The Department of Defense is pleased to forward review comments (attached) developed to support EPA's Response to the National Research Council recommendations document "Health Risks from Dioxin and Related Compounds Evaluation of the EPA Reassessment." In accordance with your guidance the EPA documents were distributed and reviewed as a CLOSE HOLD task. The Department coordinated its science review with Service science representatives and other DoD experts.

The comments have been conveniently provided in a standard format matrix to assist the reader in cross referencing of the draft documents. The comments generally fall into categories denoted as Global, Major (M), and Science or methods (S). The review team agreed that the comments marked as Major (M), when taken in their totality, bring to bear serious concerns of the outcome for the assessment overall. A sense of the Major issues found during the review follow:

- EPA exclusion of relevant data from a key study to estimate cancer risks.

- There exist a range of inconsistencies carried through the EPA response that when taken collectively may call into question the outcome of the assessment altogether (e.g., care to respond to NAS consideration to treat dioxin as a threshold carcinogen).

- There are areas of the EPA analysis that deviate from accepted standard risk assessment practices as previously outlined in EPA guidance and policy (e.g., use of non-standard language leading to redefinition of critical terms formulated in EPA cancer guidelines, and use of assumptions about population risk to justify assumptions about individual risk when developing cancer slope factors).

- Given EPA's novel approaches used to develop cancer slope factors for dioxin we look forward to further guidance on how to use these values to estimate probabilities of cancer incidence from exposure to dioxin; (e.g., specifically the slope factors were based upon cancer mortality instead of incidence; several different slope factors associated with varying risk levels were developed for dioxin.

- Comprehensively, and in development of toxicity values for assessing risk of dioxin we noted that the carcinogenic properties of dioxin were not assessed using a reference dose method. Acknowledging that this is EPA's policy determination; the wealth of data presented in response to the NRC review justifies harmonization of cancer and non-cancer effects to develop a reference dose, and it is our opinion

that it is not necessary to default to slope factors for dioxin cancer risk.

If there are any questions or if an EPA office is interested in discussing any of these points please feel free to contact me directly. The granting of the two-week extension was greatly appreciated and I look forward to advancing your office expert comments to support the Charge Questions as soon as possible.

Respectfully,-

Robert (Bob) Boyd -

Research Directorate (BioSystems) -
Office of the Director, Defense Research & Engineering -

Department of Defense Comments on the Draft *EPA's Response to "Health Risks from Dioxin and Related Compounds Evaluation of the EPA Reassessment" Published by the National Research Council of the National Academies,* January 2010

Comments submitted by: Robert Boyd | Organization: Department of Defense | Date Submitted: 03.26.2010

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1		Global, 5-51, Text Box 5-1.	Before addressing specific issues in EPA's response, we would like to point out some reoccurring issues and inconsistencies noted inour review. All of the implications of these findings for the qualitative and quantitative analyses and conclusions could not be determined during the time allotted for this review. The major points are briefly outlined in the following global comments. As but one example (explained in detail below), EPA's "proof" in Text Box 5-1 is a logical tautology, i.e., its assumptions include the premise it intends to prove.	The document to needs to be edited to the critical analysis and responses so that its authors and editors can ensure logical consistency in at least the main text of the document. We recommend that several logical inconsistencies, including a tautology, as well as the inconsistent use of definitions that deviate from EPA agency guidance be corrected. Before EPA releases this document to the public, **we strongly recommend that it correct these errors and the analyses that depend upon them.** As dioxin risk is also the basis for risks for a number of dioxin-like chemicals, it is especially critical that all documents related to the toxicity of dioxin be accurate.	S/M
2		Global	**Although EPA says it accepts low-dose nonlinearity, it does not follow the procedure for risk assessment that is presented in its cancer guidelines.** For cancer, a published analyses that demonstrates a dose-dependent metabolism that results in nonlinearities at low doses appears to be supported. This conclusion is further confirmed by the calculation of exposures associated with specific risks, an unnecessary step if the low-dose curve is linear as defined by EPA's cancer guidelines, i.e., risk is proportional to exposure. The approach for the dioxin cancer assessment does not use the approach in the EPA 2005 cancer guidelines for chemicals for which	Unless compelling reasons are presented, we recommend that the cancer guidelines be followed and the reference dose (RfD) method be used for establishing the cancer risks for dioxin. For dioxin, appropriately implementing the conclusion that low-dose cancer risks are nonlinear has an additional advantage of harmonizing the U.S. assessment with those of other countries, e.g., Canada and the European Union (EU). Estimating an RfD from the point of departure (POD) is expected to change the estimated risks for dioxin and dioxin-like chemicals.	S/M

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			there is evidence of low-dose nonlinearity, i.e., to calculate an RfD.		
3		Global	**The data set for TCDD is robust, and appears to be a prime opportunity to harmonize the cancer and non-cancer risk assessment**, yet this was not done. Since it is postulated that both cancer and non-cancer endpoints are mediated through Ahr interactions, this seems a reasonable approach.	Discussion relative to why cancer and non-cancer benchmarks are not harmonized should be included.	S/M
4		Global	**Multiple "oral slope factors" are presented that without implementing guidance are not useful for many programs that utilize IRIS toxicity values.** Because of the nonlinearities, the document presents separate "oral slope factors" for a series of cancer risk levels, though such slope factors only have a logical meaning for linear extrapolations. **This seems to be a new method for estimating risks**, i.e., risk-specific, multiple, "oral slope factors". We are not aware of any EPA document or review process that has evaluated this **novel and major change in EPA's risk assessment procedures**.	The presentation of risk-specific multiple slope factors needs to be highly reconsidered. We view this as a new risk assessment procedure and policy which should not be utilized on an *ad hoc* basis without the appropriate procedures for public comment and external peer review. If the multiple slope factors are retained guidance for their use should be included in the document.	S/M
5		Global	**It appears that the most relevant human data for cancer risk assessment from its key study were discarded.** The document states that, for cancer risks, the epidemiological data are the key studies, and selects one study for quantitative analysis. It also acknowledges that the pharmacokinetics (PK) and pharmacodynamics (PD) differ between chronic exposures with	We recommend that the dose-response curve for cancer risks be based on those doses for which the cancers were found and be revised accordingly. **We see these changes as necessary because in our view it is not logical to state that the high and low doses have biologically distinct**	S/M

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			limited variation and high-level exposures due to accidents. Nevertheless, the data from higher doses were not used because they are not consistent with the dose-response functions for the data at the lower exposures – a natural and expected consequence of the PK and PD differences at low and high doses that the document presents. This decision, however, eliminates the exposures where most of the cancers were found, i.e., the data that should comprise the basis for the dose-response function for cancer in humans. **EPA's Science Advisory Board (SAB) cited these issues in its comments regarding EPA using this same procedure when EPA discarded the higher dose of the epidemiological data in EPA's draft assessment of ethylene oxide.** Furthermore, discarding the data from the higher exposure levels is not the same for epidemiological studies as for animal bioassays. The usual procedure for animal data, as practiced by EPA, rests on the assumption that the dose-response function is the same at high and low doses – that is clearly not the case for this chemical. EPA has already presented data that demonstrates that the same dose-response function would not be expected to occur for dioxin. As such, the dose-response function should be fit to those data where the cancers were found, i.e., the higher doses.	**processes and then to attempt to make the high and low doses conform to the same dose-response function.** . By discarding much of the data, the power and quality of the study is also changed, this in turn, *de facto* **changes the basis on which these data were initially selected by EPA as appropriate for estimating risks**.	

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			Finally, elimination of higher data points is not an unbiased decision, as a previously published analysis (Crump et al., 2003 that is reviewed in this EPA document) states that the slope of the dose-response function increased as each of the highest dose groups were successively omitted. Crump et al. also state that the power of the study is significantly reduced by omitting some of the highest exposures. Thus, omitting some of the higher exposures was already known to increase the estimated risk while also increasing the uncertainty of the analysis by decreasing the power of the studies observations.		
6		Global	**The document redefines "linear" and "nonlinear" in a manner that is inconsistent with EPA's 2005 cancer guidelines, as well as inconsistent within the document.** The redefinitions are clear when they are presented (which is near the end of the document), but these new and non-standard definitions are not be transparent in the rest of the document, especially when this document frequently refers to risk assessment methods in EPA's cancer guidelines that have a much simpler and a different definition of linear and nonlinear. The text presented on page 5-49 does not well justify the departure from the cancer guidelines, and as the guidelines have been approved as all-agency guidelines, they	**We do not believe that fundamental risk assessment terminology should be redefined in a chemical-specific document.** We recommend that terminology from the cancer guidelines be utilized consistently in the document. If the current redefined terms are retained in the document their use needs to be better justified, used consistently in the document and definitions introduced early in the text.	S/M

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			should not be ignored without a compelling reason. **The assertion that "Linear above Threshold Model" is linear directly conflicts with EPA's cancer guidelines,** and violates their intent.. The cancer guidelines are very explicit, as stated in this document's footnote on page 5-49, for the purposes of the cancer guidelines, and hence for the purposes of low-dose extrapolation, *all threshold models are nonlinear*. **Moreover, the term "linear" is not used consistently in this document.** Several examples occur in section 5.2.3.4.1.2., some of which are discussed in more detail in the comments below. Furthermore, as these definitions are presented at the end of the document, the reader can not be expected to understand the novel use of these common terms in the prior sections. Therefore, as presented, we do not believe that the definitions are consistent with any of EPA's previous definitions of these terms. Our interpretation of the cancer guidelines is : Any dose-response function for which low doses are a straight line through the origin, i.e., no threshold, are linear. **All other dose-response functions, specifically all functions with a threshold, are nonlinear.** Consistent definitions of critical terms is one purpose for developing guidelines and guidance. Frequently redefining terms leads to confusion to the reader, as it is difficult to determine which definitions are being		

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			used in a document, discussion, etc.		
7		Global	**An inappropriate dataset was chosen for the chronic RfD.** For noncancer risks, the document concludes that the human data are the most relevant. However, the studies selected do not meet EPA's criterion (page lvi) "for noncancer, information is required regarding the appropriate time window of exposure that is relevant for a specific, nonfatal health endpoint…" For a chemical such as dioxin, where the document states that body burden or area under the curve (AUC) is the appropriate dose metric, there must be more than an acute exposure (as in the exposures for these studies) to attain the body burden. This has been the prior practice of EPA in estimating risks, e.g., that reproductive risks for these chemicals are not based on the exposure on a particular day, but rather are based on the averaged exposure that would lead to an estimated body burden. Furthermore, the analysis acknowledges that the biological and physiological parameters that are associated with toxicity at acute and high levels of exposure differ significantly from those at chronic levels of exposure. Thus, the Seveso studies demonstrate the dangers of exposures that may occur during accidents; clearly, these levels of exposure to dioxin should be avoided. **However,**	Recommend that EPA retain the estimate based on the acute exposures, **and should label this an RfD for acute exposures**. EPA should use the wealth of data it has presented to estimate a chronic exposure RfD. Toxicologists and risk assessors – and EPA in the past, e.g., for water quality – have made such distinctions.	S/M

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			other epidemiological data, which are supported by substantial data from laboratory studies, just as clearly demonstrate that chronic exposure to lower levels of dioxin are more tolerated by mammals than effects from high-level exposures due to accidents.		
8		Global	**We disagree with the characterization for TCDD as "carcinogenic to humans" for all doses; and believe that two classifications should be presented.** The data as presented in the document strongly suggest that dioxin is carcinogenic only at very high doses. As EPA's current cancer guidelines allow for different descriptors for different exposures, we believe that this is a case where that option should be implemented. Thus, we believe that dioxin should be classified as "likely to be carcinogenic to humans" at least for lower, chronic levels of exposure. We also request further clarification of the response to the NAS's request to "explain whether this conclusion reflects a finding that there is a strong association between dioxin exposure and human cancer or between dioxin exposure and a key precursor event of dioxin's mode of action…," on page 5-3. Stating that the EPA's decision is based on a "qualitative weight-of-evidence carcinogen classification" does not account for the many areas of concern, including inconsistent tumor sites and several negative epidemiology studies.	The abundant data that demonstrate different toxicities at high and low exposure levels, both acute and chronic should be utilized to differentiate the descriptor for dioxin. We suggest that "carcinogenic to humans" be limited to very high exposures and that lower exposures be classified as "likely to be carcinogenic to humans".	S/M

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9		Global	Much discussion is devoted to the hazardous interactions between TCDD and the Ahr; however, some of these interactions produce beneficial effects (e.g. induction of CYP1A1 and MFOs).	It would be useful to provide a brief background on the beneficial biological purpose of the Ahr, and why it is conserved in mammals.	E
10	Figure ES-2 Figure 2-3	Lvii 2-234	Although we agree with their inclusion, this figure is inconsistent with the inclusion of NTP studies, since they were not published in the peer-reviewed literature. As such, inclusion of NTP studies appears biased.	Recommend changing the text in the first diamond to reflect study quality or endpoint relevance instead of a strict peer review criterion.	E
11	3.3.1	3-5, line 11; 3-56, Table 3-3.	The statement that, "**TCDD is very slowly metabolized** compared to many other organic compounds, with an elimination half life in humans on the order of years following an initial period of distribution in the body" [bold text is original] is outdated and inconsistent with the rest of EPA's document and models. As stated several times in the document, and as published data from EPA's laboratories (Emond 2005) states, for higher levels of exposure, i.e., the types of exposures on which the RfD is based, "the half-life is only weeks." This is particularly important as, in the footnote of Table 3-3, EPA repeats the assertion that the half-life in humans is greater than 7 years for the doses used in the animal bioassays, e.g., very high levels. **By using greater than 7 years instead of weeks to estimate the human equivalent dose from animal bioassays, EPA will greatly underestimate the original exposure and**	The statement should be corrected to be consistent with the data and other statements in the document where EPA states that at low and chronic levels of exposure, the half-life is long, but at high and acute levels of exposure, the half-life is comparable to many chemicals and in the range of weeks. It appears that EPA has updated its conclusions based on more recent data, but has either not updated its calculations or has not updated its text. In either case, it is not clear which has occurred when such inconsistencies exist in the main text. **Any calculations that are based on this inaccurate statement should be re-estimated before the document is released for review.**	S/M

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			therefore greatly overestimate the potency of this chemical. Through the relative potency method (TEF), the toxicity of a large number of chemicals is estimated in dioxin-equivalent doses. Thus, this inaccurate estimation will have a larger effect on risk assessments than for most chemicals.		
12		3-33 Eq. 3-20 Also 5-51 line 50	This is one of many discussions in the document where the definition of linear from the cancer guidelines is not used, nor are the definitions presented in section 5 used. As this section describes, a critical aspect of the Emond et al. PBPK model that was used is the induction of the enzyme CYP1A2. Production of this enzyme is "in the form of a Hill-type function". Inspection of the equation shows that the response is not linearly proportional to dose. The various forms of the Hill equation *are inherently nonlinear* by all mathematical definitions of the term "linear" as, in its most reduced form, the independent variable (usually a form of dose or concentration) is present more than once with the same exponent.	**We recommend that he low-dose extrapolation be performed by the RfD procedure, as stated in EPA's 2005 cancer guidelines for nonlinear, low-dose functions.** The dependence of the model on the Hill equation reinforces the conclusion of EPA and others that the dose-response function is nonlinear.	S/M
13.		3-43	The PBPK model that was developed by EPA scientists was tested with data, both to optimize the parameters and (with different data) to test the predictions. The "minor modifications" made by EPA for the purposes of the dioxin reassessment **do not appear to have undergone any validation against actual data. Although this document asserts that the changes have a small effect on**	If the adjusted models have not been tested with data and have not undergone sensitivity analyses (neither is presented in this document), the modified model should not be used. **If, as asserted, the modifications make little difference in the results, changing the model for no quantitative result can only increase the uncertainty and lower the**	S/M

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			the results, this can not be accurate for all conditions, as even the original model has some limitations as described in the sensitivity analyses presented in the published papers. Indeed, this document uses the analyses in the paper for the unmodified PBPK model for its uncertainty analysis, rather than providing information on its modified model.	**confidence in the model.** The data should be reanalyzed using the model as published and as validated. Alternatively, EPA may choose to repeat the validation studies of the original model with its modifications to ensure that the statements, e.g., about sensitivity on page 3-49 are still accurate.	
14	4.2.4.2	4-15	Based upon the text, it appears model fit was determined through professional judgment rather than through statistical analyses. Regardless, specific criteria used for judging nominal fit are lacking.	Recommend that clearer language regarding the specific criteria used in judging nominal fit of dose response curves be provided.	E
15	Figure 4-4	4-51	The legend is sparse and the graph is difficult to interpret. Magnitude of human variability reflects static uncertainty value, and is not any reflection of the data. It is inconsistent to develop RfDs for each study.	Recommend either graphing endpoint-specific LOAEL and NOAEL values relative to BMD/BMDLs or the graph has little value.	E
16	5.1.2.1.1.	5-6, Temporality	Temporal responses between exposure and effect do not infer causation. They are circumstantial and required at best. Neither is prolonged latency a requirement.	Please note that exposure must precede effect, and that effect may manifest following prolonged latency following exposure, but is not necessarily a requirement.	S
17	5.1.2.2.	5-9 Specificity	It is stated that absence of specificity does not detract from causal evidence, yet none is provided. In fact, it is stated throughout that the mechanism is poorly understood. Moreover, if tumor formation is tissue specific, and all cohorts are exposed in the same manner, it is not clear what else could explain the relatively weak increases in	The paragraph needs to be edited. Recommend separating "mechanism" from "mode of action" (i.e. "mechanism of action", see also p. 5-14). The contradictions in the text need to be resolved. Acknowledge the insufficient human epidemiological data and variability in animal response. Stronger causal data may be found	S

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			overall cancer incidences. Interesting relationships and hypotheses are presented, but more is needed for any statements regarding causality.	in the controlled animal data.	
18	5.1.2.3.4	5-18	It is stated that other studies have not ruled out involvement of the Ahr in the mediation of adverse effects, yet sections of the text cite studies in which Ahr negative knockout mice have shown to produce adverse effects at high exposures (Fernandez-Salguero et al. 1996). Moreover, since it is recognized that the mechanism for carcinogenicity is unknown, it cannot be stated that AhR interactions are a necessary early event (see also comment 2).	Please modify the text accordingly.	E
19	5.2.2	5-22, line 18	The choice of the percent response, i.e., the benchmark response or BMR, for the POD for extrapolation is not justified here, except to state that, in the 2003 modeling, the choice made no difference. According to EPA's cancer guidelines, the POD should be "near the lower end of the observed range, without significant extrapolation to lower doses."	We recommend tha the document justify the selection of an ED_{01} based on the data in the study, not the properties of the dose-response function that were selected.	S
20	5.2.3.2.6.8.	5-23	Bias in the blood-based measure could occur through additional and unplanned exposures (e.g. through TCDD contaminated feed, as recognized in the text).	We recommend some recognition that the kinetics could be influenced from other additional TCDD exposures, particularly from data reported from early studies.	E
21	5.2.3.2.6.11	5-44	If it is postulated that TCDD acts as promoter (e.g. phorbal esters), the logic is unclear why the log-linear extrapolation is used.	Please provide evidence that the dose response curve is not known at lower exposures. If so, the extrapolation to a $BMDL_{01}$ is probably unsupported because of great variability at the	S

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				tails. If data are available, then consider modifying the slope accordingly.	
22	5.2.3.3.	5-45	The BMDL provides the 95% confidence intervals of the dose response data. As such, they parameterize the variation of the model and do not represent "uncertainty". Uncertainty, by definition, is what is not known.	Recommend tephrasing to "variability".	E
23	5.2.3.4.1.2. Low-dose extrapolation: threshold or no threshold?	5-48	This section appears to be an attempt to redefine "linear" and "nonlinear" for EPA's 2005 cancer guidelines. While the guidelines admit that the definition used is a "narrower sense than its usual meaning in the field of mathematical modeling", redefining the terms can only lead to confusion. In particular, including "Linear above Threshold Model" as linear (page 5-50) is in direct conflict with EPA's cancer guidelines and violates their intent. The cancer guidelines are very explicit. As stated in this document's footnote on page 5-49, for the purposes of the cancer guidelines, and hence for the purposes of low-dose extrapolation, all threshold models are nonlinear.	**Basic terminology from agency guidelines should not be redefined in a chemical-specific document.** Per the EPA cancer guidelines: Any dose-response function with a threshold is nonlinear for the purposes of estimating low-dose cancer risks.	S/M
24	5.2.3.4.1.2.	5-50	The definitions presented here of types of models are not useful as some dose-response functions would fit more than one definition. The "threshold" model is part of three other models. As it is not clear if "linear above a threshold" is considered "linear", the definition of "nonlinear" is also not clear. If we assume that EPA intends the	The non-standard definitions presented in this section do not consider the considerable effect the presence of a threshold has on both risk assessment and risk perception and we believe should not be used. One of the two mutually exclusive groups used to divide carcinogens from EPA's 2005	S/M

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			"linear above a threshold" to be considered "linear", then all of the definitions include the "zero at zero" model, as described in the paragraph after the definitions. As not all dose-response functions are "zero at zero", however, these definitions are confusing, as no one definition describes a coherent set of models. By (1) redefining "linear" to include "linear above a threshold" and (2) proposing that all classifications of models include thresholds, the document proposed definitions that have no useful function under current guidance. Prior to the 2005 cancer risk guidelines, EPA assumed all carcinogens had no threshold. EPA's 2005 guidelines divide carcinogens into two mathematically, mutually exclusive groups, "linear" and "nonlinear", and present different methods for the risk assessment of each group. By EPA's standard definitions, all "linear" functions must not have a threshold, and all threshold functions must be "nonlinear". Some functions that do not have a threshold are also nonlinear.	guidelines, "linear" or "nonlinear" should be used.	
25	5.2.3.4.1.2.	5-50	Traditionally, individual risks have been used in risk assessment. Using population risks to impose conditions on individual risks is not consistent with current practice. According to EPA's cancer guidelines, decisions	Unlike other IRIS documents, this document considers population risks in addition to the standard individual risks. We believe that **EPA should clearly state if it is intending this discussion to mark a change in policy.** The document should also explain why or how	S/M

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			regarding low-dose extrapolation procedures depend (in this case) on the existence of a threshold for the individual risk, not population risk.	the lack of a population threshold would affect existence of an individual threshold. Furthermore, the conclusions should not be based on the limited number of examples that conform to the thesis presented.	
26	5.2.3.4.1.2.	5-51, Text Box 5-1.	**The analysis in the text box doe no appear to be correct. It is a logical tautology.** The text states as its premise that each individual in the population has a threshold and that this analysis is to examine the resulting population threshold. However, by setting the limits of integration for the thresholds, T, from 0 to δ, EPA has defined some members of the population to have no threshold, i.e., T = 0 is the lower limit of integration. **By assuming that some individuals in the population may not have a threshold for this response, the population risk has been defined to have no threshold.** Thus, the rest of the "proof" is unnecessary. Furthermore, it assumed that the thresholds are "uniformly distributed". A uniform distribution is highly unlikely, as it assumes that the proportion of people with a given value for a threshold are always the same, i.e., the number of people with a threshold at the 99th percentile would be the same as the number of people with a threshold at the 59th percentile. **By assuming a uniform distribution, it has been ensured that the probability of**	If the section on population risks is retained, it should be edited to increase its validity. If part B of the text box is retained, a citation it should provided for the fundamental assumption that the response would be logarithmically proportional to dose near a threshold. Alternatively, EPA could clearly state that, if this condition were true, then the analysis might have utility, but that many dose-response functions are not expected to have this property.	S

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			individuals in the population having a no threshold is as likely as any other value for an individual's threshold. The assumption of a uniform distribution for T, along with the other assumptions in the example, ensures a biased estimate of the population threshold, unless the true threshold is less than or equal to the value of ($\delta - T$). Assuming that δ is small relative to T and that (as stated) $\delta > T$, integrating between the limits of 0 and δ will result in most of the probability mass for the distribution on T to be much less than T. For part A, assumes that the response is proportional to ($\delta - T$). This is only accurate for the case defined as "linear above a threshold". If, for example, the response were proportional to $(\text{dose})^2$, then the integral would be of $(\delta - T)^2$, with a different outcome. Under these conditions, it is not clear that the slope will be zero for the population threshold. Part B appears tobe unnecessary. There is no *a priori* reason to believe that the response is logarithmically proportional to dose near the threshold – or any other part of the dose-response curve. We assume that this function was used because it is one of the few, in addition to the linear above a threshold, for which the desired property is true.		

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27	5.2.3.4.1.2.	5-51, line 51	The Hill equation is not linear at low doses. The tangent to the Hill equation is used to estimate one of the parameters. The equation is not a straight line for any value, although the linear approximations for parts of the curve are useful for estimating some toxic parameters.	The statements should be corrected to be mathematically accurate.	S
28	5.2.3.4.1.2.	5-51, line 52	The Michaelis-Menten equation is not the linear form of the Hill equation. It is the form where the Hill exponent is equal to 1.	Statement needs to be corrected.	S
29	5.2.3.4.1.2.	5-51, line 53	The statement, "Linearity … is a fundamental conserved characteristic in living systems" requires a reference, we question its accuracy. As noted in many publications including EPA's physiologically based pharmacokinetic (PBPK) analysis presented in this document as well as EPA's analysis of using (body weight)$^{3/4}$, most living systems rely on an allometric scaling that is not linear, even by the definitions presented herein. Moreover, many of the examples EPA presents in this document assume that "living systems" are log-linear that is not the same as linear.	This assertion should be removed or provide explanation why allometric scaling is not justified for this chemical. The broad term "living systems" warrants better definition.	S
30	5.2.3.4.1.2.	5-52 including Text Box 5-2.	This very limited discussion of receptor binding is dependent on a very narrow set of conditions, not all of which would be expected for many of the well studied receptors. The discussion, including that in the text box, assumes a Hill exponent of 1, i.e., the Michaelis-Menten equation. Many well-known examples, e.g., hemoglobin, have receptors for which the Hill exponent is greater than one (in that case, 4) and yet the basis for receptor binding	In this discussion of receptor binding, equally valid alternative examples should be included. Such examples are readily available, but can be provided upon request.	S

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			analysis is still the law of mass balance. Volumes, e.g., *Methods in Enzymology*, Volume 249, 1995, have been written on the possible variations that have different properties than those assumed for these examples.		
31	5.3	5-66. 5-93, Table 5-19.	As stated, all of the epidemiology studies are based on cause of death, and therefore, are related to cancer *mortality*. EPA's risk estimate procedures, are based on cancer *incidence*. Cancer incidence is also the basis for several regulatory programs. **It appears, however, that EPA has neither adjusted for the difference between cancer incidence and cancer mortality nor has it appended a qualifying note to its oral slope factors.** We expect that people will use the cancer potency factors assuming that they are estimating cancer incidence when they are estimating cancer deaths. Note that, when data for both mortality and incidence were available (Table 5-19., Becher et al.) "steeper dose-response [were] seen for cancer mortality". Steeper dose-response functions would result in higher cancer potencies.	Ideally a slope factor useful for estimating the probability of cancer incidence would be presented in the document, as several Federal and State programs regulate carcinogens on this basis, not mortality. The use of mortality data without adjustment should be justified, especially as the information it presents indicates that mortality data may yield higher risk estimates than the incidence data, at least for this chemical. EPA should ensure that its oral slope factors clearly indicate that the risk estimates are for cancer mortality not cancer incidence. This is particularly important for summary tables, e.g., Text Box ES-1 and EPA's IRIS database.	S/M
32	Appendix B		From our review of Appendix B, we believe that the criteria used to include or exclude studies from the dose-response assessment may not be consistently applied. **Study selection and conclusions appeared to be based heavily on results that showed positive associations**. For example, in Table B-5 the Collins et al., 2009, is the most recent study with study size and follow	All studies should be evaluated on an equal basis. All epidemiological studies have limitations, and vague criteria should not be used to selectively include or exclude data. For example, if EPA believes that there should be sufficient time between exposure and observations for cancer to develop, it should define a time for this latent period. Ideally, the	S

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			up large enough to yield precise estimates of risk and ensure adequate statistical power. Individual serum samples with TCDD analyses available for 280 former workers. Although the study demonstrates an exposure-response relationship with TCDD, "The study found no association between TDCC and death from most types of cancer." Nevertheless, this study was excluded due to insufficient follow-up of cohort with no evaluation of possible latent effects.	latent period should be chemical-specific. For dioxin, where chemical accidents have, according to the document, led to some increase in cancers, the period of time for those to become statistically above background should be sufficient for all studies. Similarly, as all of the worker cohorts had concurrent exposures to other chemicals, what were the quantitative criteria for inclusion or exclusion? If such information is not provided, the qualitative determination appears too subjective. As has been suggested before and by others, EPA should consider using some of the meta-analytic techniques to combine results across studies. **Given the extensive resources EPA has used to analyze virtually all of the reasonable data (animal and human), it would seem appropriate to combine the results to determine if the data are consistent and, if they are, to reduce the uncertainty in the risk estimate.**	