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C O N T E N T S

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Proceedings.....Page 3

1 DR. ROBERTS: Welcome back to the
2 Scientific Advisory Panel. Today's meeting will
3 extend our discussions on determination of the
4 appropriate FQPA safety factor on the OP pesticide
5 cumulative risk assessment.

6 I would like to start out as we did
7 yesterday by introducing our designated federal
8 official, Mr. Paul Lewis, and ask him if he has
9 any announcements or instructions for the panel
10 today.

11 MR. LEWIS: Thank you, Dr. Roberts. And
12 welcome, everyone, to our second day of this FIFRA
13 Scientific Advisory Panel meeting. I just want to
14 again review for the members of the panel and the
15 public that this meeting follows requirements of
16 the Federal Advisory Committee Act. Such that
17 being the case, all materials are available to the
18 public in our public docket. Some major
19 background materials are available and posted on
20 our scientific advisory panel website.

21 Thank you, again, to members of the
22 panel and for the public for participating in

1 today's meeting. I'm looking forward again to very
2 challenging and interesting dialogue that will
3 occur during the course of today's discussion.

4 Dr. Roberts.

5 DR. ROBERTS: Thank you, Paul.

6 I would like also to introduce the panel
7 in part because we may have some members of the
8 audience who weren't here yesterday and also
9 because we have two members of the panel that are
10 joining us today.

11 So let me again ask as we did yesterday
12 beginning to my right, which I guess will be Dr.
13 Hattis this morning, and ask each member of the
14 panel to state their name, affiliation and area of
15 expertise, and we'll just go around the table in a
16 counterclockwise fashion.

17 Dr. Hattis.

18 DR. HATTIS: Dale Hattis, Clark
19 University. I'm a risk analysis modeler. I
20 specialize in issues of variability and
21 uncertainty, and I particularly have done some
22 work on pharmacokinetics comparing children of

1 various ages and adults based on pharmaceutical
2 data.

3 DR. POPE: I'm Carey Pope from Oklahoma
4 State University. My area is neurotoxicity,
5 neurotoxicology of organophosphorus compounds.

6 DR. SULTATOS: My name is Les Sultatos.
7 I'm from the department of pharmacology and
8 physiology at New Jersey Medical School. And I'm
9 a pesticide toxicologist.

10 DR. ELDEFRAWI: Amira Eldefrawi. I'm a
11 professor in the University of Maryland School of
12 Medicine, department of pharmacology and
13 experimental therapeutics. My expertise is in
14 neurotoxicology, my specialty, and with a focus on
15 insecticides and also toxins.

16 DR. BIGBEE: Good morning. My name is
17 John Bigbee. I'm from the Virginia Commonwealth
18 University, department of anatomy and
19 neurobiology. My field of interest is
20 developmental and noncholinergic roles for
21 acetylcholinesterase, the noncholinergic
22 mechanisms that regulate morphogenic events during

1 development.

2 DR. REED: I'm Nu-May Ruby Reed. I am
3 from California Environmental Protection Agency.
4 I'm a staff toxicologist in the department of
5 pesticide regulation. I do pesticide risk
6 assessment.

7 DR. HARRY: I'm Jean Harry from the
8 National Institute of Environmental Health
9 Sciences. Expertise is in the area of
10 neurotoxicity.

11 DR. MCCLAIN: I'm Michael McClain. I'm
12 a toxicologist. I have spent most of my career in
13 the pharmaceutical industry doing pharmaceutical
14 development. I have worked for Hoffman LaRoche
15 for 28 years. For the last three years, I have
16 been working as a consultant in toxicology doing
17 mostly pharmaceutical development, and I have my
18 consulting company, McClain Associates.

19 DR. LAMBERT: I'm George Lambert from
20 the Environmental Occupational Safety and Health
21 Science Institute at U of BNJ (ph)
22 and Rutgers, and I am director of the childhood

1 center for neurotoxicology and exposure
2 assessment. And I'm a pediatrician neonatologist,
3 pediatric environmental health specialist.

4 DR. MATSUMURA: I'm Fumio Matsumura
5 from the University of California, Davis. My area
6 of expertise are molecular toxicology on the
7 pesticide toxicology mode of action. My Ph.D.
8 thesis a long, long time ago was on malathion.
9 That's how I started. And this topic is my
10 interest.

11 DR. NEEDLEMAN: I'm Herbert Needleman.
12 I'm professor of psychiatry and pediatrics at the
13 University of Pittsburgh. And my area of interest
14 is in neurotoxins in child development.

15 DR. THRALL: Good morning. I'm Mary
16 Anna Thrall. I'm a professor of veterinary
17 pathology at Colorado State University.

18 DR. PORTIER: Good morning. I'm Chris
19 Portier. I'm the director of the Environmental
20 Toxicology Program at the National Institute of
21 Environmental Health Sciences.

22 DR. ROBERTS: My name is Steve Roberts.

1 I'm a professor at the University of Florida in
2 toxicology and serve as the director for the
3 Center for Environmental Toxicology there.

4 And it's also my pleasure to serve as
5 the chair for today's panel.

6 We have with us again this morning, I'm
7 pleased to say, Ms. Sherell Sterling, who is the
8 acting director of the Office of Science
9 Coordination and Policy, as well as Ms. Marcia
10 Mulkey, who is the director of Office of Pesticide
11 Programs.

12 Good morning. And I wanted to ask you
13 if you had any comments or anything for us before
14 we launch into the questions today.

15 MS. STERLING: For me, just good
16 morning. Welcome. Thank you again, and we look
17 very much forward to the discussions that we're
18 about to hear.

19 MS. MULKEY: And I will also limit
20 myself to a greeting and thanks, although I want
21 to offer specific and special greetings and thanks
22 to those members who have joined the panel since I

1 had the opportunity to say something similar
2 yesterday morning. It is very nice to have you
3 here too.

4 And also to tell you how very much we at
5 the agency are looking forward to today's
6 discussion among you.

7 DR. ROBERTS: Thank you.

8 Dr. Dellarco, will you be posing the
9 questions to the panel today?

10 DR. DELLARCO: Yes, I will.

11 DR. ROBERTS: Good morning. Do you want
12 to go ahead and begin with the first question?

13 DR. DELLARCO: We have asked questions
14 under three topic areas that concerns the common
15 mechanism, again, our analysis's focus, on the
16 inhibition of acetylcholinesterase.

17 And the first question concerns the role
18 of acetylcholinesterase in development.

19 Question 1.1 says, please comment on the
20 extent to which the report adequately summarizes
21 the current state of knowledge.

22 Does the scientific evidence support the

1 conclusion that perturbation of the cholinergic
2 nervous system during development by inhibiting
3 acetylcholinesterase can potentially lead to
4 deficits in the structure and function of the
5 central and peripheral nervous system.

6 DR. ROBERTS: Dr. Bigbee, I realize you
7 just got here, but can you lead off our discussion
8 in response to this question?

9 DR. BIGBEE: My interest in this, in
10 cholinesterase, is its noncholinergic role in
11 neurodevelopment and how it can function as an
12 adhesive protein during development.

13 And this adhesive function of
14 acetylcholinesterase is entirely independent of
15 its cholinergic ability. Complete elimination of
16 its activity does not perturb this ability to
17 promote axonal (ph) outgrowth, neuronal migration
18 and also to some extent neuroproliferation.

19 And so I guess my first comment, my
20 first question is this idea of common function,
21 and that since not all OPs are the same, that, in
22 our studies we have shown that different

1 inhibitors, if you treat developing systems mostly
2 in vitro with inhibitor compounds, that different
3 inhibitor compounds have very, very different
4 effects on this morphogenic ability of
5 acetylcholinesterase.

6 And the reason for that, we propose, is
7 because these inhibitor compounds perturb an
8 adhesive domain on the surface of
9 acetylcholinesterase and thereby prevent its
10 morphogenic abilities.

11 So a question that I have or a concern
12 would be that the different OPs and their
13 different structure as they interact with the
14 cholinesterase molecule might all produce
15 inhibition, but, because of their different
16 structure, could potentially change the
17 configuration of the molecule.

18 And by changing the configuration of the
19 molecule, could potentially alter this surface
20 adhesive domain and thereby affect this
21 morphogenic ability of AChE.

22 And I think it would be an interesting

1 and an important discussion to have in the report
2 this potential difference or potential effect of
3 the different OPs because of their structure in
4 affecting this surface domain.

5 DR. ROBERTS: Dr. Eldefrawi, did you
6 have any comments that you wanted to add on this?

7 DR. ELDEFRAWI: Well, I was delighted to
8 communicate when I came in this morning because I
9 really didn't know much about adhesion molecules.
10 So I'm anxiously waiting to hear that.

11 In addition, definitely, children need
12 more protection. And because they are exposed
13 more to organophosphates whether playing in the
14 dust or in their homes or in the gardens or
15 proximal planted trees or flowers, therefore, if
16 the exposure is more, then they are more liable to
17 have brain effects than in the adults.

18 DR. ROBERTS: Dr. Pope.

19 DR. POPE: The cumulative risk
20 assessment of organophosphorus anticholinesterase
21 is based on their common mechanism of toxicity.
22 Even though it has been shunted around here about

1 cholinesteration inhibition, most people realize
2 it is not just cholinesterase inhibition. There
3 is a sequence or a cascade of steps that are
4 important and can be modified.

5 Anyway, that common mechanism is
6 phosphorylation of the enzyme leading to
7 accumulation of acetylcholine and consequent
8 cholinergic signs of toxicity.

9 Acetylcholine and acetylcholinesterase
10 have been proposed to play a role in the
11 development of the nervous system. A possible
12 adverse effect of the OP anticholinesterases is
13 therefore abnormal neurodevelopment.

14 Section 2 A of the report adequately
15 describes the available information regarding the
16 roles of acetylcholine and acetylcholinesterase in
17 neurodevelopment. That's one of the questions.

18 The scientific evidence does not in my
19 opinion, however, provide a strong support for the
20 conclusion that perturbation of the cholinergic
21 system during development by inhibiting
22 acetylcholinesterase can lead to deficits in the

1 structure and function of the nervous system.

2 As stated in the report, neuromodulatory
3 roles for both molecules were proposed decades
4 ago. Of particular importance to the risk
5 assessment of OP toxicants, more recent
6 information suggests that some OP inhibitors can
7 modify neuronal growth in vitro.

8 It should be stressed, however, as noted
9 in the report that some anticholinesterases do not
10 apparently have any effect on neurite outgrowth.

11 Some studies suggest that
12 neurodevelopment may be affected in vivo by some
13 OP toxicants. Most of these studies utilize
14 unrealistic exposure conditions such as exposing
15 animals to chlorpyrifos and 100 percent DMSO. And
16 thus, the relevance of such of these effects are
17 uncertain.

18 These findings general suggest, however,
19 that such neurodevelopmental changes are not
20 tightly coupled to inhibition of
21 acetylcholinesterase activity per se, and thus do
22 not constitute endpoints elicited by the common

1 mechanism of toxicity.

2 And I think further consideration of the
3 cumulative risk assessment process is therefore
4 not warranted if the risk assessment is based on
5 the common mechanism.

6 DR. ROBERTS: Dr. Brimijoin.

7 DR. BRIMIJOIN: I think Dr. Pope has his
8 finger on a key issue here.

9 I mean, as the question is worded, the
10 answer has to be yes. The question is strictly
11 worded here as, does the scientific evidence
12 support the conclusion that perturbation of the
13 cholinergic system during development by
14 inhibiting AChE can potentially lead to deficits
15 in the structure.

16 It's really asking is there enough
17 evidence out there for us to consider that this is
18 a large enough unknown.

19 So just as it is flatly stated, I would
20 have to say the answer is yes. But Dr. Pope is
21 absolutely right, I believe, in indicating that
22 the evidence falls way short of what is needed to

1 demonstrate that the simple inhibition of AChE and
2 a resulting buildup in acetylcholine itself is or
3 likely to be pure and simply a factor that would
4 perturb neurodevelopment.

5 In that way, what he said is absolutely
6 right. And he has properly brought the discussion
7 away from the fascinating but still speculative
8 basic science down to the question of what are the
9 implications of this science for this cumulative
10 risk assessment in terms of a common mechanism of
11 action.

12 I guess I would qualify this, not that
13 we need further complexity, but I would qualify
14 what Dr. Pope just said by saying that it is --
15 we're moving just slightly away from the explicit
16 focus of the defined common mechanism when we talk
17 about agents that might exert toxicity through
18 their actions on the very same molecule within a
19 few anstroms, in fact, of the active site.

20 We're not talking about actions of these
21 compounds on totally unknown or hypothetical
22 entities in the nervous system, but the same

1 protein.

2 And frankly, if we had enough data to
3 show that even a subset of the OPs, because of the
4 way they interacted with AChE, were indeed putting
5 the organism at risk for developmental
6 abnormality, in that case, I would have to say
7 that although it isn't maybe within the actual
8 letter of the statute or charter that we have here
9 to focus on AChE inhibition, in that case, I think
10 we would immediately want to broaden the
11 definition of common mechanism to include this
12 type of action.

13 So it is because of that that I would be
14 hesitant to say, well, the evidence is too weak to
15 even consider this as a factor.

16 And as Dr. Bigbee, I apologize for
17 missing his presentation, but I know fairly well
18 the science that he is presenting and am convinced
19 of its relevance, as Dr. Bigbee is pointing out,
20 some molecules are going to interact with AChE in
21 such a way that they may in deed affect its
22 associated functions, which I'm at least an

1 agnostic on this. I think that there is a very
2 strong possibility it has associated functions.

3 For all that, I think that the jury is
4 out, but I would urge us to keep the idea that
5 perturbation of AChE broadly speaking by at least
6 a subset of the OPs has potential for being a
7 developmental risk.

8 DR. ROBERTS: Thank you. Let me ask the
9 last associate discussant for opinion, and then
10 we'll open this to panel discussion.

11 Dr. Harry, what is your opinion on this.

12 DR. HARRY: I'm not sure I can follow
13 those guys.

14 I'm thinking a little more in the
15 document. There has been a lot of guidance here on
16 things to put in.

17 And while you can always make a
18 suggestion that there can be more in the document
19 and maybe some of these other issues should be
20 raised within this first part of the document
21 itself, I think it clearly lays out that there can
22 be potential, but it doesn't necessarily

1 demonstrate it.

2 And you might want to take the
3 opportunity to take a couple of the issues that
4 were raised, put a few more references in that are
5 the basic biology behind why we would assume this
6 would be happening.

7 As far as it goes into the examples of
8 the chemical specific that you are going after
9 right now, I think does a very nice job of
10 presenting those.

11 So my comments go from concepts to more
12 details on the report. But I think with just a
13 little bit of tweaking of a little additional
14 references and background it covers most of those
15 issues.

16 DR. ROBERTS: Let me open this issue,
17 then, to discussion among the panel at large.

18 Dr. Lambert.

19 DR. LAMBERT: From what I hear and I
20 know, it appears that OPs can act through this
21 pathway, through this mechanism and cause toxic
22 effects.

1 The question that I don't think is asked
2 is is this the only way that it can occur and is
3 this going to be a biomarker sensitive enough and
4 specific enough to identify the risk of OP for
5 children.

6 And I think that's surely not proven
7 here.

8 DR. ROBERTS: Dr. Portier.

9 DR. PORTIER: I'm not sure how to state
10 my question, because I have a question to the
11 panel about the question. That's where I'm a
12 little lost.

13 The question asks, is it reasonable to
14 assume, and you are saying there is potential
15 evidence. I think from the point of view of EPA,
16 and I'll speak for myself, but I think I would
17 like to have some discussion about the weight of
18 the evidence in support of that assumption.

19 Is it zero evidence, is it some
20 evidence, is it fairly strong and emerging
21 evidence?

22 The reason for that, I think, again,

1 from my perspective, is thinking about what FQPA
2 requires. It is a question of stating that this
3 is not possible or the strength of the evidence
4 that this is not possible is fairly strong, that
5 would lead to the use of not a 10X or not a 3X for
6 that particular aspect.

7 And so while we had some interesting
8 debate on various parts and pieces of it, I would
9 like some discussion of what the overall strength
10 of the evidence, what you think it would be.

11 DR. ROBERTS: Dr. Brimijoin.

12 DR. BRIMIJOIN: Well, I don't know if
13 this will satisfy you, Dr. Portier. Let's just
14 maybe very briefly recapitulate some of the pros
15 and cons. What I see is there is a set of data
16 largely from in vitro work that do suggest a key
17 potential to disturb -- of some of these compounds
18 at least, a set subset of them, to disturb
19 neuronal development with implications that it
20 might extend to the brain, the actual and the
21 intact animal or child. And then there is some
22 opposing evidence.

1 Maybe Dr. Bigbee will want to add to
2 this. But I would list some of the evidence in
3 favor of this idea as, and I apologize for
4 reiterating what he may have said, findings by
5 Lawyers Group (ph) and Bigbee and others that in
6 vitro systems, a subset of these compounds really
7 do in a fairly profound way affect neurite
8 outgrowth.

9 Secondly, it is antedating that work or
10 studies by neurobiologists such as Mume and Poo
11 (ph) that show that acetylcholine has important
12 effects on axonal guidance as neurons are
13 developing and growing. So you could expect that
14 marked perturbations in acetylcholine levels
15 locally would be potentially disturbing.

16 Thirdly, there are the associated, the
17 radical changes in cholinesterase expression at
18 key developmental windows. I mean, they are
19 associated with key developmental events in the
20 brain.

21 Fourth, there are observations by
22 several groups, including mine, a variety of means

1 of suppressing the expression of
2 acetylcholinesterase that cause fairly substantial
3 changes in again the growth properties of
4 individual neurons or neuronlike cells in tissue
5 culture.

6 There are the observation by Slotkin and
7 his group which I don't think are overwhelmingly
8 solid, but, on the other hand, they cannot be
9 dismissed, that there are small but very
10 persistent and profoundly disturbing changes in
11 DNA protein expression patterns in the brain after
12 doses that can be characterized as maybe not
13 environmentally relevant but on the other hand
14 aren't associated with a whole lot of measurable
15 direct effect in the brain so it didn't seem to
16 get too much percentage inhibition to get these
17 effects.

18 There are also developmental changes
19 mentioned in the document here in fruit flies
20 resulting from genetic disturbances or knockout of
21 genes. All of that is on one side.

22 Against it, though, is the remarkable

1 persistence of at least apparently normal
2 development or hardly -- nothing like the radical
3 change that you might have anticipated, I
4 anticipated, from the knockout in mammalian
5 system.

6 So that ability of a mouse that is
7 totally lacking in AChE to develop an actual
8 brain, and I looked at these brains -- I suppose
9 if I wanted -- I don't know why I wasn't smart
10 enough to decide it was worth publishing our
11 observations that we couldn't find any
12 abnormalities, I tried very hard to find
13 structural neurochemical abnormalities in the
14 brains of the total knockouts. And there's
15 nothing obvious.

16 So that certainly tells me that in the
17 mammalian nervous system, probably in children,
18 there is a huge potential for at least
19 compensation for what may be an auxiliary
20 developmental function that is disturbed when the
21 enzyme is out.

22 So it is a mixed bag. And if you forced

1 me to make a decision, and I think we are in a
2 position or EPA is in a position of having to make
3 decisions, I think there is enough concern that at
4 least some OPs will have in common an ability to
5 affect development by their actions.

6 DR. ROBERTS: Dr. Portier would like to
7 respond and then Dr. Bigbee.

8 DR. PORTIER: One quick question for
9 you. I did go back last night and look at the
10 knockout animal papers, in Chi's (ph) paper.

11 In Chi's paper, you are right. They
12 note absolutely no abnormal pathology in the brain
13 anywhere.

14 But they do note that the nol (ph)
15 azygous animals begin to radically shake at three
16 days of age and start to actually walk in circles
17 and have abnormal gate very rapidly so that the
18 lack of seeing the pathology from OPs in animals
19 does not in fact preclude the lack of a
20 development -- behavioral or developmental effect.

21 Is that correct?

22 DR. BRIMIJOIN: It is certainly true,

1 and, of course, this is all about, I think, Dr.
2 Harry and Dr. Padilla and others, Carey Pope,
3 would probably stress, the fact that our ability
4 to detect the consequences of minor disturbances
5 in brain structure and function is still limited.

6 The early neurotox studies were based on
7 does the animal still have a head, can it walk at
8 all, that kind of thing. And we're a long way
9 from getting to what would the animal's SAT score
10 be.

11 And Dr. Slotkin's group has shown us
12 that we have to look a little farther than just
13 see what's the size of the hippocampus if we want
14 to pick out changes.

15 So I think as neurobehavioral studies
16 become more sophisticated, there is a potential
17 discover, things that aren't immediately obvious
18 to the untrained eye but are, nonetheless, of
19 profound importance. That's less than a dooms day
20 scenario.

21 What do I really believe? I really
22 believe that acetylcholinesterase has a minor role

1 in formation of brain structure. That's just a
2 gut feeling.

3 DR. ROBERTS: Dr. Bigbee?

4 DR. BIGBEE: I think something that Dr.
5 Brimijoin said as far as a potential minor role,
6 the -- and it gets to the point that the
7 literature supports the noncholinergic role for
8 acetylcholinesterase in a couple of very
9 well-defined systems, not necessarily throughout
10 the entire neuraxis.

11 So that the Dorthru Ganglion (ph) system
12 and the Thalamocortical Projections are uniquely
13 high in this development spike of
14 acetylcholinesterase.

15 And those two systems have been probably
16 the most mind experimental protocols.

17 And so it is not like it is all
18 throughout the entire nervous system. These two
19 systems are uniquely showing this high
20 developmental expression.

21 So a total brain acetylcholinesterase
22 activity may not completely give us a picture of

1 what is happening in some specific subsections or
2 some specific systems.

3 I think it's important to continue to
4 point out that this developmental role or this
5 structural morphogenic role is completely
6 dissociated from the enzymatic activity of the
7 protein that studies that have point mutations
8 where they have eliminated the activity or in some
9 certain -- some inhibitors, that measuring the
10 enzyme activity may not be the best measure of
11 measuring this morphogenic role. And I think
12 that's an important point.

13 Another thing about the knockout systems
14 that always worries me a little bit is that the
15 animals that do survive are those that have been
16 clever enough to figure out a way to get around a
17 knockout.

18 It is a little bit dangerous sometimes
19 to assume that the animal is somehow -- that the
20 acetylcholinesterase, to put a function on it just
21 because it has been knocked out developmentally,
22 experiments where once the animal has committed to

1 its expression and then knock it down by antisense
2 technology or conditional knockouts are perhaps a
3 little bit more telling about that.

4 But as Steve was saying, too, I think
5 that the role, this developmental role is probably
6 a very subtle difference in that it has potential
7 for the axonal growth guidance and steering. But
8 it is certainly not some of these more growth
9 morphological, like Steve said, without a head
10 sort of structures.

11 But I think it is important to keep in
12 mind that we really are talking about two
13 independent parts of this molecule. It's a
14 multifunctional, multidomain molecule. One is its
15 catalytic activity and one is this adhesive
16 morphogenic role.

17 DR. ROBERTS: Dr. Bigbee, not to put
18 words in your mouth, but in your opinion, you
19 think that the potential neurodevelopmental
20 effects of OPs, or ones that have been observed,
21 are more likely to be due to the noncatalytic --
22 interactions with noncatalytic portions of the

1 molecule?

2 DR. BIGBEE: I think that is one. Then
3 the other would be by having an excess of
4 acetylcholine developmentally can also have its
5 effect through acetylcholine receptors.

6 So if we're talking just about the
7 acetylcholinesterase molecule itself, the effect
8 there is on this adhesive domain, I believe.

9 DR. ROBERTS: I believe Dr. Hattis was
10 next and then Dr. Eldefrawi.

11 DR. HATTIS: I think -- when I read it,
12 I'm not an extensive expert in this area, but the
13 discussion I think is not unreasonable as it
14 stands as a marshalling of the qualitative
15 evidence for concern about cholinesterase
16 inhibition in developing babies and young
17 children.

18 And if anything, my concern is enhanced
19 by the presence of these other mechanisms of
20 effect, the effect by way of increasing the
21 acetylcholine levels transiently or on a longer
22 term basis with possible consequences for receptor

1 adaptation and the adhesion properties, where it
2 may in fact not be directly a function of the
3 inhibition of the catalytic activity itself but at
4 least this is a set of molecules that is known to
5 bind irreversibly to that enzyme, and so it is of
6 greater suspicion than your random set of other
7 chemicals that happen to be floating around in the
8 environment.

9 So at least my index of suspicion is
10 raised about the chemicals even if it turns out
11 that important aspects of their activity is not
12 captured by the raw inhibition potency. It still
13 gives me enough uncertainty that I think concern
14 is warranted.

15 I think the discussion needs to be
16 improved, and perhaps this will help enhance the
17 analysis with two supplemental discussions.

18 First, I think there should be a clear
19 articulation of reasonable hypotheses about which
20 dosimetrics for cholinesterase inhibition could be
21 important for the developmental pharmacodynamic
22 actions.

1 So I think that one really does need to
2 seriously do an analysis of the pharmacodynamics
3 from the available data and any additional data
4 that can be marshalled.

5 For example, it is not impossible that
6 the best dosimetric for predicting effect could be
7 some peak levels of cholinesterase inhibition on
8 one day or several days of successive exposure.
9 Alternatively, an AUC measure of the integral of
10 percent inhibition by time could prove to be the
11 closest causally relevant predictor of
12 developmental effects. There are also a few more
13 complicated hypotheses that I'll mention a bit
14 later.

15 In any event, given each of these and/or
16 other plausible measures of internal delivered
17 dose, I think EPA should discuss the roles of
18 activating versus detoxifying enzymes' activities
19 and other factors.

20 For example, for measures of acute peak
21 cholinesterase inhibition, I expect that
22 activating enzymes would prove to be very

1 important for those OPs that need activation.

2 But the detoxifying enzymes such as the
3 esterases will be less important. The opposite
4 would tend to be the case if AUC integrated
5 percent inhibition by time over an extended period
6 of dosing is more important for causing
7 developmental effects.

8 In that case, activating activity would
9 be somewhat less important and detoxifying enzyme
10 activities for both parent chemical and the active
11 intermediates would tend to be more important.

12 The in vitro data I think -- that you
13 just mentioned I think can contribute to this
14 discussion if analyzed quantitatively.

15 What dose by time metrics for the
16 cholinesterase inhibition best explain the effects
17 that can be observed that are thought to be
18 related to developmental changes in vitro.

19 It might be a lot quicker to get
20 information on that subject. And it's a subject I
21 think that has not been as fully explored in the
22 document as it perhaps could have been if in fact

1 the in vitro data contained a bunch more
2 quantitative measures of both cholinesterase
3 inhibition and duration that could be inferred.

4 DR. ROBERTS: Dr. Eldefrawi and then Dr.
5 Needleman and Dr. Thrall.

6 DR. ELDEFRAWI: I'm going to talk about
7 my special expertise, which I did before
8 yesterday. And that is neurotransmitter
9 receptors.

10 That included the first receptor ever to
11 be purified about 30 years ago. We purified the
12 nicotinic acetylcholine receptor. These are large
13 size receptor, 25,000.

14 And when it is activated, it opens its
15 central channel. And then if the dose is very
16 high, the acetylcholine dose, it changes
17 confirmation right away and closes the ionic
18 channel.

19 On the other hand, the muscarinic
20 receptors are much smaller, (inaudible) 100,000.

21 And they don't desynthesize that fast.
22 What they do is downregulate their numbers so that

1 they can fight the excess effect of the
2 acetylcholine that is released by the nerve.

3 DR. ROBERTS: Dr. Needleman.

4 DR. NEEDLEMAN: The question divides
5 into two parts. Doesn't it?

6 The second part is, given the scientific
7 evidence, is it reasonable to assume that
8 perturbation of the cholinergic nervous system
9 leads to deficits in the structure and function of
10 the central and peripheral nervous system.

11 The answer is, unequivocally, yes, it
12 does.

13 The first question is, please comment on
14 the extent to which the report adequately
15 summarizes the current state of knowledge.

16 What we just heard this morning is that
17 it does not adequately summarize the current state
18 knowledge.

19 This problem belongs in the realm of
20 behavioral teratology. It is a field that has
21 been around for 60, 70 years.

22 And the principles of that are at lowest

1 dose, the most sensitive measures of toxicity are
2 in behavior.

3 And while the document pays lip service
4 to behavioral analyses, it doesn't include it at
5 all in the risk analysis. It just mentions the
6 papers that we have discussed and then goes on to
7 look at a peripheral enzyme to measure a central
8 effect.

9 Now, it is clear that AChE is a marker
10 for toxicity. In any marker, you are required to
11 furnish certain measures of its utility. That is,
12 its sensitivity, its specificity, its predictive
13 power positive and negative, its correlation with
14 the outcome that you want to know.

15 None of this has been done. And that
16 leads me to say that there is -- the reason that
17 we're here is to decide if there is enough
18 uncertainty or enough certainty to avoid the
19 obligatory tenfold safety factor.

20 I think it is clear hat there is enough
21 uncertainty that you cannot do that.

22 DR. ELDEFRAWI: If I may, I saw the

1 picture that I brought in yesterday.

2 For today's invited speakers and guests,
3 I would like very quickly just to explain what
4 that picture is.

5 You see on way up left corner, there is
6 a cell end that is releasing acetylcholine.
7 However, that's the end of the neuron -- I'm
8 sorry, there is a nicotinic receptor sitting up
9 there around green circles. And the nicotinic
10 receptor when activated, it inhibits the release
11 of the transmitter of that neuron.

12 Then the big large neuronal end, that
13 does not receive the transmitter. The transmitter
14 in this case is glutamate or gaba.

15 These studies were detected by
16 electrophysiological methods by my colleague in
17 the University of Maryland, Dr. Edson Albuquerque.

18 He's an electrophysiologist. So he can
19 measure single events. So the presynaptic
20 preceptors are important, as well as, of course,
21 in most cases, the postsynaptic receptors.

22 DR. ROBERTS: Dr. Thrall then Dr.

1 Matsumura.

2 DR. THRALL: I was just going to suggest
3 that maybe we could make this discussion more
4 simple if we could ask the agency to take out the
5 phrase, by inhibiting acetylcholinesterase
6 inhibition or by inhibiting acetylcholinesterase.

7 Obviously, that's the biomarker, but it
8 looks like there is a whole and other component to
9 this. If we could just take out that phrase, that
10 might simplify this.

11 DR. ROBERTS: Yes, but I think sort of
12 -- having that phrase in there has sort of
13 stimulated, I think, some very interesting
14 discussion about the potential for what inhibiting
15 cholinesterase really means.

16 There is at least apparently two
17 potential modes of action that could be defined as
18 inhibiting cholinesterase.

19 And there is some implications, I
20 suppose, in the risk assessment in terms of which
21 of -- the weight of evidence, which of those is
22 more plausible because, of course, the potency

1 estimates and everything are based on the
2 catalytic activity of the enzyme, which is one
3 mode of action.

4 DR. ROBERTS: Dr. Matsumura I think is
5 next and then Dr. Pope.

6 DR. MATSUMURA: I basically agree with
7 Dr. Needleman's statement, that we would like to
8 look at more behavioral results and analysis in
9 the final document.

10 Certainly, there must be some data where
11 -- a generation treatment on all those -- at least
12 some doses to show that some test has been run to
13 look at some sophisticated changes.

14 I agree with Dr. Pope's position as
15 well, that the roles of behavioral changes may be
16 so subtle and that we are a little worried about.

17 I have been working on the autism in the
18 last two years. They are really, really
19 dedicated. You can't find anything really a
20 little bit effect on noxtocian (ph). I'm not even
21 sure whether that can really be tied to gross
22 behavioral problem, which we just can't find the

1 molecular biological clue about the autism. So
2 I'm on the side of a little more cautious.

3 But at the same time, I would like to
4 look at the perspectives once more. And if we
5 look at the chlorpyrifos, looking at those two
6 papers by Slotkin's group, .1 milligram per
7 kilogram I see effects in behavioral as well as
8 the other effect.

9 So if you do that, then when you look at
10 the probabilistic model, at the 99.9 percent, it is
11 one hundredfold margin, so the difference safety
12 factor if we accept that is the most sensitive
13 method.

14 So the question is, is this one
15 hundredfold enough to cover that unknowns. And I
16 would like to really look at the overall
17 perspectives. And certainly the agency did a
18 pretty good job really looking at the old types of
19 the exposure.

20 So the point to me is that if there is
21 one hundredfold difference in the 99.9 percentile,
22 the question really is this real. There are lots

1 of other types of options in the intricate on one
2 side. The other side is that, yes, we agree with
3 the regulatory agencies that they have to make
4 some decision and that we have to ask really to
5 check is this real.

6 Are we really close enough, 100 times
7 safety factor here. Is that in the reason that we
8 should be really jumping on or not.

9 So that's a question I would like to
10 raise.

11 DR. ROBERTS: Dr. Pope.

12 DR. POPE: There has been a lot of
13 excellent points brought up on in the discussion
14 on this topic. Some of these points are well
15 taken.

16 Dr. Thrall's suggestion that we might be
17 able to alleviate the problem by getting rid of
18 the phrase or the idea of inhibition of
19 acetylcholinesterase I think is the pivotal part
20 for me. The way I see it, that's what the whole
21 process is based on.

22 And while the role of acetylcholine

1 itself as a neuromodulator, I can see that as
2 being part of the process.

3 However, the point I was trying to make
4 is that if you have compounds that are inhibitors
5 of acetylcholinesterase that do affect some of
6 these processes in vitro and others that are very
7 potent cholinesterase inhibitors that don't, then
8 I don't see how this could be part of the process
9 of cumulative risk assessment based on cholinergic
10 toxicity.

11 DR. ROBERTS: And by inhibiting
12 cholinesterase, you mean the asteratic part of the
13 molecule --

14 DR. POPE: That's what I mean.

15 DR. ROBERTS: We have to be very careful
16 about our semantics and what we're talking about
17 because the cholinesterase as a protein versus --
18 most of our methods in our potency assessment is
19 based on the asteratic attributes and activities
20 in the molecule as opposed to perhaps some other
21 functions in the molecule.

22 Dr. Brimijoin.

1 DR. BRIMIJOIN: Just a very small
2 addition. Basically, I agree with you, Carey,
3 although, I still wonder if the evidence gets more
4 solid whether we'll have to broaden the notion of
5 what is a common mechanism. But right now I think
6 we have to go with what we know happens.

7 But I would like to make the small
8 point, I think Dr. Bigbee will agree with me, say
9 so if you don't, John, that this sort of other
10 action on the acetylcholinesterase molecule, which
11 I think we're imagining might involve a
12 disturbance of interactions, that protein and
13 other protein molecules in the vicinity maybe is
14 not impossible, but it is very unlikely that any
15 of these pesticides could have that kind of action
16 without also causing AChE inhibition.

17 So that putative site is so close to the
18 catalytic gorge that to date any molecule that is
19 known to interact with that area of the surface,
20 including the snake toxins that can't even get
21 into the active site, do have a profound
22 inhibition of acetylcholinesterase activity. So

1 we would expect that to be a common feature.

2 It is possible that somebody may
3 discover a weird molecule in the future that can
4 block these adhesive functions by just sort of
5 coming near that zone or just disturbing the
6 interaction without preventing access of the
7 substrate, without disturbing the function.

8 But that's very unlikely to happen with
9 an OP.

10 DR. BIGBEE: I agree. There is really
11 no evidence that an OP is binding to that or
12 interfering with the site.

13 DR. ROBERTS: For the record, that was
14 Dr. Bigbee.

15 I have Dr. Harry next and then Dr.
16 Sultatos and then Dr. Hattis.

17 Let me remind the panel. I think what
18 we're really sort of being asked here, at least in
19 the second part of this, is this an endpoint that
20 is plausibly related to the mode of action that is
21 being addressed in this cumulative risk
22 assessment.

1 I think they need a pretty clear
2 articulation from us in terms of does the science
3 support linking this endpoint with this mode of
4 action.

5 Dr. Harry.

6 DR. HARRY: That was somewhat of my
7 point that I was going to make in the sense that I
8 think the discussions that have gone on leads into
9 the first question about is there an adequate
10 representation of the scientific knowledge and
11 data for that.

12 And the agency could sit there and write
13 five or six review papers if we start going into
14 all of these things. I do think they address
15 these compounds rather nicely. A little more of
16 the background could help, as I said, in the
17 original comment.

18 But the other question that is here is
19 somewhere along the line I assume the advisory
20 panel accepted this as a biomarker of a common
21 mechanism of action in the adult, right, for
22 looking at these pesticides.

1 Now, the question is, we're now asked to
2 make the assumption that that will cross over to
3 the developing organism. There seems to be some
4 discussion there.

5 But to come back and say is this a
6 viable mechanism by which they can look at to do a
7 cumulative risk assessment given the fact that
8 they have also looked at each individual one of
9 these compounds for their most sensitive endpoint
10 which has included behavior and everything else.

11 I wasn't here for the presentation
12 yesterday, and I sort of quickly tried to glance
13 through the slides. But with the questions that
14 have been raised, it seems like we still come back
15 to asking for the behavior.

16 So I was wondering if I could ask the
17 agency for a question of, if you are looking at
18 these levels of inhibition, what is the relative
19 changes that you see in behavior?

20 Can you give us some sort of feel for
21 what you see is what you expect to see -- of the
22 data that you have, would you see it higher than

1 this.

2 If we can have a framework, that might
3 help address some of the questions that some panel
4 members have.

5 That may be another question further
6 down, but it seems a framework that is getting in
7 the way of things right now.

8 DR. ROBERTS: Dr. Dellarco, do you want
9 to respond?

10 DR. DELLARCO: I'll take the first stab,
11 then I'll ask Dr. Padilla and Dr. Baetcke to add
12 to this.

13 But in general, what we see in the data
14 that we have when you look at clinical signs, they
15 typically occur at much higher doses than where
16 you can see cholinesterase inhibition. Typically,
17 you can see cholinesterase inhibition occurring at
18 lower doses.

19 Now, there are exceptions, or you see
20 them occurring about at the same levels. But we
21 don't see the behavioral effects occurring at
22 doses lower than where we can detect significant

1 cholinesterase inhibition.

2 I would like to try to summarize what I
3 have heard so far to make sure I understand it.
4 And i want to put it in very simple terms. Maybe
5 it is best we wait until all the deliberations are
6 over with. I'm trying to understand what the
7 panel is saying on this question.

8 DR. ROBERTS: We're sort of circling
9 around. I'm hoping our opinion is going to become
10 more crystallized as our discussion continues.

11 So let's let the panel sort of go
12 through that process. And if we're not where we
13 need to be at the end of that discussion, then I
14 would ask you to do that, because I think it is
15 very important that we make our opinion as clear
16 as we can.

17 Dr. Sultatos and then Dr. Hattis.

18 DR. SULTATOS: I have a question for, I
19 guess, Dr. Bigbee or Dr. Brimijoin.

20 Is the adhesive site that we're talking
21 about here the peripheral binding site on
22 acetylcholinesterase?

1 DR. BRIMIJOIN: Near it.

2 DR. BIGBEE: And including it.

3 DR. BRIMIJOIN: Overlapping it on the
4 surface, outer surface.

5 DR. SULTATOS: Because occupying the
6 peripheral binding site does in fact inhibit
7 acetylcholinesterase. It is just a different
8 mechanism of inhibition. It is an allosteric
9 modification of the active site. So it's not a
10 phosphorylation, but you still inhibit
11 acetylcholinesterase.

12 DR. BRIMIJOIN: But the reason it is
13 difficult to fold that into the common mechanism
14 is that nobody is proposing that it is the
15 inhibition of the activity that is responsible for
16 the cellular effects.

17 DR. ROBERTS: Dr. Hattis, then Dr.
18 Portier.

19 DR. HATTIS: I just have two brief,
20 further comments that I didn't say before.

21 This first goes to the knockout mouse.
22 In my view, the knockout mouse evidence is

1 surprising, but doesn't, I think, completely argue
2 against important effects of transient
3 fluctuations of the acetylcholinesterase activity
4 or inhibition, because the transient fluctuations
5 present a substantially different potential for
6 adaptation than in the case of the heterozygous
7 and homozygous knockout mice, which have the
8 opportunity to develop their connections and
9 feedback control processes in a more consistent
10 basis.

11 Finally, I want to suggest that the
12 mouse with an apparently recovered whole brain
13 cholinesterase activity is not necessarily the
14 same as an unexposed mouse, and could have in fact
15 persisting effects due to the fact that some of
16 its cholinesterase molecules could continue to be
17 inhibited.

18 Imagine that you have a bunch of
19 synapses where the cholinesterase that were
20 present prior to the exposure and those molecules
21 continue to be inhibited unless they are
22 resynthesized by the same cell.

1 But new synapses may well have lots of
2 newly synthesized and therefore completely
3 uninhibited acetylcholinesterase enzymes.

4 And therefore, you are talking about a
5 situation that even though -- if -- you have 10
6 percent residual inhibition in that situation is
7 not the same thing as if you have just inhibited
8 10 percent uniformly.

9 And so, that's part of my concern to
10 develop better dosemetrics. Perhaps one of the
11 neuroscientists either from EPA or on the panel
12 could flush out my understanding of that because
13 I'm not absolutely sure.

14 But my impression is that the
15 cholinesterase molecules would have to be made
16 within the particular cells that are participants
17 in a particular synapse in order to be working.

18 DR. ROBERTS: Dr. Portier.

19 DR. PORTIER: Dr. Dellarco, I need some
20 clarification again. There was a question you got
21 yesterday that sort of we didn't get an answer.
22 We did partially about DNT studies.

1 As I understand it, you have two DNT
2 studies in hand. Is that correct? Full DNT --

3 DR. DELLARCO: Full DNT studies.

4 The report on page 7 in a footnote
5 summarizes the status of the DNT studies. We have
6 already gotten the chlorpyrifos DNT study. That
7 was reviewed quite a while ago and discussed.

8 We have completed the review of
9 dimethoate. I believe that we have given you that.

10 Malathion, we have completed the
11 cholinesterase review, but the scientists in our
12 organization are still going over the other
13 measures and the DNT. So that's not available
14 right now.

15 For methyl parathion, I believe, that's
16 the same situation.

17 So we have gotten several DNT studies
18 for the cholinesterase data, but not necessarily
19 all the other neurological measures.

20 And again, the status is on page 7.

21 DR. PORTIER: I just found it. I didn't
22 read the footnote.

1 So then in terms of -- again, a
2 clarification issue. In terms of behavioral
3 effects from fetal exposure into juvenile and
4 adult life, the total body of data consists of the
5 DNT studies you have in hand, the Slotkin studies
6 on chlorpyrifos, and a few other --

7 DR. DELLARCO: And the literature.

8 DR. PORTIER: -- there's things in other
9 -- not necessarily mammalian systems.

10 Is that pretty much the gist of the
11 information?

12 DR. DELLARCO: I think so.

13 I think that's a reasonable summary of
14 it.

15 DR. PORTIER: I will note one thing
16 again for the record that I'll put in my response
17 here, that Dr. Sass's comments yesterday about the
18 analysis of the malathion data does concern me.

19 In looking at those tables in the
20 analysis that was done there relative to the
21 analysis done by Slotkin, Slotkin log transformed
22 the data. In the malathion study, they did not.

1 Slotkin did an analysis of variance to find these
2 effects, which is a much more powerful,
3 statistical tool. In the malathion study, that
4 did not appear to be done.

5 I think when you look at these DNT
6 studies for behavioral effects, I would strongly
7 suggest that they be reanalyzed with a log
8 transform and a full analysis of variance so they
9 are comparable to Slotkin's study and can be
10 easily compared across the various OPs.

11 DR. ROBERTS: Thank you, Dr. Portier.

12 Dr. Dellarco, we're not there yet, but
13 I'm hoping we can get some closure on this
14 question fairly soon.

15 Let me ask Dr. Bigbee or Dr. Pope, since
16 they have a lot of experience in this area and
17 have been listening attentively to our discussion.

18 If either one of them want to volunteer
19 to sort of capsulize our response so far, the
20 short answer.

21 We have given them a lot of suggestions.
22 I think that there is -- I have heard varying

1 opinions on the degree to which the report
2 adequately summarizes the current state of
3 knowledge. There have been some suggestions about
4 aspects that need to be added, and we can
5 certainly include that in our report.

6 But the second question is a pivotal
7 one. Is a very important one. And I think we
8 need to be very clear in how we respond to this.

9 So not to put you on the spot. Dr.
10 Bigbee, do you think you could sort of capture the
11 --

12 DR. BIGBEE: I think the key word, and
13 Dr. Brimijoin said this, is potentially. That's
14 the word.

15 And potentially, it is there. It can
16 cause deficits in structure and function,
17 potentially.

18 And another thing as far as the
19 behavioral studies, the two major systems that
20 have been looked at are sensory systems.

21 And sometimes the abnormalities in the
22 sensory system are a little bit harder to

1 determine than motor systems.

2 So I just see that great big potentially
3 word there, and I think we -- my main is concern
4 is that there needs to be information, more
5 information in the document as far as our
6 discussion today, but that certainly with the
7 potential there, I think we have to give that a
8 lot of weight.

9 DR. ROBERTS: So potentially, yes, but
10 potentially not. And the document really doesn't
11 cover the scientific strengths and weaknesses of
12 that -- the evidence for that linkage. Is that
13 correct?

14 DR. BIGBEE: Yes.

15 DR. ROBERTS: Does anyone else have a
16 different viewpoint or want to try and summarize
17 it differently?

18 Dr. Dellarco.

19 DR. DELLARCO: Can I try to summarize it
20 in really simple terms, make sure that I'm not
21 misinterpreting anything?

22 DR. ROBERTS: Absolutely.

1 DR. DELLARCO: From listening to the
2 discussions, particularly the comments that Dr.
3 Brimijoin, Dr. Pope and Dr. Bigbee have made, this
4 is my understanding, that the basis of the
5 cumulative assessment was done on the ability of
6 these 30 OPs to act on the same site of the
7 acetylcholinesterase molecule. And phosphoryly,
8 it didn't. Thus, inhibited (ph).

9 However, when we moved to the developing
10 system, there may be other actions on that
11 molecule, and there may be subgroups of OPs and
12 how they affect that molecule based on their
13 structural characteristics -- maybe a chemical
14 kind of OP specific kind of thing.

15 So although we can say we have a common
16 mechanism for cholinergic toxicity, we can't
17 necessarily say for all 30 of these OPs we have a
18 common mechanism for neurodevelopmental toxicity.

19 However, it's not unreasonable to assume
20 that the inhibition of acetylcholinesterase may
21 not be a bad biomarker of effects because it is --
22 again, it is affecting -- if it's acting on that

1 molecule through another action, it is probably
2 going to be inhibiting it in the way that -- in
3 terms of the catalytic function.

4 So as we look at common mechanisms of
5 neurodevelopmental effects, there may be subgroups
6 there. Is that what I'm hearing?

7 And this doesn't mean we shouldn't be
8 concerned about neurodevelopmental effects and
9 continue to look at OPs, particularly on a
10 chemical by chemical basis as data continues to
11 emerge and we continue to understand mechanisms
12 and effects.

13 DR. ROBERTS: I think that's certainly a
14 path forward. Let's see whether the panel agrees
15 with that description and assessment.

16 Anyone want to weigh in on that? Dr.
17 McClain.

18 DR. MCCLAIN: Listening to the EPA
19 presentation yesterday morning, I got a much more
20 clearer understanding of how you are actually
21 focusing this.

22 And once I had that understanding, my

1 opinion on some of these questions did change.
2 Because I confused, like I think perhaps some
3 other are confusing, the limitations and the focus
4 on the common mode of action, which is the
5 inhibition of acetylcholinesterase, all of the
6 other effects, the developmental teratology, the
7 toxicity, the carcinogenicity and what ever other
8 studies have been done with these compounds would
9 have been included in the risk assessments and the
10 tolerances for each of the individual's OPs.

11 So I know I was very confused until I
12 heard your presentation. And I think your point,
13 and you have done it versus succinctly, that you
14 have to make the distinction between what you are
15 evaluating on the common mode of action and any
16 other potential toxicity of these 30 OPs that are
17 handled on an individual basis.

18 And you can't bring in all of the
19 effects of those 30s into this cumulative risk
20 assessment.

21 So I think the way you have just
22 expressed it now I have a much better

1 understanding of that yesterday morning. And I
2 think that's the way, the perspective that we need
3 to take on this.

4 DR. ROBERTS: Other view points? Dr.
5 Brimijoin.

6 DR. BRIMIJOIN: I want to say something
7 I hope it simplifies rather than complicates.

8 Despite the evidence that there may be a
9 structural kind of basis for developmental
10 abnormalities caused by acetylcholinesterase
11 inhibitors, in other words, other sites -- other
12 mechanisms than simply raising acetylcholine
13 levels locally, despite that interesting evidence
14 emerging from all these in vitro studies, I'll
15 just say, personally, if you force me to come
16 right down to the question, would inhibition of
17 acetylcholinesterase and a resulting rise in
18 acetylcholine levels in certain regions of the
19 brain have the potential for causing lasting
20 effects on either the brain structure or the
21 function, I would have to say that I already think
22 there is enough potential for that, that enough

1 uncertainty about that possibility that EPA would
2 be wise to incorporate that into their thinking
3 about what is an appropriate safety factor for the
4 developing organism. Just on that basis alone.

5 And we must not lose site of the fact
6 that OPs do inhibit acetylcholinesterase.

7 And one further point of information is
8 that in the knockout mice, the one thing that has
9 been seen that I'm aware of, and I don't know if
10 it has made its way into the papers published yet,
11 but is very substantial and I guess permanent
12 changes in the level of acetylcholine receptors in
13 the brain.

14 So the animal has adapted, but the brain
15 is different, and in a way that perhaps you and I
16 wouldn't want our children's brains to be
17 different.

18 DR. ROBERTS: And not to put words in
19 your mouth, but I assume from your remarks that
20 you think that including this endpoint, meaning
21 neurobehavioral effects in this cumulative risk
22 assessment, which is based on a common mode of

1 action involving cholinesterase inhibition is
2 appropriate based on existing scientific
3 information --

4 DR. BRIMIJOIN: Yes, I do.

5 DR. ROBERTS: Dr. Pope.

6 DR. POPE: Just one quick question to
7 Steve. That's whether the receptors are
8 permanently altered in the heterozygotes or just
9 the homozygotes.

10 DR. BRIMIJOIN: I wish I knew the
11 answer. I don't, but I think they probably are,
12 but I don't know.

13 DR. ROBERTS: Dr. Lambert.

14 DR. LAMBERT: Just a clarification from
15 the agency.

16 Are we also trying to address that is
17 this going to be the bottom line for assessing the
18 potential developmental neurotoxicology potential
19 of these class of chemicals?

20 DR. DELLARCO: In the context of
21 cumulative assessment, but just in general?

22 DR. LAMBERT: Right.

1 DR. DELLARCO: I think what we're
2 hearing today will be very helpful, not only to
3 how we look at this issue in the cumulative
4 assessment, but how we continue to look at this
5 issue in individual chemical assessments on the
6 OPs.

7 Does that respond to your --

8 DR. LAMBERT: I think most everybody
9 around the table agrees that it is an important
10 pathway of toxicity.

11 The question that some of us have, I
12 think, is is it the most sensitive and specific
13 and is it so sensitive and so specific that will
14 capture risk to the human child.

15 That's much more difficult.

16 DR. DELLARCO: The other point I'll
17 raise is that, as stated yesterday, the bulk of
18 these developmental neurotoxicity studies will be
19 in by 2003. We don't have many of them. And we
20 will continue to look at them as they come in and
21 appropriately revisit chemical assessments. We
22 will be looking at that as that data and knowledge

1 continues to emerge.

2 DR. ROBERTS: Dr. Portier.

3 DR. PORTIER: I'm going to agree with
4 Dr. Brimijoin. I think he did an excellent job of
5 summarizing very clearly my views.

6 And based upon that, Dr. Dellarco, I
7 would argue that waiting for the -- I don't know
8 if you are going to have to put this risk
9 assessment out before you get those DNT studies in
10 2003, but I would argue that without those DNT
11 studies we don't have sufficient weight of the
12 evidence to argue that there isn't a consistent
13 behavioral reduction that is also potentially
14 linked to the acetylcholinesterase inhibition.

15 And I think that's a key issue.

16 DR. DELLARCO: Can I respond?

17 DR. ROBERTS: Please.

18 DR. DELLARCO: There is one important
19 premise in the report. And that is the mechanism
20 is the inhibition of acetylcholinesterase. That's
21 the precursor event. And if we account for
22 age-dependent sensitivity, we should account for

1 the behavioral effects that are associated with
2 that mechanism.

3 DR. ROBERTS: Dr. Portier will respond,
4 and then Dr. Pope.

5 DR. PORTIER: I guess I have a
6 difficulty with that question, with that response,
7 since the correction factors you are using across
8 the OPs to develop the overall exposure index are
9 based upon the adult studies and not upon a
10 potential for specific sensitivity in the infant
11 that is beyond the acetylcholinesterase inhibition
12 that led to the toxicity in the adults that you
13 had observed.

14 And that's the question here, is that
15 whether the neurobehavioral effects above and
16 beyond what occurs in the adult are something that
17 we need to be worried about on a per
18 acetylcholinesterase inhibition measure.

19 And that's the thing that hasn't been
20 demonstrated because we haven't seen enough DNT
21 studies and behavioral responses to decide whether
22 that is a common difference, a common effect

1 across many of these OPs or not. That's my
2 opinion on it.

3 DR. DELLARCO: I have a question for Dr.
4 Portier.

5 What you are saying is that, although,
6 we have accounted for in the relative potency
7 factors the potential for the young to respond at
8 lower doses to cholinesterase inhibition, you
9 don't consider that adequate because you feel that
10 behavioral effects can occur at doses lower than
11 that?

12 DR. PORTIER: No. The issue is I don't
13 know.

14 We haven't established the question of
15 whether a 10 percent acetylcholinesterase
16 inhibition in an infant leads to an equivalent
17 toxicity of a 10 percent cholinesterase inhibition
18 in an adult.

19 There are indications that a particular
20 inhibition in an infant may lead to a different
21 outcome in an adult than you have ever seen in an
22 adult.

1 That's an added risk. And it is that
2 issue, I think, that plays an important role in
3 this debate.

4 DR. ROBERTS: Did you want to respond,
5 or do you want to move on?

6 Dr. Pope.

7 DR. POPE: Just a brief comment about
8 Dr. Lambert's question about sensitivity and also
9 the recent discussion here is that generally
10 speaking the acetylcholinesterase, for example, 10
11 percent toxicity -- I mean toxicity associated
12 with 10 percent inhibition really isn't there.

13 There is no toxicity associated with 10
14 percent inhibition. Generally, the synapse has
15 excess enzyme levels, and most people think that
16 there is some degree of inhibition that can be
17 tolerated before you alter cholinergic
18 neurotransmission.

19 As I say that, I am thinking I have a
20 little uncertainty regarding the very young
21 central nervous system, so I'm not really as
22 confident there. But that is something that

1 should be considered.

2 There is generally safety built into the
3 synapse because of excess enzyme.

4 DR. ROBERTS: Dr. Hattis.

5 DR. HATTIS: I think when we're talking
6 about the effects of 10 percent inhibition in
7 adult animals on a long-term continuing basis, I
8 think it does beg the question about whether that
9 that's the right dosimeter for predicting effects,
10 these likely developmental effects and, you know,
11 that could in fact have an effect of transient
12 inhibition that could be greater than that that
13 could result from one or a few doses that you
14 wouldn't capture with that chronic, that
15 longer-term measure.

16 Or, it could be that even a rather
17 modest inhibition, maybe less than 10 percent, in
18 fact turns out to have some marginal change in the
19 numbers of connections that get made or don't get
20 made because of marginal changes.

21 The developing organism is a situation
22 where lots of things could be at the edge. It is

1 not necessarily so that we have functional reserve
2 capacity for all of the important cells and all of
3 the important places doing all the important
4 functions.

5 So I think it is at least an issue of
6 concern to try to do some pharmacodynamics based
7 on either in vivo or in vitro studies. And that's
8 part of the uncertainty -- the relationship
9 between the pharmacokinetic measure -- the
10 cholinesterase inhibition and the pharmacodynamics
11 is I think still an uncertainty that that remains
12 from the current database, despite the fact that
13 one has never seen obvious changes, these
14 behavioral changes that have only been observed a
15 few times as far as I can tell.

16 And the database is just not very
17 impressive to be able to conclude firmly that 10
18 percent inhibition in adults is without important
19 effects in -- you know, for this one dosimeter is
20 without important effects in developing organisms.

21 DR. ROBERTS: About 10 minutes ago we
22 were on the brink of clarity for our panel

1 response to this question I think after Dr.
2 Brimijoin spoke. So I'm going go back to Dr.
3 Brimijoin to recapture that moment and see if we
4 can come to some closure on this particular
5 question and move on.

6 Some of the other comments are good
7 comments that people are making, but I think they
8 may fit in elsewhere in our discussion. I would
9 like to sort of move things forward. So let me go
10 back to Dr. Brimijoin and then I'm going to ask
11 Dr. Dellarco whether we have put together a good
12 response.

13 DR. BRIMIJOIN: I was starting to feel
14 that we were kind of drifting away from the point
15 here. I think we have heard a lot of important
16 points made, but I'm listening very carefully
17 trying to filter it all.

18 And I really haven't had any input
19 coming in here that seems to -- I'm not hearing
20 disagreement among the panel. I'm hearing all
21 kinds of caveats and finer points being raised.

22 But I'm hearing a consensus that the

1 panel agrees with the idea that there is enough
2 information out there, even there is enough
3 information in the document itself, and there is
4 enough information out there for us to have a
5 level of concern that there are, there is a
6 potential developmental risk from the action of
7 OPs to inhibit acetylcholinesterase activity.

8 And there may be a variety of mechanisms
9 by which other things can happen as well, but
10 there is a level of concern that this exists.

11 And so in that sense, we have already
12 reached a consensus on the formal answer to the
13 formal question. I think what may be bothering
14 some of the panel members, such as Dr. Portier, is
15 that what was not asked in this question is, oh,
16 well, in fact, I can't find it, strikingly,
17 anywhere in this array of questions put to us, I
18 can't find -- is it there, just a flat question,
19 does the panel agree with the agency's proposal
20 specifically to go with a threefold FQPA safety
21 factor with compounds that are shown to have a
22 certain degree of extra sensitivity.

1 We aren't asked that. I think we should
2 have been. If we were, Dr. Portier would be, I
3 think, very much on the point to be saying, we're
4 not sure that a amount of additional inhibition
5 here is the same thing in the neonate as the
6 adult.

7 I think that's a question that does need
8 to be dealt with.

9 Personally, I think the EPA has struck a
10 middle ground here in saying, yes, we do have to
11 make an FQPA adjustment. Yes, indeed, we do. But
12 maybe not an extreme one.

13 But as for the purposes of this
14 question, I suggest we have already reached
15 consensus. And it is time to move on to the
16 remaining questions.

17 DR. ROBERTS: Okay.

18 Dr. Bigbee, as the report coordinator,
19 for this particular session, do you have a pretty
20 good sense of what the panels's response might be?

21 DR. BIGBEE: Yes. And certainly, I
22 appreciate everybody's input.

1 DR. ROBERTS: So basically, as I hear
2 it, the answers to the questions are: There is
3 some other discussion that needs to be added; and
4 is it reasonable to assume it would lead to
5 deficit in the structure and function, the answer
6 is, yes, but there would be lots of sort of
7 qualifications associated with that that would
8 appear in the discussion.

9 Dr. Eldefrawi.

10 DR. ELDEFRAWI: I have a stupid
11 question, but I'm interested to know the response,
12 if there is.

13 How about the old people, not with
14 Alzheimer's or other diseases, but are they as
15 susceptible or more susceptible than the younger
16 people or not. I really don't know.

17 DR. ROBERTS: That issue was raised,
18 actually, in our last discussion, at our last SAP
19 meeting. And perhaps we can talk about that at
20 the end of this one. But I would like to sort of
21 keep us focused on the questions. That was an
22 issue, however, that was raised at the last review

1 or go-over on the cumulative risk assessment.

2 Dr. Needleman.

3 DR. NEEDLEMAN: Just to amplify what Dr.
4 Brimijoin said, the unasked question in question 1
5 is: Is the data adequate enough to certify
6 certainty for the prescribed threefold safety
7 factor.

8 That should, I think, be in the first
9 question.

10 DR. ROBERTS: I suspect we'll get the
11 opportunity later on to discuss what the
12 appropriate uncertainty factor might be given the
13 various uncertainties.

14 But I think this was a pivotal question
15 about whether or not this endpoint needs to be
16 included this cumulative risk assessment.

17 And my understanding, and please correct
18 me if there is any disagreement from this panel,
19 but it seems that the response is yes, this is an
20 endpoint that should be included in this
21 cumulative risk assessment which is based on
22 cholinesterase inhibition.

1 Is there any disagreement with that?

2 Dr. Dellarco, have we finally --

3 DR. DELLARCO: I just want to come back
4 to one issue that Dr. Portier raised about the
5 benchmark 10 response that is being used in the
6 assessment for our point of departure.

7 When you make uncertainty and safety
8 factor determinations, you have to look at all
9 aspects of the assessment and weigh the biases in
10 the assessment with respect to the input
11 parameters where there is conservatism and where
12 there is not and make that decision.

13 So as you think about that benchmark 10
14 response, I would ask you to consider that, as I
15 stated in my talk yesterday, that's in light of
16 the 10X interspecies factor and intraspecies
17 factor, 100X.

18 That's considered as a group factor in
19 this assessment.

20 DR. ROBERTS: Are we ready to move
21 forward to the next question? I would like to at
22 least get through 2.1 before we take a break this

1 morning.

2 DR. DELLARCO: We're going to move to
3 our second topic area, which includes the
4 interpretation of the animal studies with respect
5 to age-dependent sensitivity to
6 acetylcholinesterase inhibition.

7 This is question 2.1. Please comment on
8 the extent to which the report adequately
9 discussed and summarized the current understanding
10 of age-dependent sensitivity to cholinesterase
11 inhibition, the prevailing views in the scientific
12 community concerning the biological factors
13 involved and the role esterases may play as a
14 major factor accounting for the potential
15 increased sensitivity of the immature rat.

16 DR. ROBERTS: Dr. Harry, would you mind
17 leading off our discussion on this question?

18 DR. HARRY: I think you are going to end
19 up with a lot of different comments about the same
20 way we did in the last one, because it is asking
21 for whether there is a sufficient amount of
22 information available that you can provide in the

1 document.

2 Within the framework of how the document
3 was formed and I think the level at which it was
4 focused on, it gave enough understanding of the
5 differences but maybe not all the details that
6 could be possible that I'm sure other members of
7 the panel can pull out for you to expand upon some
8 of that discussion.

9 I did have a couple things. And they
10 may cross down in some other questions. Since I'm
11 not on those, I will sort of say them as they will
12 cover over, but I won't expand upon them.

13 But when I was going through this, one
14 of the things that I was finding it a little
15 difficult, and again, I'm focusing on what you
16 have written in the document, I found it a little
17 difficult to understand how you were handling the
18 detoxification of the animal with the modes that
19 you had, the cumulative dosing versus acute
20 dosing, and then also the rebound or the apparent
21 rebound loss of inhibition going on.

22 And that may be a dilution factor or

1 things like that, but I think that that needs to
2 be in the document in a transition to explain that
3 a little more, because right now it is sort of a
4 what-type question and exactly how you are looking
5 at those two endpoints there.

6 The other -- this may come down on time,
7 but I think it also comes in here. When you are
8 looking at the role of these compounds and what
9 they will do on the esterases to decrease them is
10 the fact that you have very little data and you
11 have very little data at which you can compare
12 quite often as in the dose that was given, the
13 route of administration, the timing of doing the
14 esterases.

15 So, like I said, other people have more
16 knowledge of the basic biology behind this. I
17 think what was presented in the document was
18 focused on these OPs, the knowledge that you have
19 about them and presented rather clearly.

20 The problem is you don't have a whole
21 lot of information to be working with. But it did
22 present some concepts that those are being taken

1 into consideration with risk assessment.

2 DR. ROBERTS: Thank you, Dr. Harry.

3 Dr. Sultatos, did you find the
4 discussion adequate or are there things that you
5 think need to be addressed?

6 DR. SULTATOS: I think there are things
7 that need to be addressed and added. I think the
8 discussion of the biological factors that might
9 result in age-dependent toxicity of certain OPs
10 and specifically the A esterases and carboxyl
11 esterases could be significantly improved by
12 presenting a more balanced interpretation of the
13 available data.

14 I think the report summarizes evidence
15 that supports important roles for A esterase and
16 carboxylesterase in the increased sensitivity of
17 the immature rat, but it ignores observations or
18 interpretations that might confound that view.

19 As a result, I think the document
20 overstates the degree to which the mechanism of
21 age-dependent toxicities of OPs are understood.

22 And I think it is most apparent, at

1 least for me, with regard to three issues.

2 First, the document summarizes several
3 studies that have reported correlations between
4 the temporal patterns of development of A esterase
5 and carboxylesterase activities and OP
6 sensitivity.

7 But it doesn't talk about some of those
8 same studies which have reported a decreased
9 capacity for activation in the immature rat.

10 It was touched upon a little bit in the
11 presentation yesterday, but there is nothing said
12 about it in the document.

13 Immature rats do have reduced capacity
14 to detoxify certain oxons, but they also have less
15 oxon present because they are producing less oxon.

16 So I think this is a confounding factor
17 that needs to be discussed. And it may implicate
18 other factors involved in the differential
19 toxicity between immature rats and adult rats.

20 It also may have some bearing on one of
21 the later questions when we're talking about or
22 we're discussing possible relevance of animal

1 studies to human studies.

2 So I think there needs to be a
3 discussion about this decreased capacity of
4 immature animals to metabolically activate the
5 OPs.

6 The second issue is that the report
7 presents evidence in support of a role for A
8 esterase and detoxification of certain OPs and in
9 age-dependent sensitivity. But it doesn't discuss
10 evidence that might be contrary to that view.

11 Out of the 30 or so OPs that we have, to
12 my knowledge, there are only three that have been
13 identified as being substrates in vitro for A
14 esterase. Those are paraoxon, chlorpyrifos oxon
15 and diazoxon (ph).

16 Over the past 5 or 10 years, there have
17 been a number of studies based largely on kinetic
18 analyses that have questioned roles, the role of
19 A esterase in the detoxification of these three
20 compounds in vivo.

21 Essentially, there is some evidence to
22 indicate that these reactions are not very

1 favorable kinetically.

2 In addition, with the development of a
3 knockout mouse by Clem Furlong, A esterase
4 knockout mouse, he has reported that paraoxon --
5 in the knockout mice, there is no altered
6 sensitivity for paraoxon. So we know that A
7 esterase does not place an important role in the
8 detoxification of paraoxon, which is the oxygen
9 analog from parathion.

10 While Furlong's group has reported that
11 the knockout mice do have an increased sensitivity
12 towards chlorpyrifos oxon and para -- I'm sorry,
13 diazoxon, and that's included in this report,
14 Furlong has also reported that there is only a
15 slight increase in the sensitivity of the knockout
16 mice when the parent compound is given, which
17 would be chlorpyrifos and diazinon.

18 And even then, it is only at fairly high
19 doses of chlorpyrifos and diazinon.

20 So I think that that suggests that there
21 may not be an important role for A esterase in the
22 detoxification of chlorpyrifos oxon or diazoxon in

1 the knockout mice when the parent compound is
2 administered, the chlorpyrifos or the diazinon.

3 So I think there needs to be some
4 discussion of that.

5 And the third issue, in looking at table
6 2, the document states that the temporal pattern
7 of A esterase and carboxylesterase activities
8 correlate reasonably well with studies on OP
9 sensitivity.

10 But the report doesn't discuss the
11 possible exception to this correlation, which I
12 mentioned yesterday, which is methyl parathion.

13 Methylparaaxon is not a substrate for A
14 esterase. And according to table 2, it has
15 limited interaction with carboxylesterase.
16 Therefore, we should expect limited age-dependent
17 sensitivity if we buy into the role of A esterase
18 and carboxylesterase in age-dependent sensitivity.
19 But with methyl parathion, it's age-dependent
20 sensitivity, according to what is reported in
21 table 1.

22 It is almost the same as that of

1 chlorpyrifos following acute exposure. And it is
2 age-dependent toxicity after repeated
3 administration. Probably even exceeds that of
4 chlorpyrifos.

5 So I think these observations could
6 suggest involvement of other factors in
7 age-dependent sensitivity at least for methyl
8 parathion. And I think that a discussion of that
9 needs to be included in the document.

10 DR. ROBERTS: Thank you, Dr. Sultatos.

11 Dr. Pope.

12 DR. POPE: Yes, I have some of the same
13 comments as Dr. Sultatos regarding the esterases
14 and their role in OP toxicity.

15 One thing about most -- as far as I
16 know, all the studies evaluating carboxylesterase
17 -- many of the studies evaluating this esterase is
18 an age-related sensitivity. There are correlation
19 studies evaluating the inherent activity at a
20 certain age group with its acute sensitivity to
21 the pesticide. And there are no mechanistic
22 studies really out there.

1 The paraoxonase activity is
2 highly-correlated with age-related sensitivity,
3 but paraoxonase appears to have no real role in
4 parathion toxicity, for example.

5 The report mentions some toxicodynamic
6 factors that may be important, such as
7 differential receptor modulations, and also
8 mentions the feedback inhibition of the
9 presynaptic regulation of acetylcholine release,
10 which I personally think is important in higher
11 sensitivity in younger animals.

12 But that's going to be only important
13 with when you are evaluating sensitivity at really
14 high exposures.

15 I think roughly speaking the report does
16 an adequate job of describing the information
17 pertaining to differences and sensitivity based on
18 cholinesterase inhibition.

19 DR. ROBERTS: Thank you, Dr. Pope.

20 Dr. Brimijoin?

21 DR. BRIMIJOIN: I really don't have much
22 to add. I think Dr. Sultatos did an excellent

1 job. But what I'm hearing is that he has some
2 very specific suggestions about some additional
3 information, different points should be raised,
4 should be incorporated in the document. And
5 undoubtedly, we'll be able to capture that in the
6 report.

7 But with those qualifications, I would
8 agree that we're sort of close or on track here.

9 DR. ROBERTS: Just to throw in my
10 comment, I think as a follow up to some questions
11 and comments I think that Dr. Lambert made
12 yesterday, I think there is -- probably the
13 section on developmental aspects of P450 could be
14 beefed up a little bit. There is a fair amount of
15 information on P450 isoforms and at what points
16 they come on line.

17 And if that could be tied with what
18 information is available about those various P 450
19 forms in terms of bioactivation or detoxification
20 of these compounds, that might be useful.

21 Any other comments or suggestions?

22 Dr. Hattis.

1 DR. HATTIS: I just want to apologize.
2 I read most of my answer to this question in the
3 previous discussion, and I'm sorry to have
4 confused people.

5 But essentially, the only thing I have
6 really to add here is that the relative
7 importance of different activating and
8 inactivating systems depends on the dosimeter that
9 you think is causally relevant to the behavioral
10 effects.

11 And one at least needs to discuss the
12 different implications of different reasonable
13 hypotheses about that.

14 DR. ROBERTS: Any other suggestions from
15 panel members in response to 2.1?

16 All right. Perhaps then we should try
17 and tackle 2.2 before a break, which would keep us
18 on schedule.

19 DR. DELLARCO: Please comment on the
20 timing of administration, in other words, the
21 developmental stages treated, and the differential
22 found between adults and the young animal.

1 DR. ROBERTS: Sort of an open-ended
2 question.

3 Dr. Pope, do you want to tackle that
4 one?

5 DR. POPE: Well, obviously, the timing
6 of exposures is critically important if you are
7 going to evaluate age-related differences in
8 sensitivity.

9 The report describes a number of
10 studies, some with prenatal, some with postnatal,
11 some with combined prenatal and postnatal
12 exposures.

13 Based on cholinesterase inhibition, the
14 studies utilizing exclusively prenatal dosing
15 appear to me to consistently report equal or
16 lesser effects in the developing organism than in
17 the dam.

18 As indicated in the report, this may in
19 some cases be due to the timing of biochemical
20 measurements relative to the exposures. If you
21 wait long enough, you are not going to see a whole
22 lot of inhibition in the younger animals because

1 they are recovering faster while it may not really
2 be an indicator of reduced sensitivity.

3 In essence, more extensive
4 cholinesterase inhibition is often noted in young
5 animals compared to adults to a number of OP
6 toxicants, postnatal animals.

7 With acute relatively high exposures, a
8 number of organophosphorus insecticides, for
9 example, chlorpyrifos and methyl parathion are
10 more toxic to young individuals based on acute
11 sensitivity, lethality, cholinesterase inhibition.

12 The ability to recover just as in
13 prenatal animals between exposures and tissues
14 from postnatal animals is probably very important
15 in this regard.

16 If acetylcholinesterase molecules are
17 being synthesized faster in immature animals, they
18 will recover faster following each cholinesterase
19 inhibitor exposure.

20 Because of the relatively short
21 maturation period in rodents, however, repeated
22 dosing studies have the confound of a changing

1 baseline. In essence, the animal is becoming less
2 sensitive to the pesticide throughout the dosing
3 period.

4 Thus, lesser age-related differences in
5 sensitivity with repeated compared to acute
6 exposures may be due to both inherent differences
7 in recovery potential and to decreased sensitivity
8 as the dosing period progresses.

9 DR. ROBERTS: Dr. Brimijoin.

10 DR. BRIMIJOIN: Actually, I still
11 couldn't tell, I thought a lot about this
12 question, and I couldn't tell what you are asking
13 or why you are asking it and how it is different
14 from what we have already talked about.

15 So I think Dr. Pope has done a brave job
16 of plowing forward with a response to a question
17 whose purpose is obscure.

18 Would you like to clarify your purpose,
19 and maybe we could give you a little bit more
20 help?

21 DR. DELLARCO: I actually think Dr. Pope
22 was on the mark in what we were trying to get at.

1 Because when we were looking at the animal
2 studies, just the empirical observations, we drew
3 certain conclusions about prenatal exposure and
4 what we see in the fetal tissues versus maternal
5 issues.

6 And what we were seeing in the postnatal
7 direct dosing studies with respect to -- it
8 appeared that as the young animal was maturing,
9 that differential was disappearing.

10 We just wanted confirmation, did you
11 agree with those conclusions.

12 DR. BRIMIJOIN: So basically, yes.

13 I wondered if you were asking for more
14 specifically like, do we accept the idea that a
15 21-day rat is equivalent to a one-to-two-year-old
16 human, which is a key question sort of lurking in
17 the background.

18 Do we think that a -- the dosing, how to
19 handle this window of time between the birth of
20 the rat and weaning it.

21 Do we consider that equivalent to third
22 trimester, and what kind of dosing regimen would

1 be appropriate.

2 And I guess -- we had a discussion about
3 that yesterday. And I think we're all aware of a
4 certain sense in which this lineman is correct,
5 but the questions about -- actually, the
6 limitations of the model when it comes to modeling
7 the very last stages of human development -- I
8 certainly agree with what Dr. Pope has just said.

9 Since I'm on the spot, I'll just raise
10 one other question. Maybe this is the right time
11 to throw it in, or perhaps it should have been
12 tossed in at 2.1, which is: In looking at these
13 differences, which I'm convinced are real, that
14 there are some compounds that are showing a
15 definite age-related sensitivity in your model,
16 and we have had some nice data, mostly presented
17 by Dr. Padilla, about possible mechanisms, at
18 least possible mechanisms that would account for
19 these differences, and one of the things that has
20 emerged is a consistent theme that when you go
21 from acute dosing to repeated dosing at the very
22 youngest ages, there are some chemicals that

1 behave differently, that chemicals which on an
2 acute dose are -- the newborn or the very young
3 are much more sensitive, and on repeated dosing
4 that tends to go away, the explanation being that,
5 this is something easy for us to accept, the idea
6 that there is more rapid replenishment by new
7 synthesis. The brain is adding to its
8 cholinesterase pool.

9 In looking at those data, though, at
10 first I'm just completely convinced, that makes
11 great sense. I think it basically does make sense.
12 But there is a puzzle that I would like someone
13 else to comment on, maybe Dr. Padilla.

14 If we have some chemicals which are
15 showing heightened sensitivity in the very young
16 on acute dosing, but when we do the repeated
17 dosing model, that differential is sharply
18 reduced.

19 And then we have chemicals like
20 methamidophos which don't seem to show this
21 age-related sensitivity in the acute dosing
22 model.

1 We had something like maybe malathion as
2 an example of case 1 and methamidophos as an
3 example of case 2.

4 So with malathion or maybe chlorpyrifos
5 where we see the age-related sensitivity sharply
6 with the acute dose and it goes away with repeated
7 dosing. Metamidophos, we don't see it in either
8 case.

9 If we don't see it in the acute dosing,
10 though, and there really is a much more rapid
11 replenishment in the very young, why doesn't the
12 age sensitivity reverse itself when you go from
13 acute dosing to repeated dosing with a chemical
14 like that?

15 So if there really is such, as I believe
16 there is, dramatic resynthesis, why doesn't that
17 give the young an advantage with a chemical that
18 doesn't show the differential sensitivity in acute
19 dosing?

20 DR. ROBERTS: Dr. Pope would like to
21 respond, apparently.

22 DR. POPE: In a way, we had a paper from

1 1993 that looked at intermittent dose in the
2 chlorpyrifos. We actually did see that.

3 If you spread the doses of chlorpyrifos
4 out far enough, at the end, the adult is showing a
5 lot more neurochemical changes.

6 DR. BRIMIJOIN: Do you have anything to
7 add to add to that?

8 DR. PADILLA: I actually have not looked
9 at the repeated methamidophos study. So I don't
10 know what the interval was. I don't know when
11 they did the cholinesterase inhibition. So I
12 really can't report on it.

13 But you are right. If everything else
14 was equal, it seems like you might be able to see
15 that sort of less sensitivity in the young after
16 repeated dosing.

17 DR. BRIMIJOIN: Just having added this
18 confusion, I'll just come back and say I basically
19 agree with what Dr. Pope has said.

20 DR. ROBERTS: I was just looking at
21 Table 1 in the document. The acute was done at
22 PND 17, whereas in some of the other ones it was

1 done -- and of course, there was no difference,
2 but some of the other ones were done at PND 11,
3 acutely, and they did see a difference.

4 We're not necessarily having an equal
5 basis of comparison, unfortunately, from the data
6 set.

7 My impression, again, this is to
8 emphasize something that Dr. Pope said, the
9 problem with the model is that the development
10 proceeds so rapidly that you can't repeat a dose
11 at different stages.

12 Because to repeat a dose, you move
13 through these developmental stages. And I think
14 that makes it very difficult to try and get
15 quantitative estimates of sensitivity at varying
16 stages. Because to do any kind of a repeated
17 dose, which I think we all agree is perhaps more
18 relevant, you are spanning developmental stages.

19 So ultimately, you are only capturing,
20 perhaps, what is relevant at the end.

21 What do you think about that, Dr.
22 Padilla?

1 DR. PADILLA: There is also the aspect
2 of how much each dose in each age carries over to
3 the next day.

4 And if methamidophos is one of these
5 compounds that the effects are really gone in both
6 the adult and the pup by the next day, then what
7 you are measuring at the end of the repeated dose,
8 of course, is just the result of the last dose and
9 not the cumulative effect.

10 That's the other factor that you have to
11 factor into that.

12 DR. ELDEFRAWI: I thought we were
13 looking at cumulative risk assessment. That means
14 it should apply to all the OPs in use. Am I
15 correct or am I wrong?

16 If some of them are affected by repeated
17 dose and some are not, the organophosphate
18 insecticides.

19 DR. ROBERTS: I don't know. Does
20 someone want to respond to that?

21 Dr. Dellarco.

22 DR. DELLARCO: I'm trying to understand

1 what the question is. Could you restate the
2 question?

3 DR. ELDEFRAWI: The repeated exposure
4 versus an acute exposure or whatever for certain
5 organophosphates but not others, they have
6 different effects.

7 DR. DELLARCO: You are saying that for
8 some of these OPs we can only see this increased
9 sensitivity only after an acute and not repeated.
10 In some of them we see after both acute and
11 repeated. So how does that play a role in the
12 cumulative.

13 DR. ELDEFRAWI: Yes.

14 DR. DELLARCO: When we look at exposure,
15 we're doing daily estimates and we're also looking
16 at exposure over a 7-day rolling average too.

17 It is kind of difficult for us to make a
18 linear extrapolation into our exposure analysis
19 from just these studies.

20 And the way that we're looking at acute
21 and repeated is more with respect to developmental
22 stages that were exposed and their sensitivity.

1 That's the point we're trying to make.

2 It appears somewhat as an animal
3 matures, this seems to be going away.

4 DR. ELDEFRAWI: Could the toxicity be
5 due to inhibition of acetylcholinesterases or are
6 there other targets that are causing these
7 symptoms.

8 Because if it's only some of the OPs,
9 then it doesn't apply to all the organophosphate
10 anticholinesterases. That's what I'm trying to --

11 DR. DELLARCO: You are saying this may
12 be a characteristic that's not particularly shared
13 among all these OPs?

14 DR. ELDEFRAWI: Shared amongst all -- I
15 understand it is not.

16 DR. DELLARCO: Yes.

17 DR. BRIMIJOIN: Dr. Eldefrawi, I think
18 maybe we're -- we're not talking about different
19 mechanisms of action or things that would be
20 outside the common mechanism.

21 We're talking about just differences in
22 the life-span, the rates of metabolism, the depot

1 effects and other things, which will vary from one
2 chemical to the next.

3 And the EPA has factored these things in
4 to its regulatory scheme from the data base. So
5 it shows how effects do build up or don't build
6 up.

7 You can have 100 drugs that act by an
8 identical mechanism, and each one of them will
9 have its own unique pharmacokinetics and
10 metabolism rates.

11 DR. ROBERTS: Does anyone else on the
12 panel have anything to add to Dr. Pope's response
13 to this question?

14 Dr. Harry.

15 DR. HARRY: I think your comment about
16 this being a broad question that would be open for
17 a lot of comments back on it is true.

18 And the one that was coming to mind, as
19 I was hearing the discussions over there and also
20 reading through the document on the changes that
21 happened, and again, I'm sorry, I wasn't here
22 yesterday, so I haven't looked there, is this

1 potentially raising a question of do you have the
2 optimal design for exposure in your DNT testing
3 that you have out there?

4 DR. DELLARCO: No. It really wasn't
5 getting -- what it was trying to get at is you
6 look at your animal studies. That's what you
7 have. You don't have human studies.

8 But at some point in the assessment when
9 you get to the characterization, you are going to
10 need to make some extrapolations or predictions
11 about children. And in our cumulative assessment,
12 as I showed yesterday, we have different age
13 groups that we're looking at.

14 So we just want to know to what extent
15 can we draw conclusions about the sensitivity of
16 different children's age groups in our cumulative
17 assessment like the less than one year and infants
18 versus the one to two year olds and so forth just
19 based on what animal data we have that has looked
20 at administration of these OPs to different
21 developmental stages.

22 DR. ROBERTS: With that explanation, are

1 there any other comments we want to make on 2.2
2 before we go to break?

3 DR. HATTIS: I guess we'll just notice
4 that we're going to talk about the enzyme
5 development in children versus humans in another
6 question.

7 DR. ROBERTS: That's correct.

8 And Dr. Pope, we may want to preface
9 your comments with sort of a brief statement of
10 what we understood the question to be, and then
11 respond, because it is kind of a broad and
12 open-ended thing.

13 If there are no other comments in
14 response to this particular question, let's go
15 ahead and take a break. Let's reconvene at 10:45.
16 And we'll take up question 2.3.

17 (Thereupon, a brief recess was taken.)

18 DR. ROBERTS: Dr. Dellarco, could we
19 proceed with question 2.3.

20 DR. DELLARCO: We're going to move to
21 question 2.3.

22 Please comment on the extent to which

1 comparative cholinesterase data on six OP
2 pesticides, chlorpyrifos, diazinon, dimethoate,
3 methamidophos, malathion, methyl parathion, may
4 represent a reasonable subset of different
5 structural and pharmacokinetic characteristics of
6 the cumulative group of OP pesticides to define an
7 upper bound on the differential sensitivity that
8 may be expected at different life stages of the
9 immature animal.

10 DR. ROBERTS: Dr. Sultatos, what do you
11 think? Is this a reasonably representative data
12 set?

13 DR. SULTATOS: Well, the document
14 suggests that the age-related changes in
15 sensitivity to certain OPs is largely a function
16 of pharmacokinetic factors. And I think I probably
17 agree with that.

18 So to me, the answer to this question or
19 to answer it, you have to consider whether or not
20 the pharmacokinetic characteristics of the
21 remaining members of the cumulative assessment
22 group are sufficiently different from the six

1 indicated in the document so as to lead to
2 juvenile, adult differential toxicity greater than
3 three.

4 And it seems to me that based on the
5 lack of information in the open literature
6 regarding the pharmacokinetic characteristics of
7 the remaining pesticides, specifically, with
8 regards to their metabolism and volumes of
9 distribution, I have to conclude that there is not
10 enough information available to know whether or
11 not the six insecticides indicated in the document
12 are representative pharmacokinetically of the
13 cumulative group.

14 So consequently, I don't think it can be
15 concluded that those six OPs can serve as an upper
16 bound for the possible different age-dependent
17 sensitivity of other OPs.

18 DR. ROBERTS: Dr. Reed, what do you
19 think?

20 DR. REED: I pretty much agree with what
21 was said, but since I have written something out,
22 I might as well read it to you.

1 The current available data on direct
2 postnatal exposure, six OP pesticides, shed some
3 light to the potential differential sensitivity of
4 OPs during stages of development.

5 The agency is to be commended for the
6 extensive effort in addressing these rather
7 complicated issues.

8 However, the complex interplay of many
9 factors, pharmacokinetics, but also
10 pharmacodynamics, that are chemical and
11 (inaudible) age specific that leads up to the
12 inhibition of brain cholinesterase inhibition will
13 give substantial uncertainty for predicting the
14 upper bound of the differential sensitivity for
15 all of the OP and their evaluation.

16 It is understood that the age
17 sensitivity issue is somewhat important,
18 especially for azinphos methyl, since the agency's
19 presentation showed that azinphos methyl has 27
20 percent contribution to the food exposure of one
21 to two years old. And I think that's sort of --
22 part of the reason that the question was phrased

1 making sort of comparison or mention of azinphos
2 methyl and malathion.

3 Well, specific to the relationship
4 between the two, azinphos methyl and malathion,
5 the impossibility to predict the sensitivity
6 pattern based on being in the same chemical
7 subgroup is obvious and not necessarily limited to
8 the age-related sensitivity issue of brain
9 cholinesterase inhibition.

10 The improbability to extrapolate between
11 OPs of the same subgroup can be illustrated merely
12 among the adult female rats without the age
13 factor.

14 A simple question is what considerations
15 would predict the magnitude of more than three
16 hundredfold difference of the two phosphoryl
17 dithioates (ph).

18 Based on the agency's final cumulative
19 OP risk assessment in June 11th, 2002, the
20 relative potency factor is 0.1 for azinphos methyl
21 and 0.0003 for malathion.

22 I looked at another phosphoryl

1 dithioate, methatathion (ph) that has a relative
2 potency factor of 0.32. And there is a threefold.

3 So now we have, just based on the
4 relative potency factor and brain cholinesterase
5 in female rats, we have such a spread in
6 differences in potency. And I look at that, and I
7 decided I really cannot make an upper bound
8 decision putting the age factor into it.

9 And I also make the observation that in
10 another situation where I look at the
11 impossibility of extrapolating (ph) the
12 sensitivity pattern of brain cholinesterase
13 inhibition between two chemicals just within the
14 adult female rats, the chemicals that are
15 metabolic activation pairs like acephate and
16 methamidophos, and there is a more than tenfold
17 difference in relative potency, again, this does
18 not have age factor in it.

19 For these two chemical metabolic
20 activation pairs, for these two chemicals, with
21 the rich database available for methamidophos, the
22 agency's document say that it's not possible to

1 determine whether acephate would show comparable
2 responses in adult and young rats.

3 And so I felt that we're going through
4 the same path as I personally have taken when I
5 was working on methyl parathion. And even now our
6 group in California is going through
7 cholinesterase policy rediscussion or updating
8 many of these issues, that we look at so many
9 pharmacokinetic parameters, and I look at the
10 polymorphism of any enzyme that I can think of,
11 important enzymes for metabolism, and I came up
12 empty in terms of using that to quantify the
13 interindividual differences or age differences in
14 any of these.

15 So I came to the same conclusion, too,
16 with the agency that I decided to come back and
17 just look at the how many fold, quantitative, how
18 many fold difference is based on toxicity outcome.
19 And that's where I think the agency's threefold
20 came from, one to threefold.

21 My comment on that is that there is a
22 place for that kind of assessment, but I think if

1 we are going to come up with that threefold from
2 that type of comparison, then, as I mentioned
3 yesterday, I think benchmark dose is important,
4 and one of the data set, I believe, would come up
5 to be fourfold instead of threefold.

6 So my conclusion is that I think
7 threefold is, just based on that type of analysis,
8 would not be sufficient to identify an upper bound
9 of uncertainty factor that the agency is
10 considering.

11 But I do have another issue I think is
12 fairly important. I would not know where to place
13 it, but since the FQPA uncertainty factor also
14 addressed, as the agency interpreted, addressed
15 the exposure, I thought it is interesting, and
16 mostly in the context of what had been brought up
17 as comments at many of these SAP meetings, I kept
18 hearing people saying, the 99.9 percentile of
19 exposure is really unreasonable and cannot be
20 substantiated.

21 DR. ROBERTS: Dr. Reed, are you starting
22 to get sort of into an exposure issue as opposed

1 to --

2 DR. REED: In terms of uncertainty
3 factor overall.

4 DR. ROBERTS: Right. But can we come
5 back to that point maybe later on when we talk
6 about --

7 DR. REED: Yes.

8 DR. ROBERTS: You will have the
9 opportunity to broach that issue then.

10 I gather, then, from your comments that
11 you also do not think that the six necessarily
12 captures the upper bound?

13 DR. REED: Right.

14 DR. ROBERTS: Great. Thank you.

15 Dr. McClain?

16 DR. MCCLAIN: This is a difficult
17 question. And this is where the uncertainty factor
18 comes in, is on this particular judgment. So it
19 is a matter, I think, of looking about how certain
20 or uncertain we are, but this is basically where
21 the uncertainty factor is introduced.

22 And I think when you take a look at this

1 question, there is a couple ways that can be
2 interpreted.

3 First is the question asked, can we
4 predict the toxicity from the six OPs that we have
5 data for. Or is it a question of predicting the
6 degree of enzyme inhibition that may occur or the
7 differential enzyme inhibition that may occur
8 after direct dosing of the adults and the juvenile
9 animals.

10 I think with respect to the first
11 interpretation, it is certainly not possible to
12 predict the toxicity of the chemical based on the
13 toxicity of another chemical. One could only make
14 some very generalized conclusions.

15 But what is being asked here is more
16 limited. And that is, can EPA define the relative
17 range of enzyme inhibition based on the amount of
18 information that they currently have.

19 And I think you need to consider a
20 couple things here. First, there is no inherent
21 difference in the sensitivity of the
22 cholinesterase enzymes between the young and

1 adult. And its binding characteristics, they are
2 the same.

3 Second, the difference between
4 inhibition of the cholinesterase between newborns,
5 pups and adult animals is primarily due to two
6 factors as we have discussed here, one of which is
7 the rate of enzyme regeneration, and the other is
8 the rate of detoxification by the various enzymes
9 that are present, the esterases and the cytochrome
10 P 450s.

11 And we'll be discussing some of the
12 enzyme situations a little later on. And this
13 certainly is an area where the information is
14 deficient because really the detoxification
15 enzymes seem to drive the differences with age
16 more so than any other factor.

17 Now, these factors are, the enzyme, the
18 rate of detoxification, the rate of regeneration
19 of the enzyme, these, of course, are going to be
20 the same with respect to any one of the
21 organophosphates that you test.

22 And the main difference, then, between

1 compounds is going to be the relative rate at
2 detoxification, which certainly could differ and
3 does differ between the compounds. But in
4 general, the six OPs for which data are available
5 for cholinesterase inhibition of young and adult
6 animals indicate that they are qualitatively
7 similar.

8 And for these compounds, the ratio of
9 CHE inhibition of the adult as compared to the
10 juvenile, in this case the pup rat, would have
11 sensitivity which range in several cases from no
12 difference at all up to a threefold difference.
13 And I think this is where the uncertainty factor
14 comes in. And I basically agree with the choice
15 of the agency.

16 And I think the other thing that needs
17 to be taken into account here, when you are
18 dealing with the prediction and the uncertainty of
19 this particular aspect, is that the one to
20 threefold factors that we're dealing with are
21 based on the direct dosing of the adult and the
22 juvenile animals, which is an appropriate way to

1 get some sort of an assessment of the difference.

2 However, under realistic conditions of
3 exposure, that is the treatment of the dam, the
4 pregnant dam or the lactating dam, the inhibition
5 of cholinesterase is invariably higher in the
6 adult as compared to either the fetus or the
7 neonatal or juvenile animal. And I think this
8 needs to be taken into consideration.

9 I think in the human infant, the level
10 of enzymes that detoxify the OPs will be near the
11 adult levels, and we'll discuss this again in a
12 little more detail later, but by six months of age
13 they are generally metabolically competent. And
14 this would be at the point in time where you would
15 begin to have dietary consumption of pesticides.

16 And I think these types of differences
17 observed between pups and humans when you consider
18 the six months of age are probably going to be
19 different. We use our models to predict, but
20 there is limitations on doing that.

21 And I think overall the prediction of
22 the range of enzymes inhibition is more limited

1 than the predictation of toxicity. And I think
2 the uncertainty factor based on this is
3 appropriate at this time.

4 But one of the things when you take a
5 look at this data, and we'll discuss this a little
6 bit more, too, when you look at the differential
7 inhibition of the enzyme between the various age
8 groups, I would raise a question, is this a matter
9 of exposure or is this a matter of increased
10 sensitivity. And I don't think the two are
11 equatable.

12 But that's my comment.

13 DR. ROBERTS: So we have a difference of
14 opinion. In your opinion, the data set is
15 sufficient to establish an upper bound for
16 sensitivity --

17 DR. MCCLAIN: Acknowledging that this is
18 where the uncertainty factor should be.

19 DR. ROBERTS: Dr. Pope.

20 DR. POPE: Well, to me, there seems to
21 be little data to support the conclusion that six
22 compounds would represent 30 compounds, basically.

1 If all 30 OP pesticides had exactly the
2 same mechanism of toxicity and not just a
3 mechanism in common, there would probably be
4 sufficient information on the six. However,
5 that's not the case.

6 If 24 other OP toxicants have not been
7 evaluated, there is probably a high degree of
8 uncertainty that all those compounds are going to
9 behave in the same way as the other six.

10 And thus, the comparative data for the
11 six representative compounds may not adequately
12 represent the other 24 compounds, and caution
13 should be used in that assumption.

14 DR. ROBERTS: Thank you, Dr. Pope.

15 Let me, then, ask other members of the
16 panel for their opinions on this.

17 Dr. Hattis, then Dr. Matsumura.

18 DR. HATTIS: Basically, I agree with the
19 earlier speakers in saying that I'm in general
20 uncomfortable with using a term like bound because
21 it connotes a defined upper limit when we --
22 unless, in fact, we have some good reason to

1 believe that values above X are not possible.

2 I would rather have a distributional
3 treatment. But the distributional treatment has
4 to be preceded by some better definition of the
5 relative potencies in the pups of various ages
6 relative to the adults.

7 And the current treatment -- I have been
8 told privately that EPA is working on better
9 treatments of these data. But for the record, you
10 can't estimate relative potency appropriately, I
11 think, by taking a number like 89 percent in
12 inhibition in the pups and directly dividing it by
13 a 39 percent observed inhibition in the adults for
14 the same dose because even if there were no
15 residual cholinesterase activity, 100 percent
16 inhibition, that calculation couldn't get you an
17 answer more than about 2.5.

18 If you -- you can treat -- the ideal
19 treatment in cases where you have enough dose
20 levels to calculate ED 50 or to apply Woody
21 Setzer's types of models in calculating ED 10, you
22 should use those.

1 And I have no problem with using an ED
2 50 or an ED 10 depending upon what is possible.

3 Where you have only one dose point to
4 work with, you still can apply a simplified
5 version of the exponential model that is basically
6 the original model that was suggested earlier.

7 And basically, if you do that for this
8 particular case where you have 89 percent versus
9 39 percent just for illustration, instead of the
10 two point threefold difference that is indicated
11 by the straightforward calculation, you get
12 approximately fivefold. So it does make some
13 difference.

14 It makes more difference in that case
15 than in some other cases. And I haven't a
16 complete handle on all of the things in Table 1,
17 but essentially all of those calculations need to
18 be redone, and then you need to do some kind of
19 distributional treatment to describe the data.

20 DR. ROBERTS: Your original comment was,
21 though, that you did not --

22 DR. HATTIS: I don't want to speak in

1 terms of bounds --

2 DR. ROBERTS: You don't think it
3 necessarily sets an upper bound?

4 DR. HATTIS: Right. I don't want to
5 speak in terms of bounds. At best, with a good
6 deal of work, one can define upper confidence
7 limits for the observed data.

8 DR. ROBERTS: Dr. Matsumura and then Dr.
9 Needleman.

10 DR. MATSUMURA: This question whether
11 it's really -- reasonably representing all
12 organophosphates, I'm not sure, because I have
13 experience such as the fenitrothion, which makes
14 such a huge difference between the parathion and
15 the fenitrothion.

16 And when you follow that kind of logic,
17 it took a long, long time to understand why those
18 two are different. And I guess the G S A -- G S T
19 is one of the big functions which was not really
20 considered.

21 Actually, I like Dr. Padilla's
22 experiments very much. That's a good way to go.

1 That's a good solid progress. But like D D B P,
2 which is one of the topics, the exposure that you
3 really wanted to study but did not, they are
4 affected by G S T.

5 And the glutathione really affect many,
6 many of those OP toxicities; and there is no
7 question, particularly dimethyl type chemicals
8 and those halogenated and, of course, the
9 double-bonded chemicals such as the D D B P.

10 And it is not represented here. And I
11 mentioned about the carboxylamidase, which is not
12 covered here either.

13 Of course, we have to keep working. And
14 you are doing a good job going to that direction.

15 With a few more additions, you may have
16 reached that goal. But at this particular stage,
17 I have to side with everybody, Dr. McClain, Dr.
18 Reed and Dr. Pope, that it is not there yet.
19 That's my opinion.

20 DR. ROBERTS: Dr. Needleman and then Dr.
21 Portier.

22 DR. NEEDLEMAN: Just a short response to

1 Dr. McClain's statement, that the children's
2 behavior is not a measure of their sensitivity.

3 It is true. Children live closer to the
4 ground. They put their hands in their mouth more
5 often. They have higher metabolic rates. They
6 take in more water per kilo than adults. They eat
7 more fruit than adults. That increases their
8 risk. And that factor should be included in the
9 risk analysis.

10 Not to do that is to put them at
11 increased jeopardy.

12 DR. ROBERTS: Dr. Needleman, did you
13 want to weigh in on this particular question,
14 though, in terms of whether or not the subset
15 represents a reasonable upper bound or --

16 DR. NEEDLEMAN: No. I think it is
17 well-said, well-handled. I agree with Dr. Pope.

18 DR. ROBERTS: Dr. Portier?

19 DR. PORTIER: Yes and no. And I'm going
20 to go straight to the statistical issue.

21 Under the assumption that there is a
22 common distribution for sensitivities across

1 chemicals between the adult and the juvenile,
2 then, in fact, with six observations in a
3 population of 30 possible observations, six
4 observations should be enough to get you the mean
5 and the standard deviation with sufficient
6 accuracy to estimate some range of possible values
7 for the difference between sensitivities in
8 juveniles and adults across an entire distribution
9 of 30 compounds.

10 Regretfully, that's not what was done in
11 this analysis. And in fact, the interpretation
12 you are using in applying these factors to your
13 analysis for the differences between juveniles and
14 adults is in fact to do it on a chemical specific
15 basis.

16 Hence, in order to be able to do that,
17 you actually need the numbers for every single
18 chemical, because you are not presuming a common
19 distribution and so you are not presuming a common
20 upper bound. And the only way to get at what you
21 are asking is to do the individuals.

22 DR. ROBERTS: Dr. Brimijoin.

1 DR. BRIMIJOIN: I'm going to give it an
2 unsophisticated response here. We have heard I
3 think very intelligent and informed reactions of
4 people comfortable with statistics and population
5 distributions.

6 But I'm talking my gut feeling is that
7 the answer is flat out no. It is a huge data gap.
8 And I think in the case of the compounds, that we
9 don't have this developmental data for at all. We
10 should revert to, in fact, the default FQPA factor
11 of 10.

12 DR. ROBERTS: Other opinions?

13 Dr. Lambert.

14 DR. LAMBERT: Would it be helpful to
15 poll the committee on this question if there is a
16 divergent --

17 DR. ROBERTS: I don't know that we need
18 to poll the committee, but I think -- I certainly
19 want to give everybody who has an opinion the
20 opportunity to express it for the record.

21 DR. LAMBERT: No.

22 DR. ROBERTS: Thank you. Very

1 succinctly stated.

2 Dr. Hattis.

3 DR. HATTIS: I want to add one other
4 thing for the record.

5 A particular challenge for the proposed
6 distributional analysis comes from cases like
7 malathion where there is no detectable
8 cholinesterase inhibition in adult animals in some
9 -- in the brain, I believe. But there is
10 appreciable inhibition at comparable and lower
11 doses in younger animals. I think that was
12 pointed out in discussion at the public session.

13 Simply -- the temptation is simply to
14 exclude those cases, but there is a problem with
15 excluding them. Because excluding those analyses
16 could risk biasing the analyses because you have
17 excluded the very case where there is a suspicion
18 that the difference between adults and pups could
19 be big.

20 So some kind of truncated distributional
21 analysis is in order. And good statisticians know
22 how to do that.

1 DR. ROBERTS: Last call for folks to
2 express an opinion.

3 Dr. Eldefrawi, were you signaling me?

4 DR. ELDEFRAWI: No.

5 DR. ROBERTS: I think the panel response
6 on this is reasonably clear. So let's go ahead
7 and proceed, then, to the next question, which is
8 3.1.

9 DR. DELLARCO: This is our last topic
10 area. This concerns the relevance of the animal
11 findings to children.

12 The first question is: Please comment
13 on the maturation profile of A esterase and the
14 uncertainties surrounding these data in young
15 children. Because no human data are available on
16 the maturation profile of carboxylesterases,
17 please comment on what should be assumed in
18 humans, especially children age one to two years,
19 given the animal data and what science understands
20 in general about detoxification maturation
21 profiles.

22 DR. ROBERTS: Dr. Hattis, are you ready

1 to respond?

2 DR. HATTIS: Basically, we have done
3 some research in this area, although nothing is
4 directly applicable without modification to the A
5 esterase or let alone the one that hasn't been
6 measured. I thought I might put up for you some
7 of the data.

8 The panel, I think, has the paper that
9 has this table in it. But basically, the thrust
10 of the observations -- this is results from an
11 analysis of a data base of pharmaceutical data,
12 and it's basically observations of half-lives of
13 about 30 odd different drugs.

14 This is some individual data. There
15 should be a table that is in one of the slides.
16 Again, even this slide is not easy to read.

17 But essentially, these are, essentially,
18 from the overall regression analysis for a total
19 of 41 different drugs for 135 different data
20 groups.

21 Essentially, what we find is that
22 premature neonates are about fourfold on average

1 -- or geometric mean, I should say, larger.

2 These are sort of one standard error
3 limits on the mean on that typical result. Longer
4 in half-life than adults.

5 That difference comes down to about
6 twofold for full term neonates and ages up to
7 about 2 months. By two to six months of age, the
8 difference is no longer statistically detectable
9 in general. By the time you get to six months to
10 two years, the typical case is that the half-lives
11 are somewhat shorter.

12 And thereafter, you have pretty close
13 correspondence on average to adult levels.

14 The same basic pattern happens -- there
15 was another slide that was like that that may not
16 have gotten saved that shows a finer breakdown by
17 different pathways.

18 In any event, this general pattern is
19 similar to the hypothesized pattern from the
20 limited data that we have for A esterase.

21 It doesn't guaranty that this pattern is
22 going to be seen for the unknown metabolic routes,

1 but I think it is the reasonable best case. So
2 basically, under this kind of thing you expect
3 some increase pharmacokinetic sensitivity for very
4 young infants under six months -- between six
5 months and two years, which is about the period
6 that was inquired specifically in the question.

7 You don't expect much enhanced
8 sensitivity to increased concentrations of the
9 parent chemical.

10 You could get some increase in
11 generation of the active metabolite if those are
12 produced by particular P 450 metabolic route.

13 So that's basically what comes out of
14 our information. There is also some information
15 that we have on individual values, and what you
16 see is that you get individual values that exceed
17 the -- even tenfold larger than mean adult values
18 in some individuals early in life.

19 That tendency to have increased
20 variability relative to the adults in half-lives
21 does also tend to disappear by -- relatively
22 early in childhood, two to six months of age

1 folks.

2 DR. ROBERTS: Thank you, Dr. Hattis.
3 Does that conclude your response to this question?

4 DR. HATTIS: Right.

5 DR. ROBERTS: Dr. Lambert?

6 DR. LAMBERT: I took a pretty similar
7 approach in trying to answer some of the issues on
8 animal extrapolation to human that they've asked
9 also.

10 And the agency should be commended for
11 the document in their attempt to look at FQPA 10X
12 for the OPs. The agency wishes for the SAP to
13 comment on the metabolism of the OPs and in
14 particular to A esterase. The overall premise is
15 that OP neurotoxicities correlate with the
16 capacity to decrease acetylcholinesterases.

17 Therefore, the expression and the
18 turnover of the choline esterases may indicate the
19 relative susceptibility of the developing human to
20 the OPs.

21 The effect of OPs on the esterase
22 appears to be dependent on the metabolism OPs to

1 the reactive metabolites of some of the OPs to
2 oxons. Therefore, it would be informative to
3 examine the entire pathway, and not just look at A
4 esterase.

5 To begin with a general comment, a
6 developing human is not equivalent metabolically
7 to a rodent at any stage during development. To
8 try to correlate any stage of a rodent's
9 development and make it equivalent to a human's at
10 any stage of development, for example, in the P
11 450, is just not -- there is no comparisons.

12 This is easily shown with the expression
13 of cytochrome P 450s that are expressed in the
14 human, and there are some P450s that are expressed
15 in humans that aren't even expressed in the
16 rodent. Those that are co-expressed in the rodent
17 and the human have different metabolic profiles as
18 far as developmental expression.

19 And most of this data is generated in
20 the liver looking at the liver expression of these
21 proteins and very little, if any, into the brain,
22 where equal or greater would be anticipated.

1 Therefore, trying to draw any
2 conclusions from an animal study metabolically to
3 a human is very difficult.

4 A esterase may be a little less complex.
5 But if you are looking at the entire metabolism
6 of the OPs, that is going to be very difficult to
7 come up with any reasonable comparisons that is
8 accurate and similar.

9 The OPs are essentially -- some of them
10 are initially metabolized by the P 450s to oxon
11 metabolites. It appears the P 450s that are
12 involved are primarily the 3a family and possibly
13 2D6. The family three enzymes' overall activity
14 is generally thought to be increased during the
15 newborn period, infancy and early childhood stage
16 of life.

17 Family three development is primarily
18 composed of in the human P 450 3 A4 and 3A7. The
19 3A7 is the fetal form of family three, which is
20 not expressed at all in the rodent and as
21 expressed, if at all, in very low concentrations
22 in the adult.

1 And we essentially don't know anything
2 about the ability of the human P 4503 family to
3 metabolize these in vivo.

4 And particularly, looking at the fetal
5 forms of the family, we have no data that I'm
6 aware of, these findings are somewhat substrate
7 dependent in the family three. And again, their
8 ability to metabolize OPs during development is
9 not available. That data is not available.

10 But the fact that these enzymes are
11 activating some of the OPs to active metabolites
12 are higher in the newborn and during early
13 development, it would indicate that they may be
14 putting the child at higher risk, the fetus,
15 infant and early childhood.

16 In regards to cytochrome, P4502D6's
17 expression is decreased, almost nonexistent in the
18 newborn's liver, and then approaches adult levels
19 within a few weeks of life.

20 The expression of these enzymes in the
21 human brain during development has not yet been
22 extensively studied, but it would be important to

1 look at.

2 In regards to A esterase animal data,
3 there is only data in the serum and not any data
4 as related in the human, and there is no data
5 looking at A esterase activity in the human liver
6 or brain.

7 There are no data about the maturation
8 profiles of carboxylase in the human.

9 From the studies reported in the
10 document, it appears that A esterase in the serum
11 in both human child and animal are not expressed
12 in early development, but develops to the adult
13 level by one or two years of age according to what
14 is given to us in the document.

15 This would again indicate that a child
16 is going to make some of the oxons at a higher
17 level, have active metabolites. And decreased
18 ability to deactivate would be a concern and put
19 the child at risk.

20 There are critical lack of data in
21 regards to the human that prohibit accurate
22 assessment of these pathways in the human. The

1 capacity of the P450s in the human liver and brain
2 are not known. In particular, the capacity of
3 3a7. Also, the expression of A esterases and
4 carboxylesterase in the human are not known.

5 DR. ROBERTS: Dr. McClain.

6 DR. MCCLAIN: I think this, as I
7 mentioned before, is a particularly critical
8 issue, is the detoxification enzymes for the OPs
9 and their development both in the animals and
10 humans since this seems to relate to -- probably
11 would be the most important factor in the
12 differential inhibition.

13 I did go back to this section on this
14 question and read some of the papers that are
15 referenced here. And of course, this question is
16 specifically addressing the issue of the A
17 esterases.

18 And the one paper here that did have
19 data on the human developmental aspects, the
20 Augustton and Barr paper essentially show that at
21 birth in humans the enzyme activity is about 20
22 percent of the human adult.

1 And as you get to about six months of
2 age, these are up around 70, 75 percent. And it
3 would be consistent with Dr. Hattis's information
4 that he showed that the clearance was about
5 equivalent at about six months of age. So by six
6 months of age, they would be, you know, close to
7 the adults.

8 And the other question was the
9 development of the carboxyesterase. There is no
10 data available for that with respect to the
11 development in human. However, in the literature
12 that we were provided, there are a number of
13 esterases. And they generally show a rather rapid
14 increase after birth up to six months of age.

15 It is likely that the carboxyesterases
16 would follow a pattern similar to the others.

17 DR. ROBERTS: Thank you.

18 Dr. Pope.

19 DR. POPE: Well, the carboxylesterases
20 and the A esterases have been shown to be
21 important in the detoxification of some OP
22 toxicants, and may contribute to age-related

1 differences in sensitivity.

2 However, some studies suggest that other
3 metabolic factors may also be important
4 contributors to age-related sensitivity. The
5 entire spectrum of activation, detoxification of
6 the OP toxicants should be evaluated in relative
7 sensitivity.

8 Determination of activities of all
9 processes in human tissues would be ideal, but
10 difficult to obtain. While the relative
11 contribution of blood and tissue detoxification
12 could be estimated and is estimated in animal
13 models, information is unknown in humans. Thus,
14 this kind of constitutes an uncertainty in how
15 young children may respond to OP toxicants based
16 on relative metabolic processing.

17 Both carboxylesterase and A esterase
18 activities increase during postnatal maturation in
19 rodents. Some studies suggest that esterases also
20 develop in humans during the first year of life.
21 These studies focus exclusively on A esterase,
22 however, and only in the blood. Thus, the

1 knowledge of carboxylesterase expression is absent
2 in any tissues of rodent models, and expression of
3 A esterase in other important detoxification
4 tissues, like the liver, is also missing.

5 One could assume that liver esterases
6 may also coincidentally develop along with the
7 blood esterases, but there appears to be no direct
8 evidence.

9 It seems reasonable to assume that by
10 two years of age, liver and blood detoxifying
11 esterases have developed to adult levels based on
12 developmental profiles on experimental animals,
13 but there is no information to confirm that.

14 Data in human should be collected, if
15 possible, at least with blood carboxylesterases to
16 limit this uncertainty.

17 DR. ROBERTS: Let me open it to other
18 members of the panel for comments.

19 Seeing none, I would just like to
20 comment or second Dr. Lambert's information. We
21 have done a little bit of work in my laboratory on
22 perinatal and prenatal metabolism comparing rats

1 and humans in terms of P450 and asteratic
2 metabolism. Unfortunately, not with
3 organophosphorus pesticides.

4 But with the compounds we were looking
5 at, there was nothing alike between humans in
6 utero and perinatal and rats.

7 So it is an issue. There may be more
8 similarities as development proceeds to
9 approximately the one to two year age range, which
10 seems to be the focus, but earlier than that.

11 I think there is some real question
12 marks about using information from rats to
13 extrapolate to humans to the extent that -- when
14 metabolism isn't a key aspect.

15 Any other comments or things people want
16 to add to this?

17 Dr. Dellarco, was our response
18 reasonably clear?

19 DR. DELLARCO: Yes.

20 DR. ROBERTS: Let's go ahead and take
21 3.2.

22 DR. DELLARCO: Please comment on the

1 extent to which the biological understanding of
2 observed age-dependent sensitivity to
3 cholinesterase inhibition in laboratory animal
4 studies informs our understanding about the
5 likelihood of similar effects occurring in
6 children. In particular, what can be inferred
7 from animal and human information regarding the
8 potential for different age groups to show
9 increased sensitivity if exposed to cholinesterase
10 inhibiting pesticides.

11 Does the scientific evidence support the
12 conclusion that infants and children are
13 potentially more sensitivity to organophosphorus
14 cholinesterase inhibitors.

15 DR. ROBERTS: Big question.

16 Dr. Brimijoin, what do you think?

17 DR. BRIMIJOIN: We're now getting to the
18 point where the rubber really is meeting the road.

19 Actually, this is really a continuation
20 of the other question. It really is about asking
21 us to what extent we believe that the animal data
22 we have available, the data we have available,

1 which are largely animal data, apply to infants
2 and children.

3 And that means, first of all, whether we
4 think the types of age-dependent sensitivity that
5 we see in animals really occur in children,
6 infants. Whether the kinds of mechanisms that have
7 been suggested to explain the age-dependent
8 sensitivity in animals apply to humans in general.
9 And then I guess even more specifically, whether
10 it is the same relative importance of all these
11 variables.

12 And of course, when you are faced with
13 so many things at once, the tendency is just to
14 throw up your hands and say, how could we ever
15 know.

16 And so, I'm not sure that I can really
17 inform this debate. Certainly, not based on my
18 own specific knowledge of the relevant metabolic
19 and pharmacokinetic parameters here. But I would
20 say, I would take a stab at this, I think it would
21 be very hard to argue against the idea that the
22 existence of age-dependent sensitivity as seen in

1 animals would not be reflected by something
2 roughly similar in humans.

3 And so I consider that the scientific
4 evidence that we have now certainly offers a
5 strong presumption that infants and children are
6 potentially more sensitive to OP cholinesterase
7 inhibitors than adults are.

8 So what I consider to be the debatable
9 questions are, first of all, what is the exact
10 extent or magnitude of this age dependency. Is it
11 in the roughly threefold range that we have been
12 seeing for some compounds in rodent models? Is it
13 twofold? Is it tenfold? Hard to say.

14 Second, I think we have to ask what are
15 the exact ages at which these putative changes in
16 sensitivity will occur in humans.

17 How do we line up or do we line up at
18 all the different stages of human development with
19 the various phases that have been identified in a
20 rodent model.

21 So in particular, I guess a very
22 critical question, much the agency has focused us

1 on, is the extent to which a one to two year old
2 child which seems to be at special risk of
3 exposure because of behavior patterns and such,
4 how closely we can model that case with, let's
5 say, a weanling rat.

6 A third question is whether the
7 underlying mechanisms of this age-dependent
8 sensitivity are not only similar in general, but
9 similar in specific terms.

10 And we have heard from Dr. Lambert in
11 particular how at least some of the metabolic
12 effects, particularly those involving the P 450
13 system, we have to say flat out that they are not
14 similar. There is different enzymes involved,
15 different expression patterns, different substrate
16 preferences and so forth.

17 So even if we conclude that these
18 mechanisms are in general similar, we have to
19 recognize that there could be important
20 differences.

21 And looking for the general similarity,
22 I think the existing data where we have data in

1 human and animal together do support the idea that
2 there is some commonality, that there is a
3 developmental profile in the maturation of the A
4 esterase family in particular, which if not
5 identical in human rodent is fairly similar.

6 So I think to that extent we bridge the
7 species gap. We know much, much less about the
8 carboxylesterases, or the B esterases as Dr. Pope
9 has pointed out.

10 We can make a guess. If I were going to
11 set up a hypothesis, my working hypothesis would
12 be it will follow the same pattern. But it is
13 striking how little we know about that particular
14 and possibly important variable, a variable that
15 might be especially important with some OPs and
16 much less important with others.

17 Finally, the issue of enzyme synthesis
18 and replacement about the extent to which fetuses,
19 infants, human infants will parallel the
20 developing rat in showing much higher rates of
21 resynthesis of acetylcholinesterase. Again, we
22 have no data and very unlikely to be able to get

1 such data any time soon, if ever.

2 So it is speculative, although, again, a
3 working hypothesis would be that from everything
4 we know about the metabolic rates in children in
5 general, it would be a safe bet that there is at
6 least some degree of differential.

7 Is it as large as in the rat? Is it
8 even larger? Cannot say.

9 I recognize that the panel here has to
10 take some position on this matter, even if it's a
11 determined decision that it can't take a position.

12 More than that, the EPA doesn't even
13 have that luxury. They have to take a definite
14 position. So we have to make or recommend
15 decisions in the absence of a complete data set.

16 So I, with some and typical academic
17 misgivings and concerns, would come down with the
18 idea that the agency's basic approach of this is
19 sensible in the absence of more information with
20 all the caveats that have been mentioned.

21 However, I think that instead of just
22 wringing our hands about the absence of relevant

1 human data and saying how hard it is to get it, I
2 think we should actually do something about this.

3 These data gaps should be closed to the
4 extent possible. And there are at least two basic
5 ways that they could be closed in a relatively
6 short period of time.

7 One is a much more extensive application
8 of in vitro assays with human blood along the
9 lines that Dr. Padilla has been using in her
10 rodent studies to identify the potential role of A
11 and B esterases in determining sensitivity, E C 50
12 values for OPs, but not limited necessarily to
13 that approach. So that's the right place to
14 start.

15 And getting blood samples is a minimally
16 invasive procedure. And to the extent we can
17 learn things from studying actual human tissues
18 such as that, accessible tissues, I think it
19 behooves us, the scientific community and the
20 agency, to push for that information under the
21 broadest possible scale with all of the relevant
22 compounds.

1 And secondly, I want to raise again the
2 idea that surfaced yesterday that I think we
3 shouldn't contend ourselves -- or it's a false
4 dichotomy to say we don't trust the rodent as a
5 model for humans and we can't inject these things
6 willy-nilly into humans, especially children, so
7 we're stuck. I don't think we are stuck. There
8 are other primates out there.

9 Primate research is encumbered with
10 ethical problems, but the kinds of experiments
11 that would need to be done to establish
12 maturational profiles of these key detoxifying
13 enzymes, the kind of experiments that would need
14 to be done to show that in a primate, preferably a
15 higher primate, that there is or is not a more
16 rapid recovery of inhibited enzyme.

17 It is not a horrendous experiment. It
18 is not even a terminal experiment. You might not
19 want to do it on children, but the monkeys will
20 survive.

21 So I think there should be deliberate
22 thought given to pushing to get the most relevant

1 animal data that we'll be more comfortable in
2 extrapolating the human case.

3 Those are my preliminary remarks.

4 DR. ROBERTS: Thank you, Dr. Brimijoin.

5 Dr. Lambert, do you have anything to
6 add?

7 DR. LAMBERT: Let me finish up with the
8 line he was going, and then I'll go back into my
9 original.

10 It is kind of like in the -- I would
11 agree with everything that Dr. Brimijoin stated.

12 As far as looking at kids, it is kind of
13 like in the FDA issues with use of anti-hyperous
14 and other drugs that are used in children that
15 have never been adequately tested in children.

16 Some of the experiment in those drugs
17 are going on, but we're not looking at kids to
18 determine are we doing harm or benefit in the
19 children getting those drugs and what are the
20 optimal and safe use of those drugs.

21 And similar, the experiments,
22 essentially, when you expose a general population

1 to a chemical, the experiment is on. And what we
2 need to do is identify methods in ways to try and
3 determine the outcome in the general population.

4 And yesterday, we talked a little about
5 the exposure. In next month's epidemiology, there
6 are a whole bunch of abstracts on kids' exposure
7 to organophosphates in the July 2002 issue.

8 Some suggesting that kids in the
9 peripheral -- in the rural, some around the farms
10 are exposed to higher levels and some that aren't.
11 There is dichotomy of information.

12 But in general, my comments are, the
13 scientific data does support the conclusion that
14 infants and children are potentially more
15 sensitive to organophosphorus cholinesterase
16 inhibitors.

17 The animal data is very helpful in
18 exploring and understanding potential mechanisms
19 of action.

20 In the field of toxicology, an almost
21 universally-accepted concept is that extrapolation
22 from the animal to the human for purposes of

1 quantitative risk assessment is very difficult and
2 one of the most difficult areas of all toxicology
3 extrapolation of data from the developing
4 toxicology literature to the human.

5 And we can go back to thalidomide and we
6 can go through all the usual examples of that.

7 The reason is that there are species and
8 age-specific differences in P K P D and also end
9 organ sensitivity, of course.

10 There are a few to no neurobehavioral
11 studies that have been done in the human exposed
12 to OPs during development. Although, we know we
13 are.

14 In addition, the complexities and
15 capacity of the human brain in comparison to the
16 animal would imply that even if there are no acute
17 or irreversible nerve behavior effects in an
18 animal model, that the human may manifest
19 neurobehavioral effects that cannot be determined
20 or seen in the animal such as subtle learning
21 disabilities.

22 Due to the total lack of data on looking

1 at the neurodevelopment of function of children
2 with chronic high exposure to OPs, drawing any
3 comparison from neurobehavioral studies in the
4 animals is risky.

5 The human during development may be at
6 greater risk due to enhanced metabolism OPs to
7 oxon, altered sensitivities to the OPs and
8 potential long-term and irreversible changes.

9 There is a clear need for additional
10 studies. And this is all documented in the
11 agency's report.

12 DR. ROBERTS: Thank you, Dr. Lambert.
13 Dr. McClain.

14 DR. MCCLAIN: I definitely think it is
15 possible that humans could show some differences
16 in sensitivity for enzyme inhibition with age as
17 compared to rats. How this would actually
18 compare, we don't know exactly. But I think
19 whether or not this makes a difference is based on
20 exposure. I think the bottom line of the issue
21 that we're dealing with here has to do with
22 exposure.

1 And I think what makes this cumulative
2 risk assessment that EPA has done in the case of
3 the OPs, especially well done, is that the
4 exposure via the dietary route has been very well
5 characterized for all age groups, probably a more
6 comprehensive performance on this than they have
7 ever done before.

8 It indicates that milk is not a
9 significant source of OP in nursing infants. And
10 for children, a comprehensive and data specific
11 exposure assessment has been made with respect to
12 dietary exposure.

13 And overall, the dietary exposures are
14 very, very low in children. And this provides
15 data, I think, with respect to the margin of
16 safety by the dietary route, which is quite clear.

17 DR. ROBERTS: Dr. Reed.

18 DR. REED: About modeling and human
19 response with animal studies, I totally agree with
20 all the opinions being said in terms of in the
21 absence of data that we just have to make such an
22 assumption that there is a good likelihood that

1 humans, young ones, are going to be more sensitive
2 as shown by the animal studies.

3 My only concern is quantitatively
4 whether we could also assume that human young ones
5 would have a threshold of 10 percent
6 cholinesterase inhibition in the brain as sort of
7 a benchmark.

8 And my concern came from the fact that a
9 lot of neurobehavioral parameters, things that
10 perhaps are a great more -- sort of greater
11 importance to humans that learning ability or
12 cognitive memory type of thing has not been
13 tested.

14 Therefore, I cannot say whether going
15 from the animal to studies quantitatively at the
16 10 percent level is sufficient.

17 DR. ROBERTS: Thank you.

18 Dr. Hattis.

19 DR. HATTIS: I just basically want to
20 say that I support what Dr. Brimijoin said at the
21 outset.

22 I think there is much more reason to

1 believe that there is purely pharmacokinetic extra
2 sensitivity in the human neonate than at the
3 somewhat later phases of development that where
4 the exposures for dietary sources are higher.

5 For the neonate, however, it is very
6 likely that there is some exposure by
7 particularly inhalation routes that could still
8 give enough to make the extra sensitivity in that
9 initial period relevant to the cumulative
10 assessment.

11 The water pathway as well is a possible
12 source.

13 But the animal data do give us some
14 extra reason to believe in pharmacokinetic
15 sensitivity early on. It's a little bit more
16 questionable on the basis for the period of
17 maximum exposure.

18 DR. ROBERTS: The responses so far have
19 all been fairly consistent. Let me ask the panel
20 members if anyone else has a different opinion.

21 Dr. Needleman.

22 DR. NEEDLEMAN: As I sit here, the fable

1 of the blind-folded man and the elephant keeps
2 manifesting itself before my eyes.

3 EPA has presented us with this elephant
4 and blind-folded us and asked us to describe what
5 it is. The two pediatricians here see the elephant
6 as a child's brain. The toxicologists and
7 molecular biologists see it as a collection of
8 enzymes and proteins.

9 I think that we must focus on child
10 development as the outcome of interest.

11 EPA has selected a single outcome,
12 acetylcholinesterase, and is betting its money on
13 that.

14 It employs it as a surrogate for other
15 more direct measures closer to the outcomes of
16 interest. That is, the function of the child,
17 which is what we're interested in.

18 Now, we have this peripheral AChE
19 levels. We don't know how they correspond to AChE
20 at the critical site, the neuron, the neurite
21 glia. And to assume the single measure of the
22 peripheral enzyme may serve as a surrogate for

1 measures of disturbed anatomy or behavior, which
2 is my interest, in the absence of studies of, once
3 again, the degree of correlation between the AChE
4 levels and the other outcomes, specificity
5 sensitivity, predictive power positive and
6 negative, is to introduce an unmeasured amount of
7 uncertainty into the analysis.

8 And then to apply this exclusion, they
9 will only consider other outcomes in the
10 cumulative analysis as they relate to AChE
11 inhibition -- is a mistake, I think.

12 AChE inhibition is not the mechanism of
13 toxicity or the precursor of antitoxicity. It is
14 a measure of toxicity. And until it is documented
15 according to some of the criteria I suggested and
16 probably others, it is a risky business.

17 Let me talk a minute about exposure
18 prevalences --

19 DR. ROBERTS: I want to focus on this
20 particular question and then when we finish after
21 we get done with the last one, I think we're going
22 to open it up to more, for individuals to raise

1 points related to this. I just want to be sure.

2 The question here is does the scientific
3 evidence support the conclusion that infants and
4 children are potentially more sensitive to
5 organophosphorus and cholinesterase inhibitors.

6 DR. NEEDLEMAN: I think I'm coming to
7 that. I would be happy to wait, whichever you
8 prefer.

9 DR. ROBERTS: You know what is on your
10 mind more than I do, but again, I want to focus
11 the response to this question now. And if there
12 are other issues related to this, but not directly
13 addressing this, you will have the opportunity to
14 make that.

15 DR. NEEDLEMAN: Let me go ahead. If you
16 think I'm wrong, you will know.

17 I think there are factors which
18 condition the way we examine this that important
19 to make visible and bring up for discussion.

20 One is exposure. The OPP discussion of
21 exposures is incomplete. There are important
22 epidemiologic data on rates of exposure in the

1 literature. And they are not cited in the
2 document.

3 Larry Needum (ph) and the people at CDC
4 measured 12 analytes in 1,000 subjects in the 1984
5 NHANNES study. 82 percent tested positive for
6 chlorpyrifos.

7 In Cienna, Italy, Apria tested six
8 alkylphosphate (ph) analytes and found positive
9 tests in over half of the children. That's a
10 nonfarming, nonindustrial area.

11 In Minneapolis, Saint Paul, 90 children
12 were tested. Positive detections were found in
13 98 percent of the children. Similar results were
14 found in an urban sample on newborns at birth,
15 meconium. 20 infants were studied by Robin Wyatt
16 (ph) and the name is Barr. And they found that 19
17 out of 20, as I told you yesterday, had positive
18 DEDP. And 20 out of 20 had positive DEDDP.

19 So those are very high exposure rates,
20 and they cannot be shrugged off.

21 I want to talk about one particular
22 issue in brain development that I think needs to

1 be thought of when we discuss the findings of
2 behavioral alterations in rodents.

3 That's the issue of spearing of cortical
4 function. It's a well-known phenomenon. That is,
5 if you lesion a brain, there are recuperative
6 powers that take place. And the animal may appear
7 normal.

8 But if you later challenge the animal
9 with other tasks, they would be deficient, because
10 the cortex often comes in and takes over the
11 function that was lesioned and then is no longer
12 available for the later task.

13 It's a well-developed thing. It has
14 been in the literature for 70 years. And I think
15 it applies to the need for long-term studies of
16 application of neurotoxicants to immature
17 organisms or children.

18 I will close by saying we can learn
19 something from history, too. 26 years ago in
20 Crystal City, EPA convened under a court order a
21 task force to write the criteria document for lead
22 in children.

1 And after two days of vigorous
2 discussion, the EPA presented -- the first pass of
3 the EPA document said that five micrograms per
4 deciliter was an acceptable level for lead in the
5 air in the United States.

6 Now, five micrograms for cubic meter,
7 excuse me, is about what Los Angeles was showing
8 in a bad day. They wanted to say that that was
9 safe for the entire country.

10 There were two days of very rigorous
11 discussion, and the science advisory board told
12 EPA not to revise the document, to tear it up and
13 begin again, which they did. And they came back
14 six months later. There was a second session. The
15 document was improved, but still did not pass
16 muster, and they were told to go back and come
17 back with a better version. They did.

18 And the document called for a standard
19 of 1.5 micrograms per cubic meter, which became
20 the standard for this country, and that was
21 resulted in the removal of lead from gasoline.
22 And in 1976, the mean blood lead in this country

1 was 15. It is now less than 3.

2 And in this month's environmental health
3 perspective, there is a kind of metric study from
4 Centers for Disease Control which says that the
5 monetized benefit to a one year cohort of children
6 in this country, the children born in 1998, the
7 monetized benefit for lowering their blood level
8 over what it would have been had this not happened
9 was between 118 and 300 billion dollars for that
10 one cohort.

11 I think there is a historical lesson in
12 that in terms of what science can produce in terms
13 of threshold effect values and in terms of the
14 potential benefits to society.

15 DR. ROBERTS: Does anyone else want to
16 weigh in on 3.2 that we haven't heard from yet in
17 terms of whether or not the evidence supports the
18 conclusion that infants and children are
19 potentially more sensitive to OPs?

20 DR. HATTIS: As you have rephrased it
21 there, the sensitivity -- there is a distinction
22 to be made between sensitivity to the

1 cholinesterase inhibition, which I identify as
2 purely the pharmacokinetic and the pharmacodynamic
3 part which is sensitivity to the effects that
4 result from the cholinesterase inhibition, which I
5 think by any standard there is just too little
6 information on to be confident that we're -- that
7 we know enough to say that the exposures that are
8 consistent with that 10 percent effect level in
9 the --

10 DR. ROBERTS: I think you are reading
11 more into the question than was there.

12 Anyone else on this particular question?

13 Dr. Dellarco, were the responses
14 reasonably clear?

15 DR. DELLARCO: We can move on to the
16 last question or do you want to take a break?

17 DR. ROBERTS: Actually, I was going to
18 propose that we take a break for lunch before we
19 take on the last question.

20 Members of the panel have expressed
21 interest after we finish the questions in perhaps
22 commenting on areas related to the issues that may

1 not have been captured in the questions.

2 I have tried with varying degrees of
3 success to forestall those comments until the end
4 of the session. But I would like them to have the
5 opportunity to do that. So I'm concerned that if
6 we -- so there is, I think, a block of time that
7 we still need to cover.

8 So let me suggest that we take a break
9 for lunch for an hour, meet again at 1 o'clock.
10 We'll deal with the last question and then have
11 open discussions.

12 (Thereupon, a luncheon recess was
13 taken.)

14 DR. ROBERTS: We have one more question.

15 DR. DELLARCO: This is our last
16 question.

17 Please comment on the conclusions
18 regarding the faster recovery in the young animal
19 of acetylcholinesterase activity. Because there
20 is no human information on the recovery of
21 acetylcholinesterase in children compared to
22 adults, please comment on the extent to which

1 recovery of acetylcholinesterase in children
2 should be factored into conclusions regarding
3 potential risk to children.

4 DR. ROBERTS: Dr. Elderfrawi --

5 VOICE: She is off chasing some wayward
6 disk.

7 DR. ROBERTS: Dr. Harry, you are the
8 representative among the discussants that is
9 presenting. Are you ready to respond to this?

10 DR. HARRY: My question is do you want
11 this short as I prepared as after everybody else
12 or do you want me to prolong it until they get
13 here?

14 DR. ROBERTS: You might need to stall
15 just a little bit. Try not to get too expansive.

16 DR. HARRY: To directly address this
17 question, it was asking a comment on the
18 conclusions regarding that. And I guess we go
19 back to the same thing in the fact that when I was
20 reading through the document as well as looking at
21 the slides this time, I'm not real sure that I saw
22 exactly what conclusions you were drawing from

1 that.

2 Information was provided regarding what
3 appears to be a faster recovery. However, there
4 is little discussion regarding the dynamics of
5 exactly how that happens. And I think we had
6 mentioned that earlier, whether it is a dilution,
7 what is the components behind the recovery.

8 And that that's actually rather
9 important as trying to understand this biological
10 impact of which to then a cross-over to say is
11 this conservative enough now to take and to take
12 into consideration when we're talking about
13 children.

14 However, it reflects the data that you
15 have on most of this. So it is not that anything
16 was missed. I think it reflects the appropriate
17 data.

18 Now having said that, I think what is
19 interesting and as was mentioned a lot earlier by
20 Steve in the last question was that the -- it is
21 very difficult to assume that there would be
22 something that would be happening in a rodent that

1 would not be an underlying component that would
2 happen in higher mammals also at least to take
3 into consideration.

4 The other thing that come out is the
5 compensatory ability of the developing organism
6 continues to show itself in a lot of different
7 factions, and that has been examples today with
8 the knockout animals as well as some genetic
9 mutants.

10 We often see lots of things in there.
11 And in order to take this to the human, you
12 probably need to understand more about exactly
13 what is driving that recovery. It was
14 interesting, while there is a limited
15 characteristic of what represents that recovery
16 and there is an example of speculation of what it
17 may mean or what may be driving it, very little
18 data is available to you for the whole dynamics of
19 that transmitter system as in what is truly
20 involved, whether it is metabolism, whether it is
21 the turnover, the enzyme activity, its receptor
22 number, receptor binding and that type of thing.

1 And that information would be very
2 helpful to you. I know you are looking for more
3 information. I'm not telling you anything you
4 don't already want.

5 But as far as the compensatory
6 mechanisms which come into regard here, I would
7 say that one should assume that such adaptive
8 mechanisms will also be taking place in the human.
9 And it is difficult to even say that you should
10 discount any of that.

11 So while I would agree that there is no
12 human information, you should take this into
13 consideration when you are thinking about the
14 humans. I have to honestly say I'm not real sure
15 exactly what you are taking into consideration
16 from the little bit of data that you have.

17 So it is a mindset for how you are
18 looking at that information. But I think you are
19 going on a body of scientific knowledge and all
20 the other information that you have of trying to
21 pull that out.

22 DR. ROBERTS: Thank you, Dr. Harry.

1 Dr. Eldefrawi, your comments on response
2 to question 3.3?

3 Do you want to take a minute to get
4 settled, or do you want me to ask someone else?

5 DR. ELDEFRAWI: My disks go away again
6 today. I don't know.

7 DR. ROBERTS: Let me ask other members
8 of the panel, then, on responses on question 3.3.

9 Dr. Brimijoin, do you have a response to
10 question 3.3?

11 DR. BRIMIJOIN: Actually, I did prepare
12 a response, but I think -- I basically included
13 that response in my response to question 3.2,
14 which is that I do think it is quite likely that
15 there is an accelerated recovery in children, that
16 this is something we have no direct data on in the
17 human case.

18 This is something that is amenable to
19 study in other animal models, including those that
20 might be most relevant to the human case such as
21 primates or even higher primates since it could be
22 done as a blood base study involving injection of

1 OPs in measuring rates of return of plasma and
2 erythrocyte cholinesterases carefully measured. I
3 think that would be valuable.

4 That's really the essence of my view on
5 this question.

6 DR. ROBERTS: Thanks. Let me, then,
7 open it to the panel. Are there other members
8 that would like to respond? Dr. Pope and then Dr.
9 Hattis.

10 DR. POPE: Well, the recovery of
11 cholinesterase activity, I think, can be an
12 important determining factor in age-related
13 sensitivity. It is, I think, only an important
14 factor really when you have repeated dosing. It
15 is a cumulative risk assessment that's based on
16 primarily on repeated dosing. This should be an
17 important factor to consider, that is to make the
18 younger animal actually less sensitive than the
19 adults.

20 One thing that doesn't come out, I think
21 Dr. Hattis mentioned this before, is the
22 functional status of the enzyme molecules that are

1 there. As I do when we treat animals, we will
2 take tissues out and measure total cholinesterase
3 activity. That doesn't really tell you where
4 those enzymes are located in the animals' tissues
5 and how they may be affecting neurotransmission.

6 And there have been several reports over
7 the last few years that suggest that
8 anticholinesterase may induce the synthesis of
9 acetylcholinesterase and it may not be functional.
10 So you may get a kind of a false perception of
11 increased rapid recovery in the younger animal
12 when it may not be really functional recovery.

13 DR. ROBERTS: That's a good point. Dr.
14 Hattis and Dr. Eldefrawi.

15 DR. HATTIS: I think that's well and
16 economically stated. I'm going to be less
17 economical. Say it in ways that are maybe clear to
18 different people.

19 The answer to the question depends upon
20 -- again depends upon one's judgment about the
21 casually relevant dosimetric relating
22 cholinesterase inhibition.

1 If the most causally relevant dosimeter
2 is peak levels of inhibition, then the relative
3 faster rate of regeneration in younger animals
4 doesn't matter much.

5 If it is in fact an AUC type measure
6 integral of percent inhibition times time, then it
7 matters a lot.

8 We don't know which is actually likely
9 to be true based on the current analysis, which is
10 one of the reasons for pursuing the issue of
11 pharmacodynamic modeling a little bit more
12 intensively as the data become available. It may
13 be that the data are not really adequate for that.
14 Maybe the in vitro data can shed light on that.

15 Some very tentative theoretical
16 reasoning that might lead one to place somewhat
17 greater initial weight on the peak dose hypothesis
18 is based on this idea that the cholinesterase
19 molecules associated with these synapse, mostly in
20 the postsynaptic membrane, I gather, or attached
21 to the postsynaptic membrane, are likely to have
22 minimal exchange rates with molecules floating

1 free in the intercellular fluid or attached to
2 other cells.

3 In this case, the apparent regeneration
4 of whole brain cholinesterase following an acute
5 acetylcholinesterase exposure --
6 anticholinesterase exposure, sorry, would be a
7 function of both the establishment of new synapsis
8 involving wholly new molecules and a likely slower
9 rate of resynthesis of uninhibited AChE molecules
10 in the cell body and then possibly somewhat slow
11 transport of those new cholinesterase molecules
12 down the long axon to the synapse.

13 In light of this, it is likely that
14 after an acute inhibition event, a greater degree
15 of inhibition will persist in preform synapses
16 that would be expected from the recovery of whole
17 brain acetylcholinesterase activity.

18 And I don't have a clue as to what the
19 relative rates of that are, the resynthesis
20 through generation of the synapse and maybe other
21 places versus, as you said, the inhibition of the
22 preexisting molecules.

1 But in any event, this has the potential
2 to lead to a differential change in the activity
3 of older neuro pathways relative to newer pathways
4 either weakening or strengthening of things in
5 ways whose effects I can't predict in advance.

6 DR. ROBERTS: Dr. Eldefrawi.

7 DR. ELDEFRAWI: I did ask my questions
8 during the session, so I don't have anymore to
9 ask. Thank you.

10 DR. ROBERTS: Thank you.

11 Other members of the panel who would
12 like to respond to this particular question? Dr.
13 Brimijoin.

14 DR. BRIMIJOIN: I wonder if I could ask
15 Dr. Hattis for a little more clarification, just
16 to make sure I understand, since we'll be writing
17 this report together, and our this discussion
18 might as well be heard by the audience.

19 I'm coming from a background where
20 things like dosimetry and such terms are -- I have
21 a tenuous grasp on them, but if I understand you
22 correctly, when you are talking about dosimetrics

1 and dosimetry, you're talking about what measures
2 of effect we're choosing to apply and how they
3 might differ, how they might respond differently
4 or show different things depending on the nature
5 of the dosing itself, whether it was repeated or
6 single. Is that right?

7 DR. HATTIS: That's almost right. But
8 what I'm mainly focusing on is the cholinesterase
9 inhibition as an intermediate parameter between
10 the dosing schedule and the ultimate action in
11 terms of changes in the structure and function.

12 And so what I'm talking about between
13 peak dose and AUC is not necessarily in terms of
14 the concentration or the actual amount of the
15 anticholinesterase that is in the brain, but in
16 terms of the inhibition.

17 DR. BRIMIJOIN: So in that case, it
18 seems to me -- so you are raising the interesting
19 question. It's a biological question about --
20 we're really focusing on the developing nervous
21 system here. Is it worse to have a transient and
22 relatively severe decline in acetylcholinesterase

1 activity or is it worse to have the same or
2 possibly even greater area under the curve of a
3 milder inhibition that is sustained for a long
4 period of time, which I think is a question we can
5 answer, as you astutely point out. That's a
6 subject for further research.

7 But with that perspective, it seems to
8 me that if we do focus on the repeated dosing
9 instance as EPA has explicitly chosen to do as the
10 most reasonable scenario in the actual field, it
11 is that if we are talking about differences in
12 rates of recovery, which in some cases may be
13 significantly slower in the adults than in the
14 newborns, then we're actually likely to have both
15 things going on, namely, that although we might
16 have a case where the bolus injection would have
17 given comparable levels of inhibition, if we
18 repeat that dose in an organism which has a slower
19 recovery rate, the actual depth of the curve will
20 be lower even if the individual ratchets in the
21 curve are no larger.

22 DR. HATTIS: If you are talking about

1 the long-term accumulation of inhibition as the
2 result of many doses over an extended period, then
3 the rate of regeneration matters. That's right.

4 If are you talking about the peak or
5 trough inhibition following a single event, then
6 it matters less.

7 DR. ROBERTS: So what I'm hearing is
8 that there is at least in principle the
9 desirability of including that information, but
10 how to include that information. I mean, how to
11 include differential recovery is hampered by
12 fundamental lack of information.

13 DR. HATTIS: Yes. You have to basically
14 have a dynamic model of cholinesterase inhibition
15 in the relevant brain and recovery.

16 And it is possible that there is enough
17 information to do that, but it would most
18 certainly be aided by additional dynamic modeling
19 exercises -- maybe even some additional, you know,
20 exercises in data collection, because it is
21 possible that the neuroscientists have not been as
22 interested in these modeling enterprises as

1 basically quantifying --

2 DR. BRIMIJOIN: As they should have
3 been.

4 DR. HATTIS: I'm trying to say this very
5 gently that sometimes biologists don't have the
6 same orientation toward quantitative issues as
7 some random risk assessors trying to look over
8 their shoulder and use their results.

9 DR. ROBERTS: Any other comments in
10 response to this question?

11 Dr. Bigbee and then Dr. Matsumura.

12 DR. BIGBEE: There is data in the adult.
13 I don't believe in the young. And this is results
14 from Mona Zurick's (ph) laboratory, that
15 inhibition of the acetylcholinesterase leads to
16 the expression of a novel transcript, a novel
17 splice variant, which she calls the read through
18 form. And this enzyme is active, but it is a
19 soluble monomer.

20 If you were to look at total AChE
21 recovery, you would be measuring this novel read
22 through transcript. But it wouldn't be placed in

1 the membrane or at the synapse as precisely as the
2 normal synaptic form.

3 That's shown in the adult. I don't
4 think there is any data for young ones.

5 DR. ROBERTS: Thank you.

6 Dr. Matsumura.

7 DR. MATSUMURA: My position is similar
8 to Dr. Harry. Yes, it happens. It is probably
9 fundamental. And probably that may happen in the
10 humans too, real young child, but it is
11 interpretation.

12 If you think every compensatory or
13 repair process is good for that animal, then we
14 have a problem. We cannot make that kind of
15 blanket statement just simply because those young
16 animals can recover quicker so that's not a
17 problem.

18 You cannot make that kind of a
19 statement. So what I mean is that the
20 distribution packaging -- lots of people assume
21 that the recovery is due to just the quick
22 synthesis. It may not. Proteins must be

1 phosphorylated, packaged right. It could be
2 having splice variance.

3 There are many, many ways that the
4 proteins could show the increase in functions for
5 that time of duration. But it is not always that
6 compensatory or repairing mechanisms good for the
7 animals.

8 All I'm saying is that we cannot say
9 always that the fact the young animals can recover
10 quickly does not mean that it is always more
11 poisons, problems disappear there.

12 DR. ROBERTS: Any other comments?

13 Dr. Dellarco, do you have any follow-up
14 questions on this? Was our response on this
15 reasonably clear?

16 DR. DELLARCO: Yes.

17 DR. ROBERTS: Great. Thank you. This
18 concludes the responses by the panel to the
19 questions posed to it.

20 Before we move on, I would like to point
21 out that Dr. Portier had to leave over lunch. He
22 was not able to participate in discussion of this

1 last question or subsequent discussions.

2 He did ask me, though, to communicate to
3 the agency that despite his pointed comments
4 earlier, he is in fact very pleased with the
5 effort in the document that you folks have
6 produced.

7 So I wanted to communicate that final
8 message to you from Dr. Portier.

9 I had promised the panel the opportunity
10 to make some perhaps more general comments. And
11 let me say at the beginning that it is not my
12 intent to open up the cumulative risk assessment
13 in total to comments.

14 SAP has been consulted on numerous times
15 about the cumulative risk assessment, including as
16 recently as just a few months ago. So I think we
17 should let -- our suggestions are on record. I
18 think we should let them stand.

19 The topic for this particular session is
20 the determination of an appropriate FQPA safety
21 factor in evaluating sensitivity and
22 susceptibility to the mechanism of toxicity.

1 And within that subject area, there are
2 perhaps some comments that in the judgment of the
3 panel might be useful for the agency that don't
4 fall in the context of the specific questions.

5 So what I would like to do is to provide
6 the panel with the opportunity to make those
7 questions now. And I suspect it is going to
8 impossible to avoid some sort of ping ponging
9 around on different subjects, but I would like to
10 the extent possible for us to focus on one subject
11 and make whatever comments we're going to make and
12 then move on.

13 Intuition tells me that one of the
14 subjects that panel members might want to comment
15 on is the scientific underpinnings regarding the
16 specific choice for an FQPA safety factor made in
17 the document that we reviewed.

18 In other words, did the data with what
19 it offers and what -- its limitations support the
20 choice made by the agency.

21 So I will at this time entertain
22 comments from panel members on that subject if you

1 want to weigh in or if you have an opinion to
2 express.

3 Dr. Brimijoin.

4 DR. BRIMIJOIN: This is a question. It
5 might lead to a comment -- but since we still have
6 the EPA representatives here, and Dr. Dellarco,
7 for example, in particular, put her on the spot.

8 I mean, you have heard from the panel
9 various levels of comfort and or discomfort with
10 the proposal to in general apply a threefold
11 safety factor, F Q P A factor into the RPF's or
12 benchmark doses of certain compounds.

13 I guess you have heard from us that we
14 think a tenfold safety factor is more appropriate
15 for the compounds where you have no data at all.

16 I would like to ask a very practical
17 question of you, which is whether you have done
18 calculations that show what would be the ultimate
19 impact on the viability of the, let's say,
20 currently registered chemicals, if you went to a
21 uniform FQPA factor of 10 as opposed to three, I
22 would just like to have some sense about whether

1 we are skating the edge of something that makes an
2 enormous difference in whether any chemicals can
3 ever be used or -- you don't have to name
4 chemicals and companies, but as to whether there
5 will be a radical change in the landscape
6 depending on whether you finally end up with
7 factors of three or factors of 10.

8 Do you think you could answer that
9 question?

10 DR. ROBERTS: Let me offer the agency
11 the opportunity, since this doesn't relate to a
12 particular scientific issue, but sort of the
13 consequences of scientific decisions.

14 If you want to respond to that as a side
15 bar rather than in this session, certainly that's
16 okay with the chair.

17 DR. DELLARCO: We can only respond to
18 that to a certain extent.

19 And based on the understanding of
20 exposure to these OPs and their relative toxic
21 potency, you would have the same contributors that
22 we identified yesterday. They would still be the

1 major contributors.

2 DR. ROBERTS: Dr. Dellarco, I actually
3 had a clarification. And it came from a comment
4 that you made yesterday, and maybe I didn't
5 understand.

6 By applying the factor in a sense sort
7 of early in the calculations to the potency
8 factor, then it really gets carried -- it really
9 gets applied regardless of the age group. Is that
10 true or does it get applied specifically for the
11 margin of exposure for that age group such that it
12 would not get applied for adults?

13 I guess it really just depends on where
14 this gets plugged into the process, how it
15 translates out through the calculations. That was
16 just something I didn't understand.

17 DR. DELLARCO: We incorporated the 3X on
18 the RPFs, and we did it across all age groups,
19 even the adults, simply because the
20 one-to-two-year-old age group is most highly
21 exposed.

22 DR. ROBERTS: I'm sure it is more

1 convenient from a calculation standpoint to do it
2 that way, but of course, it does distort a little
3 bit the comparisons and the margins of exposure
4 from different age groups. I just wanted to get
5 that clarification.

6 DR. PERFETTI: You are absolutely right.

7 It does sort of distort the other age
8 groups, but our feeling was is that we knew that
9 the one to twos were the most highly exposed, and
10 that all of the other exposures were within
11 acceptable ranges.

12 So I guess we should have made clear,
13 and I will make clear now, that the exposures for
14 the other age groups are much exaggerated by about
15 1.2 overall.

16 DR. HATTIS: I'm not understanding that.

17 DR. PERFETTI: Because of the software
18 and the way it runs, we could not selectively put
19 the factors on the RPFs and then apply it only to
20 one age group. We had to apply it to all of them.

21 And if you wanted to know what the
22 actual exposures were, you would have to then go

1 back and hand calculate exposures for other age
2 groups.

3 DR. HATTIS: You could do a post
4 processing. This is the estimated exposure that is
5 in raw milligram per kilogram equivalents of the
6 standard chemical, and this is what you get if you
7 apply various FQPA adjustments to different age
8 groups.

9 It might be easier to do a post process.

10 DR. PERFETTI: Believe me. We thought
11 about it.

12 DR. ROBERTS: Thanks. Any other
13 comments. Dr. Reed?

14 DR. REED: Maybe I should ask sort of
15 for a clarification first.

16 My understanding by reading the document
17 is that the FQPA safety factor would apply based
18 on your consideration of not only on the
19 toxicological part of it, but also the exposure.

20 And so my earlier comment was within
21 that context, in that the question was posed as is
22 3X enough considering the toxicological part of it

1 with an understanding that the exposure is
2 extremely conservative or at least we don't have
3 uncertainty in that sense that we know how to
4 estimate.

5 And I think that is an important point
6 to bring up, especially now that the panel is
7 pretty much in agreement in terms of threefold not
8 being sufficient to address the toxicological part
9 of it.

10 Especially in that context, I think it
11 is important to take a look at the exposure and be
12 very sure that we don't have any underlying
13 uncertainties that would come with it.

14 And my comment is it is a good practice
15 and you have been doing this in expressing the
16 exposure in a range with the different
17 percentiles. But it was sometimes looked at as,
18 okay, then one might have a choice of taking at
19 the 95th or 99.9 and so forth and it depends on
20 how we look at the data in the outcome.

21 What I did, and I think it would be of
22 interest to you, what I did was to take what was

1 presented in that table with different age groups
2 and different dietary exposure levels at different
3 percentiles.

4 What I did was to take that number and
5 assuming that all that exposure actually came from
6 only one commodity and one pesticide, not one
7 commodity, multiple pesticides or modical
8 commodity, modical pesticides, which is quite
9 cumulative risk assessment as well.

10 So as sort of putting meaning to number
11 is what I was trying to get. I think it is a very
12 important point so that the people would
13 understand what does 95th mean outside of the
14 consideration of statistics. Because if you do
15 the statistical sort of consideration, you would
16 say, well, 95th is probably more certain. And
17 since we have all the real good data in there and
18 95th might be a more firm number and 99.9 might be
19 pretty far out on the distribution.

20 So that's what I did. I took the
21 exposure value and attributed that, all of it, to
22 one chemical, and one commodity in this case --

1 because azinphos methyl has 27 percent
2 contribution. I think you are more interested in
3 looking at azinphos methyl because of the lack of
4 data about young ones' sensitivity.

5 So I went back to the PDP data. We're
6 making sure that we're not using something that is
7 extremely unlikely as, say, tolerance, less than
8 one percent chance.

9 I went back to 1999's PDP data. I
10 looked at two commodities. One is azinphos methyl
11 in apple. The single serving survey would have
12 76.2 percent of detect, so it's not an unlikely
13 event in terms of being detected to have residue.
14 And of course, there is a range of residue level.

15 What I did was to take the highest,
16 which is 0.55 PPM for the single serving apple,
17 and back calculate with that exposure level, and
18 now you know the residue concentration. You
19 assume a body weight for one to two years, 10 or
20 15 kilogram.

21 Then what I come up with is a
22 consumption, a different percentiles of exposure

1 that you come up with a cumulative risk
2 assessment.

3 For the 95th percentile, a child one to
4 two years, so it would eat less than two ounces of
5 apple, if you attribute all the exposure only
6 come from one commodity, one pesticide, and so
7 that 95th becomes not representative, in my mind,
8 not representative of high end at all.

9 So you go up to 99th, 99.5 and 99.9.
10 And I think it might be good for the agency to
11 present sort of a meaning to the number in such a
12 way so that a reader could understand what does he
13 mean by 95th percentile exposure and what is 99.9
14 exposure.

15 What I did also with pear, for single
16 serving pear you have 43.2 percent detect, which
17 is, you know, again, not a rare event. By the
18 way, I still eat apple and pear, and I haven't had
19 any concern about that. So it was not about the
20 commodity. Not about the pesticide.

21 You have a detection range. Pear, for
22 single serving pear, you have actually higher

1 concentration than the apple.

2 So at the 95th percentile, if it is all
3 attributed to pear and only coming from the
4 exposure of azinphos methyl, it would amount to
5 about one ounce of pear per day at the 95th.

6 So I don't think it is very quote,
7 unquote conductio (ph) or capturing the high end
8 at all.

9 It's sort of justifying for both taking
10 a look at it, but also for making perhaps a risk
11 management decision later on after the risk
12 assessment to decide where you want to take the
13 decision based on what percentile.

14 DR. ROBERTS: Dr. Eldefrawi.

15 DR. ELDEFRAWI: I was wondering, the
16 pear or the apple, is it peeled or is it eaten
17 with the skin?

18 DR. REED: Could someone comment on that
19 with the P D P data on a single serving survey?

20 DR. PERFETTI: Actually, in the P D P
21 data, the fruit is washed, lightly washed. So it
22 would be with the skin. But in our software

1 program, the DEEM, there are provisions made for
2 both peeled and unpeeled fruit.

3 DR. REED: I guess the difference
4 between peeled and not peeled is really dependent
5 on whether a chemical is systemic or not. If it's
6 systemic, then peeling probably is not going to
7 make any difference.

8 DR. ROBERTS: Right.

9 You did make mention, before I get to
10 Dr. Hattis, who is next on the list, that the
11 opinion of the committee is that threefold is not
12 sufficient. And I don't know that we have
13 established that, which is sort of the purpose for
14 our discussion now. I just wanted to point that
15 out.

16 Dr. Hattis.

17 DR. HATTIS: I think part of the
18 argument on whether threefold is really plenty or
19 tenfold should be retained goes to the sufficiency
20 of the evidence for assuring safety. And part of
21 that discussion, you know, relates to the claim,
22 the perception that is created by these margin of

1 exposure numbers of the order of 100 or somewhat
2 more or somewhat less.

3 I think it is worth remembering what the
4 100 was for and, to some extent, you know, what
5 its limitations are. Because the one hundred is
6 usually thought of as tenfold for between species
7 differences and tenfold for among human
8 differences.

9 The tenfold for between species
10 differences, however, is based upon measuring dose
11 in terms of milligrams per kilogram of intake in
12 the animals.

13 And as it happens, that's not the most
14 predictive dosimetric for toxicology in general
15 for chronic effects.

16 For acute effects, it is in fact the
17 best dosimetric for things like L D 50s. They
18 scale across species more or less like that.

19 But for effects that take several doses
20 to produce or internal levels, it turns out that
21 pharmacokinetic processes, elimination processes
22 tend to scale on average with body weight to the

1 three quarter power. And between rats and humans,
2 that use is up about fourfold of that tenfold.

3 Secondly, so that you are typically --
4 there is only about two-and-a-half fold left or
5 twofold left of conservatism in that interspecies
6 factor once you take the average pharmacokinetic
7 differences into account.

8 Then if you compare effective doses in
9 humans with animals after making this correction
10 of body weight to the three quarter -- taking the
11 body weight to the -- you still get substantial
12 variability from chemical to chemical in
13 toxicologically equivalent doses. And this is
14 based on a series of comparisons by Paul Price
15 with anticancerations with not exactly the same
16 endpoints in animals and people. But it's worth
17 mentioning that for rat single species you get on
18 average about, human potency, about .8, what you
19 would predict on the body weight to the three
20 quarter basis.

21 But the observed confidence limits
22 around that, that is the -- is basically there is

1 a geometric standard deviation of about threefold
2 that describes the distribution of equivalent
3 animal and human doses.

4 So what that means is that where your
5 best expected value is close to one, your 95th
6 percentile is for human potency that would be
7 about just a little less than fivefold more than
8 the animal, the prediction of human potency that
9 you would get from the animal based upon the body
10 weight to the three quarter power scaling.

11 So essentially -- you shouldn't expect
12 that that tenfold is in fact -- is going to be on
13 balance, a little conservative, but it is -- it
14 comprises much less than a 95th percentile of that
15 particular distribution. So it has some
16 conservatism built-in it, but not a great deal.

17 The tenfold for human interindividual
18 variability I found from a database of
19 observations may well not be doing the full job
20 that people expected to be doing, that essentially
21 the human interindividual variability from my
22 limited data sets, which are generally not

1 including the full range of sensitivities, would
2 not be sufficient, usually -- would not be
3 sufficient to get you from a dose that is causing
4 10 percent incidence of effects to a dose that is
5 causing 10 to the minus 5th incidence of effects a
6 large fraction of the time.

7 It will most of the time, but again, it
8 is not a lot of the time. And if we build in the
9 fact that my interindividual variability
10 observations don't include really a large number
11 of effects that would be distinctive for early
12 life exposures, then there is some argument for an
13 additional safety factor for developmental type
14 exposures that could be associated with
15 developmental changes.

16 Going more explicitly to the legal
17 language that Ruby was raising, I have to say that
18 I don't think that a reasonable standard of
19 "adequate" evidence is met on the pharmacodynamic
20 side.

21 I think you could conceptually
22 distinguish between the pharmacokinetic side and

1 the pharmacodynamic.

2 In the pharmacokinetic side, I think we
3 have some insight that would lead to us suggest
4 that -- if we have no pharmacokinetic information
5 for the chemical and no pharmacodynamic
6 information, then maybe you should be retaining
7 the full tenfold safety factors.

8 Where you have some pharmacokinetic
9 information, there is a possibility that you
10 should make a lower adjustment in recognition of
11 the fact that you have eliminated some of the
12 uncertainty by the pharmacokinetic comparison.
13 But we don't have very wonderful pharmacokinetic
14 information in the humans.

15 In fact, for the very young humans,
16 there is good reason to suppose that there is an
17 extra fewfold prolongation of half-lives, at least
18 for newborns and up through several months of age.

19 By the time you get to the age that you
20 have been focusing on for the greatest exposures,
21 I think it is quite right that we don't have very
22 many examples of unusually prolonged half-lives in

1 that case.

2 That doesn't mean it couldn't happen.
3 But we just don't have much observational data
4 that supports that. I don't want to make an
5 overall policy suggestion, but I do want to
6 suggest that Ruby is right, that if you want to
7 apply some understandable standard of adequacy of
8 evidence on the pharmacodynamics side, as a
9 general matter, I think that some considerable
10 skepticism needs to be retained.

11 We have some, but rather limited,
12 pharmacokinetic information, so that there is an
13 argument that could be made that you have some
14 evidence on that front, but whether it is entirely
15 sufficient or whether the pharmacodynamic concern
16 is sufficient that you want to retain the whole
17 tenfold for pharmacodynamics is certainly a
18 possibility.

19 DR. ROBERTS: Anyone else like to
20 express an opinion on this issue?

21 Dr. Reed.

22 DR. REED: Could you just clarify. What

1 I think I'm looking at is that there are certain
2 things that you can clarify more and get you out
3 of that uncertain mode. And I think exposure,
4 especially dietary exposure, is one.

5 If you could clarify what the exposure
6 express, then you might be able to say, because I
7 know so much of it, I don't have to include that
8 in the uncertainty consideration.

9 DR. ROBERTS: Anyone else on this issue?

10 DR. LAMBERT: Are we taking it for
11 granted that the panel feels that 10X is the
12 appropriate or we're not going to discuss it?

13 DR. ROBERTS: I'm not taking that for
14 granted.

15 VOICE: If you want to express an
16 opinion, speak.

17 DR. LAMBERT: As far as I'm concerned
18 with what Dale had stated, I think you can take
19 into exposure the concepts, but I think what we
20 have for kids right now on exposure is probably --
21 in the food chain, water and food is probably
22 pretty good as far as we have been discussing a

1 couple times.

2 In inhalation and drift off of fields
3 and things like that, that's a much different
4 database, which I don't think there is adequacy at
5 this point. But there may be in the very short
6 term. But some of the initial abstracts that are
7 coming out, at least in some of the studies, are
8 suggesting that there is a significant higher
9 exposure in those kids living in and around farms
10 using these chemicals.

11 But if you just take what Dale had said
12 as far as the pharmacokinetic and then put it into
13 the formula, the dynamic aspects of potentially a
14 more susceptible organ system in a child,
15 particularly with potential of having long-term
16 effects on the brain, I would think that due to
17 the inadequacy of what we have in front of us and
18 as we just stated today that we felt that much of
19 the data was lacking and there was in some of the
20 pharmacokinetic aspects that the 10X factor would
21 still be in play.

22 DR. ROBERTS: Anyone else want to

1 venture an opinion on this? You are not compelled
2 to do so. Just offering the opportunity.

3 DR. MATSUMURA: Just a clarification.

4 This particular discussion is not going
5 to be a part of this answering session. Right?
6 So it is more a free discussion rather than --

7 DR. ROBERTS: It would be covered under
8 a comments section at the end of our report.

9 DR. MATSUMURA: I was thinking the
10 perspectives. At least most of those are
11 registered pesticides. It has been used for 20,
12 30 years. And of course under the FIFRA, most of
13 those people, all of us are being exposed.

14 So my overall feeling is that
15 organophosphates or phosphorous pesticides and
16 carbamates, they are not that huge problems that
17 something that we have seen like organochlorine
18 and all those pesticides just simply because their
19 actions are rather ephemeral, exception, delayed
20 ataxia, all those, the chronic type, the
21 organophosphates which have been eliminated,
22 leptiphos (ph) and EPN and all those chemicals

1 have been already eliminated, and even the methyl
2 parathion is gone.

3 So my feeling is that at least
4 perspectives, I may go along with the agency's
5 currently recommendation for this particular case
6 with some reservations as expressed.

7 That's my feeling looking at the more
8 comparative ways. I really do not see such a
9 social disaster like the lead poisoning or mercury
10 or those which stay in the body for long, long
11 time like cadmium arsenic.

12 I don't see that. Metabolically, they
13 are eliminated rather quickly. That's my feeling.

14 DR. ROBERTS: Thank you, Dr. Matsumura.
15 Last call.

16 DR. HATTIS: I don't see evidence of a
17 wide spread disaster either, obviously. But I'm
18 not sure we would know. I'm not sure anybody knew
19 about lead, you know, at a comparable stage in the
20 development of the issue.

21 And that was in the face of mean blood
22 lead levels of the order of 19 or 20 or something

1 like that, that you perhaps can give that.

2 In any event, the policy choice was made
3 by the Congress to a degree that said that unless
4 we are pretty damn sure, we're supposed to retain
5 this factor.

6 DR. MATSUMURA: My point is the
7 persistence in the animal data. As the active
8 form, how long those chemicals persist in the
9 body. So what I can -- immediately, that's
10 clearance, is not comparable to anything like PCBs
11 or lead or mercury.

12 These are the ones which half-life is
13 rather short. That's what I'm saying. Just
14 overall feeling.

15 DR. HATTIS: It is quite right that the
16 persistence is much less and that's a factor
17 arguing for less concern than was in the case of
18 either lead or the organochlorines.

19 On the other hand, there are these
20 mechanisms that are at least possible whereby you
21 have a transient change leading to long lasting
22 effects.

1 DR. ROBERTS: Dr. Needleman.

2 DR. NEEDLEMAN: Can I pick up on what
3 Dale said about lead, because I think the history
4 is instructive.

5 When childhood lead poisoning was first
6 reported, there was great skepticism that there
7 was such a thing, that children could have lead
8 poisoning was disputed.

9 Once it was accepted that, yes, kids
10 could get lead poisoning, it was thought there
11 were only two outcomes, you either died or you
12 recovered completely with no residua.

13 Then it was accepted that there were
14 long-term effects. Now we are talking about 1943.
15 But in order to have long-term effects, you had to
16 have signs of brain edema, vomiting, convulsions,
17 stupor.

18 At that time the toxic dose was
19 established at 60 micrograms per deciliter. Then
20 it was shown in the 70s and 80s that children who
21 had no visible symptoms but had elevated body
22 burdens had lower IQ scores.

1 And the threshold for effect shifted
2 downward to 30, 25. And then CDC and NAS said it
3 was 10 or lower in 1980, I think.

4 Now there is data that shows that blood
5 leads below 10 are associated with measurable
6 deficits in IQ. And the reason for that is better
7 outcome measures and better epidemiology.

8 There is a reciprocal relationship
9 between the quality of the studies and the
10 effective dose.

11 DR. ROBERTS: Dr. Harry.

12 DR. HARRY: Sorry. This is a quick
13 comment on the history. And while it was
14 appreciated, and I think we do remember that, we
15 also have to realize that we're not starting from
16 that same point. We are using those refined
17 techniques now. We are looking for those subtle
18 differences in animals as well as in the
19 epidemiology study.

20 So I don't think any of us are going to
21 forget the steps with the lead. And I'm not real
22 sure that assuming that taking a 3X versus a 10X

1 factor is going to take us back to the times of
2 not recognizing that there are risks, because we
3 do have those refined methods that we're using
4 across the board now.

5 DR. ROBERTS: Dr. Needleman I think
6 would like to respond.

7 DR. NEEDLEMAN: I just have to dispute
8 what you said about the quality of the outcome
9 measures. I don't think we're applying the same
10 specific measures of function, behavioral
11 function.

12 DR. ROBERTS: Are there any other
13 comments on this particular issue? Anyone else
14 want to weigh in?

15 Mr. Lewis has suggested that I summarize
16 our comments on this. And I'm reluctant to do so.

17 We did have some folks express the
18 opinion with different explanations for why they
19 thought an FQPA safety factor of 10X would be more
20 appropriate. And we had one panel member express
21 an opinion that the 3X was appropriate.

22 That essentially, I think, captures the

1 discussion so far, although, many of the panel
2 members, maybe even numerically most of them, did
3 not express an opinion on this issue.

4 Dr. Harry.

5 DR. HARRY: As a point of clarification,
6 on each one of these compounds, you have an
7 individual evaluation that you have done. Right?

8 How is this cumulative risk assessment
9 going to influence an individual chemical's risk
10 assessment?

11 MS. MULKEY: Let me try that. It is not
12 really how it influences the risk assessment.

13 The individual chemical risk assessment
14 does not, except to the extent that the same
15 issues are relevant and they appear there, it does
16 not adopt or borrow from this risk assessment.

17 But to draw a conclusion from whether
18 the tolerances which are, of course, are all set
19 on individual chemicals about whether they meet
20 the statutory standard, the reasonable certainty
21 of no harm standard, you have to have evaluated
22 the individual chemical's risk assessment and

1 drawn your conclusions based on that.

2 And then the statute says you have to
3 consider the cumulative risk associated with -- if
4 that chemical is part of a group that has a
5 chemical, a common mechanism.

6 So before a final determination can be
7 made about whether a particular tolerance meets
8 the standard, the reasonable certainty of no harm,
9 you have to have considered the individual
10 chemical risk assessment and considered the
11 assessment of the cumulative risk from the class
12 of compounds.

13 So the individual chemical risk
14 assessment looked at the same data, was informed
15 by the same underlying information, as well as a
16 lot of other information. But it was not per se
17 influenced by this risk assessment.

18 DR. HARRY: I was just wondering how
19 this influenced that and also to bring back the
20 fact that in each one of the individual ones you
21 do look at all the behavioral outcomes, you look
22 at everything that may happen there, adult and

1 developmental as you have them in.

2 And then this is sort of an extra
3 component of information of how things might be
4 additive to evaluate how do I now look at these
5 things of how they may build up and work with each
6 other.

7 DR. DELLARCO: Exactly.

8 DR. ROBERTS: Then let me now open it.
9 Are there any other scientific issues related to
10 whether and how to use information on the
11 sensitivity of children and incorporate that into
12 the cumulative risk assessment? Any comments on
13 that area that individuals on the panel might want
14 to make? This is sort of our last offer for
15 comment.

16 DR. HARRY: Could you say that again?

17 DR. ROBERTS: Now moving beyond the
18 issue of the specific FQPA safety factor, but,
19 again, within this topic of how the agency should
20 view and use data relevant to a determination of
21 sensitivity of children and incorporating that
22 information into the cumulative risk assessment,

1 are there any comments that people want to make
2 that weren't covered previously in our response to
3 the questions?

4 Dr. Pope.

5 DR. POPE: I would like to ask the EPA
6 people if -- with the single compound risk
7 assessments, are any of the compounds regulated on
8 the basis of something besides cholinesterase
9 inhibition?

10 DR. DELLARCO: Yes. Because all
11 toxicities are considered. And typically in those
12 assessments, they go for the sensitive endpoint.
13 It may not necessarily be cholinesterase
14 inhibition or cholinesterase inhibition in the
15 brain.

16 MS. MULKEY: In most cases it is
17 sensitive, isn't it?

18 DR. DELLARCO: In most cases, it is.
19 But again, all compartments are looked at and
20 selected.

21 DR. POPE: I didn't say brain
22 cholinesterase inhibition. I said cholinesterase

1 inhibition.

2 DR. DELLARCO: Pardon?

3 DR. POPE: Cholinesterase inhibition in
4 any tissue. Are there single compounds that are
5 regulated on the basis of a noncholinesterase most
6 critical endpoint?

7 DR. DELLARCO: In the case of
8 chlorpyrifos, the FQPA safety factor was retained.
9 Although the R F D endpoints were based on
10 cholinesterase inhibition, a 10X factor was
11 retained because of other toxicities that were
12 observed in the developing nervous system that may
13 not have been due to the cholinergic system.

14 DR. POPE: But the RFDs were all based
15 on cholinesterase inhibition?

16 DR. DELLARCO: I think mostly all the
17 RFDs. Karl, can you --

18 DR. BAETCKE: This is Karl Baetcke.
19 There may be a few exceptions. But for most, it
20 is based on cholinesterase. What I can't recall
21 is when you get into the chronic studies, there
22 may be other endpoints for the long term.

1 DR. DELLARCO: But also, you have to
2 keep in mind when the FQPA decisions were made for
3 certain OPs, a factor, whether it was 10 or maybe
4 3X, was retained because of the consideration of
5 other toxicities.

6 DR. ROBERTS: Dr. Reed.

7 DR. REED: While we were looking at the
8 single and the modical chemical exposure, I was
9 curious to know if by applying different
10 uncertainty factor to single versus to modical,
11 would it create something so that -- I think
12 people conceptually are looking for cumulative
13 risk being greater than single chemical risk,
14 because conceptually it is cumulative, meaning you
15 have other exposures that come into play, but are
16 there situations where you might have risk for
17 single chemical turn out to be greater than
18 cumulative risk.

19 And is that sort of confusing in terms
20 of that comparison.

21 MS. MULKEY: It depends on whether you
22 are looking at your cumulative risk before or

1 after you've regulated your single chemical.
2 That's part of what makes that question
3 complicated.

4 I suppose it is -- our effort is to have
5 completed at least enough work on the single
6 chemical that we understand its entire profile.

7 In most instances, we have not only
8 completed the risk assessment for the single
9 chemical, we have completed risk management.

10 This is more of a science question, I
11 probably shouldn't try to answer it. I think it
12 is theoretically possible that you could have an
13 endpoint in a single chemical that was far more
14 sensitive than your common mechanism endpoint. So
15 you could have a single chemical where your risk
16 gave you much greater concern than the cumulated
17 -- the risk from the cumulated exposure of the
18 class as it related to the common mechanism
19 endpoint.

20 I don't know whether that theoretical
21 prospect exists for this class of chemicals.

22 DR. ROBERTS: I think that's right.

1 DR. MATSUMURA: Theoretically, yes, many
2 OPs can affect the carboxylesterases. There are
3 some report clearly to show those joint kind of
4 actions. Iso malathion, for instance, is going to
5 affect on the purity of a chemical. One component
6 of the same compounds or different OPs (ph) can
7 inhibit the carboxylesterase.

8 I'm quite sure Dr. Padilla has addressed
9 that, too, right? Some compounds could affect the
10 A esterases, too, via competition. So
11 interactions are there, theoretically.

12 DR. ROBERTS: This is the last call for
13 comments.

14 Seeing none, I would like to thank the
15 members of the panel for their time and effort in
16 preparing for this meeting, for their excellent
17 comments and discussions.

18 I would like to thank the agency for,
19 obviously, their very hard work in preparing this
20 analysis, their presentations and very useful and
21 candid discussions with us on the technical
22 issues.

1 And of course I would like to thank the
2 SAP support staff for putting this meeting
3 together. There are a lot of logistical details
4 associated with assembling a panel, getting the
5 materials to the panel, getting everybody here and
6 so forth. They do a terrific job for us. I would
7 like to thank all of them for that.

8 We're going to close this session now.
9 And I would ask the members of the panel to meet
10 just to cover some administrative details in terms
11 of preparing the minutes from this meeting.

12 Is there any other announcements or
13 anything anyone would like to say before we finish
14 for the day?

15 MR. LEWIS: Just briefly, I want to
16 thank Dr. Roberts for serving as chair for our
17 meeting over the past few days, and again,
18 thanking the panel for your thoughtful
19 deliberations over the past two days.

20 The panel will now work in preparing its
21 minutes for the discussion for the past two days.
22 We anticipate having the report, the minutes

1 available in approximately two to three weeks.

2 Thank you.

3 DR. ROBERTS: If there are no further
4 announcements, this session of the FIFRA
5 Scientific Advisory Panel is now closed.

6 - - -

7 [Whereupon, at 2:30 p.m., the
8 meeting concluded.]

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