <b>submitted</b> 110:5 119:5 137:2 225:10 326:14 373:12 <b>subsection</b> 135:7 <b>subset</b> 21:22 270:11 <b>subsets</b> 270:4 271:19,19 <b>subside</b> 54:6 <b>substances</b> 395:2 <b>substantial</b> 84:11 84:14 117:10 209:15 317:3 346:15 <b>substitute</b> 131:19 <b>subtypes</b> 181:9 <b>sub-chronic</b> 334:15 <b>success</b> 55:13	<b>sum</b> 260:20 266:11 355:9,11 <b>summarize</b> 17:11 215:13 248:2		
<b>strongly</b> 149:17	210:22 212:10 213:10 216:7 221:11 222:8 224:17 229:14 233:1 237:16,17 237:22,22 242:6 242:15 246:4 247:12,22 248:14 249:14,21 250:5 253:11,12 257:8 257:10 284:8 319:1 344:21 347:12 349:10,16 349:19,20 350:3 350:11 351:3,11 354:22 356:18 357:19 359:17 365:5,13 366:14 366:14 368:2 369:16,19,20 370:3,4 372:6,8 372:11,13 385:11 387:14 394:6,13 395:22 396:11,14 396:18,19,19 397:4,5,6,10 398:9 399:3,10 400:1,3 401:1,9 402:15 403:6,8 413:3,17,18 414:4 414:10 416:10,13 420:1,4,16 421:18 422:2,14,18	<b>studying</b> 168:12 <b>stuff</b> 59:6 69:14 127:16 183:4 222:11 277:13 307:11 <b>subgroup</b> 187:13 187:14 188:4 189:5 <b>subgroups</b> 191:14 191:16 <b>subject</b> 255:19 329:14 <b>submit</b> 139:7 228:21 282:10 <b>submitted</b> 110:5 119:5 137:2 225:10 326:14 373:12 <b>subsection</b> 135:7 <b>subset</b> 21:22 270:11 <b>subsets</b> 270:4 271:19,19 <b>subside</b> 54:6 <b>substances</b> 395:2 <b>substantial</b> 84:11 84:14 117:10 209:15 317:3 346:15 <b>substitute</b> 131:19 <b>subtypes</b> 181:9 <b>sub-chronic</b> 334:15 <b>success</b> 55:13	<b>sum</b> 260:20 266:11 355:9,11 <b>summarize</b> 17:11 215:13 248:2		
<b>struck</b> 374:13 378:19 380:5	210:22 212:10 213:10 216:7 221:11 222:8 224:17 229:14 233:1 237:16,17 237:22,22 242:6 242:15 246:4 247:12,22 248:14 249:14,21 250:5 253:11,12 257:8 257:10 284:8 319:1 344:21 347:12 349:10,16 349:19,20 350:3 350:11 351:3,11 354:22 356:18 357:19 359:17 365:5,13 366:14 366:14 368:2 369:16,19,20 370:3,4 372:6,8 372:11,13 385:11 387:14 394:6,13 395:22 396:11,14 396:18,19,19 397:4,5,6,10 398:9 399:3,10 400:1,3 401:1,9 402:15 403:6,8 413:3,17,18 414:4 414:10 416:10,13 420:1,4,16 421:18 422:2,14,18	<b>studying</b> 168:12 <b>stuff</b> 59:6 69:14 127:16 183:4 222:11 277:13 307:11 <b>subgroup</b> 187:13 187:14 188:4 189:5 <b>subgroups</b> 191:14 191:16 <b>subject</b> 255:19 329:14 <b>submit</b> 139:7 228:21 282:10 <b>submitted</b> 110:5 119:5 137:2 225:10 326:14 373:12 <b>subsection</b> 135:7 <b>subset</b> 21:22 270:11 <b>subsets</b> 270:4 271:19,19 <b>subside</b> 54:6 <b>substances</b> 395:2 <b>substantial</b> 84:11 84:14 117:10 209:15 317:3 346:15 <b>substitute</b> 131:19 <b>subtypes</b> 181:9 <b>sub-chronic</b> 334:15 <b>success</b> 55:13	<b>sum</b> 260:20 266:11 355:9,11 <b>summarize</b> 17:11 215:13 248:2		
<b>structure</b> 45:22 55:4 67:18 68:7 84:8	210:22 212:10 213:10 216:7 221:11 222:8 224:17 229:14 233:1 237:16,17 237:22,22 242:6 242:15 246:4 247:12,22 248:14 249:14,21 250:5 253:11,12 257:8 257:10 284:8 319:1 344:21 347:12 349:10,16 349:19,20 350:3 350:11 351:3,11 354:22 356:18 357:19 359:17 365:5,13 366:14 366:14 368:2 369:16,19,20 370:3,4 372:6,8 372:11,13 385:11 387:14 394:6,13 395:22 396:11,14 396:18,19,19 397:4,5,6,10 398:9 399:3,10 400:1,3 401:1,9 402:15 403:6,8 413:3,17,18 414:4 414:10 416:10,13 420:1,4,16 421:18 422:2,14,18	<b>studying</b> 168:12 <b>stuff</b> 59:6 69:14 127:16 183:4 222:11 277:13 307:11 <b>subgroup</b> 187:13 187:14 188:4 189:5 <b>subgroups</b> 191:14 191:16 <b>subject</b> 255:19 329:14 <b>submit</b> 139:7 228:21 282:10 <b>submitted</b> 110:5 119:5 137:2 225:10 326:14 373:12 <b>subsection</b> 135:7 <b>subset</b> 21:22 270:11 <b>subsets</b> 270:4 271:19,19 <b>subside</b> 54:6 <b>substances</b> 395:2 <b>substantial</b> 84:11 84:14 117:10 209:15 317:3 346:15 <b>substitute</b> 131:19 <b>subtypes</b> 181:9 <b>sub-chronic</b> 334:15 <b>success</b> 55:13	<b>sum</b> 260:20 266:11 355:9,11 <b>summarize</b> 17:11 215:13 248:2		
<b>structures</b> 336:9 347:7	210:22 212:10 213:10 216:7 221:11 222:8 224:17 229:14 233:1 237:16,17 237:22,22 242:6 242:15 246:4 247:12,22 248:14 249:14,21 250:5 253:11,12 257:8 257:10 284:8 319:1 344:21 347:12 349:10,16 349:19,20 350:3 350:11 351:3,11 354:22 356:18 357:19 359:17 365:5,13 366:14 366:14 368:2 369:16,19,20 370:3,4 372:6,8 372:11,13 385:11 387:14 394:6,13 395:22 396:11,14 396:18,19,19 397:4,5,6,10 398:9 399:3,10 400:1,3 401:1,9 402:15 403:6,8 413:3,17,18 414:4 414:10 416:10,13 420:1,4,16 421:18 422:2,14,18	<b>studying</b> 168:12 <b>stuff</b> 59:6 69:14 127:16 183:4 222:11 277:13 307:11 <b>subgroup</b> 187:13 187:14 188:4 189:5 <b>subgroups</b> 191:14 191:16 <b>subject</b> 255:19 329:14 <b>submit</b> 139:7 228:21 282:10 <b>submitted</b> 110:5 119:5 137:2 225:10 326:14 373:12 <b>subsection</b> 135:7 <b>subset</b> 21:22 270:11 <b>subsets</b> 270:4 271:19,19 <b>subside</b> 54:6 <b>substances</b> 395:2 <b>substantial</b> 84:11 84:14 117:10 209:15 317:3 346:15 <b>substitute</b> 131:19 <b>subtypes</b> 181:9 <b>sub-chronic</b> 334:15 <b>success</b> 55:13	<b>sum</b> 260:20 266:11 355:9,11 <b>summarize</b> 17:11 215:13 248:2		
<b>struggled</b> 32:10	210:22 212:10 213:10 216:7 221:11 222:8 224:17 229:14 233:1 237:16,17 237:22,22 242:6 242:15 246:4 247:12,22 248:14 249:14,21 250:5 253:11,12 257:8 257:10 284:8 319:1 344:21 347:12 349:10,16 349:19,20 350:3 350:11 351:3,11 354:22 356:18 357:19 359:17 365:5,13 366:14 366:14 368:2 369:16,19,20 370:3,4 372:6,8 372:11,13 385:11 387:14 394:6,13 395:22 396:11,14 396:18,19,19 397:4,5,6,10 398:9 399:3,10 400:1,3 401:1,9 402:15 403:6,8 413:3,17,18 414:4 414:10 416:10,13 420:1,4,16 421:18 422:2,14,18	<b>studying</b> 168:12 <b>stuff</b> 59:6 69:14 127:16 183:4 222:11 277:13 307:11 <b>subgroup</b> 187:13 187:14 188:4 189:5 <b>subgroups</b> 191:14 191:16 <b>subject</b> 255:19 329:14 <b>submit</b> 139:7 228:21 282:10 <b>submitted</b> 110:5 119:5 137:2 225:10 326:14 373:12 <b>subsection</b> 135:7 <b>subset</b> 21:22 270:11 <b>subsets</b> 270:4 271:19,19 <b>subside</b> 54:6 <b>substances</b> 395:2 <b>substantial</b> 84:11 84:14 117:10 209:15 317:3 346:15 <b>substitute</b> 131:19 <b>subtypes</b> 181:9 <b>sub-chronic</b> 334:15 <b>success</b> 55:13	<b>sum</b> 260:20 266:11 355:9,11 <b>summarize</b> 17:11 215:13 248:2		
<b>struggling</b> 37:2	210:22 212:10 213:10 216:7 221:11 222:8 224:17 229:14 233:1 237:16,17 237:22,22 242:6 242:15 246:4 247:12,22 248:14 249:14,21 250:5 253:11,12 257:8 257:10 284:8 319:1 344:21 347:12 349:10,16 349:19,20 350:3 350:11 351:3,11 354:22 356:18 357:19 359:17 365:5,13 366:14 366:14 368:2 369:16,19,20 370:3,4 372:6,8 372:11,13 385:11 387:14 394:6,13 395:22 396:11,14 396:18,19,19 397:4,5,6,10 398:9 399:3,10 400:1,3 401:1,9 402:15 403:6,8 413:3,17,18 414:4 414:10 416:10,13 420:1,4,16 421:18 422:2,14,18	<b>studying</b> 168:12 <b>stuff</b> 59:6 69:14 127:16 183:4 222:11 277:13 307:11 <b>subgroup</b> 187:13 187:14 188:4 189:5 <b>subgroups</b> 191:14 191:16 <b>subject</b> 255:19 329:14 <b>submit</b> 139:7 228:21 282:10 <b>submitted</b> 110:5 119:5 137:2 225:10 326:14 373:12 <b>subsection</b> 135:7 <b>subset</b> 21:22 270:11 <b>subsets</b> 270:4 271:19,19 <b>subside</b> 54:6 <b>substances</b> 395:2 <b>substantial</b> 84:11 84:14 117:10 209:15 317:3 346:15 <b>substitute</b> 131:19 <b>subtypes</b> 181:9 <b>sub-chronic</b> 334:15 <b>success</b> 55:13	<b>sum</b> 260:20 266:11 355:9,11 <b>summarize</b> 17:11 215:13 248:2		
<b>stuck</b> 392:19 421:13	210:22 212:10 213:10 216:7 221:11 222:8 224:17 229:14 233:1 237:16,17 237:22,22 242:6 242:15 246:4 247:12,22 248:14 249:14,21 250:5 253:11,12 257:8 257:10 284:8 319:1 344:21 347:12 349:10,16 349:19,20 350:3 350:11 351:3,11 354:22 356:18 357:19 359:17 365:5,13 366:14 366:14 368:2 369:16,19,20 370:3,4 372:6,8 372:11,13 385:11 387				

179:17 184:22	234:10 395:15	204:21	273:14 276:21	305:8,9,11,18
189:15 190:15	409:18	<b>synthetic</b> 12:15	280:6,13 282:10	306:10,15 307:9
191:17,19 194:4	<b>surprising</b> 106:5	196:3 299:11	282:12 284:9	307:14 311:14
254:3 395:12	126:2	<b>system</b> 7:14,14	285:16 289:12,17	312:5 314:22
<b>sure</b> 29:2,17 50:7	<b>surprisingly</b>	12:19 23:1,2,2,14	289:21 298:5	319:3 323:4,18
51:11 66:19 70:11	109:16	33:4 54:7 66:7	301:7,17,19 311:9	324:5 327:7 360:4
81:1 83:13 84:9	<b>surrounds</b> 309:18	67:3 72:11 75:20	329:8,13 337:18	361:6 374:3 380:7
111:1 119:12	389:21	78:4 81:20 89:15	337:21 340:4	380:10,12 402:9
127:15 135:12	<b>survey</b> 8:9,13 112:7	90:12 117:13	346:13,14,17	414:4 416:8
161:5 175:3 181:5	<b>survival</b> 348:2,3	130:9 137:21	357:10 362:14,17	419:16 422:19
181:11 189:18	<b>Susan</b> 2:2 7:15 35:4	138:13,21 176:2	362:20 378:15	<b>taken</b> 13:3 116:5
219:2,4 227:21	<b>susceptibility</b>	180:5 184:16	382:8,15	120:20 123:15,17
230:6 245:14	344:18 347:22	187:11 192:20	<b>system's</b> 277:2	195:6 201:10,13
319:12 320:3	397:18	198:11,14 201:1	387:2	202:18 204:21
321:6,10 348:13	<b>susceptible</b> 146:4	201:20 220:21		211:22 222:22
401:15 402:9	<b>suspect</b> 52:2,15	224:11 233:16	<b>T</b>	239:8 264:6
404:3 406:19	53:8 338:16	236:8 238:17	<b>T</b> 2:13 184:1	274:17 276:12
411:17 423:22	<b>sweet</b> 48:10,19	246:6,13 248:7,9	240:19,21 247:17	298:12 307:1
<b>surface</b> 78:18	<b>Swenberg</b> 135:18	248:13 251:3	247:17	327:3 332:3
103:5,20 104:2,12	139:16,17 157:12	257:11 259:15	<b>table</b> 16:18 18:16	361:11 362:13
116:19,19 261:5,7	157:21 158:2,17	272:22 273:9	22:4 36:14,22	378:6 389:18
262:11 263:3	161:2 182:12	275:1,9,11 277:18	91:5 134:3 255:8	<b>takes</b> 64:21 65:22
284:1,18,19,22	185:12	278:9 279:19	256:7 269:1,5	130:8 410:19
285:2,3 327:17	<b>switch</b> 218:14	286:5 288:19	271:11 272:20	<b>take-home</b> 223:15
331:17 337:18	323:9 324:15	289:13 298:8,20	297:1 303:17,19	<b>talk</b> 11:16 80:7
360:12 379:17,20	<b>synapses</b> 347:5	299:4 301:9,12,15	326:1 377:3	99:22 139:22
379:20 380:19	<b>syndrome</b> 153:7	301:22 327:5	383:20 423:4	184:13 189:3
<b>surge</b> 142:9 145:9	<b>synergistically</b>	329:10 330:9,13	<b>tables</b> 14:12 15:12	259:5 260:4,6
145:13 147:4,13	355:13	331:5,8 346:13,14	340:3	287:5 325:1 330:5
148:10 184:21	<b>Syngenta</b> 82:1	348:19 350:2	<b>tags</b> 418:18	369:7
187:12 188:3	84:10 85:21 94:19	355:7,15 356:4	<b>tails</b> 59:7	<b>talked</b> 12:5 60:21
189:15 190:3,9	97:1 110:14,19,21	364:15	<b>take</b> 10:14,19 30:10	86:8 95:18 151:5
191:17,18 192:21	127:21 133:19,19	<b>systems</b> 13:2,4,4,6	33:19 34:12 35:2	288:1 411:21
195:5,13 197:1,2	134:6,11,18	13:18 15:4 17:13	37:22 38:4 45:10	<b>talking</b> 24:5 31:14
197:3,9,12 198:18	136:16 138:17	21:22 22:9,12,14	46:19 56:22 57:11	35:10 42:21 44:19
199:3,7,12 202:7	156:7 237:16	23:8 24:2 54:3	60:6 70:13 71:11	61:18 65:12 81:1
212:8 214:20	245:5 258:3,4	55:19 56:3,7,10	75:11,22 76:14	87:18,22 92:5,19
215:1,2,4,10	262:16,18 263:12	56:15,16,20 71:4	83:1 85:15 86:20	135:3 161:11
216:13 217:7	285:11 303:11	71:15 74:5 75:7	93:1 95:12 96:7	162:12 246:15
220:1,4 230:1,12	327:8 340:6,6	75:10 86:16	115:4,17 116:15	258:6,8,21 261:10
230:13 231:6,7,14	381:8 397:10	101:16 103:13	117:4 127:14	295:9 296:20
232:4 384:18	420:17	180:19 236:3,8	164:22 182:17	297:19 315:2
394:19 395:13	<b>Syngenta's</b> 256:1	262:10 263:3,9,15	193:5 195:22	317:11 338:20
<b>surges</b> 147:10	<b>synthesis</b> 198:3	263:19 264:12,19	202:20 243:9,21	400:19
231:3	255:3	265:3 269:11,16	245:20 259:4	<b>tandem</b> 203:18
<b>surprised</b> 166:14	<b>synthesized</b> 171:15	269:21 270:3,5	269:14 300:20	<b>tangent</b> 233:12
192:7 231:16	<b>synthesizing</b>	271:13 272:6,12	301:7 304:22	<b>Tanguay</b> 156:9

<b>tank</b> 106:16	<b>tenfold</b> 228:10	344:16,21 349:8	106:13 112:6	70:9,22 71:17
<b>tap</b> 304:16 363:9	310:16,17 415:16	351:1,8	141:15,15 144:17	74:2 76:13 78:5
<b>target</b> 23:20 87:9	<b>tens</b> 22:22	<b>testes</b> 348:22	153:5 179:16	79:21 80:10,13,18
175:4	<b>tenuation</b> 230:3	<b>testimony</b> 364:22	184:12 208:9	81:12 84:17 85:7
<b>targeted</b> 21:13	<b>ten-day</b> 292:11	<b>testing</b> 217:14	229:7 246:22	85:8,11,21 86:7,8
289:11 391:13	<b>ten-year</b> 107:19	314:10 346:6	259:8 266:4 267:5	91:19 92:3,11
<b>targets</b> 150:22	<b>terbuthylazine</b>	357:20 381:1,5	268:15 278:20	93:11,19 95:10,12
151:5	120:14 131:21	<b>testosterone</b> 136:11	300:17 305:17	95:15 96:5,7
<b>task</b> 106:1 254:12	132:7	203:22 205:16	306:14 318:9	113:12,16 119:8
<b>taste</b> 329:1	<b>Teresa</b> 2:9 7:9	206:2 209:6	321:20 324:19	123:13,21 126:9
<b>team</b> 351:17	<b>term</b> 17:19 27:21	224:10,18 225:12	358:14 364:1	128:7 129:7
<b>technical</b> 51:20	33:1 37:19 39:20	<b>tests</b> 291:18	388:5 393:1	132:22 133:6,10
222:7 325:7	45:12 53:5 255:18	<b>Texas</b> 136:4 163:1	410:10,12	143:4,17 155:13
419:12	255:18 271:6	<b>text</b> 389:17,20	<b>things</b> 18:17 29:15	155:19 156:19
<b>techniques</b> 178:14	311:20 312:6,22	<b>TGAC</b> 159:3	34:20 44:2,11,14	157:21 159:15
291:4	313:1,5,6 314:1	<b>thank</b> 5:3 10:1	45:9 52:19 54:15	161:12 162:21
<b>technologies</b> 83:12	315:8 335:6	11:21 30:3 53:19	54:19 61:21 63:19	163:2 164:15
85:10 109:14	<b>termed</b> 412:20	91:2 97:3 99:10	64:11 67:5 74:2	165:8 166:17
111:13,19	<b>terminated</b> 109:21	105:5,12 124:6,7	76:13 77:7 78:9	167:20 176:19
<b>technology</b> 85:13	<b>termination</b> 190:21	133:17 139:17	86:6 87:5 92:21	177:3,8 178:15
130:5	199:6	155:12,17 176:4,5	95:21 102:8	182:11 183:5
<b>teeth</b> 121:16	<b>terms</b> 21:2 23:3,13	182:4 183:8 184:7	126:22 127:20	194:5 202:2 204:4
<b>tell</b> 43:8 61:11,15	35:1 41:10 49:20	194:13 218:10	128:2,14 129:22	206:12 220:12
70:12 129:3 202:9	55:22 73:13 83:3	220:19 221:2	143:6 157:10	221:20 223:22
203:10 206:6	86:18 91:16,20	223:11 229:2	175:5 181:18	228:9 231:14
217:19 231:9	93:14,16 124:10	236:18,22 237:1,3	217:12 224:4,18	233:9,14 234:3,19
237:15 274:11	197:20 202:5	256:7 257:22	236:1 243:10	236:6 238:9 244:5
<b>telling</b> 194:1 364:3	209:21 210:7	258:1 294:12	284:3 290:7,8	246:17 249:5
<b>tells</b> 417:2 420:6,9	216:15 217:13	302:4 323:12,15	293:7,10 296:5	254:12 255:7
<b>temporal</b> 23:21	219:6 226:16	325:2 339:10	300:15 303:18	256:10 257:3
71:7,8,11 77:16	233:20 239:9	364:17 368:11	305:7 343:7	260:18 265:10
77:17 78:17 95:7	241:1,6 245:8	372:17 373:1,2,5	354:19 355:11	266:11,12 270:15
95:17 142:21	248:19 295:21	378:16 379:7,8	365:6 397:21	272:8,10 275:2
282:20 373:16	296:3 300:10	380:21 383:3	418:22	276:1 282:14
399:19	371:8 381:4	398:5 404:7 425:9	<b>think</b> 5:1 10:2 14:1	285:16,18 287:4
<b>temporality</b> 95:11	416:13	425:15	14:20 18:7 21:2,8	288:9 289:14
<b>temporally</b> 70:3,5	<b>terraces</b> 104:14	<b>thanks</b> 25:19 96:13	22:3 23:5,21	293:3 294:5 295:6
152:13	<b>terribly</b> 59:19	99:10 113:2	24:20,21 27:13	295:8 297:9,15
<b>ten</b> 61:12 62:7	66:11 192:7	118:22 321:3	28:7,8,22 29:12	298:18 299:15,19
109:5,8 168:2	<b>test</b> 48:1 64:7	<b>theory</b> 24:18	29:14 31:20,21	301:6 302:14
233:21 235:2	111:16 188:5	<b>Theresa</b> 218:10	32:4,9,11,20 33:4	304:2,12,15
263:21 265:3	225:10 226:8	<b>thin</b> 19:2 338:22	37:1 38:20 39:11	310:21 316:18,22
276:13 310:7	291:12 292:3,8,18	<b>thing</b> 22:19 26:21	39:16 42:18 48:16	317:4 318:13
<b>tend</b> 68:8 75:4	370:17,21 371:4	28:1 40:15 41:18	51:12,18 52:1,5	320:6 321:19
182:13 186:3	371:15	44:8 46:3 60:5	54:16 55:5,12	323:3 328:3,4
270:13 299:21	<b>tested</b> 198:19,22	66:22 67:10 74:16	58:3,9 64:4 65:3	336:2 337:12
<b>tendency</b> 395:21	238:2 296:21	84:17 89:4,14	65:14 68:16 69:6	338:4 339:22

340:17,22 341:22	<b>thousand</b> 319:15	56:6 69:8,10	194:1,12,16	<b>tissues</b> 179:5 181:9
343:8 349:12	321:11	80:10 81:9 82:20	199:20 208:18	204:22 205:7
354:19 355:7	<b>thousandfold</b> 309:7	84:9,22 85:12	209:8 211:16	<b>titrated</b> 253:6
356:17,22 357:3	310:13 311:1,11	89:13 90:21 267:4	215:22 217:9	<b>today</b> 11:4 12:14
357:11,22 358:10	312:3	<b>Thursday</b> 338:20	221:19 230:8,15	43:15 94:15 99:17
358:10 363:21	<b>thousands</b> 22:21,22	<b>thymus</b> 243:10	230:17 231:5	99:22 115:21
364:8 365:19	49:22	<b>tidier</b> 189:20	234:18 235:19	123:5 125:11,17
366:11,16,18	<b>three</b> 10:17 12:18	<b>tie</b> 34:22	236:14 239:10	126:3,8,10 129:8
367:5,12 368:1,5	17:19 30:19 53:2	<b>tied</b> 125:12	240:13 241:13	134:14,22 138:5
375:22 376:10,19	59:14 67:11 76:2	<b>ties</b> 237:12	242:21 244:4	139:21 142:8
379:13,16 381:8	111:3 136:18,22	<b>tiger</b> 355:16	245:1 247:2,5,9	156:21 187:14
382:14,22 383:13	137:1 138:2 140:8	<b>tight</b> 10:6	248:12 250:14,14	188:19 189:4
383:22 392:3	148:21 165:15	<b>tightly</b> 52:18	250:17,19 254:13	193:22 194:7,11
394:3,6 399:18	169:18 170:16	<b>till</b> 101:18,18,19,19	255:16 264:3	194:16 202:22
401:17 405:16	184:20 191:14	102:22 103:9,14	265:13 267:13,17	231:8 237:3
406:18 407:10	195:11 202:14	183:13	274:6 288:20	238:11 244:8
408:16,21 411:11	206:9 207:2	<b>tillage</b> 100:14,17,19	290:8 293:15,16	296:13 303:12
412:13 413:2,10	239:21 240:2	101:3,4,6,18	293:19 297:17	318:22 339:5
416:13 417:7	247:7 255:5	102:3,10 103:3,10	298:10 299:16,18	355:8 366:11
419:18 420:3	262:12 271:3	103:13 104:13	299:19 304:1	368:1,18,21 377:7
421:1,14 422:7,7	273:5 286:4,5	107:1 112:5,8,11	315:22 323:13	378:19 381:6
422:10 423:12,16	309:1,16 326:21	112:15,16 126:17	331:14 334:8	393:15 394:7
423:18 424:3,17	329:9 337:2 362:6	<b>tilling</b> 101:10	335:10,15,19	395:11
425:7	383:16 390:12	<b>Tim</b> 303:10	345:5 346:17	<b>today's</b> 43:12,16
<b>thinking</b> 64:18	392:13 393:4	<b>time</b> 6:19 10:13	350:4 353:21	101:2 425:9
67:10 85:7 87:6	411:1	11:5,15,16 13:13	356:10 358:13	<b>token</b> 255:7
216:22 222:10	<b>threefold</b> 310:19	16:2,4,5 20:6,19	368:3 371:3	<b>told</b> 94:5 113:10
280:21 317:10	310:20	20:20 21:1 27:11	372:12 375:10	120:17 369:4
379:13,19 382:19	<b>three-day</b> 14:7	35:18 39:22 40:9	381:21 391:13	<b>tolerant</b> 107:4
416:18	17:10 18:20 19:15	41:5,19 50:8 52:6	397:21 400:5	109:15 111:19
<b>third</b> 40:8 41:3	19:16 32:13	59:11 61:2,4,8,12	404:3 406:10,11	<b>tolerate</b> 48:11
55:2	292:10	61:16 84:19 85:3	406:13 417:10,17	49:11
<b>thirds</b> 135:11 420:4	<b>three-hour</b> 214:4	85:15,17 93:6	419:5,20	<b>tolerated</b> 238:2
<b>Thirty</b> 271:15	<b>three-month</b> 88:17	94:12 95:3,14	<b>times</b> 14:4 15:20	<b>Tomatis</b> 344:3
<b>thorough</b> 141:19	<b>three-node</b> 40:18	102:19 105:10	43:13,14 46:15	<b>tomorrow</b> 93:1
178:6	40:21 41:1 52:13	108:14 109:1,10	47:4,8 94:5 116:2	296:14 338:19
<b>thoroughly</b> 288:20	52:17	111:9 114:4	133:14 156:15	339:1 366:6
349:8 367:21	<b>three-year</b> 111:9	116:19 119:13	158:19 166:11	425:12
374:21	<b>threshold</b> 61:2 62:2	123:22 130:8	169:19 170:14	<b>tonight</b> 216:19
<b>thought</b> 63:3 67:1	343:3 425:2	135:22 136:12	190:14 250:22	<b>tool</b> 64:6 103:8
93:22 181:4	<b>thresholds</b> 259:2	143:12 144:3	251:1 294:21	106:3 107:2
187:10 234:7	<b>throwing</b> 25:13	150:5 159:5	417:20 418:2,20	112:19 229:22
257:9,20 272:8	<b>thumb</b> 366:7	173:20 178:7,7,12	<b>timing</b> 71:10 265:5	338:4 374:2
295:14 318:2,3	<b>Thurman</b> 3:18	181:22 182:10	265:18 346:20	<b>toolbox</b> 114:16,22
404:14 423:7	11:7,9 25:6 28:3	185:8 186:11	<b>tired</b> 338:13	<b>tools</b> 114:16,21
<b>thoughts</b> 86:6	29:9,10 31:18,19	187:3,7,7,10	<b>tissue</b> 168:13	379:5
176:14 374:5	34:2,11 35:12,16	188:9 189:10	222:21	<b>top</b> 17:5,6 19:1

20:5 33:21 37:17 51:3 103:5 128:3 223:5 240:10 263:13 264:21 267:10 268:3 269:8 293:7 308:5 313:4 316:5,9,16 <b>topic</b> 136:2 194:14 236:6 262:9 384:3 <b>topics</b> 135:2,13,13 <b>total</b> 86:22 89:16 89:20 90:5 113:7 125:7 260:1 266:11 268:4 269:17 330:13 331:2 362:16 <b>totally</b> 88:11 285:8 <b>tox</b> 81:11 132:17 348:1 <b>toxic</b> 346:3,4 355:14 <b>toxicities</b> 178:16 <b>toxicity</b> 95:13 170:3,4,12,21 171:2 257:14 346:9 349:7 350:12 <b>toxicologic</b> 138:11 184:9 186:2 <b>toxicological</b> 7:7 87:17 259:1 314:10 333:15 338:21 <b>toxicologist</b> 5:21 6:9 7:8 9:8 303:10 312:17 380:16 <b>toxicologists</b> 31:22 <b>toxicology</b> 5:20 6:13 9:4,10 92:5 119:2 134:11 137:17 150:14 256:4 258:7 305:10 319:1 339:19 341:6 385:9,11 <b>track</b> 90:7 139:12	252:13 <b>tract</b> 7:4 <b>trade</b> 373:8 <b>tradeoff</b> 80:2,5 <b>tradeoffs</b> 80:18 <b>traditional</b> 150:13 <b>traditionally</b> 110:5 <b>tragedies</b> 115:13 <b>trained</b> 419:2 <b>training</b> 326:11 <b>transcript</b> 4:22 198:1 <b>transcription</b> 176:13 <b>transfected</b> 175:2 <b>transferred</b> 204:22 <b>transformed</b> 163:5 <b>transgene</b> 159:1 <b>transgenic</b> 158:20 159:3 196:13 401:11 402:19 414:18 <b>transient</b> 199:13 346:19 <b>transition</b> 137:9 183:2 184:5 <b>translate</b> 95:16 <b>translational</b> 235:22 <b>transparency</b> 141:17 333:14 372:15 <b>transparent</b> 119:16 <b>transport</b> 83:19 <b>transportation</b> 130:8 <b>transporting</b> 84:13 <b>treat</b> 200:10 203:4 <b>treated</b> 165:12 185:15 186:22 187:15,17 190:6 190:19 192:12 195:22 197:17 201:4,13 202:14 221:19 402:19 <b>treatment</b> 185:17 187:19,19 188:2	188:10 189:14 190:3,8 191:3 192:2 198:16,20 199:6,9 203:8 207:8 208:3 209:4 213:21 215:5,12 215:17 217:2 223:18 229:14 234:14 277:20 327:6 328:10,15 328:21 329:6 333:4 380:1,6 395:1 396:3 401:22 <b>treatments</b> 108:7 108:11,18 109:1,3 109:11,17 111:5 <b>treatment-related</b> 235:4 <b>trees</b> 360:15 <b>tremendous</b> 117:17 <b>trend</b> 209:7 235:10 267:16,22 268:7 268:11,13 285:7 285:10 381:19 <b>trending</b> 192:15 260:12 267:22 <b>trends</b> 29:11 260:12 267:6 272:14 283:1 <b>trials</b> 108:6 <b>Triangle</b> 149:21 <b>triazine</b> 86:22 96:19 97:15 105:14 116:10 120:12 131:19 133:13 164:2,3 175:18 327:13 <b>triazines</b> 132:19 171:5 176:3 326:19 <b>tricks</b> 88:21 <b>tried</b> 78:15 112:11 222:13 340:21 <b>trifling</b> 118:5 <b>trigger</b> 47:10 90:16 <b>triggered</b> 316:3	<b>trihalomethanes</b> 121:17 <b>trips</b> 85:20 101:10 <b>trouble</b> 343:7 <b>true</b> 12:8,9,16 13:15 14:11 15:13 15:16 16:8 20:22 26:1 29:22 37:5,6 44:22 63:9 64:2 66:6 70:9 112:11 219:17 274:16 278:11,18 279:9 279:11 281:6 282:4 288:13 291:9 292:8 294:7 305:5 321:18 400:16 401:10 <b>truly</b> 275:4 282:17 <b>trust</b> 135:5 <b>truth</b> 26:14 63:11 64:1 <b>try</b> 52:6 55:5,9 67:2 69:12 74:14,15 105:19 110:11 136:19 139:13 163:4 185:19 186:16 188:12 194:6 210:21 237:8 299:13 303:13 365:15 372:17 374:3 413:9 <b>trying</b> 52:8,12 66:3 67:7,17 73:7 77:7 226:9 274:2 286:22 289:1 295:6,7 304:11 314:5 320:1 327:10 419:21 <b>tube</b> 226:5 <b>TUESDAY</b> 1:13 <b>tumor</b> 140:14 150:20 164:19 165:6 388:11 391:20 393:5,11 395:5 396:1 397:7 397:11 399:11	402:20 403:12 424:14 <b>tumorigenesis</b> 400:9 <b>tumors</b> 142:1 143:10 152:8 154:10 157:8 343:22 384:22 385:21 388:19 389:1,10 391:7 394:22 396:7,20 398:20 401:5 402:18,22 <b>tune</b> 314:20 <b>turf</b> 360:15 <b>turn</b> 5:2 11:6,20 43:7 99:5 105:11 123:11 137:15 138:10 139:15 161:2 171:4 273:20 283:16 384:20 387:3 409:18 410:1 <b>turned</b> 88:12 137:18 <b>turning</b> 62:8 281:21 <b>turns</b> 174:4 238:9 240:22 <b>Twain</b> 118:1 <b>twice</b> 342:10 343:12 383:12 <b>twist</b> 123:11 277:1 <b>twisted</b> 122:6 <b>twisting</b> 122:19 <b>two</b> 5:5 10:4,18 11:10 12:12 16:4 16:11 17:21,22 18:4 19:11 30:19 33:6 36:18 39:17 43:8,11,14,17 46:5,13,15 54:14 67:17 70:17 77:19 78:16 91:3 94:15 94:16,22 107:19 108:13 118:22 122:14 134:18
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

135:10,13 139:7	286:2 299:3	398:22	154:15,15	270:14
145:19 149:5,19	329:22 365:5	<b>unclear</b> 349:5	<b>undertaken</b> 376:3	<b>unsurprisingly</b>
157:4 158:6,18	388:11	393:18,22	<b>undertook</b> 168:11	270:17
165:15,17 166:1	<b>types</b> 18:1 52:22	<b>underestimate</b> 25:1	<b>under-powered</b>	<b>unusual</b> 144:7
166:20 167:17	67:5 149:9 173:19	<b>underestimates</b>	420:10	159:7,8 181:19
173:5 174:1,7	174:6 175:17	57:19	<b>unexplained</b>	211:14
183:8 186:20	186:1 257:20	<b>underestimating</b>	161:18	<b>unusually</b> 119:3
194:18 198:19	261:7	16:14 19:8,21	<b>unfinished</b> 378:14	<b>update</b> 95:4 339:21
199:5 211:6	<b>typical</b> 18:11	24:16 26:14	<b>unfortunate</b> 375:8	340:10 362:12
214:12 218:18	104:10 235:6	<b>underestimation</b>	<b>unfortunately</b>	409:20
220:13 229:1,9	243:11,11 247:20	20:4	232:16 345:15	<b>updated</b> 361:13
232:9 233:6	310:15	<b>underlie</b> 194:4	354:12 392:22	<b>updates</b> 364:12
234:18 239:2	<b>typically</b> 124:17	197:15	397:3	<b>uphill</b> 279:3
246:4 249:14	246:15 263:5,22	<b>underlining</b> 238:20	<b>unheard</b> 129:14	<b>upper</b> 12:8 13:8
255:12 257:16	276:9 277:11	<b>underlying</b> 150:20	<b>Union</b> 120:5 127:7	<b>upside</b> 409:18
260:6 261:7	<b>t-test</b> 111:15	152:7	127:10	410:1
267:18 272:15	<b>T.V</b> 326:11	<b>underpin</b> 313:9	<b>unique</b> 54:7 104:10	<b>upstream</b> 276:21
273:5 278:7 281:1		<b>underpowered</b>	115:5 235:21	<b>uptake</b> 180:8
281:9 285:17	<b>U</b>	417:3	261:2 282:7	<b>upwards</b> 294:7
290:12 295:16,19	<b>ubiquitous</b> 331:16	<b>understand</b> 38:12	395:19	411:9,11
296:4 298:18	<b>Ueda</b> 158:6 401:4	40:22 51:5 80:9	<b>unit</b> 425:4	<b>urge</b> 397:22
308:17 310:18	<b>ugly</b> 37:16 43:3	82:11 83:14,15	<b>United</b> 33:16 132:9	<b>urinary</b> 244:9
313:19 322:21,21	<b>ultimate</b> 77:15	86:10,11 98:15,18	378:20	248:10,16
324:6 326:7 339:9	374:8	113:15,19 115:1	<b>unity</b> 351:7	<b>urine</b> 163:21
339:12,20 355:17	<b>ultimately</b> 77:9	115:13 136:19	<b>universe</b> 265:21	243:22 244:1,20
356:5 368:15	89:21 200:10	158:9 161:6 178:1	<b>universities</b> 108:3	245:20 246:18
372:3,14 381:14	295:22 328:11	192:15 228:4	110:10 111:6	250:12,16 251:6
388:3 390:16	379:4	249:17 258:10	<b>university</b> 6:3,8,14	251:10 359:15,19
392:10 393:4	<b>unable</b> 343:13	260:13 283:1	6:16,20 7:11,16	360:3
396:12 400:22	344:9	290:3 294:2	8:3,15,17 9:7,11	<b>usage</b> 128:10
401:9 402:14,17	<b>unaffected</b> 190:21	297:19 299:1,9	9:16,19 57:10	<b>use</b> 3:8 11:13 34:3
403:6,11 411:1	191:3	300:7 318:12,17	75:13 99:18	36:1 37:4 39:4
413:17,18 414:4,5	<b>unaware</b> 275:8	320:4 336:22	110:15,21 136:4	44:19 45:2 48:22
414:10 416:9,13	<b>uncertain</b> 250:10	379:16 406:20	153:10 163:1	50:19 51:19 52:7
418:22 420:3,18	<b>uncertainties</b>	418:20 419:2,22	193:21 210:13	52:21 56:4 57:4
<b>twofold</b> 353:9	150:18 310:19,20	<b>understanding</b>	218:11 349:14	58:13 60:7 64:5
<b>two-fold</b> 166:7	401:7,11 416:21	49:1,4 132:14,17	<b>unknown</b> 151:11	69:15 70:21 71:16
<b>two-node</b> 53:14	<b>uncertainty</b> 45:6	140:3 159:6 275:5	291:20	71:22 72:14,15
<b>two-pronged</b> 294:6	72:1 73:15 80:20	275:19 280:6	<b>unlock</b> 236:10	74:9,21 76:2,10
<b>two-step</b> 334:5	82:3,4 93:11	287:16 299:5	<b>unnecessary</b> 282:6	76:10,15 77:5
<b>two-thirds</b> 118:16	95:22 246:3	307:5 356:19	316:20	87:4 89:1 103:13
270:7 362:19	281:15 282:2	374:11,15 375:17	<b>unrealistic</b> 86:15	105:22 107:8
<b>type</b> 28:1 32:2	283:7 309:7 311:2	382:8 386:18	<b>unreasonable</b>	108:14 113:22
51:13 54:6 65:1	319:14 320:11	391:14 406:20	385:18	114:3,6 120:6,12
78:5 140:14	321:11,16,22	407:17	<b>unsafe</b> 358:20	120:12 122:8,9
161:19 165:20	322:1,18	<b>understands</b> 98:10	360:18 361:2	125:6,9,11 130:11
195:3 211:14	<b>unchanged</b> 154:4	<b>understood</b> 150:22	<b>unsurprising</b>	130:12,13 131:10

151:21 159:9	131:6,10	241:14,17 243:3	241:13 242:21	<b>vulnerability</b> 188:9
174:3 203:12	<b>U.S</b> 1:1 8:8,12	243:21 244:20	248:12 289:13	188:15,17
204:3 222:16	102:11 111:6	260:14 268:12	<b>vertical</b> 46:9	<b>vulnerable</b> 24:2
225:18 227:19	116:11 152:18	270:11 271:22	<b>vertically</b> 302:15	34:20 289:12,17
249:21 259:6	325:14 345:22	279:9,12,18	<b>Veterinary</b> 6:7,17	289:20 332:4
260:20 261:1	357:15 384:8	281:11 282:22	<b>viability</b> 170:5	337:19
262:13 268:4,9		308:17 311:17,19	<b>view</b> 295:20 331:11	
280:15 283:9,13	<b>V</b>	311:20 312:7,13	377:17	<b>W</b>
284:11 299:18	<b>vaginal</b> 143:20	313:8,9 314:22	<b>vindicated</b> 123:6	<b>waiting</b> 25:5 298:2
312:16 313:17	185:8 187:9 191:8	316:12 322:10	<b>violates</b> 365:22	411:17
333:8,15 334:16	191:12,22	336:18,19	<b>violation</b> 332:11	<b>walk</b> 141:12
336:5 338:3 352:6	<b>validate</b> 280:21	<b>variability</b> 30:9	<b>violations</b> 329:8	<b>wall</b> 349:3 358:12
353:12 356:15	<b>validation</b> 370:15	50:16,17 52:22	<b>viral</b> 356:3	419:4
359:10 360:10	370:17 371:15	55:3,10 70:4,6,20	<b>Virginia</b> 9:4 153:10	<b>want</b> 4:9 20:18
369:21 370:3	<b>validity</b> 377:18	93:11 251:12	<b>virtually</b> 19:13	24:19 27:14 29:10
371:16,22 372:6	<b>valuable</b> 112:19	275:6 291:17	149:9 373:9	43:5 45:6 48:14
<b>useful</b> 21:19,20	275:4	329:15 337:20,22	<b>visit</b> 83:17	49:13 61:3,11
85:6,8 91:12,14	<b>value</b> 13:10 14:11	370:20 371:4	<b>visiting</b> 84:12	62:6 66:17 69:1
221:21 239:5	15:14,14,17 16:9	<b>variable</b> 30:13	<b>visualize</b> 196:16	74:2,15 79:11,12
246:10,17 281:13	20:22 24:16,18	281:22 299:4	<b>visually</b> 33:15	82:22 83:5 89:13
336:8	37:6 39:9,20 42:2	<b>variables</b> 64:12,22	<b>vitro</b> 1:8 5:8 136:7	92:15 105:5
<b>user</b> 372:15	43:9 47:11,17,18	<b>variation</b> 225:14	136:20 149:7	113:13 133:11,11
<b>users</b> 333:19	47:19,20,21 48:3	228:7,9	151:10,18,19	142:5,18 168:17
381:17 411:11	48:6,13 63:7	<b>variations</b> 12:12	168:3,4,18 169:3	180:14 182:13,22
<b>uses</b> 58:21 254:15	66:19 78:12 98:10	<b>varies</b> 70:2 371:2	176:2,18 216:6,7	184:12 194:13
290:13 331:16	98:15,18 103:1	<b>variety</b> 104:19	222:19 387:14	202:1 204:3
358:21 379:4	113:14 114:10	164:18 172:7	<b>vitro-in</b> 175:8	212:10 216:18
<b>USGS</b> 70:11 84:9	173:5 224:15	389:15	<b>vivo</b> 151:14 163:9	217:22 218:13
268:12 331:19,22	239:13 253:13,14	<b>various</b> 56:5 77:21	164:8 168:6 175:8	233:22 235:17
356:9	269:10 273:22	179:2 181:8	175:11 201:1	237:3 259:21
<b>usually</b> 30:18 52:7	278:11,11,14	272:17 274:6	222:8 387:14	271:10 275:5,6,15
106:14,17 108:12	291:1 301:8,11	286:6	400:22	277:12 293:14,19
162:2 186:1 224:9	306:6 308:5 309:5	<b>vary</b> 275:16	<b>VMP</b> 262:18 266:4	297:11 298:1
321:15	310:6 311:4,9	<b>varying</b> 75:14,14	266:9 269:12,16	300:12 317:5
<b>utero</b> 256:14,19	313:22 315:4,9	76:18	270:8 274:14	318:9 325:2 326:9
<b>utilities</b> 325:9,11	336:17 337:5	<b>vegetative</b> 104:14	281:3 290:19	327:3 330:5
325:12,20 327:7	<b>values</b> 12:8 13:11	<b>vehicle</b> 203:5	<b>VOICE</b> 300:16	333:22 342:14
328:14,21 329:7	13:16 14:9,11	221:19 222:12	<b>voiced</b> 272:9	348:11,12,15
329:19 331:12	16:18 18:5 20:19	253:12	<b>volume</b> 54:4	358:14 365:15
333:21 334:4	21:6 23:15 37:18	<b>verbal</b> 326:4,13	103:21 105:7	367:4 368:17
335:21 336:4,7	38:13,16,18 39:6	<b>verify</b> 195:15	251:6 382:3	379:17 404:9
363:4	39:10,15 40:14	<b>version</b> 116:3	<b>voluntary</b> 262:17	405:7 406:19
<b>utility</b> 98:10 126:2	41:20 44:9 45:11	189:2 416:5	263:12,16,20,22	421:9 425:9
328:11	45:19 46:7 58:14	<b>versus</b> 14:15 29:14	265:5	<b>wanted</b> 30:5 31:19
<b>utilize</b> 128:17	59:22 60:6 67:19	30:18 124:11	<b>volunteers</b> 378:21	39:21,22 42:11
<b>utilized</b> 110:13	88:14 209:18	153:14 187:19	<b>Vroom</b> 368:15	47:8 69:4 99:22
<b>U.K</b> 9:7 119:20	239:20 240:9	188:15 226:10	373:4,5,7 380:21	111:1 160:11

164:22 167:2	273:9,14 275:1,6	379:17,18,20,21	126:11 243:19	294:16
185:18 189:18,22	275:7,9 276:3,3	380:13,19,20	297:22	<b>Welcome</b> 5:5
256:12 287:5	276:20,20 277:2	381:1,2 382:1,8	<b>weakly</b> 175:12	<b>welcoming</b> 182:8
295:15 304:9	277:18,19 278:3,5	382:21,21 383:1	<b>weather</b> 128:14	<b>wells</b> 284:3,10,10
321:5,10 369:3	278:8,9,18 279:1	<b>waters</b> 56:8 329:16	<b>website</b> 116:8	<b>well-being</b> 236:2
371:16	279:2,19 280:1,8	331:17 361:14	364:14	<b>well-described</b>
<b>wants</b> 4:12 372:6	280:13,14 281:16	<b>watershed</b> 34:4	<b>websites</b> 110:9	173:4
<b>warning</b> 259:6	282:10,12 283:10	75:4 277:7 278:22	<b>weed</b> 98:21 101:5	<b>went</b> 29:20 35:6
<b>Washington</b> 1:17	284:1,2,6,8,9,14	330:1 340:5 361:9	103:8,11 105:15	39:9,18 74:21
339:18	284:18,19,22	361:9 362:8	107:10,13,21	96:15 109:6
<b>wasn't</b> 10:6 58:18	285:2,3,15,15,16	<b>watersheds</b> 57:5	108:1 109:20	154:20 195:14
74:7 111:1 130:22	286:1,5 288:19	275:15 276:9,22	112:9 125:14,21	221:9 291:21
223:20 240:6	298:5,20,22 299:4	279:21 280:17	130:20	292:18 296:8
285:8 350:6	299:4 300:18,19	361:12,16 362:1,4	<b>weeds</b> 100:17 103:6	314:13 317:17
<b>water</b> 1:8 5:8 8:10	300:20,21 301:7,9	363:13,20	106:19 107:11	323:21 353:14
11:8 12:19 26:4	301:12,14,17,19	<b>waterways</b> 100:21	112:12 124:15,16	388:6
33:4,22 35:22	301:22 304:20	103:19 357:18	125:1 130:21	<b>weren't</b> 58:15
39:13 54:3,4,5,7	306:16 307:6,7,22	<b>water's</b> 38:10	<b>week</b> 18:8 78:15	192:7
54:22 55:19 56:1	308:9,13,19 309:8	<b>water-soluble</b>	87:18 105:6 118:8	<b>we'll</b> 5:17 10:14,16
56:3,7,10,10,15	310:1,20 311:5,9	380:12	367:6 379:14	10:18,19,20,21
62:3 67:3 70:2	311:22 312:11	<b>water/static</b> 271:18	<b>weekly</b> 12:22 15:8	11:2,2,22 12:9
71:2,4,15 72:11	313:14 314:9	<b>wave</b> 230:19	21:9 71:15 74:12	24:3 69:8 75:15
72:12 74:5,8 75:7	315:5,16,19 316:8	<b>way</b> 13:12 20:13,18	74:17,17,19 77:6	76:2 77:3 91:22
75:10,20 78:4,8	317:2,15,20,22	23:17 24:19 27:22	122:4 316:6	93:7 96:7,8 97:1
78:19 81:20 83:16	318:7,19 319:22	28:12 36:20,20	<b>weeks</b> 15:6,11 16:4	124:3 133:21
83:18 85:14 89:15	320:12,22 321:4	37:13 39:18 40:21	16:11 18:4 39:17	135:11 136:21
89:22 90:4,10	321:12 322:13	42:13,15 45:1	61:8 62:4,8,8	139:4 141:11
94:18 95:18 101:1	324:12 325:4,8,9	52:9 53:22 58:4	189:16 190:7	142:8,19 155:14
101:11 103:20	325:10,13,15,18	82:4 99:2 100:14	213:5 221:8 247:7	162:21 176:6
104:2,12 105:16	326:5 327:6,7,17	100:15 110:3	274:22 303:22	178:18 182:16
117:4,13 119:2	328:3,7,14,20	118:16 141:2	355:17	183:12,13,14
121:3,11,12,15,18	329:8,19 330:8,12	160:6 169:20	<b>weigh</b> 106:2	184:4 188:3 194:6
121:20 122:2	330:19 331:5,10	171:11 187:1	<b>weight</b> 59:10 94:9	228:22,22 229:2
129:3 131:7,14	332:1,6,7,9 333:3	216:22 219:10	103:20 114:1	232:10 234:4
134:20 258:15	333:4,10,18,21	227:8 230:14	115:19 149:16	236:19 256:7
259:9,10,16,21	334:1,4 335:21	234:14 256:21	150:6 154:1	258:20 261:21
260:2 261:6,8,8,8	336:4 337:5,18	264:11 282:12,18	206:11,13,16,22	262:13 297:17
261:9,10,12 262:7	340:4,5 352:3,12	295:20 300:10	207:2,3,4,4 233:1	318:17 325:21
262:10,10,11,14	355:18 356:11	305:6 311:6	235:8,12 294:22	368:6 406:14
263:2,3,9,10,15	357:10 358:2,6,8	312:17 313:3	313:19 322:19	409:20 410:14
263:19 264:5,8,12	360:12 361:10	342:12 364:12	357:7,7 389:14	423:22
264:19 265:2,8	362:4,11,14,17,18	382:6 397:16	400:10 411:16	<b>we're</b> 5:10,12 10:3
268:17 269:11,16	362:21 363:9	412:20 414:12	415:19 422:1,1,3	10:8 11:9 17:7
269:20 270:2,5,6	364:15 373:19	417:3 420:15	422:15	19:20 20:19 21:19
270:11,12 271:13	375:16 376:4,16	424:19,22	<b>weighted</b> 267:17	22:2 23:3,6 25:5
271:13,19 272:6	377:10,15 378:10	<b>ways</b> 29:15 36:18	274:7 337:6	27:17 28:4 29:15
272:11,13,22,22	378:13,14,15	72:10,16 97:11	<b>weighting</b> 291:1,1	31:17 32:12 34:18

34:21 44:4 45:1 46:3 57:11,17 59:19 61:18 63:17 64:18 69:17,18 70:3,14 71:3,6,18 72:5,15,18 73:16 73:20 74:11 75:6 75:11,15,22 76:8 76:10,15,20 77:7 78:3,10,11 80:14 82:21 86:18 87:9 87:18 88:21 89:15 92:16,19 93:19 94:6,12,22 95:2 96:2,18,21 114:12 116:17 126:22 134:17 137:9 138:5,10,15 139:12 143:11,13 146:2 151:8,18 156:21 159:18 162:11 166:14 175:3 178:10,16 180:17 182:7,8 188:4 189:3,4,6 210:8 217:12 218:4 224:11 226:7,8 230:6,22 232:5 235:3 243:4 249:8 255:7 257:12,19 258:11 260:4 264:22 290:7 292:3 295:6 297:7 302:20 304:11 310:21 311:19 312:2 314:8,10 315:5 316:17 318:4 319:1,2 321:20 323:9,17 325:6,15 325:20 338:13 368:8,18 380:13 383:14,16,21,22 384:1,3 392:17 397:4 400:19 405:3 407:3,20 408:22 409:1	410:16,17 413:10 420:9 423:7,17,21 425:5,12,13 <b>we've</b> 11:5 19:12 23:10 29:11 31:20 32:4 34:14 56:17 57:2 70:18 79:9 89:18 95:18 98:19 106:21 112:4 113:3,15 114:5 137:5 168:3 231:6 232:6 235:18 237:12 239:7,15 240:15 242:12,14 244:12 250:21,22 254:18 255:2 265:20 283:6 305:7 306:22 307:1,12 308:1,2 311:16,22 315:18 316:1 324:7,22 325:11 326:17 327:17 336:15 363:18 365:4 384:4 390:15 405:17,22 <b>what-not</b> 91:7 <b>whichever</b> 218:13 <b>whiskers</b> 307:10 311:15,18 <b>white</b> 11:11 12:11 26:7 76:12 96:20 97:2,3,5 112:22 113:2 125:8 126:16 127:13 128:16 131:3,9,13 131:21 132:3,12 132:16 133:2,6 278:10,16 392:8 392:10 398:17 <b>wholesale</b> 118:4 <b>wide</b> 119:3 150:11 170:10 276:8 329:14 344:18 382:9 <b>widely</b> 106:6,7 <b>widespread</b> 331:16	<b>wife</b> 113:9 <b>Wilcoxon</b> 111:15 <b>wildlife</b> 101:13 349:21 361:22,22 <b>William</b> 2:7 9:14 <b>Williams</b> 2:17 7:1,1 160:10,11,15 161:10,17 162:7 178:20,21 404:11 404:12 <b>willing</b> 402:9 <b>wind</b> 100:19 101:12 <b>window</b> 188:8 400:6 <b>windows</b> 347:10 <b>winds</b> 102:18 <b>winter</b> 59:10,11 67:14 <b>wish</b> 105:10 135:1 354:8 377:6 408:6 417:8 <b>wishing</b> 36:22 383:10 <b>Wistar</b> 142:10 195:6,7 <b>within-test</b> 370:19 <b>women</b> 148:5,7 153:7 157:6 161:12,19 162:10 <b>wonder</b> 31:3 54:12 132:20 420:15 <b>wondered</b> 28:12 404:12 <b>wondering</b> 25:11 181:15 182:1 253:5 298:14 <b>word</b> 168:20 226:4 243:9 259:7 260:18,21 261:1 265:11 <b>worded</b> 409:13 <b>words</b> 36:12 54:2 269:19 270:12 288:7 323:8 331:20 334:16 351:9 <b>work</b> 12:5,15 13:7	71:22 72:22 100:7 105:17 106:10 113:17 151:3 156:15 159:21 182:6 217:14 218:17 236:7 262:2 269:6 272:1 279:15 284:12 286:18 287:2 294:3 299:8 300:11 307:4 315:19,21 318:15 343:21 365:16 380:9,17 389:5 400:12 <b>workers</b> 358:19,22 360:6 <b>working</b> 71:18 75:21 76:21 105:16 118:13 123:3 124:5 139:12 160:3 245:15 281:6 294:6 316:17 323:5 376:22 382:15 407:4 408:22 419:20 <b>works</b> 40:22 106:8 106:8 318:17 324:12 325:4 <b>world</b> 119:19 343:4 <b>worried</b> 63:18 112:10 <b>worry</b> 63:18 112:9 <b>worrying</b> 282:13 <b>worst</b> 277:11 <b>worth</b> 358:10 411:3 411:4,17 <b>wouldn't</b> 68:14 92:2 115:21 176:10 358:4,8 395:15 396:22 412:19 <b>Wow</b> 338:10 <b>wrap</b> 99:9 <b>wrapping</b> 70:19 282:16	<b>wrestle</b> 78:5,7 <b>wrestling</b> 72:6 <b>write</b> 388:1 423:22 <b>writing</b> 423:18 <b>written</b> 4:22 326:14 327:18 328:8 <b>wrong</b> 80:11 91:11 321:21 <b>wrongness</b> 73:13 <b>wrote</b> 118:1 344:8
<hr/> <b>X</b> <hr/>				
<b>X</b> 306:1				
<hr/> <b>Y</b> <hr/>				
<b>year</b> 14:2 19:18 20:12 21:16 22:16 22:17,18,21,21,21 23:3,3,8,9 30:14 35:6,13,17 38:10 39:16,22 40:10 47:3 54:1,15 57:4 57:5 58:9,11 60:13,15,20 70:16 88:14 94:8 107:9 107:9,10 116:9,15 137:3 139:11,12 149:15,17 152:5 263:6 264:1,6 271:16 272:3,4 286:14 287:19 330:4,14 331:6 363:1,6 368:9 404:2 <b>yearly</b> 307:2 <b>years</b> 13:4 22:1,1 22:14 30:19 46:21 54:21 56:12,18,21 57:6,7,9 60:16 62:13,14 70:17 98:22 106:6 109:5 109:8,9,19 110:2 111:3 114:19 115:3 122:7 123:3 125:10,13 126:5,5 126:10,15 130:6 136:18,22 138:2				

160:4 196:22	420:14	<b>1.0</b> 384:12	<b>100,000</b> 262:6	<b>1700</b> 230:10
224:3,3 233:21	<b>younger</b> 161:12	<b>1.1</b> 279:22 281:12	315:18	<b>18</b> 362:1
257:17 264:18	249:21	341:15 354:4	<b>1001</b> 1:17	<b>180,000</b> 261:14
269:19 273:1	<b>y-axis</b> 143:22 145:1	<b>1.17</b> 352:1	<b>103</b> 285:15	<b>19</b> 354:14
275:3 281:5	311:16	<b>1.2</b> 279:20 386:15	<b>11</b> 3:10 16:13 18:7	<b>1970</b> 160:5
285:19,21 286:13		425:13	<b>111-day</b> 249:20	<b>1970s</b> 342:18
288:19 291:13	<b>Z</b>	<b>1.28</b> 273:22	<b>12</b> 22:5,8,10 38:16	<b>1971</b> 342:18
294:9 305:22	<b>zero</b> 18:6 24:13	<b>1.4</b> 348:8	93:2 189:16 190:6	<b>1982</b> 102:17
327:15,17 332:10	47:18 59:14 61:4	<b>1.6</b> 264:14 350:16	190:7 211:13	<b>1986</b> 108:20
340:11 345:14	244:1 248:10	386:15	228:16 287:14	<b>1988</b> 113:5 309:4
378:6 396:12	251:1,2 265:13	<b>1.61</b> 332:20	335:7	<b>1991</b> 328:18 343:18
<b>Year's</b> 266:2	415:7	<b>1.67</b> 352:14	<b>12,000</b> 263:2	<b>1993</b> 262:21 263:8
<b>year-to-year</b> 55:2	<b>zoom</b> 35:1	<b>1.8</b> 255:18 279:20	<b>12-1/2</b> 335:7	275:2
55:10 56:12	<b>zooming</b> 71:3	310:7 313:6 314:1	<b>12.5</b> 311:2 320:9	<b>1994</b> 113:5 134:13
291:16		319:12,14 320:10	<b>12:02</b> 183:13	149:20 267:16
<b>Yee</b> 137:4	<b>\$</b>	322:17 355:6	<b>123</b> 118:8 119:7	268:6
<b>yesterday</b> 4:11	<b>\$1,200</b> 331:6	<b>1.87</b> 352:16	<b>125</b> 349:15	<b>1995</b> 97:16 329:9
10:5 12:4 22:3	<b>\$100</b> 331:1	<b>1.9</b> 353:21 356:15	<b>13</b> 17:4 67:11	<b>1996</b> 376:6
31:9 32:10 35:19	<b>\$180,000</b> 330:14	<b>1.92</b> 352:17	227:12 302:21	<b>1997</b> 141:4 171:12
37:11 61:22 69:14	<b>\$200</b> 330:17	<b>1:15</b> 183:14,14,17	<b>130</b> 56:16	264:16
81:16 90:16 92:4	<b>\$30</b> 112:2 330:12	184:2	<b>132</b> 263:19	<b>1998</b> 39:11
94:6 113:9 116:15	<b>\$300</b> 331:2	<b>10</b> 46:12 48:11,11	<b>134</b> 270:7	<b>1999</b> 407:6,7
142:7 143:5	<b>0</b>	62:4 155:21	<b>14</b> 16:3,11 17:4	
145:10 149:4	<b>0.01</b> 176:19	165:14 168:22	19:17 20:11 76:3	<b>2</b>
151:6 153:5	<b>0.1</b> 132:22 133:2	210:1 227:7 228:1	157:5 202:17,21	<b>2</b> 17:2 19:9,21
199:17 206:22	<b>0.100</b> 165:13	255:17 306:9	207:20,21 209:4,8	43:14 209:22
224:18 237:5	<b>0.4</b> 332:22	307:19 311:9	215:17	227:9 240:17
276:19 296:12,14	<b>000041</b> 320:19	313:1,5,15 322:22	<b>14th</b> 1:17	247:1 254:22
313:9 314:7 348:5	<b>004</b> 332:2	<b>10,000</b> 47:7 60:16	<b>14-day</b> 14:20 15:16	<b>2B</b> 343:19,19
350:20	<b>05</b> 278:6 342:5	<b>10.7</b> 18:7	<b>147</b> 362:9	<b>2.0</b> 386:10
<b>yesterday's</b> 43:13	<b>09</b> 278:4 340:1	<b>10:08</b> 96:8	<b>15</b> 16:12 119:6	<b>2.1</b> 280:8 361:6
<b>yield</b> 65:7 107:16		<b>10:09</b> 96:15	125:10 177:4,19	<b>2.2</b> 354:6
111:22 124:19,22	<b>1</b>	<b>10:25</b> 96:8	227:7 266:13	<b>2.3</b> 353:17
<b>yielded</b> 109:2,11	<b>1</b> 19:22 20:1,21	<b>10:27</b> 96:16	308:6	<b>2.6</b> 279:22 280:8
111:10	120:8 165:13	<b>100</b> 124:22 181:5	<b>15-minute</b> 96:7	281:12 351:22
<b>yields</b> 124:10,11	169:5 186:21	189:17 190:15	323:18	<b>20</b> 22:6,8,9 122:3
<b>York</b> 116:2	189:5 191:15	202:16 204:12	<b>150</b> 266:13 277:17	124:19 126:5,10
<b>young</b> 2:18 8:14,14	202:17,21 209:4	206:14 207:16	<b>150,000</b> 315:10	126:15 130:6
24:9,10 25:6,10	266:6 307:16	209:9 212:2	<b>150-some</b> 56:16	211:11 227:13
25:16,19 65:12,13	332:20 333:1	239:15 241:4	<b>152</b> 265:2	244:13 309:8
66:14 67:7,11	361:19,19	242:10 253:15	<b>153</b> 362:14,17	319:18 320:12
68:21 79:22 80:1	<b>1,000</b> 320:11	259:11 276:10	<b>16</b> 67:12 114:19	322:4,7,10 327:15
81:3 85:7 186:17	322:17	301:19 320:21	125:10 298:8	327:17 335:7
191:20 195:7	<b>1,060</b> 364:5	362:7,18,20	361:18	355:19 361:12,16
234:9,17 236:11	<b>1,172</b> 363:13,16	414:22 415:1,7,9	<b>161,000</b> 332:13	362:3,5
290:1,2 293:8	<b>1,400</b> 291:13	415:11,12,12	<b>17</b> 269:18 271:17	<b>20-fold</b> 173:8
295:2,14 297:9	<b>1,500</b> 330:10	416:22	272:4 340:17	<b>20-minute</b> 286:15

<b>20-year</b> 107:19	155:21 183:16	362:19,21 386:16	<b>4</b>	<b>5:45</b> 384:6
<b>200</b> 124:20 195:12	276:16 349:13	<b>3D</b> 34:1,1	<b>4</b> 3:6 15:21 16:8	<b>5:48</b> 425:16
201:4,13 211:7	351:16 352:21	<b>3X</b> 281:14	18:2 19:8 26:6	<b>50</b> 20:5,6 98:22
213:21 239:15	<b>2011</b> 94:7 405:4	<b>3.2</b> 386:10	179:3 342:16,20	106:6 122:7
241:4 266:13	406:14 409:3,7,19	<b>3.5</b> 111:11	363:19 412:14	174:13 185:1
312:20 355:19,20	411:6	<b>3.6</b> 385:11	<b>4B</b> 181:1,4	189:20 190:22
<b>2000</b> 119:20 135:21	<b>2013</b> 118:18	<b>3:45</b> 323:21	<b>4D</b> 181:1	209:16 211:7
137:17 149:15,17	<b>202</b> 272:21 273:11	<b>30</b> 12:19 14:20	<b>4,200</b> 325:12	213:22 227:5
149:20,20 150:4	291:13 292:3	17:18 22:6,8,9	<b>4,293</b> 111:4	230:1 312:21
151:2 152:5 153:1	296:20 297:1	23:4 97:19 125:12	<b>4,400</b> 263:8 269:11	362:6 401:18
153:8 154:18	301:6,10,10 302:7	126:5,10,15 130:6	<b>4,500</b> 14:4	402:3,13 414:19
185:5 275:2 345:8	<b>21</b> 14:22	146:21 156:1	<b>4,600</b> 331:19	414:22 415:7,10
385:7 388:5,6	<b>212,000</b> 284:5	168:22 169:9,14	<b>4.23</b> 332:12	415:12 416:22
389:18	<b>22</b> 26:6 111:7	200:9 201:12	<b>4.6</b> 109:12	<b>50th</b> 315:11
<b>2000s</b> 284:13	<b>22,500</b> 264:7	203:6 207:10	<b>4:02</b> 323:22	<b>50,000</b> 263:7
<b>2001</b> 341:20	<b>22.7</b> 269:12	208:11 215:16	<b>4:40</b> 384:3	268:19 316:2
<b>2002</b> 171:21 284:15	<b>220</b> 355:20	264:1 277:13	<b>40</b> 97:20 145:3	325:12 411:12
371:14	<b>227</b> 278:2,8,11	287:18 306:9	146:21 156:1	<b>500</b> 330:9 402:7,13
<b>2003</b> 95:9 102:17	<b>23</b> 278:1	307:20 335:7,11	227:13 363:16	<b>5100</b> 195:12
138:18 263:17	<b>23,000</b> 314:18	357:14	364:5	
264:11 271:14	<b>236</b> 109:17	<b>30-day</b> 76:3	<b>40,000</b> 306:22	<b>6</b>
345:8 384:12	<b>24</b> 111:6 169:21	<b>30-plus</b> 276:15	<b>400</b> 144:15,18	<b>6</b> 17:3 251:2
387:16 394:15	251:1	<b>300</b> 103:16 170:1	271:13	<b>6,000</b> 319:11 321:6
398:5,10 406:8	<b>24,000</b> 357:8	239:15 241:4	<b>400-plus</b> 353:16	<b>6,300</b> 275:17
409:14	<b>24-hour</b> 167:7	275:3	<b>410,000</b> 314:20	<b>6.25</b> 255:18 313:5
<b>2004</b> 119:20 158:6	<b>25</b> 16:2 46:13 192:2	<b>31</b> 266:6	<b>42</b> 102:16	<b>6.3</b> 109:2
172:3 401:4 403:6	202:15 206:17	<b>31.25</b> 15:18	<b>43</b> 354:13	<b>6.5</b> 202:15 206:17
<b>2005</b> 109:10 141:10	235:13 244:13	<b>310</b> 111:4	<b>44</b> 102:18 166:14	207:13 235:14
158:6 362:13	<b>250</b> 266:14	<b>33</b> 389:20 392:3	332:6	<b>6.7</b> 269:10,17
399:22 401:4	<b>26</b> 264:1,5,6	<b>33,000</b> 317:22	<b>440</b> 288:19	<b>6:00</b> 11:4
402:11 408:10	<b>26,500</b> 265:8	<b>34</b> 275:16	<b>45</b> 145:4 384:2,5	<b>60</b> 20:8 147:1
<b>2006</b> 109:22 111:3	<b>27</b> 1:13 16:13	<b>340</b> 3:22		174:14 179:19
116:9 259:17	183:16 333:1	<b>344</b> 140:18 145:20	<b>5</b>	275:21 324:16
267:16 268:6	<b>28</b> 14:20 202:17,17	157:6 388:12	<b>5</b> 16:8 17:3 309:6	<b>60,000</b> 411:12
271:14 278:1	203:1 206:10	<b>35</b> 3:14 23:4 272:3	354:5 402:2 403:6	<b>60-day</b> 14:21
353:9 360:7	212:14,21,22	287:18	414:21 415:8	<b>62</b> 109:19
<b>2007</b> 102:13 113:11	233:3 241:21	<b>350,000</b> 313:21	<b>5,000</b> 15:21 319:20	<b>63,000</b> 314:3
119:21 329:9	245:7	<b>36</b> 67:13	321:8	319:21
361:12	<b>28-day</b> 241:18	<b>365</b> 12:22 14:6	<b>5,811</b> 109:17	<b>65</b> 145:5 179:19
<b>2008</b> 102:20 111:3	242:3,3	58:12 60:13	<b>5-1/2</b> 235:1	<b>650</b> 102:21
119:21 122:3	<b>298</b> 311:4 322:5	265:13 307:2	<b>5.3</b> 111:10	<b>69</b> 3:18
278:14 361:12		<b>365-day</b> 12:17	<b>5.4</b> 76:12 109:11	<b>69,000</b> 314:21
362:10,13	<b>3</b>	306:3,3 308:7	<b>5.86</b> 352:1	
<b>2009</b> 259:18 276:12	<b>3</b> 17:2 19:21 168:22	<b>37-1/2</b> 335:8	<b>5.9</b> 109:2	<b>7</b>
352:2 355:16	169:5 259:16	<b>37.5</b> 242:4 260:1	<b>5:00</b> 11:2	<b>7</b> 16:4,10 202:17,21
357:4,13	267:20 335:3	<b>38</b> 43:12,13	<b>5:30</b> 11:3	209:4 215:17
<b>2010</b> 1:13 94:5	343:13 344:10		<b>5:40</b> 384:5,6,6	<b>70</b> 147:1 313:18
				322:20,21 352:19

<p><b>72</b> 165:13,18 169:20 <b>73</b> 18:6 278:14 <b>75</b> 197:9 <b>75th</b> 307:17 314:19 <b>78</b> 273:19 274:1,1 292:8 301:10,20</p> <hr/> <p style="text-align: center;"><b>8</b></p> <hr/> <p><b>8</b> 16:10 179:3 235:9 239:21 <b>8th</b> 118:12 <b>8:30</b> 1:15 425:12 <b>8:31</b> 4:2 <b>80</b> 111:8 146:2 228:2 275:21 302:12 320:13 325:13 362:13,16 367:18 <b>81</b> 329:9 <b>82</b> 367:19 <b>85</b> 177:3 <b>86</b> 351:17</p> <hr/> <p style="text-align: center;"><b>9</b></p> <hr/> <p><b>9</b> 19:8 235:9 <b>90</b> 17:18 19:12 33:1 33:2 135:4 144:1 144:2 188:2 263:1 277:16 280:12 306:9 307:20 314:21 335:11 352:19 354:7 <b>90th</b> 332:15,21 354:4,6 <b>90,000</b> 411:9 <b>90-day</b> 13:12 14:19 21:11 55:21 71:17 76:21 144:11 259:19 271:6,21 272:2 287:14 288:11,14 310:3,4 312:6,10,12 315:12 <b>90-days</b> 20:10 <b>900</b> 239:21 342:17 <b>91</b> 343:12 <b>93</b> 263:17</p>	<p><b>95</b> 108:21 273:16 292:6 301:19 302:10 <b>95th</b> 60:9 303:20 354:2 <b>95%</b> 351:22 <b>96</b> 3:20 109:10 285:16 <b>99</b> 343:13,20 <b>99th</b> 46:10,12 60:5 60:8 270:9 <b>99.8</b> 331:21 <b>99.9</b> 19:12 303:21 <b>99.9th</b> 269:9,12,17 270:9 282:21 307:18 308:5 314:16 316:14</p>			
------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	--	--	--