FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

REEVALUATION OF THE HUMAN HEALTH EFFECTS

OF ATRAZINE:

REVIEW OF NON-CANCER EFFECTS AND

DRINKING WATER MONITORING FREQUENCY

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FIFRA SCIENTIFIC ADVISORY PANEL

MEETING

SEPTEMBER17, 2010

DR. STEVEN HEERINGA: Good morning, everyone, and welcome back to this fourth and final day of the FIFRA Scientific Advisory Panel Meeting on the topic of the Re-Evaluation of the Human Health Effects of Atrazine: Review of Non-Cancer Effects and Drinking Water Monitoring Frequency.

I think since there are very few new faces in this room that we won't go around and have the Panel introduce themselves this morning. I'll just say I'm, I'm Steve Heeringa. I'm the Chair of the proceedings.

I want to thank Dr. Portier for filling in for me late yesterday afternoon, and I understand that we have gone through the Charge Question No. 4 and its subparts. Dr. Portier has left it open for any additional comments from Panel Members related to Charge Question No. 4.

Any additional thoughts overnight from people, things they would like to add on the of course, until the end of these proceedings if something comes to mind, you're always welcome to bring it forward. So don't hesitate, but in terms of sort of

the organization of our discussion, nothing else to add? Wes, Dr. Coupe, others all set? Thank you.

SPEAKER: You're okay?

DR. STEVEN HEERINGA: Okay. Well, if that is the case, I want to turn briefly to Joe Bailey, the Designated Federal Official for these meetings, just to see if Joe has anything to add before we begin.

DR. JOSEPH BAILEY: I really don't have anything to add, I just want to welcome everybody back for the last day. I think we've made good progress on the agenda so far. We're right on target, if not a little bit ahead, so .

DR. STEVEN HEERINGA: Do you want to mention hydroxyatrazine?

DR. JOSEPH BAILEY: Oh, yes, I will make one comment. Dr. Stone yesterday, I'm sorry, Mr. Stone yesterday in the discussions about the water issues made a reference to two USGS documents that have some information on hydroxyatrazine monitoring. He's going to provide me those references and the link, and I will send that out to the Panel.

I believe Syngenta has also provided a little bit of information, which I will also provide to the Panel. It did come in after the Comment period had closed, so I will treat that accordingly and send it to

you as well and put it in the docket. That's all I have.

SPEAKER: Last night I downloaded the most recent JNPR evaluation of atrazine and all of its metabolites, so I can provide that reference and the link as well.

DR. STEVEN HEERINGA: Thank you very much.

DR. JOSEPH BAILEY: Okay, good. Thank you.

DR. STEVEN HEERINGA: That's very good. So those materials will all be available to the Panel on the docket, and I think several of these things are in hard copy.

DR. JOSEPH BAILEY: It will all be electronic.

DR. STEVEN HEERINGA: Okay, thank you very much.

Okay. At this point, just to give everybody a sense of what I would anticipate for the day, it is my intent to finish by 12:00, and that gives us well over three hours of total time on two questions and wrap-up, and we should be able to do that. So that's. again, I, if it turns out that we have productive discussions that take us longer we'll do

that, but that's my aim. People are trying to plan their day here.

At this point in time, I think I'll turn to maybe Nelson to read the Charge Question No. 5 into the record or

DR. JACK FOWLE: I want to introduce myself, my name is Jack Fowle, and I'm the Deputy Director of the Health Effects Division in the Office of Pesticides.

DR. STEVEN HEERINGA: Okay.

DR. JACK FOWLE: And it clearly must be an atrazine SAP, because Anna has written saying there is a major water-main break and she's got to take a major detour.

SPEAKER: Oh, again?

DR. JACK FOWLE: So she will be a little bit late, so we'll proceed.

DR. STEVEN HEERINGA: What was it, a snowstorm last

SPEAKER: I think it was another water main.

DR. STEVEN HEERINGA: A water main, okay.

DR. JACK FOWLE: Something like that.

SPEAKER: Was there an accident at some

point in time?

DR. STEVEN HEERINGA: Okay. Well, thank you very much.

DR. JACK FOWLE: If you can put up with my scratchy voice, I can read this question, Question 5: The Agency requests the Panel to comment on important scientific factors for the Agency to consider in its analysis.

Please include in your comments specific consideration of uncertainties in estimating drinking water exposures and remaining uncertainties in atrazine's toxicological profile across life stages, particularly as they pertain to assessing risk to infants and children.

DR. STEVEN HEERINGA: Our first...thank you very much first, Dr. Fowle.

I want to turn to our lead discussant on this, Dr. Pope.

DR. CAREY POPE: Yes, good morning. So Question 5, I saw two parts of it, basically asking about uncertainties regarding drinking water exposures for young individuals and uncertainties in the toxicological profile across life stages.

I don't have a whole lot to say about the first aspect, although I did pick up a couple of

things that I would consider that evaluating treated water samples for levels seems a better approach than untreated water sources.

The other question about the duration of dosing, it would be better you know, currently, there's a 90-day rolling average in whether there may be a better duration of exposure to use. I'm still not certain whether there's in my mind a better duration to point to for either the adults or the developing individuals.

Regarding the second part of this question about the profile across life stages, I have a little bit more to say.

And by the way, Dr. Meek is not here; but she provided her information to me, and I have that as well.

DR. STEVEN HEERINGA: Yeah, she said she would do that. That's very good.

DR. CAREY POPE: So while there is a good consensus about atrazine's influence on GnRH-mediated LH surge and the reproductive or developmental toxicity, there is also some confusion, as would be expected. The Morseth, et al., study, currently used to set the point of departure, has not been replicated in more recent studies from the registrant using

relatively similar dosing strategies, repeated dosing, dietary. And, you know, in the review, it's difficult to reconcile some of these differences in these studies.

In the studies using radiolabeled atrazine, it appeared to me that, if anything, there was less uptake of atrazine across a placenta than levels noted in the dam, and these suggest that there may not be selectively higher exposures to the developmental organism during prenatal period.

A number of studies examined relative toxicity with either prenatal dosing, postnatal or peripubertal exposures to atrazine. And with the prenatal exposures, generally endpoints like preputial separation and mammary gland development were noted; but the repeated exposures were somewhere between 50 and 100 milligrams per kilogram per day. And prenatal combined with lactational exposures showed similar effects on preputial separation and prostatitis; but only 100 milligrams per kilogram per day were used.

Several studies evaluated the effects during peripubertal exposures, and again preputial separation was affected. And this, from what I could see, was the lowest dose where you saw a developmental effect, and it was at 12.5 milligrams per kilogram per

day for quite an extended period.

Testosterone levels were evaluated with a couple of studies, and I think the lowest dose, effective dose, was 50 milligrams per kilogram per day.

Thus, in this collection of studies, there's not much evidence that either prenatal, lactational or peripubertal exposures were leading to a higher sensitivity in development of organisms.

We spent quite a bit of time yesterday on a number of occasions talking about the studies with the atrazine mixture by Enoch, et al., on 2007.

And also the hydroxyatrazine metabolite has come up a number of times. I want to say here that all hydroxyatrazine metabolites are not created equally. There is a ring structure hydroxylation, which appears to be the one used in Enoch's paper that appears to be an environmental contaminant, and the one set are reported in the metabolism studies for alkyl hydroxylations, including a recent paper by, from Hotchkins Lab showing ethyl and isopropyl hydroxylations.

And I'm not sure, Dr. Lowit mentioned yesterday that there are some studies in the literature looking at the hydroxyatrazine metabolite. I'm not sure which ones she's referring to, whether they're the

ring hydroxylations or the alkyl hydroxylations. I think it could be important.

But regardless, this paper reported significant changes in mammary gland development with very low levels, down to less than 1 milligram per kilogram per day, with this atrazine mixture.

The white paper, one of the kind of overall feelings I had as I went through the white paper is that the study by Enoch and coworkers in 2007 was being kind of downgraded, so to speak, as far as its potential influence in the risk-assessment process for a number of reasons.

However, I feel that capturing the makeup of water contaminants, it in my mind is a good idea while it's obviously more complex to handle and interpret.

There's obviously some legitimate questions noted concerning the date in that paper. We've already talked about the score and the histological lesions and the reporting and the analysis of the lesions, and whether they are histological or morphometric is better.

There was obviously some low mean scores in one of the control groups in that mammary development data that kind of weakened the impact of

it.

There was little change in the effect with the higher dosages across a hundredfold dose range, which could be difficult to interpret; however, I think it's also reasonable to assume that even if results like that don't really fit very well into a risk-assessment process and trying to determine points of departure, I think it's reasonable to think that some kind of developmental alteration could occur at a certain level once a minimal level of exposure is reached. It doesn't really matter if you can have more added on top of it.

One interesting piece of information that I haven't heard and didn't key into before this morning when I was kind of looking over these papers again was a paper by Stoker and Cooper in 2007 when they looked at tissue distribution radioactivity following C14 atrazine, and the mammary gland was incredibly packed, relatively speaking, full of atrazine or metabolites. It was the highest percent of radioactivity, higher than liver and kidney; and I made a graph of this, but I'm not sure there's really much reason to show it.

DR. STEVEN HEERINGA: We can bring it up. We'll bring it up if you went through all the

trouble to make a graph.

DR. CAREY POPE: Yeah, it wasn't that much trouble.

So you can see that there's quite a range of tissues here, including tissues from the central nervous system, spleen, liver, kidney, gonads. And, you know, to me, that's pretty striking that there may be something to think about as far as accumulation of atrazine or its metabolites in the mammary gland. And this is the dam following oral dosing, 2 milligrams per kilogram. I think it's 3 hours after dosing.

It's not the developing mammary gland; but, you know, if it is, if that was the developing mammary gland, you'd think, "Wow. Maybe putting these two things together, there's something to it".

And thus while I think no other studies aside from Enoch, et al., in 2007 have used this mixture, it's a much more complicated thing to think about as far as what these metabolites are, and I think to me it kind of sends up a flag that the mammary gland may be highly exposed and may be highly sensitive during the development.

A little bit more about the hydroxyatrazine ring structure hydroxyl group, it's apparently a minimal component in the mammalian

metabolism or maybe not even a component of mammalian metabolism of atrazine; but it appears to be a substantial environmental contaminant.

I didn't, however, look at the original papers that was cited in the Enoch, et al., that refers back to the lowest concentrations of that in the water samples.

So the very low exposure levels suggest that the mammary gland effects may be sensitive endpoints following gestational exposure to atrazine and/or its metabolites. There is no clear-cut mechanism for what might be happening. These findings which apparently selected the accumulation of atrazine or its metabolites in the mammary gland provide concern for me that the high sensitivity is developing in organisms.

And as noted yesterday, I mean, I think standing alone, the Enoch, et al., paper is kind of, is standing alone. There is not much to kind of reinforce those findings, and so I think replication and extension of those findings with dosimetry and looking at individual effects on a mammary gland at low-level exposures are, are necessary to effectively influence the risk assessment.

DR. STEVEN HEERINGA: Thank you, Dr.

Pope.

And Dr. Chambers.

DR. JANICE CHAMBERS: Thank you. Just a couple of things that I certainly agree with with what Carey just said. I think the finished water will be a better reflection of what the developing organism human would be exposed to, and also the fact that an awful lot of the data we saw were just on high doses is not reflective of what humans would be exposed to. So we certainly need more low-dose information.

I guess a couple of things that I keyed into is with respect to the uncertainties you're dealing with. I think you're doing, we're seeing a lot more of the kinetic studies right now, and I think those are extremely useful in trying to determine what the internal dose of both the moms and the fetuses or the pups would be, so I would encourage doing that.

The feeding regimens we were seeing, I think it is a much more realistic paradigm for presenting the delivery or delivering the dose as it would be seen in drinking water exposures, and so I would encourage more of that. It's not drinking water, but it is an exposure that occurs over a period of time as opposed to one bolus and a gavage dosing thing; so I think that probably is useful.

The pseudo-steady state data that we saw that was presented to us and everything was very, very useful, I think, in trying to estimate what the internal dose is, which hopefully can then be related to the toxicology data.

Another thing that is going to be useful I gather that's on the mill or in the works right now is getting enough data to develop a PBK model, and that would be useful. Certainly to get that appropriate for the developing organism, we're going to need some metabolic parameters on the developing organism fetus and the infant child.

Some of the data we saw -- and I think this was from Syngenta's metabolism parameters -- only had one human sample. We're certainly going to need more than one human to get a representative number on that.

I guess one of the most equivocal things we've talked about -- and we talked about it at length yesterday and Carey just talked about it quite a bit today -- was that mammary gland issue with the Enoch paper. It's really hard to sort that out; I mean, you struggled with it, and I agreed with your concern about the conduct of that study. If it's real, it certainly needs to be dealt with in risk assessment sooner or

later. I guess Gerry said yesterday we need to determine whether it's an artifact or whether it's real. So it certainly needs to be replicated so that you can sort that out in, in the risk-assessment process.

What you just presented with respect to concentrations, that probably is not too surprising; the mammary gland, I assume, would be a pretty lipid-rich tissue and would accumulate lipophilic compounds. So that's probably not too surprising; whether the fact that it's there and the lipid is actually exerting any toxic mechanisms is hard to know.

So, again, that's a big uncertainty that I think we need to sort out. But it's out there, that paper is out there at those low doses, and some sort of replication needs to be done to determine how real that is.

DR. STEVEN HEERINGA: Thank you, Dr. Chambers.

Dr. Fenner-Crisp, Penny?

DR. PENELOPE FENNER-CRISP: A more general statement, comment in addition to the ones that the two have already made; I agree with theirs, as well.

This is all about one aspect of the

decision-making process, well, not all about, but incumbent in here is the decision on the 10x safety factor. And embedded in that assessment process is both a qualitative and a quantitative component.

The qualitative component being, do you have data, and the appropriate data, that show whether, what the toxicity profile at various life stages looks like, and there's a lot of work going on to describe that at various times.

But there is also a quantitative component in here. Once you understand toxicity profiles of various pre-adult stages, how do they compare quantitatively with the adult? And I asked Anna the other day if the Agency thought it had enough data describing the toxicity profile in the adult against which one could make comparisons, and she said yes.

So I would submit that incumbent on the Agency when they redo this discussion that that's where you start. Here is what we have acquired in the adult and it says such and so; here is what we've now done with respect to various life stages.

The toxicity profiles match up or not, as the case may be, and here are where quantitative differences may exist, and therefore this would be our

decision logic for evaluating the component of the 10x that's dedicated to the toxicology.

One of the things I found interesting about the milk data was -- or that kinetic data was the rough equivalence in plasma for the fetus and the adult, but a significant drop-off in the milk.

So one can't understand fully what the differential might be in sensitivity or tox profile comparing with an adult there. I'm not suggesting you go back and direct those pups with equivalent doses that match the kinetics in the adult; but if it comes to having to fully understand the kinetics in that life stage, that's one thing that might be appealing.

I think at this stage, we can't comment on whether or not the completed studies and those that are in the pipeline are going to be sufficient to answer all the questions on potential pre-adult toxicity and the potential for quantitative differences. So I think we have to, I would have to reserve judgment on that until those studies are finished.

DR. STEVEN HEERINGA: Thank you, Dr. Fenner-Crisp.

Dr. Pope, could you read Dr. Meek's comments into the record?

DR. CAREY POPE: Okay, this is from Bette Meek, and I'll just have to read it word-for-word: "Consideration of the value of the FQPA safety factor is seemingly best predicated on transparent and systematic consideration of the most important qualitative and quantitative uncertainties associated with both exposure and effect relevant to susceptible life stages in a context consistent with that for other pesticides.

In view of the fact that the database for atrazine relevant to the selection of this factor is still evolving, reference here is to some of the generic aspects that might be explicitly considered based on outcome of additional analysis, including for exposure this could relate to the likelihood of capturing the relevant periods of susceptibility or over- or underestimating exposure for all life stages, with the proposed monitoring strategy, including, for example, consideration of determination of TCT rather than atrazine.

"For effect, some critical questions and/or aspects to be addressed in this context include: to what extent does the database on hazard and kinetic and dynamic data inform us about potential increased susceptibility of infants and children?

Is the early key event or late adverse effect for the critical effects sufficiently protective for all age groups based on hazard characterization, including knowledge of mode of action? How protective is it, for example, an early key event protective for later adverse effects?

What is the impact to the potential reliance on a benchmark dose versus an effect level in relation to uncertainty in the characterization of the relevant dose-response relationship?

Does the degree of conservatism associated with use of a lower confidence interval for a benchmark dose increase confidence? And finally, while the epidemiological data are not considered sufficiently robust for inclusion in quantitative risk assessment, can data from any of the studies that are considered of highest quality be used to provide some idea of relative sensitivity of various age groups of the human population?"

DR. STEVEN HEERINGA: Thank you, Dr. Pope. And again, those were Dr. Bette Meek's comments, which she had written up and prepared for us.

At this point, I turn to the other members of the Panel for any comments or additional contributions on Charge Question No. 5?

Yes, Dr. McManaman?

DR. JAMES McMANAMAN: So in regards to Dr. Chambers' statement that this would be a lipophilic compound, it's unlikely to be lipophilic since it's likely that those nitrogens are charged at physiological pH and it has lots of hydrophilic residues on it; so I think it's unlikely to be lipophilic.

And if Dr. Pope could clarify the, that the C14 distribution data, that was in a lactating dam?

DR. CAREY POPE: Yes.

DR. JAMES McMANAMAN: So during lactation, there is very little adipose remaining in the mammary gland; it's almost all been de-lipidated, if you will, so it's almost all glandular structure.

Then regarding the risk assessment, it seems to me that there are two underlying aspects of this. Dr. Fenner-Crisp mentioned that there is qualitative and quantitative.

And my concern is that we are trying to - not "We are trying to do this", may be too strong -- but there is a move to try to put a square peg in a round hole, in that if atrazine were directly administered regarding the mammary gland, were directly affecting the mammary gland, then that would be a

primary target and we could expect a normal dose-response curve.

But if the mammary gland is a secondary target related to some other aspect of physiology, then I don't know that we would expect it to find a normal dose-response curve.

And so my concern is that if it has to have a dose-response curve to be considered as part of the risk assessment, then I think that we're missing, we potentially would be missing secondary effects of which there may not be a normal dose-response curve.

Dr. Rayner's study showing that F2 pups had lower weights in the atrazine-treated animals, this suggests that it is a comp...atrazine is having complex physiological effects that, again, would not expect to be a simple dose-response curve, because F2 generation, that's the grandchildren of the dam that was treated. So I think that that needs to be taken into account in assessing risk.

And if the models don't fit in a preconceived notion, then I think that they should not just be dismissed, and we should look for further explanations in terms of risk assessment.

And then there is one other thing that I want to have, make sure that it's read into the record,

and that is the Syngenta work, it's Figure 2 on Coder D. I have it on my computer, but it's the Coder 2010 D study, it's Figure 2.

And what it shows is it's the effect of increasing doses of atrazine on the weights of dams during lactation. And if we were to compare to the pair-fed dam as the control as suggested by Syngenta Group, then we have a dose-response relationship between the 100milligram per kilogram atrazine and the 50 milligram per kilogram atrazine in terms of less change in body weight. Okay? So the greatest change in body weight was the pair-fed, and then the next was 100, and the next was 50.

So if that is, if we can use that as an example, then I suggest that the Agency consider that atrazine may be having metabolic effects and that's on the adult, and I don't know that that -- it certainly wasn't part of our Charge Question; but it's come out of the data -- and that there be more studies related to potential metabolic effects of atrazine on particularly dams during lactation and possibly dams, non-lactating dams and pups.

DR. STEVEN HEERINGA: Thank you, Dr. McManaman.

Yes, Dr. Schlenk?

DR. DANIEL SCHLENK: Just to clarify on the lipophilicity issues relating to atrazine, I was just looking at the log P; it's 2.75. So it actually is fairly lipophilic; it's about 100 times more likely to be in octanol than water, so it's fairly lipophilic.

DR. STEVEN HEERINGA: Dr. Krishnan?

DR. KANNAN KRISHNAN: The biological measures of the partition coefficient don't seem to suggest that, from my recollection. But those are within a factor of 1:3, the plasma to various tissues; just an observation, recollection from the data.

DR. STEVEN HEERINGA: Dr. Horseman.

DR. NELSON HORSEMAN: I would just say it doesn't much matter. There's a lot of it in the mammary gland. And there's just about every kind of metabolite in the lactating mammary gland, lipophilic and hydrophilic and every other sort of so that doesn't really matter. Whether it's surprising or not, it's there.

DR. STEVEN HEERINGA: Any other contributions?

Dr. Bailar.

DR. JOHN BAILAR: Just to have it on the record, I would urge EPA to keep its eye firmly fixed on effects of real concern at doses of real concern.

Much of the new information we've received for this meeting falls outside one or both of those limits. I'm not saying it's irrelevant; but every time EPA uses data that are either not focused on effects of real concern at doses of real concern, they should say why it is considered relevant.

DR. STEVEN HEERINGA: Thank you, Dr. Bailar.

Just again reminding ourselves, consideration of uncertainties in estimating drinking water exposures and any remaining uncertainties in atrazine's toxicological profile across life stages, particularly assessed in infants and children. Any additional comments or input on life stage?

We heard some things, and I think the metabolism suggestion was one and there have been others. So, Dr. Pope and Dr. Chambers and Dr. Fenner-Crisp, other comments people would like to make on this particular question?

I'm going to turn to the EPA, and I'll turn to Dr. Fowle or Dr. Lowit?

DR. ANNA LOWIT: I think the only thing I would ask is implicit in the rest of the text that's not on the screen is that a lot of the water uncertainties were covered in Question 4, basically.

If there were anything that weren't covered in Question 4 that are relevant here, to make sure they get put on the record.

DR. STEVEN HEERINGA: Right, okay. And I think again if anyone has anything to add before we close these proceedings, any thoughts that come to mind, you'll certainly have a chance to bring them in. And in the preparation of the report, as you well know, there is reorganization of some of the discussion to make it match the organization of the Charge Questions. Okay.

Yes, Dr. Horseman?

DR. NELSON HORSEMAN: Again, not to drag this out a little bit, but we heard an argument here for monitoring finished drinking water, and clearly the epidemiologists would much prefer that they have that information to understand real exposure.

I wonder if given that in general primary and secondary conventional water treatment isn't designed in any sense to remove these components, the extent to which things like atrazine and soluble components are removed in conventional water treatment seems to me sort of accidental and that only tertiary treatment is designed to remove these things.

I wonder if aside from the utility of

the finished-water information for epidemiology, if this is actually the appropriate charge in terms of knowing finished water and so on.

DR. STEVEN HEERINGA: Dr. Chambers?

DR. JANICE CHAMBERS: The reason I suggested that and perhaps the reason Carey suggested that is that the epidemiology exposure information is so weak in terms of, you know, proximity to a cornfield or something like that. If you're going to get a more accurate assessment of what people are being exposed to, you need to look at the actual drinking water.

DR. STEVEN HEERINGA: Dr. Pope?

DR. CAREY POPE: Yes, I agree also with what Jan just said; but I believe someone in the last couple of days also showed some differences in the different treatment facilities as far as the incoming and the outcoming, the contents were that I thought, depending on which community water service was there, there were different clarifications of the chemicals.

DR. STEVEN HEERINGA: I think Dr. Thurman presented a comparative chart, and then I think also Syngenta chart or Dr. Hall, Mr. Hall, Dr. Hall had a chart comparing efficacy of it on about 60 different sites as to the removal.

And clearly the activated-carbon

filtration was the one that appeared to be at least producing null results, and as he went up the ladder where there was no carbon treatment, there was more likely an occurrence of atrazine.

Yes, Dr. McManaman?

DR. JAMES McMANAMAN: One last thing and very brief. I think there could be a wealth of information obtained by examining in laboratory animal studies the fecal content of atrazine. I asked this question the other day to Syngenta and they didn't have the information regarding the amount of atrazine in the fecal content; but they showed studies in which atrazine, dietary dosing of atrazine, had no effect.

Well, the only way that we can understand what those studies mean is if we understand how much is actually coming in, and a very simple procedure that could be used is by just examining the amount that was given, the amount that was absorbed, because it's just a simple subtraction.

DR. STEVEN HEERINGA: Okay. Dr. McManaman, do you feel, I thought we heard there was at least a rough estimate of the percent of excretion in fecal matter. Was this a different --

DR. JAMES McMANAMAN: That was from a gavage dose, not from a dietary dose.

DR. STEVEN HEERINGA: Thank you. Thank you, thank you.

Dr. Horseman, you have something additional?

DR. NELSON HORSEMAN: No.

DR. STEVEN HEERINGA: Any additional comments on this?

Okay. Again, we'll return and give everybody a chance for some final wrap-up comments.

Let's move on, then. I can see we're going to easily make 12:00 o'clock unless this breaks down.

But good, good. I think it's been productive, all of these discussions.

So Question 6, I'm going to rotate here. Mr. Fowle or Anna?

DR. ANNA LOWIT: Question 6: Please comment on the Agency's analysis and preliminary conclusions contained in Section 8.0 in the draft Issue Paper as it relates to the potential critical windows of exposure. Please include in your comments additional or alternative approaches or data that may inform this issue.

DR. STEVEN HEERINGA: For our integrative analysis, we'll turn to Dr. Bucher to

start.

DR. JOHN BUCHER: Thank you.

So in preparation for this, I sent some preliminary remarks around to the group earlier on, and I got a reality check back from Dr. Coupe on some of the comments I had made with respect to water systems; so I acknowledge his contributions here, and also Dr. Meek sent me some comments to integrate into this document as well.

So Section 8 in the Atrazine Issue Paper systematically addresses a number of issues. These include: the use of the LH surge suppression in the rat as a benchmark response; the strength of evidence linking the benchmark response with a variety of endpoints in human epidemiology and experimental animal studies; the comparative timing and extent of exposures with respect to the potential to suppress the LH surge in animals and humans, including kinetic and dynamic considerations; the potential for water atrazine concentrations exceeding a level of concern to be missed by current sampling procedures; and the concept that sampling frequency can be meaningfully adjusted based upon the potential for human health outcomes.

The Agency has done a good job of summarizing the situation in each of these areas with

respect to the uncertainties and limitations in both the data and in our scientific understanding of what these data are telling us.

The Agency has determined that the collected information suggests a water-sampling frequency of between a few days and four weeks based on durations of exposure considered relevant with respect to potential human health outcomes. Currently, the sampling frequency required to the registrant is once a week during the use season and once every two weeks during the rest of the year.

There are a whole series of assumptions and extrapolations that contribute to this proposed critical window of human exposure, and given the collected uncertainties that these assumptions introduce, the imprecision in this proposed sampling frequency seems fully justified.

This may be about as precise an estimate as can be obtained when starting with the experimental animal data and the exposure requirements for the LH surge suppression, as opposed to using outcomes that are more unequivocally adverse.

In this regard, the consideration of human relevance of the adversity of the LH surge suppression on the basis of both the pharmacokinetics

and the pharmacodynamics, taking into account the broader database, including data on other pharmaceutical agents that have been used to block the LH surge, is to be commended.

After all this, the proposed range of human exposures responsible for potential adverse outcomes still appears to be little more than an educated guess.

Question 6 specifically requests alternative approaches and, in fact, there is another way of approaching this that may be useful, at least when setting the boundaries of exposures that may present a concern for human health effects.

The current epidemiology database is characterized as providing suggestive evidence that the mechanisms of action thought to be operative in rats may be occurring in humans exposed to atrazine. The Agency has appropriately concluded that the limited human evidence is insufficient to establish causality and does not provide sufficient quantitative exposure information to use in a risk assessment.

However, what if one assumes that the reported human health outcomes are, in fact, due to current levels of exposure to atrazine? Although the water-sampling data may not be adequate to assure that

atrazine peaks are captured in all water systems, clearly, some of the patterns we have seen are based on rather comprehensive datasets.

These patterns of atrazine concentrations in water could provide reasonable estimations of the extent and duration of human consumption of atrazine following agricultural applications for re-emergent weed control.

I would suggest that this represents an alternative approach to getting at levels of atrazine in drinking water that may represent risks to human health.

These risks could be compared certainly on an order-of-magnitude scale against those calculated from the animal data and may provide a lower bound conservative floor from which to work and provide a different perspective on the water-sampling frequency problem.

This would put the Agency in a much better position if, in fact, the agricultural health study or the other epidemiology studies that are ongoing or may be done in the future provide further support for human health effects as the results continue to accumulate and be reported.

The other consideration when faced with

an uncertainty over a critical exposure window of a few days to four weeks is whether basing sampling frequency on human health effects is, in fact, the best course of action.

Atrazine concentrations in a stream and subsequently in the finished water supply or the community water supply that uses that steam as its water source are dependent upon many factors that vary spatially and temporally.

As was discussed yesterday, each community water system is unique in factors that affect the delivery of atrazine, such as a drainage base and size, characteristics of the soils, cropping patterns, slope, et cetera, as well as whether the community water source and water intake is directly in the steam, in a reservoir or in an off-stream storage facility.

In addition, there are many factors that affect the ability of a water-treatment system to remove atrazine from water such as use of activated carbon and the type of oxidant. It's also been shown that the amount of atrazine in the system can sometimes be related to the ongoing maintenance of the treatment plant.

So, in fact, it may be more useful to consider a strategy that I believe was reflected in

yesterday's discussion of Questions 3 and 4, which was to capture the pattern of atrazine in the source water for each community water system based on the characteristics of that particular water system, as opposed to this one-size-fits-all approach that has been put forth based on the series of health-based considerations by the Agency.

Given the collective limitations of the health outcome-based approach, this would seem prudent and would again put the Agency in a better position to take further action, should the results of ongoing epidemiology studies provide more convincing evidence of human health effects.

Thank you.

DR. STEVEN HEERINGA: Thank you, Dr. Bucher.

Dr. Coupe?

DR. RICHARD COUPE: Good morning. I don't really have much to say. I just have kind of like a, not even an opinion, really, just kind of a feeling. I appreciate Dr. Bucher putting all that together; that was really nicely done.

My feeling is that I'm really kind of somewhat conflicted as I sit here, as after we sit here for a couple of days and we've tried to and not being

a toxicologist, some of it was rather mind-numbing, trying to figure out, you know, does atrazine affect human health in any way, shape or form at levels that are environmentally significant, and it was very difficult for me to see that there was such a thing. Coming from an agricultural background, I know how important atrazine is and I was dying to ask the agricultural people some questions; but then you said, you know, keep it relative to the Charge Questions. But nothing they said was relevant to the Charge Question.

But I understand where they're coming from. You know, atrazine is very important to modern agriculture; it's also important in urban areas. I mean, we all probably use atrazine. If you use weed and feed, it's got usually atrazine, may be 24d or something else in it, we all use it. It seems a little unfair based on what we see as the health effect right now to ask the registrant to do more than they are currently doing.

You know, we have had this debate about finished water and surface water. I mean, I understand the debate, and I think, you know, let's do both. That seems a lot to ask. I don't want to lose the surface water, because when you go to the finished water,

although it's good for the epidemiologists, you lose kind of the tie to the environmental system.

And so it makes it much more difficult to predict what the environmental effects, the slopes and cropping and all that, had to do with how atrazine gets delivered to the intake. So I would hate to see us lose that, but I understand why we'd want to go with finished water.

And then that all being said, on the other hand, atrazine is used so much that it is currently found in every environmental compartment that we've looked at: it is in the rainfall, it is in the drinking water, it is in the surface water, it's in reservoirs, it's in lakes, it's in lakes and reservoirs far from any point of application; it's carried by the atmosphere.

And so it seems like we ought to, since it is such a widely used one, we do need to kind of be careful with it, 'cause what if it is having some subtle effect? What if what Dr. Bucher said is that we're already seeing the effect; it's just so broad, you know, we can't see it anymore, but it's there. I know that's a bit confusing; but that's just kind of like where I'm conflicted at at this point.

I think that's all I want to say.

DR. STEVEN HEERINGA: Thank you, Dr. Coupe. Appreciate those thoughts.

Dr. Fenner-Crisp?

DR. PENELOPE FENNER-CRISP: I should note that even being a toxicologist, it was mind-numbing.

There was a whole lot of data there; talk about supersaturation.

Obviously, I'm on board with what John has written, because we've had a chance to work on it. I wanted to add a technical comment from something that's in the chapter.

You've offered an example here of what would the numbers look like if you used that allometric scaling? It was Table 8-1 on Page 128. The thing that drew my attention was it was being based on a human female of 60 kilograms.

The average human body weight for women in the U.S. hasn't been that low for over 50 years. So I found a National Health and NCHS report that was published in 2008 that captured anthropometric reference data for children and adults for the years between 2003 and 2006.

I'll provide the citation. I don't think they published the update for 2006 to 9. But in

this, the average body weight for the U.S. female is 165 pounds. So if one chooses to go forward with allometric scaling in testing the possibilities in the quantitative component, I would suggest you update them to some reality. I found that rather startling, quite frankly.

DR. STEVEN HEERINGA: Thank you, Dr. Fenner-Crisp.

Dr. Greenwood?

DR. RICHARD GREENWOOD: Well, I, excuse me, very much agree with the tone of what Dr. Bucher presented, and I agree with the Agency that there's a lot of scientific uncertainty in estimating these critical levels of exposure in terms of critical doses, concern sort of corresponding to any critical plasma concentration and a critical time period of exposure as sort of a duration of critical plasma concentration.

And they're trying to sort this out in the absence of knowledge of any primary lesion or of the minimum disruption that will lead to various secondary lesions that we heard a lot about during this week.

And so I understand also that they've got difficulty in trying to assess human plasma areas under the plasma-concentration curve in humans that

would correspond to particular intakes of drinking water, and I will sort of come back to that at the end.

I found it difficult to assess the relevance of the information on the GnRH antagonist research, because the Mode of Action is quite different.

Really, we have no data to provide any guidance at all about what would be the minimum concentration of atrazine that would be needed over a period of exposure that would produce an equivalent reduction in GnRH level to match the antagonism of the receptor that we see with this drug.

It's very difficult to tie any of the atrazine data into that, and it's difficult to see how you would use that to identify an exposure to atrazine that would produce a similar effect at that critical period that was identified.

I think the data presented by the Agency and by Syngenta demonstrate that repeated dosing, which is the sort of case we'd have with human exposure via drinking water, would lead to some sort of pseudo-steady state if the dose was constant.

And the Syngenta data indicate that the plasma profile is very much smoother when atrazine is presented in food rather than in a discrete bolus by

oral gavage. But administration in drinking water I think would probably fall somewhere between these two scenarios, and it would be depend of course on the time and nature of meals relative to drinking the water.

So although the area under the plasma curve sort of represents internal exposure resulting from dose in it, we need to be a little careful.

It is important, I think, because this will provide a link between external exposure and site of action, and it could be important if the dose varied from day to day as it may well do in human exposure, because under the regimen of regular dosing over a fixed time with a constant dose, it's just the calculation of the area and the curve is redundant, and the plasma concentration is the only variable needed.

And I think it would be helpful for the Agency to have some idea of whether area under the curve really is important, and it's difficult to see that or to conclude that on the basis of the existing data.

If we look at the papers of Kamel and Stoker that were provided in the docket, look at the evidence they provided, then I think it's wholly appropriate to use the area under the curve as a measure of exposure, because that does give an idea of

the opportunity of exposure of individual tissues.

And the work that is being done at the minute to get good estimates of plasma-tissue partition coefficients may overcome some of the problems highlighted by the Agency in the discussion in Section 8 of the white paper, because it will give further insight into exposures of individual tissues.

I think the whole business has been slighted by the fact that the DACT binds to a range of proteins in each tissue that's being looked at, and this could be a complicating factor, depending on the amount of covalent binding in particular tissues, because then eventually for elimination of the bound material, it will depend on the time scale of turnover of proteins, and of course that can range from hours for enzymes involved in metabolic regulation to weeks for structural proteins; so it would depend on the pattern and extent of binding.

Now, this sort of binding would only become important if it was that that produced the primary lesion. I'm not sure whether we're anywhere near understanding that at all; I don't think we are.

But I do think I agree with the Agency that the physiologically based pharmacokinetic modeling approach is the ideal route if they want to take all of

these uncertainties in account and extrapolate from rodent to human.

But I think in the absence of that at the moment, the Agency is taking the best approach that's available to it, and that is to use the pharmacokinetic approach that they have used.

But it is I think one question that really should be approached, and that is to try and determine whether there really is a critical area under the curve -- that is, a critical exposure of a target site -- that leads to a given level of suppression of the LH surge, because I think at the moment if you give a constant dose over the four days, it doesn't tell you very much at all.

What you really need to do is to get the same area under the curve by different dose regimens, because there is a number of possibilities in there. One is that they're not equally susceptible or equally tolerant, if you like, on all days.

It could be, you know, you need 100 units exposure on 1 day, but only 50 on the next. Are they equally susceptible over the whole of this critical period that's being used? Do you need all four days, or is it sufficient to do Days 2 and 3?

So there could be a critical exposure

time combined with a critical level, and it would have the same nexus area under the curve; but there would be a minimum to it. There would be a minimum exposure time and that would be fixed, and then you may find that there is a minimum concentration that you need to maintain over that period.

But at the minute, I don't think any experiments are being done, really, to determine whether it's area under the curve or whether it's just a critical concentration for a critical time, and the two are different, because if you could give, for instance, a low dose on Day 1, a very high dose on Day 2, a low dose on Days 2 and 3, or you could give a moderate dose over the four days or any combination that will give the same area under the curve, but do we know whether that would actually give the same biological response? And I think the answer at the minute is no; it's just giving the design of the experiments that are being done.

So I think this could be important; it could have important implications for humans besides just another area of uncertainty, unfortunately.

But given the variability in the water sources and both temporally and spatially and all of the added variability because you got different

efficiencies of water treatment plants, and even identical water treatment plants could work with different efficiencies --

I think that's something that's been observed throughout the world -- it's difficult to see at the minute how more refined monitoring would really help to predict or catch peaks in all the individual community water treatment plants in a sort of cost-effective way.

And I think one of the things the Agency might consider - and this again is something that Dr. Bucher has raised -- is to actually look at what are the likely exposures in humans, given the information we know about the variability in water treatment plants and in the drinking water.

And it might be worth just using some simple model to try and estimate internal exposures corresponding to some of the patterns of fluctuation in water concentrations that you see. So if it's a very quick peak going over a day or two days, given the amount of water that a human would drink, what's the implication if that's then followed by three low days? Just going to some of the chemographs that are available, because we've got a lot of good data to play with, it then might be worthwhile to say: what would

happen if then we used an average concentration over the period? What would be the difference in terms of the total exposure that you'd calculate?

So at the moment I think, you know, people have been concentrating on the drinking-water variability but maybe not looking at the impact this might have, and then trying to relate that back to some of the other potential endpoints that Dr. Bucher identified.

I know that it's very difficult to try and extrapolate from rodents to humans in terms of bioavailability. It's very easy to extrapolate from rodents to humans in terms of absorption from the gut, because they're highly correlated.

But the bioavailability is quite different for many pharmaceuticals, for instance, between rat and humans. So that would need to be considered when you do any modeling. But I think Kow and coworkers in 2006 actually gave quite a nice discussion of, you know, how you might move between or, rather, some of the difficulties in moving from rodents to humans.

So I've tried not to repeat what's gone before; but I think it's pulling some of the stuff that other people have raised earlier together, and I think

I'll leave it there.

DR. STEVEN HEERINGA: Thank you very much, Dr. Greenwood.

Dr. Bucher, did Bette leave you any comments on this, or you already incorporated those?

DR. JOHN BUCHER: Bette left me a few comments that I did incorporate into the statement that I gave.

DR. STEVEN HEERINGA: Thank you.

Dr. Mumtaz?

DR. MOIZ MUMTAZ: Yeah. The use of any chemical in the environment I believe has consequences good and bad, and John has captured the Panel's views; but I also was thinking about Dr. Coupe's comments. And it is we go to community meetings, and we get that hearing is most of the time is what we hear from the public and the community.

So we should neither compromise public health or ecological health, but not impose undue restrictions on the producers of chemicals. And so we try to be as realistic as possible in what we do.

In the report and throughout the last three or four days, we have discussed only two issues; one is the LH surge, and I think I've learned enough about it hopefully, I can retain some of it to use in

the future work -- and the other one is the mixture of atrazine and its three metabolites.

So as opportunity approaches, one of the things I would like to suggest is to look at methods that can be used to get an idea about the potency of these various chemicals, just the metabolites -- and I said this yesterday about use of computational tools -- to build the weight of evidence to have some idea about what these metabolites' potency is and what their relative concentrations would be, and we discussed this in the pharmacokinetic section.

Earlier, we talked about children's and infants' health, and that's something also we have to keep in mind in terms of the sensitive populations, their enzyme levels and the quality of the enzyme changes, and so we have to keep that in mind when we think about the toxicity of chemicals in general.

And so I want to move away from the LH and look at other toxicities. I think EPA should look into neurotoxicity, hepatotoxicity by the way, there is a toxicologic profile on atrazine and it's a dated document; but it still has a lot of useful information. And there's a lot of data in animals on other toxicities, and that's something we should look at as an Agency.

And so when we do that, if we look at greatest toxicities and we are looking at using LH as the driver, it would help us make the case for the decision we are making rather than look at one and hang everything on that one tree or branch or basket or whatever the case may be.

So I would like EPA to look at other toxicities and show that this is within a range so that when we make a decision, it will be useful.

And so we all talked about PPK model that is ideal. And Karen is sitting next to me, I think, and Janice and Mel, they all have done wonderful job in promoting the PPK modeling concepts.

But ultimately it will give us an internal dose, either in a particular tissue of interest or a particular organ; but we still have to determine what is that organ which we're interested in, and so we have to look at what I call legitimate mixtures.

So it is great, you know, to have done this research on the limited mixture, but is that a legitimate mixture? Is that the actual exposure that is occurring in the environment, to the public and across the country?

As I mentioned, apart from herbicide

triazines, we use organophosphates in farms. There's a lot of other chemicals, the farm chemicals that are being used. And it will be a good idea to look at the U.S. Geological Survey data and see what other possibilities exist and look into the overall joint toxicity of those chemicals in keeping part of this, again making a realistic decision.

So having said all that, I don't want this to come as a criticism of EPA; I think they have done a wonderful job and we all, in their world, the issues are quite challenging. And we are making progress and as long we're making progress, I think we are in good shape, and I thank you for the opportunity.

DR. STEVEN HEERINGA: Thank you, Dr. Mumtaz.

Dr. Chambers?

DR. JANICE CHAMBERS: Dr. Mumtaz, you were not at the last atrazine meeting; so you didn't know that we spent several days talking about other types of toxicity. We looked at neuro and immuno and some of the other things, and the conclusion of the Agency and the Panel was that the LH surge data was really the most sensitive and most reliable database for consideration.

DR. MOIZ MUMTAZ: But, Dr. Chambers, the

problem is whether this is the primary target, and how do you, you know, the extrapolation from LH surge to actual toxicity in rats has been somewhat established; but whether that same mechanism works in humans is something which we are debating.

So I'm not saying that this is the wrong thing; I'm just telling that we should develop a maybe we should put that information as a summary in this report so that people like me can say, "Okay, EPA has done this wonderful job" and I can retract that information.

So it will be nice whenever you're presenting something to say, "We looked at all these things, and here's what we think: this is all within this certain range or order of magnitude" or whatever so that we can put the overall profile of the chemical or its mixtures in perspective.

DR. STEVEN HEERINGA: I think there were some good suggestions along those lines yesterday in the discussion of the mammary gland.

Dr. Horseman?

DR. NELSON HORSEMAN: I just wanted to say that there seems to be a sense of things maybe having it both ways, so to speak.

So with regard to the notion of

neurotoxicity, we understand maybe that the previous SAPs have looked at neurotoxicity per se; but at the same time, a neural neuroendocrine mechanism is being proposed as the underlying phenomenon that drives this change in LH surge.

So clearly you can't say that you have no neurotoxicity, but the toxicity you're using as the driver for this regulatory decision has a neural mechanism underlying it.

So I think Dr. Mumtaz's point -- and Dr. McManaman has made it, and several other people have made it -- that these may be, these effects that we're talking mostly about at this meeting may be epi phenomena of some other mechanisms that may not manifest in primary toxicity in the neural system but may drive metabolic and neuroendocrine changes. So I just want to make that distinction.

DR. STEVEN HEERINGA: Dr. Legan?

DR. SANDRA LEGAN: So in view of the discussions so far this morning, there's a lot of problems with trying to get data about an adverse effect of this pesticide in a rodent population and compare this or extend this somehow to human doses and effects and so forth.

And this is going to sound, this is a

little outside the box, but something that I think ought to be just thought about and raised, so I'm raising the issue is that out in the fields and out in the environment where the atrazine is being, you know, put on the fields, there's a lot of rodents.

There's field mice involved, et cetera, as we all know, and we're focusing on rodents here. Obviously, there are amphibians and worms, et cetera.

But having said that, there is no field biologist here on the Panel, and field biologists routinely fit birds, et cetera, including rodents, with radio frequency chips. I mean, they do it with whales and everything. So we know they can do this, and they can track, you know, where these animals roam.

And they already know what the range of where they live, you know, what the range is in their territories. Like for a mouse, it's X -- it's probably less than an acre, but who knows?

Okay, but they know. And it seems to me you could sample some of these animals. You could also establish what their range is in relation to where the atrazine, what fields. And apparently, I mean, how in Illinois or Indiana there's thousands of acres. These animals don't probably go much outside of that area where the atrazine is being used.

So you could do survival curves on animals. You could just watch until the radio frequency thing stops moving. You know, I mean, for a large length of time, there's got to be a way to do this. You could just do survival curves to see if they're surviving or not.

And if you trap, you can live-trap them and then you have a population. If you get high numbers, you can look at their reproductive systems, their brains, et cetera. You can take every piece of tissue and analyze it for atrazine and all its metabolites.

I assume. We do that in lab rats, so we just should this is, like I said, is outside the realm of what we've been discussing to some extent; but it's totally relevant if field biologists could do these things and it could be used in areas where we know there's the highest concentrations of atrazine have been used over the last X, 50 fifty years was it in some places we heard from some of the people?

So it's a thought, it's not a complete thought; but it's right there out in nature, data. And we wouldn't maybe know their exposure, but still there would be a lot of information that we could glean from that.

I think that might be useful in just trying to extend from rodents to humans out where the pesticide is in levels where the organisms are living, whatever the shape of the chemograph, et cetera, et cetera.

DR. STEVEN HEERINGA: Thank you, Dr. Legan. There is just a comment here. You know, there is a substantial amount of work on pesticides and herbicides and non-human health effects, environmental. And for those of us who have been here for ages, it seems there have been focused not only on terrestrial but also amphibian and aquatic; and I think, if I recall correctly, a lot of the emphasis on non-human or environmental effects has shifted to aquatic.

There has been some work in terrestrial; but, again, there's quite a body of work that's ongoing of that nature, including discussion of field biology and how that can play into informing exposures that are non-human.

Dr. Mumtaz - or, Dr. Krishnan and then Dr. Mumtaz.

DR. KANNAN KRISHNAN: I just, if you're done with the designated discussants, I thought I would add some comments.

I concur with Dr. Bucher's and Dr.

Greenwood's analysis and comments. I just want to add a couple. The first one relates to the use of the allometric scaling of the rodent pharmacokinetic data in relating to the duration of human exposure. Some of the results were presented in Table 8-1 and associated discussions.

I mean, I agree with those calculations to inform about the duration, the way it was done; however, but the use of such a calculation to derive a human equivalent dose here would not seem appropriate, because there are two things here when you do the allometric scaling or use of the elimination half-life. One is to inform about the possible duration to get to a steady state, if you will.

That seems appropriate to me, whereas using the allometric scaling to calculate the human equivalent dose is questionable. I'm not convinced that it's correct, because when we do the allometric scaling or when we apply the body surface scaling to calculate the human equivalent dose from the animal dose, it's to have the same parent chemical concentration in both systems.

So we are adjusting for the clearance so that there is equal parent chemical concentration. Here it's a bit tricky, because we know that it's not

just the parent chemical concentration at steady state that's of concern; it's actually the rest of it as well. So it's kind of a mix of both: the clearance of the parent chemical, as well as the clearance of the metabolites.

So you have to consider both of them together. The KEL that you do separately to inform about the duration, and then the body surface scaling that you do separately, those have to be really combined to drive it. There is some literature on it; why, we can put it in the report in terms of reference.

Then the other comment I want to make in terms of the duration considering the Mode of Action and toxicity profile on water monitoring is that I am thinking about based on the datasets, I mean, tox datasets, it's actually from a few days to four weeks which is fine, because the 28 days or a month, you know, reflects the human exposure during the cycle as the few days as the rat, four or maybe one or two days, questions are being raised.

I'm more thinking of one cycle in the rat versus one cycle in the human. But in consideration of that, I think the combined use of the steady-state consideration for pharmacokinetics as well as the similar average attenuation effect across

durations, those two key pieces put together in my mind really make a case as to whether it's really needed to decrease the duration of the monitoring frequency. I mean, that really makes, that really tells me; that's more like a textbook example.

It's actually a nice case study, the way the steady-state concentration is being used along with the similar LH across duration; so the way it's presented in Chapter 5 and the way it's brought back into 8. So based on that information, I don't see a compelling argument for less than a weekly monitoring. That's just my thought.

DR. STEVEN HEERINGA: Thank you, Dr. Krishnan.

Dr. Mumtaz, you had something?

DR. MOIZ MUMTAZ: I just wanted to follow up on Dr. Legan's comment that once upon a time when we started talking about hazardous waste sites and looking at health effects, there were a lot of studies done to look at the enzyme levels in wild animals, particularly rats and mice, on the hazardous waste sites, and some of the sites are hundreds of acres; they are not a small site. And I know not far from here, the protected Wildlife Refuge in Maryland, Dr. Ratner, does that kind of work, so there is some

database there we could look into.

DR. STEVEN HEERINGA: Okay. At this point, I think it looks like we've sort of reached the coverage on Question No. 6. I'll turn to Dr. Lowit, Nelson Thurman, any okay.

At this point in time, what I would like to do is to just go around the Panel once, and I'll start with Wes Stone to see whether there are any additional comments that you'd like to make related to these proceedings to put on the record or

MR. WESLEY STONE: Thank you, no, I'm fine.

DR. STEVEN HEERINGA: Dr. Coupe?

DR. RICHARD COUPE: Fine also, thank you.

DR. STEVEN HEERINGA: Dr. Lee.

DR. HERBERT LEE: I guess one extra comment I just sort of thought of was that mostly we've been thinking, looking at the question of are we monitoring frequently enough, looking at the water sources, and depending on duration of interest that may or may not be often enough; but on the flip side, outside of the growing season, are we monitoring more often than we need to, is another question possibly to think about. If we're not really ever finding high

atrazine concentrations outside the growing season, we may not need to have samples every two weeks. I don't think we really thought about it at all. Maybe that is worth thinking about a little bit.

DR. STEVEN HEERINGA: Thank you, Dr. Lee.

Dr. Akana?

DR. SUSAN AKANA: Is this on Question 6 or the entire meeting?

DR. STEVEN HEERINGA: The entire week.

DR. SUSAN AKANA: Oh, okay.

DR. STEVEN HEERINGA: Including Question 6.

DR. SUSAN AKANA: I woke up in the middle of last night thinking about Dr. Honda's data.

Honest. I did, I did. And I, I've been, my own personal nugget is in the HPA system; I'm still struggling with how atrazine interacts with the HPA system, and I was thinking again specifically of his figure of c-fos in the PVN.

And I woke up thinking about this, and I was slightly disturbed because in my own mind the micrograph did not include a landmark that I was looking for. So if you're in PVN and if you're talking about the CRF, I was looking at medial parvocellular.

And I didn't see the magnocenter of cells in those micrographs, and it really disturbed me.

So then what I keyed, what it keyed me to is on the flight down, I read a new paper, a 2010 paper. And it's from the King's College group; it's Kevin O'Byrne and Stafford Lightman's group, and the title of it is "Corticotropin-Releasing Factor Alters the Timing of Puberty in the Female Rat".

And I'd like to put this into my notes, because what I know of is that CRF, when you think of stress, you think of the medial parvocellular or PVN. But CRF actually is a distributed system; we find it in many interesting areas, and it's probably an integrated circuit for chronic stress.

But CRF, I specifically asked Dr. Honda did he look at areas of the BNST and the amygdala.

However, CRF is also found in the MPOA. And in this really interesting paper, they describe what apparently is well-known in the literature, is that the CRF there does have connections to the gonadotropin-releasing hormone neurons; and there are the appropriate receptors, the CRF R1 and R2. And in this paper, if you apply CRF ICV you can delay puberty, and if you give the CRF antagonist you can advance puberty.

So I think that this gives an area of connection that we were sort of searching for when we're talking about what are the upstream effects that are modulating the decrease in LH amplitude. So I think there might be more here to work with than I was originally groping for.

Thank you.

So the paper, I would like to put in my comments.

DR. STEVEN HEERINGA: Thank you; and we're sorry we disturbed your REM sleep, but I think we've all been there. So not exactly on the toxicology, but
Dr. Fenner-Crisp?

DR. PENELOPE FENNER-CRISP: I can't top that, so I'm through.

DR. STEVEN HEERINGA: Dr. Gold.

DR. ELLEN GOLD: I actually did have one comment. I like Dr. Legan's thinking-outside-the-box approach and I wanted to extend it to thinking about human studies outside the box, because I think a lot of the agricultural health studies, for example, rightly focuses on the series of applicators; but they don't include a lot of women, they aren't very diverse, as I mentioned in my comments.

And it actually is possible to study farm workers, for example. And there are thousands of farm workers, for example, working in cornfields, for example. And we've actually been able to do studies of menstrual-cycle characteristics and collect urine samples in such women.

So I would encourage in the long-term view to think again outside the human-study box that they seem to be in and extend the research beyond it, actually look at real-life populations that may have exposure that can be documented.

DR. STEVEN HEERINGA: Thank you, Dr. Gold.

Dr. Harris?

DR. SHELLY HARRIS: And I'm going to bring us back to water monitoring. I've been thinking about this for the last few days, and there's an assumption that's being made and I keep hearing around the table that the epidemiologists want measures in finished drinking water.

And we've been having a few side conversations about that and I say, "Yes, we would like measures in finished water over top of those in environment"; but I also say, "We would like both, ideally".

But realistically what can we do with those measures in finished drinking water, and we could certainly use those to improve the ecologic studies; but we've really agreed that those are not particularly useful for risk assessment. So do we want to spend a lot of time and effort improving the group-level exposure assessment for ecologic studies? And my short answer would be, "No, that wouldn't be a priority for me".

So what can we do with these low-level measures of atrazine and metabolites in drinking water supplies, and if we're going to conduct very good studies, well, we would look at those at the community level and then ideally at the top level, and then we would take additional, collect additional data on whether people filter their water or not; how much bottled water they drink; how much time they spend away traveling away from home.

So how much community water did we drink this week; the consumption in canned products such as tomatoes, another major source of water consumption in humans; and the list goes on.

So when we design those kinds of exposure-assessment studies to exposure to water or your source of water, these things all become very

important. So what's at the community level that's measured from the treatment facility may have very, very little relation at all to what the human is actually exposed to.

And I might suggest a correlation of, you know, 20 percent, if we're lucky, it might 70 percent. I'm not sure. We could look at enhanced data and those types of data in relation to some of these finished and unfinished measures and get a feel for that. And we could also conduct some really decent biomonitoring studies. And I think that some of that should be done.

But I think before really significant resources go into looking at finished-water supplies where you've got, I'm assuming, a lot of non-tapped that we should look at whether they're going to be relevant for estimating low-level human exposures. We have very little ideas of how frequently we need to do that, the windows of susceptibility and that kind of thing.

So that's sort of my wrap-up on my thoughts about that, thanks.

DR. STEVEN HEERINGA: Thank you, Dr. Harris.

Dr. Bailar.

DR. JOHN BAILAR: Nothing to add.

DR. STEVEN HEERINGA: Dr. LeBlanc?

DR. GERALD LEBLANC: Nothing.

DR. STEVEN HEERINGA: We'll go to Dr. Legan?

DR. SANDRA LEGAN: No further comments.

DR. STEVEN HEERINGA: Okay. Dr. Delclos?

DR. BARRY DELCLOS: I'm fine.

DR. STEVEN HEERINGA: Dr. Roby?

DR. KATHERINE ROBY: I just want to quickly comment that I think the discussants on this final point really did a great job of summing up both what we understand and what we don't yet understand. And with respect to the LH, we don't yet really understand what the critical window is and I think that is the bottom line, and whether new regulation or tighter regulation needs to be imposed or suggested is not sure at this point, not clear.

DR. STEVEN HEERINGA: Dr. McManaman?

DR. JAMES MCMANAMAN: Yeah, I have one last comment.

Dr. Bailar mentioned that we should be focusing on appropriate doses or physiological doses and physiological outcomes.

Since we don't know the physiological outcomes yet, I emphasize that we need more study because I think we may be looking at the LH and it may not be the appropriate physiological outcome, because physiological doses, the concentrations that we're looking at as we're focusing on atrazine not as metabolites; metabolites have a lot longer life than the atrazine itself.

So again, I think that we should be focusing on, as Dr. Bailar suggested, on the appropriate compounds and we don't know what those appropriate compounds are yet.

DR. STEVEN HEERINGA: Dr. Horseman?

DR. NELSON HORSEMAN: I have nothing to add; just thank the EPA for the quality of material that we were given, and the Panel for everything I've learned, and Steve for doing such a good job of keeping the meeting on task.

DR. STEVEN HEERINGA: Dr. Mumtaz.

DR. MOIZ MUMTAZ: I agree with Dr. Lee and Dr. Krishnan, based on the current knowledge that we probably need not monitor more often than we are currently monitoring. But while monitoring for atrazine, I would like to see the analysis extended to other chemicals present in samples so that we have a

better profile of the mixtures of atrazine, of course, within the environment.

Also that would help us educate people in terms of bio-availability of what is there. Always when I go to the meetings when I'm in a tight spot trying to explain the Committee, I use the zoo example: that we go to the zoo, we go with our parents, our children and everybody and have fun. There's no problem, even though there are dangerous animals there. But we know we'll not get exposed to unless it's California or...

The same thing is true with chemicals: just because they're there, we don't have to really worry about them. What we need to do is see if they are presenting in a completed exposure pathway, which is from the source to the sensitive population.

So when we are looking at these samples, if we do a better analysis, I know it will add to the money; but instead of increasing the frequency, do a total job with the sample I think will give a better categorization of risk.

The same argument I do with CDC all the time that is in this data they have the 160 chemicals present in my body; but I want to know which of those are present in a given sample so that we can figure out

what are the common mixes where it's potent. And it's a bigger problem than I think, but I still want to make that point.

Thank you very much. I enjoyed the participation on this Panel.

DR. STEVEN HEERINGA: Thank you, Dr. Mumtaz.

Dr. Krishnan?

DR. KANNAN KRISHNAN: You woke up in the middle of the night, but I couldn't sleep.

I had to talk to the endocrinologists before I could go to bed.

You know what I mean? Who wants to talk about the BMR or the benchmark response that we talked about the last afternoon? So I'll just make a couple of comments in closing.

And the one paper clearly makes a case for the use of the data on the attenuation of LH, despite the caveats we heard. I don't see it as a NOAEL or NOAEL as the white paper sees it. Rather, I see it as a no observable adverse perturbation level, NOAPL.

That's how I present the NAS work to my students, because it's basically no observable adverse perturbation level. It's not a no-effect level,

because, you know, you can really get to the terminologies.

But in any case, the Agency here used a one deviation, or standard deviation, from the control. That's how the BMR was defined, and we had some discussions around it.

I know it's the Agency policy to use 1SD when a biologically significant deviation of change cannot be defined or clearly defined, and I think the document brings that out. But I still continue to ask myself whether some of the additional data could be analyzed to characterize the spread in the controls at 18 hours --

I underlined even in my notebook 18 hours -- maybe more than one study to provide further support to the use of 1SD, or better define or provide better support to the BMR, because especially when we're using perturbation levels to define the benchmark doses, I think it is important to analyze it in that sense. So I just needed that.

DR. STEVEN HEERINGA: Thank you, Dr. Krishnan.

Dr. Greenwood?

DR. RICHARD GREENWOOD: I think I've said more than enough, thank you.

DR. STEVEN HEERINGA: We appreciated your comments.

Dr. Schlenk.

DR. DANIEL SCHLENK: Nothing to add.

DR. STEVEN HEERINGA: Dr. Portier?

DR. KENNETH PORTIER: Nothing.

DR. STEVEN HEERINGA: Dr. Chambers?

DR. JANICE CHAMBERS: Nothing to add.

DR. STEVEN HEERINGA: Dr. Pope?

Dr. Bucher, you have to say something since this is probably your last 10 minutes on the Panel.

DR. JOHN BUCHER: I will. I want to thank the Agency. This four years on this Panel has been very entertaining in many cases and very educational, and I appreciate the opportunity to serve.

I compliment the Agency with the atrazine review as tackling one of the most difficult scientific, social and political topics that you could take on. Six meetings may be, five meetings may be too many; but, you know, that's up to you.

And finally I want to thank Steve and the rest of the permanent Panel members for a very enjoyable couple of years, and thanks very much to Joe Bailey for reminding me that when he asks which

questions you want to respond to, you really should respond to him instead of just getting stuck with the last one as I have been, but, thank you very much.

DR. STEVEN HEERINGA: Well, thank you very much, John. As we said in our little ceremony the other day that I think all of us greatly appreciate your participation on this Panel, and I know personally I've turned to your expertise and your sort of knowledge of not only the field but also all of the players in the field. It's very, very, been very, very helpful and beneficial to this Panel, and I wish you all the best.

DR. JOHN BUCHER: Thank you very much.

DR. STEVEN HEERINGA: Okay. At this point, I'm going to turn back to Dr. Lowit, Dr. Levine for any .

DR. ANNA LOWIT: Now we want to express our appreciation to absolutely every single one of you. As you can see, we have a difficult task and some very difficult issues, and I'm amazed every time I attend one of these meetings how insightful a group of scientists can be when you get together; there's always a synergy around it, and it's quite an amazing process.

This one is no different. I appreciate that it takes an enormous amount of effort out of your

personal life and your professional life to read almost 700 pages of material, and thousands if you looked at actually some of the raw studies. So this, we really truly appreciate it, and it helps the process and helps the science, and we're going to continue to inch our way one step at a time forward.

Thank you to Dr. Bucher for your service.

Dr. Joe Bailey and Laura Bailey and the entire CP staff, another phenomenal meeting. Thank you so much for your effort.

My personal thanks to the team, and Dr. Mendez for sharing my appreciation for the team. It's an amazing group of people who have done some also another situation you get synergy of dedicated talented people, and it's pretty amazing what you can do.

With that, I think that's all.

DR. STEVEN HEERINGA: Well, thank you very much, Dr. Lowit. And I want to express my appreciation to all the members of the Panel. It's obviously a busy time of year for many of us, and to be able to gather here with so much expertise, as I say, I learn a tremendous amount every time I attend one of these meetings and I appreciate the expertise and the way that you were able to focus it during this meeting.

So the EPA Staff, again, just to reiterate the other comments from Panel members, the quality of the materials and the way it was organized, the sheer volume of material, I know we often get it on a short order; but you have to make it as current as you possibly can, and as we've seen from your work and the public commenters' work, people are working up right to the last moment often on many of these meetings.

And so that's all very much appreciated in the way that you presented it and organized it for this Panel, I'll just say thank you.

At this point, I turn to our Designated Federal Official, Joe Bailey, for comments on what will happen after this meeting is closed.

DR. JOSEPH BAILEY: Thanks, Dr. Heeringa.

I want to return some thanks back to Anna Lowit and her colleagues on bearing with me trying to plan the meeting and get everything pulled together. I think it turned out very successful.

I want to thank the public commenters for bringing forward their helpful, informative information.

I want to thank Dr. Portier and Dr.

Heeringa for chairing the meeting and keeping us on track and actually getting us ahead of time. I thought we were going to be here 'til mid-afternoon, at least.

And last but not least, I certainly want to thank each of the Panel members for working with me and agreeing to serve on the Panel. I really appreciate it, I think a lot of good information has come forward for the Agency to consider.

I will wish Dr. Bucher the best of luck with his post-SAP endeavors.

And the Panel, I'll be working with you over the next couple of months to get the meeting minutes finalized, and those will be done within the usual 90-day period. Once they're completed, they'll be available on the website and in the public docket. So, thank you all.

SPEAKER: Timeline for everybody to get the first draft?

DR. JOSEPH BAILEY: Well

DR. STEVEN HEERINGA: We'll have a break in our meeting in just a moment.

SPEAKER: Okay. I didn't want to forget.

DR. STEVEN HEERINGA: Again, all the materials that were presented before the Panel in hard

copy or electronic should be available on the docket within a reasonable period of time here.

And again, thank you to everybody who participated in this process, the EPA Scientific Staff and public commenters who worked with us on Wednesday and everything that they contributed to this process. And with that, I'll call this meeting to a close.

Permanent Panel or Panel members, if we could meet in our breakout room to plan the organization of our first draft and the timeline for that.

So, thank you everybody; have a good day.

(WHEREUPON, the meeting was concluded 10:17 a.m.)

CAPTION

The foregoing matter was taken on the date, and at the time and place set out on the Title page hereof.

It was requested that the matter be taken by the reporter and that the same be reduced to typewritten form.

Further, as relates to depositions, it was agreed by and between counsel and the parties that the reading and signing of the transcript, be and the same is hereby waived.

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I do hereby certify that the witness in the foregoing transcript was taken on the date, and at the time and place set out on the Title page hereof by me after first being duly sworn to testify the truth, the whole truth, and nothing but the truth; and that the said matter was recorded stenographically and mechanically by me and then reduced to typewritten form under my direction, and constitutes a true record of the transcript as taken, all to the best of my skill and ability.

I further certify that the inspection, reading and signing of said deposition were waived by counsel for the respective parties and by the witness.

I certify that I am not a relative or employee of either counsel, and that I am in no way interested financially, directly or indirectly, in this action.

MARK REIF, COURT REPORTER / NOTARY

SUBMITTED ON SEPTEMBER 17, 2010

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