ITER Peer Review Meeting Summary for Arsenic & Barium

An independent panel of expert scientists and risk assessors met on June 14 and 15, 1999, to review a research program on the teratogenicity of arsenic and an oral reference dose (RfD) on barium. Elf Atochem North America, Inc. sponsored the arsenic review and Chemical Products Corporation of Cartersville, Georgia sponsored the RfD for barium. This meeting was conducted by Toxicology Excellence for Risk Assessment (*TERA*); a non-profit organization dedicated to the best use of toxicity data in risk assessment. Expert peer reviewers donated their time and talents to provide an independent review of the assessments. A comprehensive overall review of the materials was provided by the combined experience of all the reviewers.

After brief introductions, the meeting began with a discussion of conflict of interest. Each reviewer certified in writing that he or she did not have a conflict (real or apparent) with the chemical under review or the sponsor, or identified the potential for such conflicts. Possible conflicts were discussed with each reviewer prior to the meeting to determine if measures were needed to manage a potential conflict (or appearance of conflict). Options included excluding the reviewer from a particular discussion and consensus, or allowing the reviewer to participate in the discussion, but not be polled for consensus. Panel members each identified themselves, summarized their backgrounds, and noted any possible conflicts. The panel agreed to each participant's participation as documented in Attachment A.

These review meetings follow a standard format beginning with a close examination by the panel members of the supporting documentation and important references several weeks prior to the meeting. At the meeting, after the conflict of interest discussion, the authors of the assessment or document briefly present their work. For chemical assessments, the panel then systematically discusses the assessment, starting with a discussion of the qualitative weight-of-evidence and a determination of whether adequate data exist on which to base a risk value. This is followed by a discussion of the appropriate critical endpoints and studies. Next, the quantitative aspects of the assessment are discussed, including proposed cancer risk estimates and non-cancer tolerable doses or concentrations. Specific questions to focus the panel's review are provided to the reviewers with their charge and are considered and discussed at the meeting.

Full discussion and participation are encouraged and agreement is reached by consensus. Consensus, for the purpose of these meetings, is defined as "an opinion held by all or most, or general agreement." The meeting was open to the public.

Inorganic Arsenic and Prenatal Malformations: A Comprehensive Evaluation for Human Risk Assessment

Sponsor: Elf Atochem North America, Inc.

Presenters:

- Dr. Craig Farr, Elf Atochem North America, Inc.
- Dr. John DeSesso, Mitretek Systems
- Dr. Joseph Holson, WIL Research Laboratories

Chair: Dr. Michael Dourson, *TERA*

Peer Reviewers:

Dr. Kenneth Bailey, U.S. EPA (retired)
Dr. Donald L. Bjerke, Procter & Gamble Company
Dr. Michael L. Dourson, *TERA*
Mr. John Fawell, Water Research Centre*
Dr. E. Sidney Hunter, III, U.S. EPA, National Health and Environmental Effects Research Laboratory
Mr. Thomas Long, ChemRisk Division of McLaren/Hart
Dr. B. K. Nelson, National Institute for Occupational Safety and Health (NIOSH)
Dr. Rebecca T. Parkin, George Washington University Medical Center, Dept. of Environmental and Occupational Health
Dr. Jennifer Seed, U.S. EPA, Office of Prevention, Pesticides and Toxic Substances
Dr. Calvin C. Willhite, California EPA, Department of Toxic Substances Control

* This reviewer was not able to attend the meeting, but provided comments.

Summary of Peer Review Panel Conclusions

Elf Atochem sponsored a review of the developmental toxicity literature on arsenic, and based on identified data gaps, supported a number of additional laboratory animal studies to evaluate the ability of inorganic arsenic to induce prenatal structural malformations. The *ITER* peer review panel reviewed the existing data and manuscripts of the new studies, and evaluated whether ingestion or inhalation of inorganic arsenic causes structural malformations. The review panel concluded that the existing human epidemiology studies were insufficient to make a determination on the ability of inorganic arsenic to induce malformations in humans, due to weaknesses in characterization of exposures, lack of reporting of birth related outcomes, and limited control of confounders. The panel concluded, based on the new, regulatory guideline-compliant studies of arsenic trioxide and arsenic acid in mice, rats, and rabbits, that repeated oral and inhalation exposures to these forms of inorganic arsenic did not induce structural malformations; even at doses that elicited frank maternal toxicity and lethality.

The peer review panel was provided with a review package that included a document written by Drs. John DeSesso (Mitretek Systems), Joseph Holson (WIL Research Laboratories), Craig Farr (Elf Atochem), and Catherine Jacobson (Mitretek Systems), entitled "Appropriate Use of Animal Models in the Assessment of Prenatal Toxicity: Inorganic Arsenic;" and copies of manuscripts of studies done by the sponsor and other

studies from the literature deemed most relevant. The panel was asked to discuss and answer six separate questions regarding the teratogenicity of arsenic. The reviewers commended Elf Atochem for providing such solid scientific data under GLP conditions and for sponsoring the forum for discussing these data. The panel agreed that Elf Atochem had designed and conducted an excellent research program that provided sufficient information to answer these questions. The panel's responses to the questions were unanimous and are summarized below.

Details of the discussions that led to these conclusions follow this summary. This discussion included suggestions for revising the document, recommendations for additional work to support the conclusions, and ideas for additional research that are of scientific interest.

Question 1 - Are the existing epidemiological data adequate to demonstrate that inorganic arsenic exposure causes or is associated with structural malformations?

No, the existing epidemiological data are not adequate to demonstrate that inorganic arsenic exposure causes or is associated with structural malformations. However, adequate studies have not been done or reported (i.e., the reported studies did not adequately report exposures or effects, or control for confounders); therefore a definitive statement regarding association or causation cannot be made using the human data.

Question 2 - In the absence of adequate epidemiological data, are regulatory guideline-compliant, dose-response developmental toxicity studies appropriate for assessing the potential teratogenicity of inorganic arsenic in humans?

The two regulatory guideline-compliant studies sponsored by Elf Atochem would be adequate for new chemicals, but in this case, where the existing animal literature indicated potential developmental effects, the additional studies sponsored by Elf Atochem are needed to address questions such as peak concentrations and route specificity.

Question 3 - Does inorganic arsenic induce teratogenic effects in animals when administered orally?

The review panel agreed to replace the term "teratogenic effects" with the word "malformations." As modified, the answer is no. Several forms of inorganic arsenic (sodium arsenate, sodium arsenite, arsenic acid, and arsenic trioxide) have been tested in several species of experimental animals (rat, mouse, rabbit, hamster) under single, repeated, and two-generation dosing protocols. When administered orally, these compounds do not induce malformations even at doses that cause frank maternal toxicity and lethality. This is most likely due to the lack of bioavailability to the target tissue.

Question 4 - Does arsenic induce teratogenic effects in animals when exposure is via inhalation of arsenic-containing dust?

The review panel agreed to replace the term "teratogenic effects" with the word "malformations." As modified, the answer is no. When rats are exposed by inhalation daily, from two weeks prior to mating through the end of gestation, arsenic trioxide does not induce malformations or other developmental effects even at doses that cause frank maternal toxicity. This is most likely due to the lack of bioavailability to the target tissue.

Question 5 - Is the present approach, combining critical analysis of the literature in conjunction with the design, conduct, and reporting of robust regulatory guideline-compliant studies, an appropriate method to assess the potential teratogenic hazard of inorganic arsenic?

Yes. The approach presented by the authors is appropriate to address the problem, and the sponsors have gone beyond the standard battery of studies normally required. Enhancements of this approach would be to strengthen the pharmacokinetic analysis.

Question 6 - Does the current scientific evidence support a conclusion that sustained exposure to ingested or inhaled inorganic arsenic at environmental levels causes prenatal structural malformations (i.e., teratogenicity) in humans?

No. At the experimental oral and inhalation doses tested, which generated frank maternal toxicity and lethality, no prenatal structural effects were induced in laboratory animals. Moreover, inhalation of arsenic trioxide produced no other developmental effects at concentrations that induced frank maternal toxicity. By the oral route (gavage and diet), developmental toxicity (post-implantation loss and/or decreased fetal weight) was seen only occasionally and at the highest dose level, which also induced maternal toxicity.

PRESENTATION AND CLARIFYING QUESTIONS

The *ITER* Peer Review meeting began with a brief presentation by the sponsors and/or authors. This was followed by questions from the panel members that were of a clarifying nature. Dr. Craig Farr from Elf Atochem North America, Inc. began the sponsor's presentation. He indicated that the development of the research program and this review were initiated in response to litigation concerning birth defect experiences of people living in the vicinity of a facility owned by Elf Atochem. The research program was designed to answer the following question: *Does the current scientific evidence support a conclusion that sustained exposure to ingested or inhaled inorganic arsenic at environmental levels causes prenatal structural malformations in humans?*

Dr. John DeSesso, from Mitretek Systems, presented a brief review of the existing human and animal studies that were available at the time the project was initiated. This review revealed that most of the epidemiology studies examined did not focus on inorganic arsenic and involved other chemical exposures. In addition to the lack of verification and quantitation of exposures, appropriate control of confounding variables was also lacking in most of the studies. The existing animal studies were designed to study neural tube defects, and not designed for use in risk assessment per se. These studies generally used i.p. and i.v. administration, lacked a dose-response design, used small numbers of

animals, and did not clearly or completely describe the methods and results, including maternal effects. Based on the multiple weaknesses in these study designs, the research team concluded that new research was needed. This review of the literature has been published (DeSesso et al., 1998).

Dr. Joseph Holson, from WIL Research Laboratories, provided a review of the new animal studies that were completed to fill these identified data gaps. Stump et al. (in press) administered a single i.p. dose of sodium arsenate or arsenic trioxide, or a single oral dose of arsenic trioxide to groups of rats. The research findings demonstrated that single i.p. administration of either sodium arsenate or arsenic trioxide increased post-implantation loss, decreased fetal weights, and increased the malformation rate, while the single oral dose increased post-implantation loss, but did not increase the malformation rate at doses that caused maternal toxicity and lethality.

Holson et al. (in press a) conducted a repeated oral-dose study by administering arsenic trioxide to rats; Nemec et al. (1998) conducted a repeated oral dose study of arsenic acid in the mouse and rabbit. In these repeated oral dose studies, arsenic acid and arsenic trioxide increased post-implantation loss and/or decreased fetal weight in mice and rats at doses that caused maternal toxicity or lethality, but did not increase the malformation rate. No statistically significant developmental effects were observed in rabbits.

Holson et al. (in press b) exposed groups of rats to arsenic trioxide in a repeated inhalation study. They reported that following this exposure regimen arsenic trioxide did not induce any developmental effects at any dose, including doses that caused maternal toxicity.

Clarifying Questions

Following the presentation by the sponsors, the peer review panel asked clarifying questions. One reviewer asked if the slide presenting a summary table of the new data referred only to the repeated dose studies and would the conclusions be different if the single-dose studies were included. Dr. Holson confirmed that the slide only included the repeated-dose animal studies, but added that based on the entire data set, the conclusions would not change.

A panel member asked for clarification on the criteria that were used to evaluate the epidemiology literature and what criteria were used to determine whether a study had adequately controlled for specific confounding variables. In response to this question, the authors indicated that the six Hill criteria presented (of the nine Hill criteria) were the most relevant in this specific case. Because none of the epidemiology studies met the criterion for temporality, the Hill criteria were not met by any study. Another reviewer asked for clarification on whether any developmental effects were reported in the large Asian cohort studies on arsenic carcinogenesis. An author indicated that only one study mentioned reproductive and developmental effects (Ch'i and Blackwell, 1968); that study reported no differences in terms of age of menarche, age of menopause, or pregnancy histories.

The panel asked a number of questions regarding the availability of pharmacokinetic data for the analysis. One reviewer asked why dosing was conducted prior to mating in the repeated-dose studies. The authors replied that this regimen was used in an attempt to ensure that the maternal arsenic levels reached a steady state prior to the critical period of gestation. They suggested that this dosing protocol did result in systemic exposure, based on the presence of arsenic in serum from the rat inhalation study, even though in the rat much of the arsenic is accumulated in the red blood cells as dimethylarsinic acid.

Two reviewers asked for clarification on the concordance between developmental effects across species and between types of effects. One reviewer asked if there was a clear relationship between malformations and post-implantation loss. The authors indicated that the maternal organism seems to be more sensitive to the arsenic treatments than the developing organism. In response to a question on the ability of fetal weight changes to predict other developmental effects, the authors replied that fetal weight change is a continuous variable and smaller changes are easier to determine statistically for continuous versus quantal variables.

DISCUSSION

Below is a summary of the discussions, highlighting the issues the panel raised and their unanimous conclusions regarding each of the questions in their Charge. The panel discussed each of the questions and reached a consensus opinion on the answer.

Question 1 - Are the existing epidemiological data adequate to demonstrate that inorganic arsenic exposure causes or is associated with structural malformations?

One reviewer began the discussion with a number of comments and suggestions on the document's presentation of the human studies. The reviewer suggested that the epidemiology discussion would be more effective if the structure of the section were laid out according to the Hill criteria used in this document. Reviewers also suggested that the revised Hill Criteria, Gordis et al. Process, or London Principles (Federal Focus, Inc., 1996) might be more applicable for evaluation of these epidemiology studies than the Hill criteria used in the draft document. They also suggested describing the timing of the exposures in epidemiology studies in relation to the critical window for humans to develop neural tube defects (the authors indicated that the window for these types of developmental effects in humans would end by gestational day 27 to 28). The panel suggested that presenting a more sophisticated review of the literature in the document could better identify problems in the exposure measures of the available human studies. The first reviewer felt that these efforts would be useful to invigorate the interest of the epidemiology community and might lead epidemiologists to incorporate birth outcomes into ongoing cohort studies evaluating the relationship between arsenic exposure and cancer.

Another reviewer asked whether any evidence of hyperpigmentation was noted in any of the epidemiology studies, since hyperpigmentation is a low dose effect that would validate that arsenic exposure had occurred in the populations examined in these studies

(all of which were of ecologic design). The authors replied that no mention of hyperpigmentation was noted in any of the studies.

One reviewer asked about the observed association for coarctation of the aorta (abnormal constriction of the aorta) seen in one study (Zierler et al. 1988). An author noted that Zierler et al. (1988) concluded that arsenic was not a cardiac teratogen even though coarctation of the aorta was noted, and that this lesion can be caused by aberrant growth of tissue around the aorta, which would not appear to be related to arsenic. This author also added that coarctation of the aorta is a common cardiovascular malformation. The panel members suggested that the document discuss this observation so that anyone (trained or untrained in developmental toxicology) can understand its value appropriately in the light of other evidence.

(NOTE - After the meeting, a reviewer examined the Ch'i and Blackwell (1968) paper and determined that the paper does not present sufficient data to determine whether any health outcomes resulting from conception are related to arsenic exposure. The study was limited in statistical power and the study authors' conclusion that no differences were detected between cases and controls regarding miscarriages and prematurities was unsupported and unconvincing.)

In summary, the panel reached unanimous consensus that the existing human data do not show an association between arsenic exposure and malformations. However, adequate studies have not been done or reported (i.e., regarding exposures, effects, or confounders); therefore, a definitive statement regarding association or causation cannot be made from the available human data.

The panel recommended:

- A more recent and relevant set of criteria (e.g., Gordis, London, or revised Hill) be used for evaluating the human data and that the discussion be restructured according to these criteria.
- The time window in human development for structural malformations such as neural tube defects should be mentioned and the authors should try to determine the exposure period for the available human studies, if possible.
- The observation of coarctation of the aorta should be mentioned and its significance should be placed in context in the document.

The panel acknowledged the weaknesses in the existing human studies and discussed possible avenues that could be taken to strengthen the existing data. One possibility included new evaluations of existing study populations (e.g., Taiwan, Utah, and Texas) which may shed additional light on developmental toxicity, and specifically malformations. Several panel members brainstormed on how scientists might use state and regional birth defects registries across the U.S. in a meta-study type design, although another reviewer pointed out that the exposures in the U.S. might not be sufficiently high to observe adverse effects. Another approach could be to try to get information on birth

outcomes in the Asian populations that have the higher exposure; in this way it is possible to determine if birth defects occur under worst-case exposures.

The panel also discussed concordance between species, as it is important to determine if the potential effects in humans mirror the early post-implantation loss observed in some of the animal studies. The authors noted that if fetal death were evaluated one should look at rabbit data, since fetal death in rabbits occurs at a later point than in rats. A reviewer also noted that the potential structural effects should not be limited to neural tube defects based on the observation that inorganic arsenic can also increase renal malformations. A presenter clarified that renal malformations were not observed in the new animal studies.

Question 2 - In the absence of adequate epidemiological data, are regulatory guideline-compliant, dose-response developmental toxicity studies appropriate for assessing the potential teratogenicity of inorganic arsenic in humans?

One reviewer commented that, in general, for a chemical that has not been previously evaluated, the guidelines developed by the regulatory agencies would be adequate to make a determination on the ability of a substance to induce developmental toxicity in animal models. However, where there is evidence for importance of peak concentrations and route specificity, a complete database would include studies to address those issues. The reviewers noted that in this case, the sponsors have gone beyond the array of required studies and sponsored additional studies; for example they have done studies in three species (rather than two) and have done inhalation, i.p., gavage, and diet dose-response studies.

Several reviewers noted that to understand why there are differences in responses by different routes, one could do additional pharmacokinetics work, but that these data are not required to determine that arsenic does not cause malformations in animal models by the oral and inhalation routes.

Another reviewer asked if it were possible to evaluate developmental outcomes in compromised animals such as older animals or those with health impairment, since in humans many women are having children at older ages where the background incidence of birth defects is increased. The authors indicated that developing animal models to mimic specific health impairments in humans is difficult and this is not currently being done in developmental toxicity studies. (NOTE - after the meeting this reviewer recommended that this limitation in current toxicological methods be mentioned in the authors' final document.)

The panel reached unanimous consensus that while the usual two regulatory guideline-compliant studies would be adequate for new chemicals, in this case, where the existing literature indicates potential developmental effects, the additional studies sponsored by Elf Atochem are needed to address questions such as disposition and route specificity. The panel concluded that the set of studies sponsored by Elf Atochem is sufficient to assess the ability of arsenic to cause malformations.

Question 3 - Does inorganic arsenic induce teratogenic effects in animals when administered orally?

To answer this question, the panel discussed a number of issues, including maternal toxicity, developmental effects, issues of dose, the recent National Academy of Sciences (NAS) report and appropriate wording for Question 3.

The panel discussed maternal toxicity. A reviewer noted that in the area of developmental toxicology it is important to determine if an agent is a "selective" developmental toxicant that induces developmental effects without altering maternal homeostasis. Orally administered arsenic does not appear to be a selective developmental toxicant in animals. Another reviewer indicated that developmental effects for some chemicals could be a concern at doses that induce maternal toxicity (e.g., ethanol). This reviewer suggested that the response to Question 3 should note that the current studies indicate that maternal toxicity may be more of a concern than developmental effects following arsenic exposure.

The Chair asked the reviewers if the decreased fetal weight at maternally toxic oral doses would indicate that ingested arsenic was a developmental toxicant. One reviewer noted that, post-implantation loss and fetal weights were observed, but that the selectivity of the response could be confirmed with maternal and embryonic tissue doses. Another panel member commented that without a multigenerational study or neurobehavioral study the database does not encompass all the potential developmental effects. The authors clarified that a two-generation reproductive study was done, in which mice were administered arsenic acid by diet. No increase in malformations was noted, but frank maternal toxicity was present (Henwood, 1990). This study has not yet been published in the open literature.

Two reviewers raised the issue of response concordance, questioning whether the lack of neural tube defects in the oral studies would indicate that one would not expect to see this same effect in other species. As a follow up question, another reviewer asked what the background of neural tube defects is in the test animals. The authors replied that it is about 3 in 10,000 in rats.

A reviewer commented that at doses extrapolated to environmentally relevant levels, the dose to the conceptus is low. The authors agreed, and noted that in one study, in which single high doses of sodium arsenate were administered to mice by oral gavage, of the 1267 animals evaluated for structural malformations, only one neural tube defect was seen (Hood et al., 1978).

One reviewer asked the authors to clarify the statement in the National Academy of Sciences report on *Arsenic in Drinking Water* (NRC, 1999), that malformations were induced by arsenic, citing the Nemec et al. (1998) oral study. The authors replied that the overall incidence of malformations and developmental variations was not increased among arsenic-treated mice in this study and that the NRC report was someone else's interpretation of the data. In the Nemec et al. (1998) study, there was no dose-response

relationship for exencephaly, total malformations, or total variations. In addition, the two incidences of exencephaly, which is a common spontaneous malformation in mice (Hood and Bishop, 1972; Murakami, 1968), were both in the same litter.

The same reviewer noted that the Rogers et al. (1981) study reported that DMA (dimethylarsinic acid) induced cleft palate in mice and asked whether inorganic arsenic can be metabolized to DMA. The authors responded that in this paper, when using very high doses of DMA (400 – 600 mg/kg/day), some effects could be forced and that all the papers with DMA have required higher doses to elicit any effects, suggesting that the inorganic form is the active form. Another reviewer added that when making a solution of DMA animals might still be getting an inorganic arsenic dose as well.

The panel discussed whether it is appropriate to group all forms of arsenic together. One panel member noted that the form of arsenic could be important depending on the bioavailability. For example, soluble forms versus arsenic trioxide would not be comparable. A reviewer also noted that the sponsors had appropriately calculated doses on an arsenic molar basis and concluded that there was no significant difference in the ability of different forms of inorganic arsenic to induce developmental effects. The review panel agreed to modify Question 3 such that it only addresses the forms of arsenic that were tested.

A reviewer raised concern that because it was not inclusive of all developmental effects Question 3 could be misinterpreted by uninformed readers. The panel discussed the wording of Question 3 and agreed to be more precise and change the phrase "teratogenic effects" to "malformations."

The panel unanimously agreed that no, sodium arsenate, sodium arsenite, arsenic trioxide, and arsenic acid do not induce malformations in animals when administered orally. These forms of inorganic arsenic have been tested in several species of experimental animals (rat, mouse, rabbit, and hamster) under single, repeated, and two-generation dosing protocols. When administered orally, these compounds do not induce malformations, even at doses that cause frank maternal toxicity and lethality. This is most likely due to the lack of bioavailability to the target tissue.

Question 4 - Does arsenic induce teratogenic effects in animals when exposure is via inhalation of arsenic-containing dust?

The reviewers asked a number of questions regarding the inhalation studies. One panel member asked for further explanation on why the structural malformations reported in the Nagymajtényi et al. (1985) study were discounted. The authors noted that there were a number of deficiencies in the study. The results reported in the study were difficult to reconcile with the reported effects, the timing of the exposure was incompletely and inconsistently reported, the reported skeletal malformations were variations consistent with growth retardation rather than true malformations, maternal status was not reported, and the paper did not address how the chamber concentration was verified. Thus, the newer study, conducted in rats under modern standards, tends to weigh more heavily than

the Nagymajtényi et al. (1985) study in mice. The panel suggested that this information be more clearly discussed in the document.

The reviewers suggested putting the high concentrations used in the newer study in perspective in terms of a physical description of the exposure conditions to provide readers with a sense of the concentration. A reviewer also suggested relating the 10 mg/m^3 exposure to rats in the newer study to current occupational exposure limits for additional perspective. Another reviewer asked if the exposure was whole-body or nose-only and whether oral exposure could be ruled out. An author replied that there would likely have been some oral exposure resulting from the whole-body inhalation exposure protocol, although the rats were wiped with wet towels every day following exposure in order to reduce oral intake.

As with Question 3 the panel agreed to specify "malformations" rather than "teratogenic effects" and to answer for the specific compounds that were tested. The panel unanimously agreed that the answer to the reworded question (Does inorganic arsenic induce malformations in animals when exposed by inhalation) is no. Arsenic trioxide has been tested in rats under repeated dosing protocols. When rats were exposed by inhalation daily, from two weeks prior to mating and throughout gestation, arsenic trioxide did not induce malformations or other developmental effects even at doses that cause frank maternal toxicity. This is most likely due to the lack of bioavailability to the target tissue.

The panel recommended:

- Text should be added to the document to clearly justify the discounting of the Nagymajtényi et al. (1985) inhalation study, which reported malformations in mice.

Question 5 - Is the present approach, combining critical analysis of the literature in conjunction with the design, conduct, and reporting of robust regulatory guideline-compliant studies, an appropriate method to assess the potential teratogenic hazard of inorganic arsenic?

The panel agreed that the approach taken by Elf Atochem is appropriate and it adequately addresses and provides the ability to answer the questions posed. Several reviewers suggested that additional kinetic analyses would help answer the question of why there are differences seen in responses by different routes of exposure in the laboratory animal studies.

The authors discussed a hypothetical kinetic model to begin to explain the alternative outcomes of i.p. or i.v. dosing studies and the oral or inhalation studies. According to the model, i.p. or i.v. dosing protocols result in a peak maternal blood arsenic concentration that exceeds the threshold for developmental toxicity. In contrast, exposure through the oral or inhalation routes would fail to generate a peak concentration above the response threshold. As support for the kinetic model, the authors presented data from Hanlon and

Ferm (1986) and Hood et al. (1987). Although the absolute concentrations of blood arsenic in these two studies were difficult to compare due to unit differences, the general shapes of the blood curves resembled those presented in the draft document.

The Chair solicited input from the panel on the ideal pharmacokinetic study that would be useful to test the hypothesis presented in the document. The panel suggested a kinetic analysis following i.v. and oral treatments using the same protocols as had been used to assess developmental effects. Reviewers acknowledged that these analyses might present some technical difficulty. It was suggested that the blood and urine data could be used as exposure indices and compared to the ACGIH Arsenic and soluble compounds BEI (biological exposure index) to give an idea of the magnitude of the exposure, and the embryo and placental arsenic levels would be valuable to compare maternal versus target doses. These data on delivered, absorbed, and target dose could then be used in extrapolating the data across species. The authors noted that in their inhalation rat study, a group of animals had been harvested on gestational day nine and that kinetic data from those animals would be available for analysis, although these are from non-radioactive arsenic and the analytical method might have limited sensitivity. A reviewer noted that inorganic versus organic arsenic data might be most useful since the difference in potency across valance states is 3- to 5-fold, while the difference in potency of inorganic to organic forms of arsenic differs as much as 1000-fold. The authors acknowledged the value of additional kinetic data to support their hypothesis and indicated that they are planning on expanding this section of the document.

The reviewers discussed the availability of PBPK models for arsenic and noted that PBPK models in various stages are available for the non-pregnant rat, mouse, hamster, rabbit, and human. One reviewer noted that developing an appropriate model could be done if the appropriate kinetic data were available. With the resulting model it would then be feasible to do the route and species extrapolations. An author added that some of the data on human metabolism have been recently reviewed in Goering et al. (1999).

The panel reached unanimous consensus that the approach taken by Elf Atochem is appropriate to address the problem. The panel thought that the sponsors have gone beyond the standard battery of studies normally required and conducted appropriate additional work.

The panel recommended:

- Additional pharmacokinetic analyses should be discussed in the document.

If Elf Atochem were to pursue additional kinetics studies, the panel suggested single dose i.v. and oral dosing at low and high doses. Measurements should include blood, urine, embryo, and placental levels of arsenic (speciation would be desirable). The panel also suggested that the sponsors investigate the potential for adjusting PBPK modeling in non-pregnant rats and determine the status of the PBPK models in rabbits and humans.

Question 6 - Does the current scientific evidence support a conclusion that sustained exposure to ingested or inhaled inorganic arsenic at environmental levels causes prenatal structural malformations (i.e., teratogenicity) in humans?

The panel reached unanimous consensus that the response to this question as it is worded is no, although several panel members commented that the phrase "environmental levels" needed further clarification. The reviewers agreed that at the experimental oral and inhalation doses tested, which generated frank maternal effects, no prenatal structural effects were induced in laboratory animals. Moreover, inhalation of arsenic trioxide at concentrations that induced frank maternal toxicity produced no other developmental effects. By the oral route (gavage and diet), developmental toxicity (post-implantation loss and decreased fetal weight) was seen only at the highest, maternally toxic concentration.

Additional Discussion

The review panel also discussed the margin of exposure analysis presented in the document. One reviewer asked about the source of the 100 ppm soil value used in the Margin of Exposure (MOE) calculation. The authors replied that this level was chosen as an illustrative soil concentration. A second panel member commented that it can be inappropriate to talk about soil arsenic levels, since the form of arsenic in the soil can vary greatly. Rather, the text should describe this as a bioavailability issue. Another reviewer echoed this sentiment, noting that the draft document cites 20% bioavailability from a smelter site, yet a conservative approach would be to assume 100% bioavailability in the absence of empirical data.

Another reviewer asked about the Monte Carlo analysis that was included in the review package and whether the exposure assumptions included consideration of bioavailability, or would be applicable across multiple sites. An author replied that the Monte Carlo analysis did not address bioavailability. The reviewer commented that upon review of the Monte Carlo analysis (Menzel et al., in press) from combined exposure pathways, even if one were to go up to the 99.5 percentile exposure, the MOE would still be very substantial. The authors noted that at these higher estimates of exposure they had lower confidence in the exposure estimates. One reviewer noted that there has been work done on *in vitro* and *in vivo* assays for bioavailability that would be useful for determining the bioavailability for specific sites. The reviewer also commented that the bioavailability would certainly be less than the neat materials used in the animal studies and as a result the analysis is already worst-case.

The panel also discussed the margin of exposure approach. If a RfD were estimated from these data the relevant areas of uncertainty would be inter- and intraspecies variation.

One reviewer asked about the implications of the steepness of the dose-response curve for arsenic effects on the interpretation of the MOE, suggesting that a steep dose-response curve gives more reason for being concerned. The reviewer added that the primary

concern is on the exposure side, where small errors in estimating the exposure could generate big changes in the MOE.

The panel recommended that the document provide further discussion of:

- Variability in environmental bioavailability.
- The expected MOE given the rat NOAELs as a starting points (for different routes).
- The steepness of the dose response curve and the implications for the MOE analysis.

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Barium Reference Dose

Sponsor: Chemical Products Corporation

Presenters:

- Mr. Jerry Cook, Chemical Products Corporation
- Dr. Cham Dallas, University of Georgia
- Dr. Phillip Williams, University of Georgia

Chair: Dr. Michael Dourson, *TERA*

Peer Reviewers:

Dr. Kenneth Bailey, U.S. EPA (retired)
Dr. Michael L. Dourson, *TERA*
Mr. John Fawell, Water Research Centre*
Dr. Ernest C. Foulkes, Professor Emeritus at the University of Cincinnati, Department of Environmental Health
Dr. E. Sidney Hunter, III, U.S. EPA, National Health and Environmental Effects Research Laboratory
Mr. Thomas Long, ChemRisk Division of McLaren/Hart
Dr. Rebecca T. Parkin, George Washington University Medical Center, Dept. of Environmental and Occupational Health
Dr. Robert Tardiff, The Sapphire Group*
Dr. Calvin C. Willhite, California EPA, Department of Toxic Substances Control

* These reviewers were not able to attend the meeting, but provided comments.

Brief Summary of Peer Review Panel Conclusions

Chemical Products Corporation developed an oral reference dose for barium and compounds based on kidney effects seen in the 1994 National Toxicology Program (NTP) drinking water studies of barium chloride dihydrate in rats and mice. The peer review panel reached unanimous consensus that available human studies were of lesser quality and the 1994 NTP study was the most appropriate choice basis for a RfD. The panel also unanimously agreed that kidney effects, rather than cardiovascular effects, are the critical effect for barium and that the high dose in the male rat reported in the 2-year NTP study (60 mg Ba/kg/day) is the appropriate NOAEL from which to derive an oral RfD. The panel approved using an uncertainty factor of 10 to account for human variability, but requested additional discussion and justification for factors accounting for interspecies extrapolation and database before approving a total composite uncertainty factor. The final value of the oral RfD for barium will be determined after the panel reviews the additional uncertainty factor discussion.

PRESENTATION AND CLARIFYING QUESTIONS

Drs. Cham Dallas and Phillip Williams of the University of Georgia wrote the assessment document and presented the oral reference dose (RfD) assessment for barium and compounds on behalf of Chemical Products Corporation. Mr. Jerry Cook of Chemical Products also attended. Barium is an alkaline earth metal that is naturally abundant in soil, water, and food. Barium has several industrial uses including pigments, ceramics, glass, aluminum refining, photographic paper, and medical diagnosis. The presenters noted that oral absorption of ingested barium is highly variable in animals and humans, but that distribution and elimination is very similar between animals and humans. Barium is primarily distributed to bone, and 90% of barium is eliminated in the feces. Human data available for hazard identification include case studies of acute poisoning, a chronic occupational study by NIOSH, a controlled clinical study, and an epidemiology study. Effects in humans following acute exposure include abdominal pain, vomiting, muscle twitching and paralysis, and renal toxicity. No effects have been observed in longer-term studies in humans. Several animal studies are available for hazard identification. No evidence of carcinogenicity has been observed. The noncancer effects observed include cardiovascular effects and renal toxicity. No adverse reproductive effects have been observed.

The presenters noted that as exposure duration to barium increases the No Observed Adverse Effect Level (NOAEL) decreases. In addition, many of the available animal studies did not identify any adverse effects, so that the high doses tested were generally NOAELs. The authors considered the human studies insufficient for developing a RfD. Therefore, the chronic study conducted by NTP (NTP, 1994) was selected as the critical study. In this study, male and female rats and mice were exposed to barium chloride dihydrate in drinking water for two years. The study was designed to assess both cardiovascular and renal effects. In rats, no effects, either renal or cardiovascular, were observed at the highest dose tested. In mice, renal effects (nephropathy), but not cardiovascular effects, were observed at the highest dose tested. In rats, the NOAEL was 60 mg/kg-day in males and 75 mg/kg-day in females; these were the highest doses tested. In mice, the NOAEL was 75 mg/kg-day in males and 90 mg/kg-day in females; the LOAEL was 160 mg/kg-day in males and 200 mg/kg-day in females. The NOAEL in male rats was used as the basis of the proposed RfD. A total uncertainty factor of 90 was proposed. The following individual factors were used: 10 for human variability, 3 for extrapolation from animals to humans, and 3 for database insufficiencies. A proposed RfD of 0.66 mg/kg-day was derived (60 mg/kg-day ÷ 90).

Clarifying Questions

Several reviewers had questions concerning the typical daily intake of barium from food and water and how the proposed RfD compares with the typical daily intake. There was a discussion about the exposure levels reported in several secondary sources including U.S. Environmental Protection Agency (EPA), World Health Organizations (WHO), and Agency for Toxic Substances and Disease Registry (ATSDR) documents. It was noted that there appears to be a discrepancy in reported daily intakes, with EPA citing WHO and reporting daily intake ranging from 300 to 1770 ug/day and ATSDR reporting daily intake ranging from 650-1770 mg/day. Dr. Williams noted that the level of exposure

from food is variable. The panel recommended that the authors clarify this discrepancy in daily intake by consulting the primary sources (and perhaps consulting with FDA for total dietary content of barium). The panel recommended that the document be revised to include a detailed discussion of normal barium intake from food and water and how the proposed RfD compares with normal barium intake.

Several reviewers asked if the presenters had considered data for different barium salts, which have different solubilities, and whether the document should state that the RfD is protective for specific barium salts. The presenters noted that most of the data available concern barium chloride or barium acetate, but that the RfD should be protective for all soluble salts. Barium sulfate is much less toxic than the soluble salts and thus, it is not appropriate to apply the RfD to barium sulfate. The panel recommended that the following statement, which had been proposed by one reviewer in pre-meeting comments, be included in the assessment document:

- It is generally believed that the gastrointestinal bioavailability of barium can vary markedly from compound to compound. For example, barium acetate and chloride salts are believed to be much more bioavailable than the barium from the sulfate. In the main, the RfD developed in this document is based on data obtained using the acetate and chloride salts. For this reason, the RfD should be applied with caution, if at all, to barium compounds similar to the sulfate salt, which have a much lower bioavailability.

DISCUSSION

Hazard Identification

The first issue discussed was the adequacy of the overall database for deriving a RfD for barium. The chair stated that he presumed the panel agreed that the database was sufficient to develop a RfD. There was no disagreement to this statement.

One reviewer noted that two human studies were not included in the document. Schroeder and Kraemer (1974) is an epidemiological study that examined cardiovascular and congenital malformation rates in 94 U.S. cities. The reviewer examined this paper, however, and did not think it would have changed the assessment. Zdanowicz et al. (1987) studied dental caries among children living in towns with different barium concentrations in water. The reviewer noted that this latter study might have had selection bias and insufficient control of confounding factors. This reviewer also noted that the assessment document should provide a better explanation of why the Japanese study (Yoshinaga et al., 1995) was considered insufficient.

The panel conducted an extensive discussion on the quality of the epidemiology studies on barium, particularly those by Brenniman and Levy (Brenniman and Levy, 1984; Brenniman et al., 1979, 1981). The discussion focused on several issues that limit the usefulness of the studies for risk assessment. One issue was the mobility of the barium-exposed population over the course of the study. The document noted that there was a

75% change in population between 1960-1970. One reviewer noted that the people moving into the study area were primarily in the 25-35 age group and that these people were possibly displacing the older population that was characterized at the start of the study. A second issue concerned the use of death certificates to determine cause of death in the mortality study. One reviewer noted that there is a high error rate in death certificates and that physicians are likely to list "cardiac failure" as the cause of death even if heart disease is not the original disease. A third issue concerns the confounding effects of water softener usage by the study population. Water softeners are known to remove barium from the drinking water. One reviewer noted that the part of Illinois where the exposed population was located has hard water and so it is likely that water softeners were used. In addition, the sponsor noted that barium has a bitter taste, increasing the likelihood that the exposed population used water softeners to eliminate taste problems. While acknowledging that the use of water softeners is a confounder in this study, a reviewer noted that it would be very difficult to quantitatively evaluate the effect of water softeners. A final issue with this study concerned accurate exposure characterization of the exposed population. One reviewer noted that although the authors measured barium concentration at the water source, they did not measure barium concentration in water at the tap. Therefore, the actual intake of barium from water by the exposed population was not known. In addition, another reviewer pointed out that the authors did not quantify the barium intake from diet, so the total barium intake by the exposed population was not known. The unanimous consensus of the panel is that these studies have serious flaws that made their use as the basis of a RfD very difficult.

The panel discussed human absorption and noted that there are few data on human absorption. The limited available data suggest human absorption is widely variable.

The panel then discussed the quality of the other available human studies including the controlled clinical study by Wones et al. (1990) and the occupational study by NIOSH (1982). Several reviewers felt that the Wones study provided a good lower bound estimate on the safe dose in humans, but it could not be used to assess how high the dose can be since it did not observe any effects at the dose tested. Likewise, the NIOSH study did not find any adverse effects in the exposed population that were clearly associated with barium exposure. However, one reviewer noted that since there was no biological monitoring (i.e., barium in urine or blood) it is not possible to state conclusively that workers were actually exposed to barium. There was also a question regarding which salt the workers were potentially exposed to; the sponsor indicated that it was both barium sulfate and soluble salts. The panel recommended that the salts issue be clarified in the final document.

There was unanimous consensus that the human studies in general, and the Brenniman studies in particular, are insufficient to use as the critical study for RfD derivation. The Wones study is a useful supporting study to provide a lower bound on safe dose, but is also insufficient as a critical study. The panel recommended, however, that the discussion of the specific faults in the Brenniman study (mobility of population, errors in death certificates, use of water softeners, no measurement of barium at tap, no characterization of barium in diet) be expanded so that the decision to not use the human studies is better

supported. In addition, the Schroeder and Kramer study and the reasons for discounting the Yoshinaga study should be added to the document.

The panel then discussed the overall quality of the animal studies and the choice of critical effect. In particular, reviewers considered the quality of the series of studies which studied blood pressure in animals as a potential critical effect (Kopp et al., 1985; Perry et al., 1983, 1989), as compared with the NTP (1994) chronic bioassay, in which kidney toxicity appeared to be the critical effect. One reviewer stated that the results of the Perry studies are not generally useful in that the technique used by these investigators, including the diet and the experimental design, are not well accepted by the scientific and regulatory community. This reviewer also suggested that the supporting document should include an analysis of blood barium levels, which do not appear to increase with time, and a comparison of these levels with *in vitro* and intravenous studies which demonstrated cardiovascular effects. This reviewer suggested that such an analysis would demonstrate that the levels needed to produce cardiovascular effects are not physiologically achievable.

The panel then discussed the NTP (1994) study and unanimously agreed that it was the most appropriate choice of critical study and that kidney pathology was the critical effect for barium. However, there was discussion on whether the changes in kidney weights observed in both the 13-week and 2-year portions of the NTP study were biologically relevant and/or adverse. One of the authors stated that in preparing the supporting documentation, he consulted with several renal toxicologists, all of whom indicated that changes in kidney weights alone were not likely to be treatment related, but rather related to a variety of other factors. Several reviewers noted that there was decreased water consumption (approximately 30% at the high dose), most likely due to the bitter taste of barium. Several reviewers also believed that the kidney effects could be due to water deprivation and suggested that the sponsors conduct a literature search for studies on the effects of water deprivation. The panel unanimously agreed that the kidney weight changes in the rats in the NTP study were not adverse, but recommended that the supporting document provide a more complete discussion of the rationale for discounting the changes in kidney weights. This discussion should examine the effects of water deprivation and should include primary references addressing the biological relevance of the changes in kidney weights.

The remainder of the discussion focused on the appropriate species and dose from which to derive the RfD. The authors selected the 60 mg/kg-day NOAEL from male rats because it was the most conservative of the NOAELs identified in the NTP 2-year study. The reviewers noted that it is important to select the most accurate NOAEL rather than the most "conservative" one. One reviewer suggested that since the male rat data represent a freestanding NOAEL, it would be more appropriate to base the RfD on the mouse NOAEL of 75 mg/kg-day (LOAEL of 160 mg/kg-day, based on nephropathy). However, after discussion, the panel agreed that the male rat NOAEL was most appropriate because there are no data to show what the effects of higher doses would be in rats, so it is not possible to determine if rats or mice are the most sensitive species. There was unanimous consensus on the use of 60 mg/kg-day as the basis of the RfD.

In summary, the panel unanimously agreed that NTP (1994) should be used as the critical study; kidney effects are the critical effect; and 60 mg/kg-day is the appropriate dose level from which to derive a RfD. The panel agreed that changes in kidney weights observed in the NTP study are not biologically relevant, but recommended that the document provide better support for this conclusion.

Dose-Response Assessment

The supporting document for the barium RfD proposed the following uncertainty factors: 10 to account for human variability, 3 to account for interspecies variability, and 3 to account for insufficiencies in the database. The panel discussed each of these factors separately.

Human Variability: The panel reached unanimous consensus that the appropriate factor for this area of uncertainty is 10. Overall, the panel felt that there were no data available to justify moving from the default factor of 10; although some of the reviewers noted that much of the source of variability in humans was the variability in gastrointestinal absorption. One reviewer noted that the caveat in the document that this factor of 10 may not cover those with decreased kidney function and diabetics should be reworded to indicate that the factor of ten would probably cover those with compromised kidney function (but not failure). Those seriously ill individuals hospitalized or on dialysis are generally not necessarily considered protected by EPA drinking water levels. Also, several reviewers recommended that text be added to this section describing the sensitivity of infants to address the concerns of the Food Quality Protection Act.

Interspecies Variability: The panel discussed the types of data available to justify moving from the default factor of 10 to a factor of 3. The authors stated that a factor of 3 was chosen because of the good agreement between animal and human studies in both the pathway and rates of distribution and elimination of barium. Most of the reviewers were not sufficiently convinced by the arguments presented in the current draft of the document that the data warranted using a factor of 3. However, there was consensus among the panel that a factor of 3 might be appropriate, if there were better support and discussion of the available kinetics data presented in the document. This discussion should address the differences in absorption between animals and humans, and should specifically be limited to comparisons between rat and human kinetics. The panel requested a review of the supporting argument for a factor of 3 before reaching a final decision.

Database: The supporting document proposed a factor of 3 for this area due to lack of a multigeneration study. The discussion focused on whether the existing data suggested a reproductive hazard for barium, necessitating a multigeneration study. The panel noted that there is only one study, Dietz et al. (1992), that examined reproductive and developmental endpoints. However, this study was not a classic developmental study because the pups were delivered and no examination of internal malformations appeared to be conducted. One reviewer felt that some of the findings in Dietz suggested a potential for reproductive effects, although at doses higher than doses that result in

kidney effects. The panel reached consensus that the appropriate factor is either 3 or 1, but that a better justification for using a factor of one would be required. The panel requested a review of the supporting argument for a factor of 1 before reaching a final decision.

The peer review panel discussed some additional comments on the barium assessment and supporting document. One reviewer noted that the document should cite EPA noncancer risk assessment methods, rather than the National Research Council.

One reviewer addressed the section that described the derivation of a TLV for barium. This reviewer noted that the existing section is incomplete, and therefore misleading. He noted that this section should either be deleted, or expanded to clarify exactly how the TLV was relevant to the derivation of an oral RfD.

A reviewer indicated that the gastrointestinal bioavailability of different barium salts will be a key issue, particularly with respect to how the RfD will be applied in site-specific situations. This reviewer suggested that the sponsor might want to conduct a pig feeding study to address questions regarding bioavailability of barium from soils or other specific media.

Finally, a reviewer noted that U.S. EPA used the Brenniman and Levy human studies as the critical study, so that it is imperative that the supporting document for this RfD give a well-reasoned and thorough critique of these studies to explain why the NTP study is more appropriate.

CONCLUSIONS AND RECOMMENDATIONS

The panel reached consensus on the following issues regarding the development of an oral RfD for barium:

- A paragraph describing the applicability of the RfD to various barium salts should be added to the document.
- Serious flaws and confounding issues preclude the use of the available human studies as the basis of a RfD.
- The chronic study by NTP (1994) is the appropriate critical study.
- Kidney toxicity, rather than hypertension, is the critical effect.
- The NOAEL from the male rat in the 2-year NTP study, 60 mg/kg-day, is the appropriate dose level for developing the RfD.
- An uncertainty factor of 10 is appropriate to account for human variability.
- An uncertainty factor of either 10 or 3 is appropriate to account for interspecies variability. If the authors select 3, then a paragraph that provides a better rationale and support for the factor is required. The panel requested a review of the supporting argument before reaching a final decision.

- An uncertainty factor of either 3 or 1 is appropriate to account for database insufficiencies. If the authors select 1, then a paragraph that provides a better rationale and support for the factor is required. The panel requested a review of the supporting argument before reaching a final decision.

The panel also made the following additional recommendations for revising the supporting documentation:

- The document should include a discussion of typical dietary intake; primary sources should be consulted to address discrepancies in existing secondary sources. The proposed RfD should be put into context of typical barium intake.
- The studies by Schroeder and Kraemer (1974) and Zdanowicz et al. (1987) should be added to the document and the document should provide a better explanation of why the Yoshinaga et al. (1995) was insufficient
- The document should include a better description of why the set of studies by Perry are not appropriate for developing a RfD, including a discussion of why the technique used by Perry is not well regarded by the scientific community.
- There should be a better discussion of why the changes in kidney weights in the NTP study are not biologically relevant or adverse. In particular, there should be a discussion on whether the changes in kidney weights were due to water deprivation and the authors should obtain references on the biological relevance of changes in kidney weights.
- The document should include a discussion on blood barium levels as compared with *in vitro* levels and levels obtained following i.v. administration that have been shown to cause cardiac effects.
- There should be a better discussion of bioavailability and relative absorption of the different barium salts. One reviewer suggested that the sponsors might want to conduct a study in pigs to address bioavailability concerns.
- The section describing the TLV for barium should be deleted.
- The document should include a better discussion of the sensitivity/ differences of young animals regarding absorption and toxicity of barium to address requirements of the Food Quality Protection Act.
- A reviewer suggested citing the EPA methods used for deriving this RfD, rather than the NRC publication.
- The issue of which salt(s) the workers in Wones et al. (1990) and NIOSH (1982) were potentially exposed to should be clarified in the document.

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Managing Potential Conflicts of Interest
***ITER* Peer Review Meeting**

June 14 and 15, 1999
(Approved by panel)

ITER peer reviewers donate their time and talents to this effort. They are selected based upon their expertise and qualifications and are employed by many types of organizations. *TERA* strives to create a balance of expertise and affiliations for each meeting. However, individual peer reviewers are representing their own expertise and views, not those of their employer. The *TERA* Board of Trustees approves *ITER* peer reviewers for inclusion in this program. A complete list of potential reviewers and more information on the *ITER* peer review program are available at http://www/tera/org/peer. Additional, *ad hoc* reviewers are selected to participate for their special expertise that may be needed for a particular chemical or discussion.

TERA requested that each peer reviewer identify potential conflicts of interest related to the review of the health risk assessment of barium (and its sponsor Chemical Products Corporation) and review of the developmental toxicity of arsenic (and the sponsor Elf Atochem). Each reviewer has signed a statement indicating that he or she does not have a conflict of interest concerning this assessment. Information regarding conflicts or potential conflicts is summarized below.

The following statements were considered by the panel and agreed upon at the meeting.

Kenneth Bailey - Dr. Bailey is a retired toxicologist from the U.S. Environmental Protection Agency. He has no conflicts and will participate fully in all discussions and polling for consensus**.**

Donald L. Bjerke -- Dr. Bjerke is a senior scientist and toxicologist with the Procter & Gamble Company's Health Care Research Center. He will participate on the arsenic panel. He has no conflicts and will participate fully in all discussions and polling for consensus**.**

Michael Dourson – Dr. Dourson is Director of Toxicology Excellence for Risk Assessment (*TERA*). Dr. Dourson will serve as panel chair for both arsenic and barium. Dr. Dourson noted that he previously chaired EPA RfD/RfC Work Group meetings on arsenic and barium, but that these were among the hundreds of chemicals discussed and he does not think this prior work would bias his review of the scientific assessments to be reviewed at this meeting. He has no conflicts and should participate fully in all discussions and polling for consensus**.**

John K. Fawell - Mr. Fawell is Principal Toxicologist and Chief Scientist of the National Centre for Environmental Toxicology, WRc plc in the U.K and has been asked to participate as an *ad hoc* reviewer for this meeting. While his colleagues performed some toxicity assessment work on methyl-HCH for Elf Atochem, Europe several years ago, he was not involved in the work and is not aware of any current or more recent work for Elf Atochem. He has no conflicts and could participate fully in all discussions and polling for

consensus. Mr. Fawell was not able to attend the meeting, but provided written comments to the sponsors.

Ernest C. Foulkes – Dr. Foulkes is a heavy metals toxicologist and Professor Emeritus at the University of Cincinnati, Department of Environmental Health. He will participate in the barium panel. He has no conflicts and will participate fully in all discussions and polling for consensus**.**

E. Sidney Hunter, III - Dr. Hunter is a toxicologist with the U.S. EPA's Reproductive Toxicology Division of the National Health and Environmental Effects Research Laboratory. He has been asked to participate as an *ad hoc* reviewer for arsenic panel because of his expertise in reproductive toxicology. Dr. Hunter conducts research on arsenic effects *in vitro.* He has no conflicts and will participate fully in all discussions and polling for consensus.

Thomas Long - Mr. Long is a scientist with the ChemRisk Division of McLaren/Hart and formerly worked for the State of Illinois. He has been asked to participate as an *ad hoc* reviewer for this meeting because of his expertise in pharmacokinetics. He has no conflicts and will participate fully in all discussions and polling for consensus**.**

B. K. Nelson - Dr. Nelson is a Research Toxicologist with the National Institute for Occupational Safety and Health (NIOSH). He has been asked to participate as an *ad hoc* reviewer for arsenic panel because of his expertise in teratology. He has no conflicts and will participate fully in all discussions and polling for consensus**.**

Rebecca T. Parkin - Dr. Parkin is an epidemiologist and Associate Professor in the Department of Environmental and Occupational Health of the George Washington University Medical Center. She has been asked to participate as an *ad hoc* reviewer for her epidemiology expertise. She has no conflicts and will participate fully in all discussions and polling for consensus.

Jennifer Seed - Dr. Seed is a toxicologist with the U.S. EPA's Office of Prevention, Pesticides and Toxic Substances. She will participate in the arsenic panel. She has no conflicts and will participate fully in all discussions and polling for consensus**.**

Robert G. Tardiff – Dr. Tardiff is the Director of the Sapphire Group. Dr. Tardiff has no conflicts and will participate fully in all discussions and consensus. Dr. Tardiff was not able to attend the meeting, but provided comments on barium, which were considered by the panel.

Calvin C. Willhite - Dr. Willhite is a toxicologist with the Department of Toxic Substances Control of the California EPA. He has been asked to participate as an *ad hoc* reviewer for his expertise in developmental toxicology and research on arsenic. He has no conflicts and will participate fully in all discussions and polling for consensus**.**