

**Department of Defense Comments on the  
Draft Toxicological Review for Dichloromethane**

Comments submitted by: Chemical  
Material Risk Management Directorate

Organization: Department of Defense

Date Submitted: 28 January 2010

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1	3.3 Metabolism 3.5 Physiologically Based Toxicokinetic Models	Global Pages 9, 12, 17, 24	The document states that, of the two pathways for dichloromethane (DCM) metabolism, the CYP pathway (page 9 line 1117) “ <i>is predominate at low exposure levels</i> ” and (line 1119) “ <i>At higher exposure levels, the CYP pathway becomes saturated and a second pathway begins to predominate.</i> ” The second pathway is the glutathione-S-transferase (GST) pathway. On page 12, line1201, it states that in humans, the saturation of the CYP pathway “ <i>appears to be approached in the 400-500 ppm range.</i> ” Since EPA asserts the mechanism for tumors requires the GST pathway, levels below the saturation of the CYP pathway should have either (a) no risk or (b) a highly attenuated risk relative to that calculated from the point of departure (POD) of the mouse data where tumors were observed, i.e., above the saturation of the CYP pathway where the additional exposure to dichloromethane is all metabolized by GST.	The human data on exposure levels for saturation of CYP and the mode of action assumed by EPA are inconsistent with a linear, no-threshold extrapolation from the POD from the mouse data. Either the model should include a threshold, or the internal dose of the GST metabolites should be attenuated based on the mouse PBTK model.	S/M
2	3.3 Metabolism 3.5 Physiologically Based Toxicokinetic Models 5.4 Cancer	Global Pages 9, 12, 17, 24	The document repeatedly (e.g., pg 17, line 1370) states that, with regard to the GST pathway, the activity is greater in mice than rats, and greater in rats than the most sensitive human, i.e., those who are GST (+/+). It states that people who are GST (+/-) have even less activity, and GST (-/-) even less. The data demonstrate that rats exposed to dichloromethane do not have statistically	If the mode of action is correct, it can no longer logically assume that people will be more sensitive than mice. If GST metabolites are required for EPA’s mutagenic mode of action and rats with more GST activity than the most sensitive person do not get cancers, it is illogical to assume people are more sensitive than rats, much less mice. This interspecies	S/M

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	Assessment		<p>significant increases in carcinogenic tumors. In 1987 EPA (page 24, line 1630) applied an interspecies scaling factor “to account for the presumed higher human responsiveness, relative to mice, to dichloromethane-induced cancer.” However the differences between the scaling factor used and presumed higher human responsiveness in 1987, versus the assumptions in this draft toxicological review are not discussed.</p> <p>Relative to the 1987 reference cited for this adjustment, the EPA web site (<a href="http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?id=49312">http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?id=49312</a>) states, “Note: EPA has updated this document, but this version is provided as a courtesy to the public as a matter of public record.” Note also that, as an External Review Draft, this reference has not been externally peer reviewed.</p>	<p>default should be eliminated as it is contradicted by the available data.</p> <p>In Section 5.4, please include discussion of different assumptions relative to human responsiveness between the supporting documentation for the 1990 IRIS assessment and the current toxicological review.</p>	
3	4.1.3, “Cancer Studies” 6.2.6. “Uncertainties in Cancer Risk Values”	Table, 4-6; 4-8;	The current scientific literature does not support the cancer descriptor that EPA is proposing, that is, that DCM is “likely to be carcinogenic to humans by all routes of exposure” and therefore, it is not justified. In fact, the literature indicates the opposite, that is, DCM is likely not carcinogenic to humans, especially at relevant environmental exposure levels as low exposures would be metabolized by a non-carcinogenic CYP pathway according to the EPA Interagency review (IAR) draft document. DCM is unlikely to be	We recommend that EPA reconsider the validity of using their proposed cancer descriptor, especially in regard to the following factors: Oral carcinogenicity data reported in animal studies; the greater sensitivity of the rodents; and the general lack of statistically significant and inconclusive data from the twelve human epidemiological studies discussed in the IAR draft document.	S

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			<p>carcinogenic to humans via the oral exposure pathway because:</p> <p>1) In a well-performed 2-year drinking water ingestion carcinogenesis bioassay in rats (Serota, et al., 1986a), the data did not exhibit any conclusive indication of a carcinogenic response.</p> <p>2) In mice, it has only been reported to induce liver tumors in a strain with a very high incidence of spontaneous liver tumors, that is, Serota et al., 1986b. These tumors did not demonstrate at dose-response effect that is expected of a positive response, and therefore were considered negative by the scientists who performed and analyzed the data. That some, but not all of the doses produced statistically significant findings as compared with the control is a much weaker finding.</p> <p>3) A very large number of consumers may be exposed to DCM in decaffeinated coffee (ATSDR 2000), yet the draft document states that the percentage of humans with liver cancer is small. Long-term occupational worker studies do not provide clear evidence of liver and/or lung tumors in DCM-exposed workers. For example, twelve epidemiological studies of cancer risk were identified in this review, of which seven were case-control studies of specific cancers with data</p>		

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			<p>on DCM exposure and four that were cohorts for which the primary solvent exposure was to DCM. These studies did not provide clear, statistically significant evidence of hepatic and/or lung tumors in DCM-exposed workers.</p> <p>4) DCM induces liver tumors by a mechanism related to GST pathway, and only after the primary pathway is saturated. Humans are much less sensitive than mice to this mode of action (MOA), as the IAR draft document states that mice are the most sensitive species, and humans are not as sensitive as rats, which do not get tumors.</p> <p>5) The significant uncertainty related to the scaling factor (7.0 for allometric scaling versus 1.0) results in a 7-fold decrease in the estimated cancer toxicity values. Lines 9060-9062 of the draft text state that "Using a whole-body GST metabolism dose metric, the resulting OSF and IUR (inhalation unit risk) for liver and lung cancer were approximately five-fold higher than when tissue-specific dose metrics were used."</p> <p>6) We agree with the EPA's conclusions that the liver cancer data derived from human studies are weak. The relevance to humans of the liver cancer data derived from animal studies has been and continues to be the subject of much scientific</p>		

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			<p>debate.</p> <p>The presence of an increased yield of liver tumors in a strain of mouse with a high background incidence of liver tumors is not sufficient to suggest that a chemical is a human carcinogen. Suggestive evidence that a chemical is a human carcinogen would require at least an increased yield of tumors in another organ or in another species with a low yield of background liver tumors.</p> <p>The results of the Serota et al., 1986b mouse study discussed in the draft toxicological review did not reveal any increase in the incidence of proliferative hepatocellular lesions in the DCM-treated female mice, despite that fact that the strain of female mice are reportedly more sensitive than males in exhibiting carcinogenicity. Thus, an increase in liver tumors in females would have been expected if DCM were carcinogenic via the oral route of exposure, especially by a mutagenic MOA that EPA claims is the case. Although treatment-related toxic effects were observed in the male and female B6C3F mouse liver following ingestion of DCM in drinking water at levels up to 250 mg/kg-day for 104 weeks, only a slight increase in proliferative hepatocellular lesions were noted and only in the male group. The lesions in the male group did not appear to be dose-related, and were</p>		

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			within historical control ranges according to the original authors' data interpretation/conclusions.		
4	4.1.3.6.1, "Case-control studies of brain cancer. 4.1.3.6.2. "Case-control studies of breast cancer. Appendix B	Pages 76-79, Lines 3023-3143.	<p>A strong association was noted (odds ratio of 6.1) for increased risk of brain cancer (that is, astrocytic brain cancer, including astrocytoma, glioblastoma, mixed glioma with astrocytic cells) with a combination of high intensity and high duration (21 years or more) of exposure in a case control study with a large sample size (Heineman et al. (1994). These results are strengthened further by the results from the Rochester, New York Eastman Kodak cohort (Hearne and Pifer, 1999). Note, however, that several of the odds ratios include 1 in the 95% confidence range and therefore would not be considered statistically significant.</p> <p>Several of the cohort studies of DCM reported an increased risk of various tumors, including in some the appearance of a dose-response relationship on the basis of years of employment or presumed high exposure levels. The results were sometimes based on a relatively small number of exposed persons (females) and varied quality of exposure data and method of exposure assessment (phone interviews, etc.). Unfortunately, these studies had limited power due to numerous confounding effects</p>	<p>Although the Blair et al. study did not report an increased incidence of brain cancer in the civilian Air Station workers, it is not clear if the controls on the Air Station Base were also exposed to jet fuel, with its known "solvent-like" effects. The potential ramifications of this possibility should be discussed further in the draft section on Hill Air Force Base workers, with an unusually large number of female workers reported to be exposed to DCM.</p> <p>Linking industrial hygiene DCM exposure civilian worker historical long-term exposure database from service records with mortality data from the National Cancer Institute database for these cancer types may yield a large cohort and should be considered. These same cohorts could be studies for potential non-cancer health impacts related to DCM exposures.</p>	S

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			Some noncancer potential impacts related to DCM exposure worth further study include the potential for ischemic heart disease (females), reproductive effects, and lower sperm count. The available data, as EPA states, can not support a positive finding in people.		
5	4.2.1.2.2 “Chronic oral exposure in B6C3F1 mice (Serota et al., 11986b; Hazelton Laboratories, 1983.”  5.3. “Uncertainties in the Oral Reference Dose and Inhalation Reference Concentration ”  6.2.6. “Uncertainties in Cancer Risk	Pages 101, Line 3664, 3667;  Page 255, Lines 7430-7431;  , 3667, etc.	DoD agrees with the original authors’ conclusions, as stated in their two year rodent studies concerning ingestion of drinking water containing DCM, that “The results gave no indications of any differences in toxic or oncogenic response between the rats and mice in response to DCM administration by the oral route” (Serota et al., 1986a). “Furthermore, the study supports the conclusion of the accompanying paper that DCM at levels in the drinking-water providing intakes as high as 250 mg/kg body weight/day does not produce any carcinogenic response in these rodents” (Serota et al., 1986b).  The toxicological review presents these authors’ conclusions regarding their results and presents EPA’s differing conclusions from the Serota et al., 1986b study, where the liver tumors in the strain of mouse used has a known high incidence of spontaneous liver tumors. It is not surprising that the percent of tumors seen in only the male mouse (and not the female mouse or male or female rat) dosed with DCM would be only slightly higher,	We recommend that EPA reconsider their use of the Serota et al. (1986b) data to derive an oral cancer slope factor.	S/M

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			<p>and thus comparable, to the percent reported in the controls. Thus, we question the suitability of the Serota et al. (1986b) mouse study data to be used to derive the oral cancer slope factor.</p> <p>DCM induces liver tumors by a mechanism related to GST pathway, as the EPA IAR draft document states humans are much less sensitive than mice to this MOA. The presence of an increased yield of liver tumors in a strain of mouse with a high background incidence of liver tumors is not sufficient to suggest that a chemical is a human carcinogen. Suggestive evidence that a chemical is a human carcinogen would require at least an increased yield of tumors in another species with a low yield of background liver tumors.</p> <p>Thus, the EPA draft document appears inconsistent in presenting species sensitivity-related conclusions and modeling solely based on carcinogenic GST mode of action.</p> <p>Although the draft authors discuss the limitations, in Chapter 6 they go on to make strong conclusions based on that dataset. In some cases, this is the sole dataset on which the EPA conclusion is based, presenting data that were not particularly supportive of the conclusion, and such uncertainties seem to be ignored.</p>		



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6	4.2.1.2.2. Chronic oral exposure in B6C3F1 mice (Serota et al., 1986b; Hazelton Laboratories 1983).	Page 101	<p>We disagree with EPA's interpretation of the data and alternative conclusion regarding the Serota et al. 1986b results, which is that DCM induced a "carcinogenic response in male B6C3F1 mice as evidenced by small, but statistically significant, increases in hepatocellular adenomas and carcinomas at dose levels of 125, 185, and 250 mg/kg-day but not at 60 mg/kg-day and by a marginally increased trend test for combined hepatocellular adenomas and carcinomas."</p> <p>According to EPA, the results for the histologic findings were restricted to mild histologic changes in the liver [vacuolization], and a slight, but statistically significant, increase in incidence in liver tumors in males only, which EPA suggested may indicate that this mouse study may not have included the maximum tolerated dose (MTD). We believe that this is unlikely, especially after reviewing the Maltoni et al. rat study, where higher doses of DCM resulted in significant rat mortality.</p> <p>EPA chose to ignore the several statistical analyses performed by the authors, and instead applied its own, single, more generic test that showed more positive values against "controls". The controls used here, however, were not those of the authors, as there were originally two control groups. By combining the two control groups, EPA negated the one positive finding of the authors that was in</p>	<p>We suggest using an alternative approach, such as the extrapolation of the NTP inhalation carcinogenic study as depicted in the draft. Although the inhalation carcinogenicity data also appears conflicting, it is preferred over the Serota et al. (1986b) male mouse data. With the large number of humans potentially exposed to DCM, we strongly urge the EPA to consider supporting additional epidemiological studies so that human data could be used instead of questionably relevant rodent data.</p> <p>If there is a lack of understanding why the authors' chose to use two control groups, the toxicological review should nevertheless, present the data as published. If EPA then chooses to combine any of the data, the document should state the rationale for doing so.</p> <p>If EPA chooses not to use the results of the sophisticated statistical analyses presented by the authors, it should clearly state why the authors' analyses are inappropriate for the data. If it chooses to use other statistical analyses that provide results that contradict those of the authors, the toxicological review should present reasons that its analyses are more appropriate and more valid than those originally published.</p>	S

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			the highest dose group and against one, but not the other, control group for that test.		
7	4.7.1 Summary of Overall Weight of Evidence	Page 194, Line 5940-5944	<p>EPA concludes “<i>Following U.S. EPA (2005a) Guidelines for Carcinogen Risk Assessment, dichloromethane is “likely to be carcinogenic in humans” by the inhalation and oral routes of exposure, based predominantly on evidence of carcinogenicity at two sites in 2-year bioassays in B6C3F1 mice (liver and lung tumors with inhalation exposure in both sexes, liver tumors with drinking water exposure in males only).</i>”</p> <p>The inhalation data appear to be appropriately summarized in this statement, but the oral exposure data are not consistent with those of the scientists who conducted the study. As the text above the table states, those scientists concluded that there was “no significantly elevated incidence compared with controls.” The data also showed no dose-response trend.</p>	<p>We believe the descriptor for the weight of evidence for DCM should be changed to “<i>Suggestive Evidence of Carcinogenic Potential</i>” based on the following.</p> <p>It is preferable to see positive results from two species, unless only one species has been tested. As EPA’s Cancer Guidelines states (section 2.2.2.1.4. Assessment of evidence of carcinogenicity from long-term animal studies.), “<i>Moreover, the absence of tumors in well-conducted, long-term animal studies in at least two species provides reasonable assurance that an agent may not be a carcinogenic concern for humans.</i>” In this case, multiple species were tested and only mice were positive by any route of exposure. Two species were negative. The particular strain of mouse that was tested is known to be sensitive to short-chain chlorinated hydrocarbons, especially for males and liver tumors. The lack of positive results in male and female F344 rats by oral or inhalation, male and female Sprague-Dawley rats by inhalation, and Syrian hamsters by inhalation demonstrate that weight of the evidence is that this chemical is not “likely to be carcinogenic</p>	S/M

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				<p>in humans”.</p> <p>As mentioned, the absence of a dose-response trend increases the probability that the study was negative as determined by the authors. In this case, dichloromethane would be positive in only one species by only one route when three species and two routes were tested.</p> <p>Finally, as discussed further below, EPA asserts that the mode of action for the liver and lung tumors in mice are by the same mode of action. If we assume that this is true, then the tumors are not biologically independent, which increases the likelihood that they are a species-and/or strain-specific phenomenon, decreasing the likelihood that dichloromethane will be carcinogenic in humans.</p>	
8	5.4 Cancer Assessment	Page 276	<p>The data used for estimating the oral cancer potency, are not a positive study. As mentioned in other comments, the scientists who performed the study and its analyses did not find either a statistically significant result. Moreover, even if (by using the different statistical analyses EPA chose) some of the data points are statistically different from the control, there was no statistically significant dose-response trend. To analyze dose-response data without a dose-response trend would necessitate ignoring some of the data.</p>	<p>EPA should not use the Serota et al. data for a dose-response analysis as they do not demonstrate a dose-response effect.</p> <p>Given that, according to the authors of the studies, the oral mouse bioassay is negative and the oral bioassay in rats is also negative, extrapolating inhalation data to a potential oral response appears questionable.</p>	S/M

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9	5.4.1.4	Pg. 271	The section states that simulations included a distribution of CYP activity from Lipscomb et al. However it seems that the GST pathway was the default at all dose levels. It is not clear how CYP activity was included in the simulations and how inclusion affected the outcome.	We recommend that text be added to this subsection to clarify how CYP activity distributions were used in the PBTK modeling and the results were impacted by including/excluding the distributions.	S
10	5.4.1.5. Oral Cancer Slope Factor	Page 273	The IAR draft states that early-life susceptibility should be assumed and the age-dependent adjustment factors (ADAFs) should be applied, in accordance with the EPA "Supplemental Guidance." This assumes that the mouse tumors associated with DCM exposure are relevant to humans, an issue that is discussed below.	If feasible, we recommend that the EPA identify whether DCM-specific ADAFs can be developed based on the scientific literature.	S
11	5.4.2.5 Cancer Inhalation Unit Risk, Consideration of combined risk (summing risk across tumors)	Global Page 287-289	<p>There are multiple consequences of the mode of action that EPA asserts for dichloromethane.</p> <ol style="list-style-type: none"> <li>1. If both lung and liver carcinogenicity have the same mode of action (as EPA states), then they are not biologically independent. If they are not independent, then their cancer risks can not be added, as the model on which combining risks is based assumes such independence, as stated by NRC (1994) and cited by EPA on page 287, line 8106.</li> <li>2. If the tumors are caused by the same mode of action, then the "two sites" of tumors used to increase the weight of evidence that dichloromethane is "likely" to cause cancer in humans is diminished as they are not independent sites but are likely to be associated</li> </ol>	<p>To the extent that EPA's conclusions depend on an inconsistent interpretation of these consequences of EPA's mode of action, they should be changed, including those listed below.</p> <ol style="list-style-type: none"> <li>1. We suggest that all of the analyses that depend on combining data from liver and lung tumors be deleted from EPA's analysis as they violate the assumptions of the model used to combine the data. Specifically, as the inhalation risk (IUR) is for the combined tumor risks, the IUR should be reduced to the higher of the individual tumor risks.</li> <li>2. As mentioned in another comment, the weight of the evidence should be changed</li> </ol>	S/M

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			<p>in a species- and dose-dependent manner.</p> <p>3. EPA's mode of action explains the lack of tumors in both rats and hamsters, i.e., that in these species the GST is insufficiently active to create a sufficiently high tissue-specific dose to cause cancer. As GST activity in all humans, even the most sensitive subpopulation, is lower than rats, people (like rats) would not be expected to have tumors. In particular, hamster cells that do not normally metabolize dichloromethane to the reactive metabolites do so when transfected with the mouse GST gene.</p> <p>4. One of the purposes of a mode of action analysis is to predict human relevance. As EPA's mode of action is dependent on GST-mediated metabolites and as humans have a threshold below which these metabolites are highly unlikely to be formed in quantities above those that did not produce tumors in rats, humans are unlikely to be at risk of cancer from exposure to dichloromethane. As EPA's cancer guidelines state, "<i>Some of the myriad ways in which information from chronic animal studies influences mode of action judgments include, but are not limited to, the following:</i></p> <ul style="list-style-type: none"> <li>• "<i>multisite and multispecies tumor effects that are often associated with mutagenic agents;</i></li> <li>• "<i>tumors restricted to one sex or species suggesting an influence restricted to gender,</i></li> </ul>	<p>to "<i>Suggestive Evidence of Carcinogenic Potential</i>".</p> <p>3. &amp; 4. The conclusions with regard to whether the hypothesized mode of action is relevant to humans (page 212, line 6436) should be changed to indicate that this mode of action is not relevant to even the most sensitive human population as, based on the rat and hamster data, the GST-mediated metabolites are highly unlikely to be formed in sufficiently high concentrations to cause tumors.</p> <p>4. &amp; 5. Given that most species have demonstrated no carcinogenic effect for dichloromethane and given that EPA's cancer guidelines state that mutagenic agents are expected to have effects in multiple species and multiple organ systems, EPA's determination that dichloromethane has a mutagenic mode of action is questionable. If it does have a mutagenic mode of action, it would be for mice only.</p>	

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			<p><i>strain, or species; ...”</i></p> <p>5. If the mode of action is not relevant to humans, then dichloromethane can not have a mutagenic mode of action for humans. Moreover, given that most species have demonstrated a lack of carcinogenicity, it is unlikely that dichloromethane has a mutagenic mode of action. As stated in EPA’s cancer guidelines, in the first bullet in the previous consequence, mutagenic agents are expected to produce cancers in multiple sites in multiple species. The opposite has been found for dichloromethane.</p>		
12	6. Major Conclusions in the Characterization of Hazards and Dose Response	Global	<p>The DoD recognizes the need to set health protective standards. Yet, a careful balance must be achieved so that potential adverse health outcomes are not overstated.</p> <p>EPA does not specifically discuss/clarify when the available data, and a review of such data, support the use of either the P450 oxidative pathway (low dose MOA) or the alternate pathway (glutathione-S-transferase (GST)). Yet a decision is made based solely on better model “fit” regardless of human relevance presented. In particular, the toxicological review is not clear in its assumptions related to dose metrics for the GSH pathway in rodents to ensure the PBTK model reflects current understanding of this specific pathway and the human relevance at low environmental exposure</p>	<p>We encourage EPA to evaluate and address the significant weaknesses, inordinately high uncertainties associated with the modeling. The specific limitations of the use of the body of literature and models/extrapolations for the estimation of dose-response relationships, identification of the mode of action (MOA); assessment of the carcinogenicity risk, and the setting of the reference dose (RfD); reference concentration (RfC) and cancer slope factor toxicity values need to be more explicitly described and addressed. We also recommend that EPA discuss and clarify its assumptions used to address limitations and uncertainties related to application of the PBTK model within a species in the “Conclusions” section of Chapter 6 and in an “Executive Summary”</p>	S

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			<p>concentrations commonly encountered. Such questions should be asked in the charge to the external reviewers as statistical and scientific questions regarding EPA's methodological approach</p> <p>EPA has not indicated its confidence in the data derived from particular supporting studies, as they have done in the past for recent chemical toxicological reviews.</p> <p>Discussion/data interpretation (to include consideration of studies with negative results) are not presented in the EPA's conclusions in Chapter 6 in regard to the apparent weakness of the animal tumor dataset (combined adenomas and carcinomas, for example, male mouse data from Serota et al., 1986b), which the EPA authors' selected for the derivation of an oral cancer slope factor (OSF)), and the relevance of these data to exposure at low environmental concentrations from DCM in drinking water solubility/limitations) and/or environmentally relevant air concentrations for indoor air vapor intrusion, etc. This is in light of the fact that low concentrations of DCM appear to follow the CYP MOA metabolic pathway and thus, do not result in tumors per EPA own discussion of these data.</p> <p>Although the animal study data are customarily at high levels of DCM exposure, the issue of dose and how the data relates to potential real-life</p>	<p>Section.</p> <p>We recommend that EPA express their overall confidence in the data they used to derive the various toxicity values, if feasible.</p> <p>We recommend the EPA discuss the relevance of the two MOAs for DCM metabolism as related to concentrations of DCM and resolve the significant conflicting discussions related to species sensitivities and the likelihood of low environmental exposure to humans resulting in a carcinogenic endpoint.</p> <p>We recommend that EPA consider providing a more balanced discussion/data interpretation (to include weight-of-evidence considerations of studies with negative results), and that the significant sources of uncertainty be clearly presented in the EPA's conclusions in Chapter 6 in regard to the apparent weakness of the animal tumor dataset, modeling uncertainties, uncertainties in distribution and elimination of DCM and/or its reactive metabolites, etc.</p>	

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Material Risk Management Directorate

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			<p>human exposures are not considered. While EPA says that there may be a statistically significant increase in the odds ratio (OR) for the incidence of adverse effects in individuals with very high exposures, those with lower exposure have almost never been observed to exhibit a statistically significant increase in OR values.</p> <p>In addition, there are numerous instances where the EPA authors discuss limitations of a dataset but then go on to make strong conclusions in Chapter 6 based on that dataset. In some cases, this is the sole dataset on which the conclusions are based, and the EPA authors have presented data in earlier sections of the IAR draft that were not particularly supportive of their conclusions. In their conclusions, however, such uncertainties seem to be ignored and are not presented.</p>		
13	6.2 Dose-Response	6.2.1. Oral RfD	<p>The calculation of increased non-cancer potency in the new IRIS Review is based on liver lesions (non-neoplastic liver foci) in a 2 yr drinking water bioassay in rats. The calculation (described briefly page 314 of the document) applied a Physiologically-based Toxicokinetic (PBTK) Model to a benchmark dose (BMD) calculation plus a composite uncertainty factor of 30: <math>3 [10^{0.5}]</math> to account for uncertainty about interspecies toxicodynamic equivalence, <math>3 [10^{0.5}]</math> to account</p>	<p>In the calculation of the recommended RfD for liver effects, a justification should be given on page 314 for the need to use uncertainty factors for interspecies toxicodynamic equivalence and toxicodynamic variability in humans. Use of these factors appears redundant with the PBTK/BMD calculations, which would appear to have already accounted for these uncertainties."</p>	S/M



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			<p>for uncertainty about toxicodynamic variability in humans, and 3 [10<sup>0.5</sup>]for database deficiencies. Uncertainty factors for interspecies toxicodynamic equivalence and toxicodynamic variability in humans are redundant with the PBTK/BMD process used.</p> <p>The calculation of the RfD presently in IRIS was based on liver lesions in an older study, also in rats. An uncertainty factor of 100 (10 for interspecies variability and 10 for intraspecies variability) was applied to the NOAEL of 6 mg/kg-day to result in the RfD of 60 µg/kg-day. Interestingly, the NOAEL in the study used in the newer IRIS review also showed a NOAEL of 6 mg/kg-day for liver lesions.</p>		
14	Appendix B: Human PBTK Dichloro methane Model	Global Page B-2, B-10	<p>There are several logical errors in the human PBTK model.</p> <ol style="list-style-type: none"> <li>1. Three distinct genotypes are averaged so that the approximate third of the population that has the genotype that has no activity and therefore no possibility of getting tumors by the assumed mechanism of action (i.e., the GST<sup>-/-</sup>) is assumed to have some probability of getting cancer via this mechanism. Averaging the most sensitive population with the totally refractory population dilutes the effect on the sensitive</li> </ol>	<p>Given the issues listed below, the cancer potencies should be recalculated.</p> <ol style="list-style-type: none"> <li>1. The three genotypes should be modeled separately; then a decision should be made as to whether the data should be combined. It would seem that, as according to the document about 1/3 of the population would be in this sensitive group, the risk assessment should be based on this sensitive population. Moreover, the PBTK model should be modified (or perhaps in</li> </ol>	S/M

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			<p>population. Moreover, this may be why the PBTK model predicts (page B-2, line 58-60, emphasis added), “<i>internal lung and liver dose in human population would have a theoretical probability of 20% for zero exposure to GST-mediated metabolites [of dichloromethane].</i>” This statement appears to say that people with no exposure to dichloromethane have a reasonably large probability of lung and liver metabolites of dichloromethane from not being exposed to dichloromethane.</p> <p>2. Some of the parameters used for estimating the distribution of body weight with age (which are assumed to have a normal distribution) have negative standard deviations -- not <math>\pm</math> a positive number, but just a negative number (Table B-2, page B-10). This is impossible by the definition of a standard deviation, and that these negative values were estimated raises issues with regard to the confidence of all of the numbers in this part of the analysis.</p> <p>3. As stated previously, EPA states that GST-mediated pathway, the relative activity is mice <math>\gg</math> rats <math>&gt;</math> most sensitive humans, GST (+/+) <math>&gt;</math> GST (+/-) people <math>&gt;</math> GST (-/-) = 0. This ranking can be observed in the liver column of Table 3-4. Yet in Table 3-11 that lists the EPA-modified parameters for <math>k_1C</math> (the first-order rate constant for GST metabolism) used in the EPA-</p>	<p>this case unmodified, as the published models apparently did not produce this result, see Table 3-6, page 30) so that people with zero exposure to dichloromethane have zero probability of receiving an internal dose of the metabolites of dichloromethane.</p> <p>2. The method for calculating the standard deviations for a normal distribution should be presented, including any computer program that was used. The process should be debugged to produce accurate values, and all of the calculations that depend on these values, i.e., all of the human PBPK models, should be run again.</p> <p>3. If the parameters in Table 3-11 accurately state the parameters used by EPA in its PBTK modeling, the parameters should be changed to more accurately reflect the data. If the parameters are incorrect in the table, the table should be corrected. The results of the PBTK model can not be reliably peer reviewed and/or reproduced until the correction is made.</p>	

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			modified PBTK model, the ranking is rat > mouse > human (+/+) > human (+/-) > human (-/-) = 0.		