PEER REVIEW OF EPA'S HAZARDOUS WASTE IDENTIFICATION RULE RISK ASSESSMENT MODEL

Breast Milk Exposure Model for the HWIR 3MRA Model

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NOTE

This report was compiled by Eastern Research Group, Inc. (ERG), an EPA contractor, under Contract Number 68-W-99-001. The report presents comments provided by peer reviewers on the *Breast Milk Exposure Model* document that is part of EPA's Hazardous Waste Identification Rule risk assessments. The actual reviewer was performed in 1998 under Contract Number 68-W5-0057.

The comments presented in this report have been compiled by topic and by individual peer reviewer. As EPA requested, this report provides the peer review comments exactly as they were submitted to ERG. Also attached are the original comments submitted by each individual reviewer.

PEER REVIEW - Breast Milk Exposure Model

1. Introduction and background

The Office of Solid Waste (OSW) is developing a proposed amendment to its regulations under the Resource Conservation and Recovery Act (RCRA) by establishing constituent-specific exit criteria for low-risk solid wastes that are designated as hazardous because they are listed, or have been mixed with, derived from, or contain listed hazardous wastes. The constituent-specific concentrations under development are to be protective from both human health and ecological effects. The Agency proposed this amendment on December 21, 1995. In addition to public comments (RCRA docket #F-95-WHWP-FFFFF), separate reviews of the risk analyses supporting the rule were conducted by the Science Advisory Board (SAB) and the Office of Research and Development (ORD). The Agency is currently evaluating the impact of these reviews and is modifying the technical information and analyses required to support the next phase of the rule development.

The goal of the exposure and risk assessment is to generate risk-based exit constituent concentrations supporting the management goal to identify low-risk listed wastes. Listed waste with concentrations below the exit concentrations would no longer be regulated by RCRA Subtitle C. The methodology under development will estimate risks through an integrated multi-media, multiple pathway, and multiple receptor assessment that characterizes potential human health and ecological exposure and risk. The assessment will calculate risk to receptor types from simultaneous exposures to a single chemical by adding exposures from potentially contaminated air, ground water, surface water, soil, and biological media. The characterization of exposures and risks are intended to provide a national distribution of individual risk from individual constituents released from the following types of waste management units: industrial landfills, waste piles, land application units, surface impoundments, and tanks. The assessment will be based on a "regional site-based" approach - a tiered design that ensures plausible scenarios are modeled and relies on actual site and receptor data, when available, rather than hypothetical site and receptor descriptions. The approach allows for maintaining correlations among dependent parameters such as climatic, hydrologic, and geologic parameters as a function of site location.

In addition to analyses to support the risk-based constituent exit levels, analyses will include: a systematic evaluation of parameters and uncertainties; understanding the part of the distribution that is above potential exit levels to see if any specific sub-populations or regions have been systematically excluded; verification of model results against existing, more rigorous scientific models; validation of components of the model, where data are available, to compare to background media concentrations and other naturally occurring levels; and several technical analyses described in the consent decree.

2. Infant Exposure

The Human Exposure module calculates exposures to human receptors from media and food concentrations. The Human Exposure module calculates exposures for two basic receptor types: human receptors (resident and home gardeners) and farmers. Human receptors may also be recreational fishers, in addition to being a resident or home gardener. Within each of the two basic receptor types, the Human Exposure module calculates exposures for 5 age cohorts: infant (aged 0-1 year), children aged 1-5 years, children age 6-11 year, children aged 12-19 years, and adults (aged 20 and up).

Infant exposure occurs via breast milk ingestion. For infant exposure via breast milk, the maternal exposure via individual pathways is summed. Therefore, infant exposures are calculated for each maternal exposure configuration: resident, home gardener, beef farmer, dairy farmer, resident/recreational fisher, home gardener/recreational fisher, beef farmer/recreational fisher, and dairy farmer/recreational fisher. The mother is assumed to be an adult (as opposed to a teenager) for the purpose of calculating maternal dose in the infant breast milk pathway. The breast milk exposure is the only pathway that is being evaluated for infants.

3. Charge to reviewers

1. Are the models physiologically sound?
   For example, are there other factors that would argue strongly against the use of linear kinetics?

2. Is the math correct?

3. Are there other models that have not been considered?
   For example, an aqueous-phase model for lead that included a bone compartment was alluded to, but could not be found in the literature.

4. If so, are there more appropriate than the ones used in the document?
   For example, the steady-state-2-compartment of Hoover et. al. (1991) is more realistic than the Smith model (Eq. 9-2) but appears to give similar results and is virtually identical to Smith in the parameters. The decision was to stay with the simpler Smith model for steady-state. An analytical solution to the differential equation for the Hoover model was not found, so the model was not considered for dynamic application.

5. Are there examples other than TCDD that can be used to assess model performance?
   (A MeHg example was developed for the nonlipophlic pathway but was not included as it was very complicated and incomplete.)

6. Do the default parameter assignments seem reasonable?

7. Is the uncertainty discussion adequate?

General Comments

Dr. Brown: The bases for selecting the models and rejecting alternatives is, in general, adequately addressed, and I am in general agreement that, within the current state of the art, the **models are fundamentally physiologically sound (Review Criterion 1).** However, limitations are significant and are recognized and addressed by the authors. The **math (Review Criterion 2)**, including development of equations and calculations, appears to have been done carefully and thoughtfully with attention to details. Strong knowledge of the underlying science, caveats, assumptions and limitations is exhibited. Choices appear to have been made on the basis of experience with, and knowledge of, the field. The equations are logically and systematically developed with the elements defined. I am unaware of **other models (Review Criterion 3)** not discussed that would **be more appropriate models (Review Criterion 4).** I am unaware of good examples, **other than TCDD to assess models (Review Criterion 5)** (except for the closely related examples cited in context by the authors). Assumptions and **default parameters (RC 6)** are generally well addressed, and I have evaluated all that were listed and can offer no substantial disagreement with any. The **uncertainty (Review Criterion 7)**, as addressed especially in the final paragraph of the document is clearly stated and I am in agreement with it. However, it is essential that this uncertainty be stressed. For example, a separated, more prominent position for these statements is recommended. My strongest criticisms of the approaches of the document concern two items which are not addressed and a third which was recognized and discussed. I state these as follows. It seems unlikely that postpartum, lactating mothers will have constant body weight or constant body fat. Many consciously attempt to lose both fat and weight, some gain weight and fat. It is a time that is likely to be different in diet and in activity, compared to the pre-partum period, and some of these differences may significantly alter the accumulation and distribution of contaminants to breast milk. Treating these factors as constant may yield significant errors. Indeed, significant body fat loss (as by diet and exercise) may tend to "dump" fat-stored toxicants with consequences that are not fully known. Some may be stored again, some eliminated more readily and some may go into the breast milk. A second concern is that the assumption is made that breast milk fat and maternal body fat are in equilibrium and equal in contaminant concentration. Significant milk fat appears to be synthesized in the mammary glands and may have significantly less contaminants than are present in general body fat stores which also may be mobilized to make milk. Therefore, this "equality" assumption may lead to bias or error in the results. I agree strongly with the authors statements that the value of breast feeding is significant and efforts to prevent unknown consequences of low levels of some contaminants, should not take precedence over this benefit. The third criticism of the described models is exemplified by the author's statements (with which I strongly agree) about many factors that are not addressed in the model equations, some of which likely will significantly affect (alter) breast milk contaminant concentrations, and more research is needed.

Dr. Fairbrother: This chapter (Chapter 9) of the USEPA's *Hazardous Waste Identification Rule Risk Assessment* describes various methodologies for estimating amounts of contaminants in breast milk, given exposure of the mother to hazardous substances. This is based on the assumption that exposure to the mother arising from combustion occurs via oral ingestion of deposited materials.
What is not clear from reading this chapter, however, is the intent of the model. The explanatory materials provided by ERG suggested that EPA is "establishing constituent-specific exit criteria for low-risk solid wastes." However, the wording in this chapter sounds like EPA is developing guidance for use by external risk assessors for calculating exposure to nursing infants via breast milk ingestion. Statements such as "Risk assessors should consult the open literature…" (p. 9-20) indicate that EPA is providing guidance.

Unfortunately, statements such as this do little to standardize how risk assessments will be done. What constitutes the "open literature?" What if more than one value is available for a particular parameter (in this case, for the half-life of a chemical in the human body)? What if no information is available for humans, but similar information exists for an animal model – how should the cross-species extrapolation be done; what type of Uncertainty Factors (if any) should be used; when should such information not be used; what type of Data Quality Objectives need to be applied to use of such information? While the intent of the chapter likely will be clarified when the entire document is assembled, questions regarding use of information from the open literature will remain. If guidance is available elsewhere for how to use such information, a reference should be given within this document; if such information is not available elsewhere, it should be incorporated here.

The first section (Section 9.1) is a review of the literature and what is known about breast milk contamination from persistent highly-lipophilic organic contaminants (e.g., PCBs, PCDDs, PCDFs), combustion-source compounds with low octanol:water partition coefficients (e.g., phenol, benzene, aldehydes), and inorganic compounds, including metals and organo-metallics. This section is complete and provides sufficient level of detail to document why certain compounds require consideration.

Section 9.2 describes the methodology for calculating the average daily dose of contaminant to the nursing infant, assuming that the daily maternal intake of the contaminant is known (or estimated through use of oral exposure models). The section discusses the pros and cons of linear versus PBPK models and, within the linear model discusses the application of kinetic information related to lactational losses or the use of simple bioaccumulation factor models. However, the final conclusion of the chapter in regard to which model is preferred by EPA is not completely clear. It appears that EPA is recommending using a linear model that incorporates elimination due to lactation as well as kinetics of maternal exposure duration and breast feeding duration (the Sullivan et al. model). While EPA acknowledges that these simple linear models are highly inaccurate for extrapolating high dose exposures (page 9-31, line 22), their conclusion that the models adequately simulate exposures at lower doses, that are likely to be environmentally relevant, is acceptable. Furthermore, the model will err on the side of conservatism. While this may lead to some over prediction of infant risk and subsequent cessation of breast feeding in situations where it may not be necessary, the risk of switching to formula feeding is less than the risks associated with false negatives (i.e., predicting lack of risk when it really would occur).

Responses to Charge Questions

1. *Are the models physiologically sound?*
   For example, are there other factors that would argue strongly against the use of linear kinetics?

Dr. Brown: Within the assumptions stated and subject to my criticisms as summarized in the “Summary Critique”, the linear pharmacokinetic model used appears to be physiologically appropriate to estimate the “average daily absorbed dose of contaminant from breast milk”.

Dr. Fairbrother: Yes, although I much prefer the model by Sullivan et al. (1991) over the steady-state model presented by Smith (1987). I think this is the model that EPA is recommending, with the modification of deleting the initial infant body burden term (equation 9-4 on page 9-18). However, it is not completely clear that this is the case and it would be helpful if EPA clearly stated this on page 9-18,

The adjustment of the Sullivan et al. model to exclude the initial infant body burden term is reasonable for approximating infant exposure via breast milk. However, the potential for exposure of the infant through body fat (presumably transferred during gestation) must not be lost for the risk assessment; i.e., the infant body fat component must be added to the exposure from breast milk to calculate total exposure of the nursing infant.

The Travis et al. (1988) model is not very sound, as it assumes linear BAFs over all ranges of maternal exposure concentrations. This assumption does not hold for many (most?) chemicals and will result in an extremely conservative estimate of infant exposures.

Dr. Shull: For the most part, the models are physiologically sound. The model for lipophilic compounds *does* take into account the physiological parameters of absorption, partitioning, elimination and mass balance by taking into account decrease in maternal body burden during lactation. A kinetic representation should be attempted for non-lipophilic substances. The presented model (Equation 9-10) for the milk aqueous phase *does not* account for chemical species with long half-lives in the body, or for the body burden loss due to lactation. These parameters are very important for non-lipophilic substances that can accumulate in the body, such as MeHg, Pb, or Cd. This is even more significant for sequestered substances such as lead; it can be released from the bone into the blood during lactation and thus into the breast milk, causing breast milk exposure to include previously sequestered lead. Gulson et al. (1998) have recently evaluated the ability of Pb to be re-released into the blood stream from bone deposits during lactation. They report the release from bone during lactation can be a significant source of lead to infants, and raise concern in situations with high levels of maternal exposure to lead. Although an existing model for non-lipophilic substances may not exist, an adaptation of the kinetic linear model (Equation 9-4) for lipophilic substances to non-lipophilic substances in the milk aqueous phase should be included in this document or at least given significant discussion. The release of lead from bone could result in significantly greater than predicted levels of lead in breast milk during lactation.

2. Is the math correct?

Dr. Brown: Yes, each equation was reviewed and all appear to be correct. I have some minor points which will be addressed subsequently when each equation is separately discussed.

Dr. Fairbrother: Yes

Dr. Shull: A review of equations and derivations presented show no errors. The models were checked for integration errors and none were found. The equations were checked for correct substitutions, algebraic substitutions, and mathematical simplifications and no errors were found. In addition dimensional analyses was performed to ensure that unit representations in parameters carried through the models correctly and no errors were found.

3. Are there other models that have not been considered?
For example, an aqueous-phase model for lead that included a bone compartment was alluded to, but could not be found in the literature.

Dr. Brown: This model is stated to be a linear, pharmacokinetic model, and subsequently (as on page 9-15) other models (including non-linear) are presented and discussed appropriately, for the most part. I agree that the discussed PBPK models are not **directly** useable for estimating infant exposure through

breast milk consumption from mothers indirectly exposed to combustion emissions. Brest milk compartments might be designed, however, and added to the models. The objection that they require unavailable data which is a serious problem for current applications. The objection, however, that specially-designed software packages would be required seems not to be a constraining objection to their use.

The placement of the section "Choice of Model: Linear vs. PBPK" (p. 9-15) is awkward and, more importantly, several of its concepts are not as well argued as are most of the concepts in the document. I strongly agree that the "adequacy of linear algebraic models for predicting human breast milk concentrations of highly lipophilic compounds is unknown" (p. 9-15). Citing Roth (1994) the authors then state that the pharmacokinetics of TCDD and related compounds "is highly non-linear and dose-dependent, although apparently linear behavior was observed at lower, environmentally-relevant doses". This appears to be a significant indictment of linear models, as used in the document. I do not understand the objection to a two-compartment model based on the statement "there does not appear to be an analytic solution that incorporates time dynamics" (however, this may be justifiable; I just don't know what the authors mean here). This may be moot since, as they state, the models may not generate significantly different predictions. To conclude this point, it would be desirable if the argument for the linear model were made stronger.

Dr. Fairbrother: Try the following PBPK models for lead:

O'Flaherty, E.J. 1991. Physiologically-based models for bone-seeking elements. II. Kinetics of lead disposition in rats. *Toxicol. Appl. Pharmacol*. 111:313-331.

Dalley, J.W., Gupta, P.K. and Hung, C.T. 1990. A physiological pharmacokinetic model describing the disposition of lead in the absence and presence of l-ascorbic acid in rats. *Toxicol. Let.* 50;337-348.

Dr. Shull: Because we did not perform a comprehensive search for other breast milk models, we are unable to provide a definitive answer to this question. However, the document does consider available model types and includes recent peer reviewed available models. The discussion of models does include the major type of model classes, non-linear PBPK, linear steady-state and kinetic models.

4. If so, are there more appropriate than the ones used in the document?
For example, the steady-state-2-compartment of Hoover et. al. (1991) is more realistic than the Smith model (Eq. 9-2) but appears to give similar results and is virtually identical to Smith in the parameters. The decision was to stay with the simpler Smith model for steady-state. An analytical solution to the differential equation for the Hoover model was not found, so the model was not considered for dynamic application.

Dr. Brown: I am not aware of such.

Dr. Fairbrother: Probably not. While these models simplify the pharmacokinetics of contaminants within the lactating female, there is insufficient evidence for most compounds to be able to parameterize a PBPK model. Assuming simple first order kinetics probably is reasonable for the low-level exposures that will be modeled for RCRA exit criteria. A strong caveat is included in the Uncertainty section, indicating that these models are very likely to grossly overestimate risk at higher exposure concentrations.

Dr. Shull: It would be easier to evaluate the choice of model if the document provided quantitative model comparisons to a non-linear model. The report references PBPK models developed for dioxins. Adding this model to the model comparison group would provide an excellent example as to the benefit of using the complicated PBPK model versus the benefit of using the easier linear models. If existing PBPK models don't include breast milk an evaluation of predicted levels in the body would still be useful.

5. Are there examples other than TCDD that can be used to assess model performance? (A MeHg example was developed for the nonlipophlic pathway but was not included as it was very complicated and incomplete.)

Dr. Brown: I am not aware of any.

Dr. Fairbrother: There are some reasonable parameters for tetrachloroethylene (PCE) that might be used, even though these exposure models initially rely on an inhalation route of exposure. It would be worth reviewing the following references to determine if sufficient information is available for use of PCE to assess model performance. Comparison could then be made to the inhalation models to determine if similar breast milk concentrations are calculated for similar absorbed doses.

Schreiber, JS. 1993. Predicted infant exposure to tetrachloroethylene in human breastmilk. *Risk Anal*. 13:515-524.

Also, see the PBPK models for lead cited above, as examples of where parameters can be found to test the model for an aqueous phase compound.

It is disturbing that the model could not be tested for methylHg. One questions how many chemicals will have sufficient data for running the model, particularly information on biological half-life.

Dr. Shull: It would seem to us that a good approach would be to assess model performance with both representative organic and inorganic substances. Lead would be a good choice for assessing the de-sequestration issue (i.e., Pb from bone). Although TCDD is a good choice for assessing the de-sequestration from body fat stores of highly lipophilic substances, others should be investigated as well (e.g., DDT, dieldrin, PCBs). For the organics, it would be extremely valuable if at some point correlations between one or more physicochemical parameters (e.g., kow for lipophilic organics) and translocation from blood into milk can be established with a series of compounds…however, such information may already exist and we are not aware of it.

6. Do the default parameter assignments seem reasonable?

Dr. Brown: I searched and found none with which I disagree significantly. It would be helpful to have the default parameters addressed more systematically; i.e., perhaps collected in a paragraph.

Dr. Fairbrother: Sullivan et al. model (equation 9-4)
Yes. However, additional guidance on how to handle half-lives of mixtures (e.g., dioxins or PCBs) would be helpful (pages 9-19 to 9-20). Should the concept of TCDD-equivalents (TEQs) be used and assume the half life of TCDD? Alternatively, would each congener have to be modeled separately? More specific guidance is required.

Fraction of Mother's weight that is fat (F_{fm}) suggests that slim women have smaller fat deposits and so would have greater concentrations of contaminants in fat stores. This is an over simplification as it assumes that intake rates, elimination rates, and metabolic rates are the same regardless of body size, weight, and configuration. This, of course, is not actually the case. More to the point, however, is whether or not this has much influence on the amount of chemical that transfers to breast milk. While the fat concentrations are higher, the total amount of chemical would be the same (given that all the assumptions stated earlier are true), so the total mass transferred would be the same. The rate constant likely would differ, however, as mobilization of fat stores would occur at different rates. EPA should explore this assumption more fully, and see if data exist to support it (e.g., similar fat concentrations of a lipophilic chemical in slim and obese women).

The Sullivan et al. (1991) model, however, assumes a constant body fat proportion of 30% for all women, regardless of whether one is considered "slim" or not, thus ignoring this potentially confounding issue. This figure seems high for a lactating female. Travis and Hattemer-Frey (1991; Physiological pharmacokinetic models. In: Statistics in Toxicology, edited by D. Krewski and C. Franklin. P. 170. Gordon and Breach, NY; reproduced with permission in: Krishnan, K. and Andersen, M.E. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes, A.W. (ed.). Principles and methods of toxicology. P. 164, Raven Press, NY) estimate body fat at 19% of body weight for the average human (which likely is an average of male and female percent fat). Documentation from where the 30% default assumption was derived would be helpful.

The default value of 365 days for duration of lactation (t_{bf}) seems unduly conservative. Page 9-29 reviews the literature on breast-feeding practices and reports that only 20% of infants are breast fed for 6 months at which time most infants are started on alternative foods and do not solely rely on breast feeding. Therefore, a default value of 275 days would appear to be adequate.

<u>Travis et al. model (equation 9-8)</u>
The primary assumption in this model is that the biotransfer factor (BTF) for breast milk is a constant, regardless of concentration. This is not true for most chemicals in other media, and likely is not true for maternal transfer to milk. Generally, linear BTF models work well for low concentrations, but become very over conservative at higher concentrations. Secondly, equation 9-9 for calculation of the BTF from the K_{ow} will work primarily for compounds with a log K_{ow} in the range of 2-5, but not for higher log K_{ow}s (this is borne out by the discussion about dixons, with a log K_{ow} of 6.6). Therefore, this model will have limited utility, being applicable only to compounds with log K_{ow}s within the 2-5 range and at low maternal exposures. I agree with EPA's recommendation on page 9-24 lines 20-22 that the Sullivan et al. model be given preference.

Contaminant concentration in the aqueous phase of breast milk – on Page 9-26 EPA states that it is unknown to what extent adequate data are available in the general literature to establish the value of the fraction of the contaminant (based on total absorbed intake) that is in the blood plasma compartment. This is an important default parameter for use of the equations for aqueous phase chemicals. Therefore, this statement is inadequate and unacceptable. EPA should research this question and provide appropriate guidance, or at least discuss it at greater length in the Uncertainty section.

It is interesting that EPA states that "Absorption estimates [for uptake from the infant gut] for most chemicals are empirically derived and available in the open literature." It has been my experience that this is not the case; it is very difficult to find absorption factors for most chemicals for adults much less for nursing infants.

Dr. Shull: In reviewing the default parameter assignments, no values seemed unreasonable and were sufficiently referenced.

7. Is the uncertainty discussion adequate?

Dr. Brown: The uncertainty discussion is very brief and other points might be stated. A general "caveat" (short) paragraph might remind the reader that the accuracy of risk analyses depend on: an appropriate (logically and mathematically correct) equation; appropriately accurate constants and input data; and correct (valid) assumptions (including equalities. When choices are to be made, the more conservative choice is to be used. If this is thought to be pedantic or unnecessary, I would suggest that all the uncertainty issues be collected in one paragraph (in addition to their current placements in context), combined with the final paragraph of the document, and set off with its own heading. The eventual application of the equations of this document must depend on decisions that take into consideration these uncertainties, which are present, but not focused on in the document, and about which I will say more in the following review section.

Dr. Fairbrother: Yes – for the Sullivan model, with the exception of a discussion of the data limitations for the fraction of contaminant in blood plasma. There is no discussion, however, for the Travis model. If EPA is assuming that the Travis model will not be used, they should state this in the Uncertainty section, and reiterate why the uncertainties are unacceptably high when using this model

Dr. Shull: The discussion of model uncertainty *does* include the to two sources of uncertainty or variance between predicted outcomes and real world exposures. Those are the inherent error of a model and the uncertainty and variance in the model inputs. The illustration of variance between the three linear models is very helpful in seeing the wide range in model outputs depending on the level of model complexity. The discussion of input uncertainty is brief and should be expanded. The use of dioxin should be carried forward to illustrate the impact of input variance on output variance. A table showing predicted outcomes using values across the range of two highly variable input parameters would be very useful.

Miscellaneous Comments

Dr. Brown: 9. Breast Milk Pathways and Breast-Feeding: Benefits vs. Risk (p. 9-1): The introduction is appropriate but little is said that relates directly to the 7 Review Criteria. However, the sentence (p. 9-1, last sentence) makes a curious and strong statement that seems to question the very relevance of assessing breast milk contaminant concentrations. Indeed, if one does not know infant dose responses to contaminants, how is evaluation of breast milk contaminant concentrations to be applied?

9.1 Chemical Contaminants in Breast Milk Arising from Combustion (p. 9.2): This is appropriate information for the document, but does not directly relate to the Review Criteria, except as it offers general support for the model. Table 9-1 (p. 9-3) collects useful information but I have strong reservations that the

"octanol partition approach" to assessing breast milk contaminants will be generally useful. It is overly simplistic to expect this factor to dominate.

9.1.1 Residues of Highly Lipophilic Organic Contaminants in Human Milk, 9.1.1.1 PCDDs and PCDFs (p. 9-4): Again, this is useful information but much is not directly relevant to the Review Criteria. However, it provides convincing support for the use of TCCD as a primary example of this class, with which I agree.

9.1.1.2 PCBs and Related Compounds (p. 9-5): This section contains information directly relevant to selection of models **(Review Criteria 1, 3 and 4)**. However, the information (p. 9-8) relating that the concentration of halogenated aromatics in milk fat is frequently slightly higher than in body fat (although the concentration ratio is seldom greater than two), is relevant to and supports my stated concerns about using body fat contaminant concentration as equal to milk fat concentrations.

9.1.2 Compounds Partitioning into both Lipid and Aqueous Phases (p. 9-8): This is relevant information, but requires minimal assessment by the seven Review Criteria. It does offer general support for the models **(Review Criteria 1)** for a variety of relevant compounds, and it does support the selected models.

9.1.3 Residues of Inorganic and Organometallic Contaminants in Human Milk (p. 9-10): This supports the requirement for inclusion of an aqueous phase component in the assessment equation **(Review Criterion 1),** with which I strongly agree.

9.1.4 Factors Influencing Transfer of Contaminants into Human Milk. (p. 9-12):
This is a most relevant topic to consider. It relates both to the appropriateness of the model **(Review Criterion 1)** and to the uncertainty of the results obtained by the models (**Review Criterion 7)**. Many of the factors listed in this paragraph are not included in the models (equations). It appears to be true and relevant that "The extent to which these variables influence the transfer of metals to milk is not well-characterized." I am concerned that these variables may also influence the accumulation of other contaminants into breast milk. They raise appreciable concerns about what is "left out" of the model (largely because of lack of knowledge).

9.2 Average Daily Dose of Contaminant to the Nursing Infant (p. 9-13): Equation (9-1), p. 9-13:

This equation defines not "intake", but rather "the amount absorbed", and it would be more appropriate to so identify the term (hDIinf).

It might be more thorough to have two terms instead of just one: "fai" [fraction of ingested contaminant that is absorbed by the infant (dimension less)]; i.e., one for the fraction... absorbed from the fat phase, and one for the fraction... from the aqueous phase. This may be moot, as when the data used is the total fraction absorbed and was obtained in an experiment with the contaminant made available in an appropriate matrix (similar or identical to milk). Having two factors causes one to evaluate the "fai" more carefully; not a bad thing to have happen.

However, the term "hDIinf" is defined as average daily contaminant intake for the infant (mg/kg-d); and it appears to be the amount absorbed.

Minor point: the "tA" in the equation is defined using the symbol AT; it would be clearer to use the same symbols.

9.2 Average Daily Dose of Contaminant to the Nursing Mother (p. 9-13):

Equation (9-1): This is a straightforward accounting of contaminant intake (mg/kg-day), taking into account, the milk ingestion rate, different distributions of contaminant in fat and water phases, exposure duration, averaging time and infant weight. It, however, combines the fraction of contaminant that is absorbed in one term (fai). One must take care that "fai", from whatever source obtained, accurately accounts for the absorption from milk by the infant. For example, if absorption were to be obtained from a feeding experiment with the contaminant present in quite different from milk, the absorption might be quite different. Perhaps, some mention to evaluate the appropriateness of any fai term could be included.
Equation (9-2): **Review Criterion 2.** The equation appears to be mechanically OK; however, it requires the assumption that the concentration of breast milk fat is "the same as in maternal body fat" (words in the report, p 9-16). Indeed, milk fat may be drawn from body fat stores but some of the milk fat is synthesized directly in the breast. This obviously creates an error which is proportional to the fraction of fat from each source. There is also the problem that nursing mothers may have significant weight changes; thus, fm may change significantly. When this is true, the value of ff consequently will not remain constant, and may change significantly. The assumption that the concentration of the contaminant in the maternal fat compartment has reached steady state may not be true; or when true, purging of body burden of the contaminant via milk ingested by the infant, would work to change any equilibrium present at the initiation of breast feeding.

Equation (9-3): The equation appears to be mechanically Ok; however, the objections noted for (9-2) equally apply since the equation is a modification of (9-2) designed to address the fact that the biological half-life of the compound may not be small, relative to the duration of exposure.

Significantly, the kinetic term (1 - e-kelim tpn) appears to seek to compensate for some of the problems I mentioned for (9-2). Elimination may well not be first order [see (9-2)] above. I appreciate the discussion (p. 9-17) which discusses some of these problems. I will examine with interest the next equation (9-4).

Equation (9-4): The equation appears mechanically Ok, and it addresses most of the concerns I have expressed above.

Equation (9-5): The equation appears Ok, and the discussion is good.

Equation (9-6): My concern, previously expressed, is that some fraction of breast milk fat is synthesized in the breast and will not have the same contaminant concentration as found in the milk fat that is derived from stored body fat (which may be equilibrated with maternal body fat contaminant). (Minor point: for consistency, d or day should be used in the definitions.)

Equation (9-7): The equation mechanically appears to be OK (minor points: the inconsistent use of term definitions can be confusing; e.g., the definition of hDIMAT is given as (mg/kg of body weight/day); or for ADD MAT, it is given as (mg/kg-day); also the latter (ADDMAT) should be mg/kg body weight per day.

Equation (9-8): This equation appears to be mechanically OK; however, it relies on unsound assumptions. I am unconvinced that the octanol-water partition coefficient adequately represents a true BTFm.

Minor points: the units are confusingly defined . For example, C milkfat should be (mg contaminant/kg milk fat); hTDIMAT should be (mg contaminant/day); BTFm should be 1/ (kg breast milk fat/day) (or could be written with -1 exponent, of course).

Equation (9-9): The equation is mechanically OK; however, as stated immediately above, I do not accept it as reliable. I appreciate the discussion on page 9-24, by the authors, including the fact that the equation predicts 10 times higher than measurements reported by Jensen in 1987. However, I do not agree with the author's statement in justification of its use (p. 9-24); i.e., " when model inputs cannot be found." If it is not valid, not having data, does not make it valid. It is too simplistic to apply the BTFm, in my opinion (I could be wrong!).

Equation (9-10): The equation appears to be a valid adaptation of equation 9-2. Equating concentrations of aqueous phase contaminants in milk and plasma seems to me to be appropriate. The limitations to its use (relating to lack of availability of data) appear to be significant. A minor point: in this equation (and in others), the definitions of units sometimes have been mixed in with equality assumptions, which is somewhat confusing.

Page 9-27:

Item 9.2.4.2 Concentration Proportionality Constant Between Plasma and Breast Milk Aqueous Phase (Pcbm): It appears to be valid to assume direct proportionality between breast milk aqueous phase and plasma concentration for contaminants; and the default value of 1, also appears valid.

Item 9.2.4.3 Fraction of Mother's Weight that Is Blood Plasma (fpm): The average plasma volume estimates appear valid; the default value of 0.046 is accurately calculated.

Item 9.2.5 Fraction of Ingested Contaminant that Is Absorbed by the Infant (fai):
Especially at low doses, the assumption "that the absorption fraction of most ingested lipophilic organic compounds will be high", appears valid, and they back this up with significant references to published data . Because of this, using fam for fai should not cause significant error, and the default value of 1, appears to be appropriate. I agree with their statement that this may not apply to metal salts and polar organics.

Item 9.2.6 Ingestion Rate of Breast Milk (Irmilk): The values cited, the rationale and conclusions and the default values appear to be reasonable and valid.

Item 9.2.7 Body Weight of Infant (Bwinf): The default value of 8 kg at 6-month-old infants and tabulated values for older infants, appears reasonable because the difference generated by reasonable variations, will be moderate.

Item 9.2.8 Exposure Duration (ED): The analysis appears valid and prudent. I agree that this is a variable with a wide range. It is optimistic to expect that searches for "local" breast-feeding practices will yield much of value (p. 9-30). The default value and upper percentile estimate is appear reasonable.

Item 9.2.9. Averaging Time (AT). The requirement that AT = ED is valid and the lifetime estimate appears valid.

9.6 Uncertainty in the Breast Milk Pathway Exposure to the Infant: I agree with the importance of the stated biases. Tables 9-7, 9-8, and 9-9 are significant and their inclusions are imperative. Presenting the data as a ratio is most appropriate, I agree that ignoring breast feeding losses can lead to significant errors.

The final paragraph on p. 9-31 is essential, succinctly stated and I had been looking for it all through the document. It should be set off in a section by itself, and appropriately titled. Perhaps it should be placed near the start of the document. In particular, I agree that the estimate of risk should not be overstated (they say "free of bias"). I agree that both time to steady state and breast feeding losses must be (not should be, in my opinion) considered.

The statement that... " the simple, linear models presented are unlikely to be accurate across a wide range of chemical properties and physiological processes". (I read this to be: compounds with disparate chemical properties and handled by different physiological processes).

I agree that the model uncertainty very likely is substantial. The assertion that in laboratory animal studies, the pharmacokinetics of TCDD and related compounds is highly non-linear and dose-dependent, is of great importance (and should not be tucked away withing a paragraph at the end of the document portion that I received.) There is some comfort to be taken in the statement that (paraphrasing) the linearity is better at lower, environmentally relevant doses. There is a stated need for more research, with which I agree.

Appendix C:

The appendix is quite useful, and the detailed and accurate development and derivation of elements is appreciated.

Minor point: (p. A-1): Although everyone knows mg/kg in this context is equivalent to ppm, it would be better to be consistent within the equation and definition.

Dr. Shull: General comments:
In general, the document contains excellent information underlying the modeling of chemical excretion into human breast milk.

The document could benefit greatly by presentation of a table showing the composition of human milk. We suggest this table give qualitative and quantitative data on humans as well as other species (e.g., cows, primates, etc.); other species might be used as surrogates for humans. The text should also give quantitative information on the *variation* of milk composition along with a description of factors that can alter fractions of milk (e.g., diet, races, stage of lactation, etc.). Some basic information on how the fractions of milk are separated -- whey vs. casein vs lipid -- would be helpful as well.

An illustrative pharmacokinetic model showing compartments with directional arrows would be helpful for readers to visualize the movement of substances among the various compartments (e.g., blood, adipose fat, milk fat, milk non-fat). These paper models would be helpful in comparing one model with another as well.

Tables 9-2, 9-3, 9-5 are missing from the review package.

Specific comments:

Page 9-1. In the section entitled 'Breast-Feeding: Benefits vs. Risk', *exposure levels* should be given. Toxicologic information is almost meaningless without placing 'effects' in the context of exposure. This is particularly the case when describing the risk-benefit relationship.

Page 9-2, ln 4. Persistent in the body, in the environment, or both? Metabolically resistant might be a better term.

Page 9-2, ln 9. Should provide a reference for this statement.

Page 9-2, ln 10. Should provide a reference for this statement.

Page 9-3, Table 9-1. Any other PAHs besides B(a)P, since PAHs are so common in combustion emissions.

Page 9-4, ln 7. Whereas TCDD is extremely toxic in certain lab animals, it has not proven as such in humans.

Page 9-4, ln 15. "…always found…" seems too strong. Even if it has been reported in 100% samples collected and analyzed, it is still too strong of a statement. Perhaps 'commonly found.' A reference should also been given.

Page 9-4, lns 9-13. Suggest expressing these concentrations on a 'whole milk' basis rather than a milk fat basis.

Page 9-4, ln 22. Please provide a reference for this statement.

Page 9-4, lns 27-29. Should provide a reference for this statement.

Page 9-5, lns 3-10. This statement seems unnecessary. EPA's document on TEFs should be referenced and a brief discussion stating why the TEF approach is applicable to breast milk.

Page 9-5, lns 12-15. Expressing concentrations on both a MF and whole milk basis would be preferable.

Section 9.1.1.2. We recommend that this section be expanded to other chlorinated compounds in addition to PCBs (e.g., DDT, dieldrin, heptachlor). There should be a substantial amount of very valuable information in the literature about the pharmacokinetics of excretion of other chlorinated compounds into milk. Even though the chlorinated pesticides are not frequently found in combustor emissions, they can certainly assist in validating the exposure models and in understanding the various parameters used to predict the movement of compounds among various body compartments including milk.

Page 9-5, ln 18. 'Levels' in what?

Page 9-6, lns 8-10. Confusing statement.

Section 9.1.2 In general, this section contains good information, but is poorly presented. The section could be improved by a series of clear statements at the beginning of the section about the factors that

control the distribution of chemicals among the various milk fractions. References to individual chemicals should be used to illustrate a specific point -- as it is, chemical-specific information is presented with no connection to a key point to be made. In addition, the information on page 9-10, ln 9-18 could be moved to the front of the section to provide readers a clearer objective of the need to understand the distribution of chemicals among fractions. Also, a statement should be made that babies consume the entirety of milk rather than only certain fractions. The section should begin with a clear

Page 9-8, ln 17. What is meant by the 'aqueous phase' of milk? Should define.

Page 9-8, ln 24. Re. 'discarded' -- additional explanation is needed.

Page 9-10, ln 1-9. I'm not sure of the point being made in this paragraph. The paragraph should begin with a statement followed by the use of chemical information to exemplify the point.

Section 9.1.3. This section is comprised of a series of statements that don't result in a cohesive description of the subject. It could be improved by making more conclusive type statements and use examples of different substances to illustrate key elements. The purpose of this section should be clearer -- is it simply to indicate that these substances are found in human milk, or that there is a scientific basis for how they move into milk, and that their movement into milk can be predicted?

Page, 9-10, ln 22. Should start this section by saying these substances are 'common' in human milk, without presenting data that confirms this. I don't think there is enough data on some of these substances to conclude they are 'common' in milk.

Page 9-11, ln 1-3. Methylated mercury has greater exposure potential via bioaccumulation in 'aquatic life', not just fish. Should state the type of developmental toxicity.

Page 9-11, ln 8. Reference for 'developmental toxicity' should be added.

Page 9-11, ln 8-10. Reference needed.

Page 9-11, ln 12: Has colostrum been defined yet?

Page 9-11, ln 8-18. The section should use examples of studies to conclude something about lead in milk. This section should be reworked.

Section 9.1.4. In general, this section presents the information in an acceptable manner. One suggestion is to carefully differentiate between factors that change the composition of milk, which then influences the transfer of substances into milk, from those that are chemical related.

Page 9-13, ln 2-3. This would be an excellent introductory statement to this section.

Page 9-13, ln 12-15. Cumbersome sentence. What 'fat' is being referred to here -- milk fat or body fat? Lipid is a better term. Milk fat is a common term in the dairy cattle literature.

Equation 9-1. AT needs to be corrected from t_A to AT.

Page 9-15. Regarding the choice of model; linear vs. PBPK. Perhaps the title should be changed -- the section doesn't really address 'choice.' I am unsure of the purpose of this section. While it contains useful information, there is no clear conclusion or guidance offered -- only general information.

Page 9-15, ln 4. "...can handle both…" needs to be reworded.

Page 9-15, ln 3. 'Determining' should be replaced with predicting or estimating.

Page 9-16, ln 23. Add 'maternal' body fat

Page 9-16, ln 27. Change words: Half life is longer (rather than large), and exposure duration is shorter (rather than small). Also, this statement should be referenced. Perhaps an example can be given to illustrate the point about times.

Page 9-17, ln 19-22. This example is unclear. It should be stated whether maternal exposure to PCDDs and PCDFs continued or was discontinued the one year post partum period.

Page 9-17, ln 23-26. Statement is unclear. Overprediction of milk concentration is at steady state -- we do not understand the contrast.
Page 9-21, ln 16 and Equation 9-7. The term f_{am} is generally referred to in human health risk assessments as the 'bioavailability' of a substance. Bioavailability in the maternal GIT or lungs will vary depending on the matrix in which the substance occurs. For consistency with other EPA documents, perhaps bioavailability should be used here.

Page 9-22, ln 17-18. Rationale for the central tendency value of 180 days should be provided.

Page 9-24, ln 14. Poor wording: "…work well…"

Page 9-31, ln 19-21. Poor wording.

Gulson, B.L.; Jameson, C.W.; Mahaffey, K.R.; Mizon, K.J.; Patison, N.; Law, A.J., Korsch, M.J.; and Salter, M.A. “Relationships of Lead in Breast Milk to Lead in Blood, Urine, and Diet of the Infant Mother.” *Env. Health Perspectives*. 106(10):667-674 (1998).