Department of Defense Comments on
Benzoapyrene IASC draft Toxicological Review and Supplemental Information June 2012.pdf

Comments submitted by: Chemical Material Risk Management Program	Organization: Department of Defense	Date Submitted: 7/16/2012

*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	Preamble; Section 7.2 and 7.3		EPA should update its BMD reference and related information presented in the preamble now that the Benchmark Dose Technical Guidance document is final.	Suggest that information in Section 7.3 relative to modeling dose response data and also Section 7.2 on modeling dose. It would be very useful to include text from the BMD Technical Guidance regarding whether to convert dose to human equivalents prior or after modeling.	E
2	Executive Summary	xxxii	DoD appreciates EPA's highlighting of key issues for the analysis in this last section of the Executive Summary. There is no default guidance for interspecies scaling for dermal exposures, but in this case, the text states that data exists on interspecies differences. EPA's cancer guidelines clearly emphasizes that, even if default guidance were available, data are to be used in preference to defaults. Since there is data, it is unclear why the data were not used in preference to the invalidated default.	For this extrapolation, the cancer guidelines should be followed and the available data used for interspecies extrapolation for dermal carcinogenesis instead of a procedure that is the default (in the absence of data) for oral exposure. This comment and recommendation also apply to Section 2.5.	S/M

3	Executive Summary	xxix	"Confidence in the Chronic Oral RfC". The authors meant chronic inhalation RfC.	Replace "oral" with "inhalation"	E
4	General	NA	Given that this is an updated profile of benzo[a]pyrene and that the EPA has endorsed toxicogenomics, it is surprising that there is no mention of microarrays or genomics in this review. There are over 40 hits using the keywords benzopyrene and microarray in Pubmed many of which examine the carcinogenicity of BaP. It would be interesting to see how the results support the common held hypotheses regarding mode of actions. See EPA Interim Genomics Policy: http://www.epa.gov/spc/genomics.htm "Genomics data may allow EPA to enhance its assessments and better inform the decision-making process". Tommasi S, Kim SI, Zhong X, Wu X, Pfeifer GP, Besaratinia A. Investigating theepigenetic effects of a prototype smoke-derived carcinogen in human cells. PLoS One. 2010 May 12;5(5):e10594 Luo, W. et al. Phenotypic anchoring of global gene expression profiles induced by N-hydroxy-4-acetyaminobiphenyl and benzo[a]pyrene diol epoxide reveals correlations between expression profiles and mechanism of toxicity. Chem Res	Please discuss why genomics data are not useful, even in a supporting role, at this stage. One possible place would be in the Literature Search/Study Selection section of the document.	O

			Toxicol. 2005 18(4): 619-29. Bartosiewicz, M. et al. Applications of gene arrays in environmental toxicology: fingerprints of gene regulation associated with cadmium chloride, benzo[a]pyrene, and trichloroethylene. 2001. Environ Health Perspect. 109(1): 71-4.		
5	1	General	The use of "*" is not defined in the tables reporting animal data.	Please add a footnote defining "*" to the Tables.	E
6	1.1.1	1-7	Figure 1-1 is a very informative array of the developmental effects following oral exposure to BaP. However, the plot shown for the body weight decrease in offspring for the MacKenzie and Angevine (1981) study combined the effects observed on PND 20 and 42. The data shown is only for PND 20, while that for PND 42 is missing. Statistically significant decreases in F1 body weight were only observed in the mid- and high-dose groups on PND 20, whereas such effects were observed at all three dose groups on PND 42.	Recommend separate plot for birth outcome for PND 42.	S
7	1.1.1	1-7	Figure 1-1: According to MacKenzie and Angevine (1981), ovarian weights were not recorded because most of these animals either had no ovaries or only remnants of ovarian tissue. However, in Figure 1-1, the effects are plotted for this endpoint as “decreased ovarian weight”.	The LOAEL designation seems appropriate; however EPA should indicate in the figure that the ovarian weights were not recorded, as it did in Table 1-2.	E

8	1.1.1	1-7	Figure 1-1: For the Chen et al. (2012) data, the X-axis legend lists that the effect was measured on post-natal day (PND) 36 and 72. This is a minor error and should read "36 and 71". For Chen et al. (2012), it is appropriate to combine the two days into a single data plat as the decrease in body weight in offspring was observed only in the highest dose group on both PND 36 and 71.	Recommend changing "measured PND 36 and 72" to "measured PND 36 and 71".	E
9	1.1.1	1-14	Figure 1-2: This figure shows the effects plot for "latency negative geotaxis" from the Chen et al. (2012) study. The effects plot rightly shows that there was an increase in this endpoint at all dose levels on post-natal day (PND) 12. However, it fails to show that the same effect measured on PND 14 was statistically significantly different from controls only at the highest dose tested of 2 mg/kg-day. There is no explanation why the PND 14 results were excluded, leaving the reader to believe that the effects probably persisted at all doses when, in fact, it only persisted at the highest dose two days later.	Recommend arraying all the effects from the various studies in the figure to provide all the information obtained from these studies.	S
10	1.1	1-15	Human studies referred to on lines 2 and 3 were for PAH mixtures not BaP alone.	Please clarify that developmental effects in humans have been reported for PAH mixtures and in animals for B(a)P.	S
11	1.1.2	1-19	Table 1-5. Table does not include MacKenzie and Angevine (1981) data on Fertility and	Include MacKenzie and Angevine (1981) data for Fertility and Testicular effects in Table 1-5.	E

			Testicular effects. The 1 mg/kg-day dose for decreased intratesticular testosterone is missing what we assume is the statistical significance notation ("*").	Add "*" to the % change of intratesticular testosterone to match the plot in Figure 1-3.	
12	1.1.2	1-19	The discussion does not distinguish between biologically and statistically significant hormone changes.	As statistically significant changes, especially in non-dichotomous parameters, are often not biologically significant, the authors should report on both, especially of the results suggest effects on parameters that are designed to vary for a variety of reasons, e.g., hormones.	S
13	1.1.2	1-22	Figure 1-3: • MacKenzie and Angevine (1981) effect levels plotted in this figure are not included in Table 1-5, but data were reported in Table 1-2. Similarly, data on Testicular Effects were not reported in Table 1-5. • The citation for sperm quality parameter is listed as Chen et al. (2011). It should be Chen et al. (2011a) as in Table 1-5. • Data for testicular changes (weight, histology) reported for Mohamed et al. (2010) and Chung et al. (2011) as well as for epididymal changes (weight, histology) reported in Table 1-5 were not included in the array.	Please plot the missing data in the Figure and be consistent throughout the text, tables, and figures.	S

			Was it because the numerical data were not reported? If so, it is unclear why data for decreases in ovarian follicles were reported in Figure 1-4 (see below) from MacKenzie and Angevine (1981) and Kristensen et al. (1995) where numerical data were not reported but plotted.		
14	1.1.2	1-23, line 27	The species being discussed in this paragraph is not identified.	Please identify the species.	S
15	1.1.2	1-26	Table 1-7: Hormone levels. In the Xu et al. (2010) study, the decrease in serum estradiol level was statistically significant at the high dose tested. The 25% reduction at this dose should be identified as such.	Modify Table 1-7 to include the statistically significant serum estradiol reduction.	S
16	1.1.2	1-27	Figure 1-4. EPA used the administered doses and not the adjusted doses in plotting the effect levels for Xu et al. (2010) in this figure.	Please plot the adjusted dose for Xu et al. (2010).	S
17	1.1.2	1-27	Figure 1-4: (a) For fertility effects, EPA plotted effect levels for “decreased F1 female fertility” from MacKenzie and Angevine (1981). The lowest dose was reported as the LOAEL. The incident data reported in Table 1-7 is for the “Number of F0 females with viable litters”, but in Table 1-4 the effect reported in	Please make the necessary corrections to Figure 1-4.	S

			inconsistently reported ad "F1 female fertility". MacKenzie and Angevine also reported statistically significant decrease at the highest dose (160 mg/kg-day) tested, making the NOAEL 40 mg/kg-day. The plot and the endpoint plotted are not correct. (b) The associated text or a footnote should state that ovarian weights were not recorded by MacKenzie and Angevine (1981) and that the effect levels they plotted for "Decreases in ovarian weight" are all inferred from the qualitative information provided by these authors. (c) The effect levels plotted for "decreases in ovarian follicles" are also inferred from the MacKenzie and Angevine (1981) study since these authors did not report numerical data for this endpoint. (d) Based on information provided in Table 1-7, doses plotted for Xu et al. (2010) should be the adjusted doses. (e) The NOAEL is not identified for the data plotted from Kristensen et al.		
18	1.1.4	1-38	Table 1-9. The low dose in the Beland and Culp (1984) study should have statistical significance assigned.	Please assign statistical significance to the appropriate incidences.	E
19	1.1.4	1-39	Relevance to humans is a major part of the	Human relevance should be included in	S/M

			MOA analysis as summarized in this document's preamble. Forestomach tumors in rodents are generally not considered relevant to human carcinogenesis. The document does not address this issue until the uncertainty analysis and by its absence in earlier sections in the document the reader is allowed to infer that the tumors are relevant.	the MOA analyses for forestomach effects and it should be noted that humans have no forestomach.	
20	1.1.5	1-57	Table 1-17. Assuming that as in Table 1-15 that "*" indicates statistical significance, none of the animal dosed groups reported in this table contain statistically significant effects.	Please add "*" as appropriate.	E
21	1.1.5	I-58	While the common accepted mode of action invokes mutations in tumor suppressors (P53) or actived oncogenes (Kras), there is also evidence that MDM2, a negative regulator of P53 (and therefore non-mutagenic) can be increased with acute exposure to BaP. Malmlöf M, Pääjärvi G, Högberg J, Stenius U. Mdm2 as a sensitive and mechanistically informative marker for genotoxicity induced by benzo[a]pyrene and dibenzo[a,l]pyrene. Toxicol Sci. 2008 Apr;102(2):232-40. Epub 2007 Dec 20.	Suggest that this reference be included and discussed.	S
22	1.1.5	1-59	In our comment on the first B[a]P draft	Please modify Figure 1-7 to represent the	S/M

			Toxicological Review, we stated that Figure 1-7 shows more than just the 4 key events described in the text, and yet is also missing other information discussed in the text. For example, it is not clear how B[a]P-mediated cytotoxicity plays a role in tumor formation. The text seemed to address this on page 1-58, lines 15-17 without stating the roles these other key events play. Figure 1-7 also does not differentiate between several potential MOAs (i.e. cytotoxicity versus mutation and promotion).	known key events specific to BaP-mediated carcinogenicity, these should be distinct from general steps in the carcinogenic process. Discuss cytotoxicity as a possible separate MOA for the cancer endpoint, or clearly link how it fits temporally within the mutagenic MOA.	
23	1.1.5	1-62, line 30	There are no data provided that demonstrate dose-response concordance and temporal relationship for mutations. We provided similar comments on the first B[a]P review on the "***Dose-response concordance and temporal relationship.***" section. If data are not available, the text should so state.	Please discuss specific data on mutations as a possible MOA for the cancer endpoint.	S/M
24	1.1.5	1-63, lines 35-37	It is agreed that there is temporal consistency between BPDE-DNA adducts and forestomach tumors, however a comparison of the dose response behavior of these two endpoints is inconsistent. If tumors were based on adduct formation, why would there be a sharp increase in tumor incidence between doses, and not a linear increase as for adducts?	Please balance the discussion amongst the various possible MOAs for the cancer endpoint.	S/M

25	1.1.5	1-67, line 8	While EPA considers "Inflammatory responses to cytotoxicity may contribute to the tumor promotion process" EPA does not consider that BaP carcinogenesis might be solely due to high level exposures at the portal of entry. Much of the data presented here appear similar to that for hexavalent chromium. For example, the lack of lung tumors following oral exposure (Table B-11) and the lack of alimentary tumors after inhalation exposure (Table B-13) argue against systemic carcinogenicity.	Please consider portal of entry effects in the discussion of other possible modes of action.	S/M
26	1.1.5	1-68, lines 18-20	We earlier took exception to the statement “infants or children are expected to be more susceptible". The expectation depends entirely on the full underlying MOA. EPA (2005, page 1-17) states that: "These empirical results are consistent with current understanding of the biological processes involved in carcinogenesis, which leads to a reasonable expectation that children can be more susceptible to <u>many</u> [*not all as is implied in EPA’s BaP text*] carcinogenic agents." Furthermore, EPA (2005, page 2-29) also states: "*Identifying and comparing metabolic process differences by age, sex, or other characteristic so that susceptible*	Please provide stronger rationale of evidence for BaP as childhood carcinogen and justify the statement "expected to be more susceptible". We suggest that the comparative data between adults and children be shown. In the absence of data, revise the ADAF discussion to be consistent with EPA cancer guidelines. Incorporate specific data that indicates that an ADAF for oral cavity tumors is not needed.	S/M

			subpopulations can be recognized. For example, metabolic capacity with respect to P450 enzymes in newborn children is extremely limited compared to that in adults, so that a carcinogenic metabolite formed through P450 activity will have limited effect in the young, whereas a carcinogenic agent deactivated through P450 activity will result in increased susceptibility of this lifestage (Cresteil, 1998). A variety of changes in toxicokinetics and physiology occur from the fetal stage to post-weaning to young child. Any of these changes may make a difference for risk (Renwick, 1998)." BaP metabolites are formed, in part, by P450 enzymes, and thus, such metabolites are less likely to be formed in younger animals. Additionally, IP injections of BaP (presented as evidence) is a mostly unlikely mode of exposure for infants. The most prevalent cancers in childern are leukemias, rhabdomyosarcomas, and pediatric brain cancers none of which have a clear link with BaP. Given that BaP could be a cancer risk to children, perhaps evidence in the literature of increased cancers in children of smoking vs children of non-smoking households(?).		
27	1.1.5	1-73	It seems that two different modes of action	We believe that per the Cancer Guidelines	S/M

			could be considered per the EPA Cancer Guidelines (2005, page 3-22, excerpted below). Several examples of non linear tumor reponse are given in the document: 1. In Tables 1-15 and 1-17 all but one of the dose responses are highly nonlinear, suggesting that more than one MOA is operating. 2. On page 1-63, lines 11-14 the adduct response also patterns the findings in tumor number; the overall response is not linear. 3. Page 1-63, lines 35-37 discusses a non linear tumor response. "Both linear and nonlinear approaches may be used when there are multiple modes of action. If there are multiple tumor sites, one with a linear and another with a nonlinear mode of action, then the corresponding approach is used at each site. If there are multiple modes of action at a single tumor site, one linear and another nonlinear, then both approaches are used to decouple and consider the respective contributions of each mode of action in different dose ranges. For example, an agent can act predominantly through cytotoxicity at high doses and through mutagenicity at lower doses where cytotoxicity does not occur. Modeling to a low response level can be	that two modes of action in different parts of the dose response curve should be considered and the document revised to reflect this consideration.	

			useful for estimating the response at doses where the high-dose mode of action would be less important."		
28	2.1.2, 2.2.2, 2.3.2, 2.4.2 and 2.5.2	2-5, 2-14, 2-23, 2-29, 2-34	The Benchmark Dose Technical Guidance has been finalized and we believe the recommend practices regarding the timing of dosimetric adjustment to human equivalent doses; either before or after dose modeling, should be referenced and briefly discussed to justify the practices used in each case. Without justification it seems like there are inconsistencies for the procedures used for B[a]P.	Please reference and discuss Section 2.1.7 of the 2012 Benchmark Dose Technical Guidance and please justify the dose adjustment being performed before or after dose-response modeling in these sections.	S/M
29	2.1.2	2-5 - 2-6	It is not clear if dosimeteric adjustments made to Chen at al. 2012 were proportional and whether this impacts dose modeling performed before or after the adjustments.	Please provide evidence that adjustments are proportional across the doses used in the Chen et al. study, in which case dosimetric adjustment before modeling the data would not have to be insured.	S
30	2.1.2	2-6	In estimating human equivalent doses, the assessment uses a BWa for 0.25 kg for rats and 0.035 kg for mice and a BWh of 70 kg for humans, resulting in DAFs for rats and mice of 0.24 and 0.15, respectively. These default BWs for rats and mice are presumable appropriate for *chronic* exposures, if the authors have not otherwise measured these parameters. EPA has not specifically stated this appropriateness for chronic exposures, or discussed whether this assumption is	Please clarify whether DAFs calculated are applicable to chronic and subchronic exposures.	S/M

			appropriate for subchronic exposures.		
31	2.1.2	2-7	Table 2-1. The array of the potential PODs is well presented and makes comparison easy. However: Almost all the studies listed in this table have exposure durations of up to 90 days. The POD_{HED} for the endpoints in this table used DAFs applicable to chronic exposures. We believe this would have some impact that should be characterized in the uncertainty analysis. Forestomach effects were not included as a potential sensitive noncancer measure. However, this table includes cervical hyperplasia as a noncancer endpoint. Cervical tumors have been reported in mice with intravaginal application (Naslund et al., 1987) (page 1-73). Gao et al. (2011) also considered the hyperplasia responses to be preneoplastic lesions (page 1-25). Furthermore, EPA considered the relationship of the cervical lesions to potential development of neoplasia as uncertain (page 1-25). Epidemiological studies (pages 2-4) have demonstrated an association between cigarette smoking and increased risk of cervical cancer (Pate Capps et al., 2009). In addition, benzo[a]pyrene metabolites and benzo[a]pyrene-DNA adducts have been detected in human	BW of the experimental animals should be utilized and not just assumptions. Please use DAFs appropriate for the exposure duration or provide rationale for using the chronic DAFs for subchronic and shorter-term exposure durations and discussion of its contribution to uncertainty. Need to provide additional justification for discounting forestomach hyperplasia as noncancer effect if including cervical hyperplasia, which may also lead to cervical tumors, is considered a noncancer effect. Alternatively, cervical hyperplasia should also be discounted as a noncancer effect given that it is a preneoplastic lesion.	S/M

			cervical mucus and cervical tissues obtained from smokers (Melikian et al., 1999; Phillips et al., 2002). If all these data show that cervical hyperplasia is a preneoplastic lesion yet it is considered a noncancer effect, it is not clear why forestomach hyperplasia was excluded as a noncancer endpoint.		
32	2.1.2	2-7	Table 2-1, footnote regarding UFs: Reference is made to an EPA document titled "Dose-response analysis of ingested benzo(a)pyrene" (EPA1991a). It seems more appropriate that the reference be to the "Guidelines for Developmental Toxicity Risk Assessment" (EPA 1991c). But even looking through this document we do not see specific guidance for selection of the UFs.	Please verify the reference cited and also more clearly justify the selection of the UFs of 1.	S
33	2.1.5	2-11	"The selection of a RfD…….induction of neurodevelopmental impairments in rats exposed to benzo[a]pyrene during a susceptible lifestage is supported by a large number of animal and human studies"	Even though the supporting studies are listed elsewhere, since this is a first time derivation of a RfD for BaP, we believe it would be useful to cite the most important of those supporting studies here.	O
34	2.1.4 and 2.2.4	2-11; 2-18	A chronic RfD and a chronic RfC were derived using developmental endpoints whose critical period of exposure is far less than that considered to be a chronic exposure duration. We have found such values very difficult to apply and communicate results from while assessing	Please reconsider using developmental endpoints as candidate RfC and RfDs, the relevant exposure timeframe is not applicable in risk assessment of chronic exposures. It would be more useful to use these studies to develop a developmental RfD and RfC utilizing specific guidance for	S/M

			risks of chronic exposures.	developmental toxicity risk assessment.	
35	2.2.4-2.2.5	2-18 to 2-19	The net difference in RfD and RfC is 350-fold. This difference is very problematic and needs to be addressed, especially since the critical effects, as determined by EPA, are both systemic and developmental. Specifically: <u>RfC vs RfD</u> RfC = $2x10^{-6}$ mg/m^3 per day. Assume inhalation rate of 20m^3/d = 4×10^{-5} mg/d = mg/d RfD = $2x10^{-4}$ mg/kg-d = $1.4x10^{-2}$ mg/d RfD/RfC (assuming equivalent absorption between routes) = 350 Furthermore, multiple statements within the ADME sections of Appendix B would indicate that this finding is not supportable by data. Page B-5, line 28 "Route of administration of BaP has little influence on the tissue distribution…" Page B-14, line 9, discussing the Roth and Vinegar (1990) PBPK model states that an increased amount of BaP is cleared by the lungs compared to liver, due to metabolic enzyme	Please consider the large difference in RfD/Cs, which is not anticipated based on toxicology of BaP. This needs to be explicitly addressed in the review. If there is ADME information to support or refute such discrepancies, this needs to be thoroughly discussed. We believe that the large difference suggests that if additional data were available a lower reference value would not result and that the UFD of 10 (but was 3 in the previous draft) is an overapplication of the UF and warrants further examination.	S/M

			induction. This might suggest that the inhalation route would be less sensitive.		
36	2.2.5 (and 2.2.1)	2-19; 2-13 - 2-14	The "Minimum Data Base Criteria" of the EPA 1994 RfC Guidelines states "...the minimum laboratory animal toxicologic date base requirement for derivation of an RfC with low confidence is a well-conducted subchronic inhalation bioassay that evaluated a comprehensive array of endpoints, including as adequate evaluation of portal-of-entry (respiratory tract) effect and established an unequivocal NOAEL and LOAEL." In our previous comments, we stated that according this EPA (1994) guidelines, the inhalation (Archibong et al., 2001; Wu et al., 2003; Wombley et al., 2004; Archibong et al., 2008; Ramesh et al., 2008) is insufficient to develop an RfC. Specifically, lung effects were not sufficiently monitored, and the duration is too short. In addition to these studies, Wolff et al., 1989 assessed lung injury after only a 4 week exposure, and Thyssen et al., (1981) did not report histological examination of the lung. A reproductive/developmental RfC could be developed, but it must be annotated as such and the lack of a general RfC must be clearly stated.	An RfC should not be developed. Recommend removing the RfC development from the document, or deriving a specifically annotated reproductive/developmental RfC.	S/M

37	2.3.2.	2-23	As presented in this section, the study selected for quantitative analyses seems to have exceeded the maximum tolerated dose (MTD). While these data may be useful for qualitative analyses, the high mortality indicates that may not be suitable for quantitative analysis.	Please justify the use of the study in terms of MTD.	S/M
38	2.3.3	2-25	Table 2-7. The estimates of risk of incurring at least the tumor types listed in the first four rows should be 0.4 and not 0.5.	Please modify the estimates of risk value.	E
39	2.4.2	2-30	A reference is necessary to justify the decision that "without data to inform a basis for extrapolation to humans, it was assumed that equal risk for all species would be associated with equal concentrations. This is equivalent to assuming that any metabolism of benzo[a]pyene is directly proportional to breathing rate and that the deposition rate is equal between species." There are data that demonstrate that deposition rates are not equal between species.	Studies should be cited to justify this major assumption regarding interspecies extrapolation of inhaled particles.	S/M
40	2.4.3	2-30 to 2-31	Some of the assumptions in this section need to be justified. We have not seen the"bounding" method used before in an IRIS assessment and believe its some support for the procedure should be	Please provide references for similar use of the "bounding" procedure such as other publications or guidance. Please provide a reference or data to support the conclusion that all the tumors were unlikely to be fatal.	S/M

			provided. The basis of the conclusion "Because the tumors were unlikely to have all been fatal, the lower BMDL10 was selected for estimating the inhalation unit risk." is not provided.		
41	2.4.3	2-31	The inhalation slope factor is well matched with that derived from oral exposures, unlike for the oral RfD and inhalation RfC.	No action needed.	S
42	2.4.4	2-32, line 3	Haber's Law was developed for gasses; the assumption that it is valid for chronic toxicity for inhaled particles requires justification.	Please justify its use of Haber's Law for inhaled particles by citations to published articles or not use it for this purpose.	S
43	2.5.3	2-36, lines 5-8	We agree with the point about incomplete mortality; however, the bolus dosing of the experimental protocols needs to be discussed, since such dosing may actually serve to decrease this same risk. Defense mechanisms might be more easily overwhelmed with bolus dosing when compared to dietary exposures, especially at higher doses.	Please balance the conflicting science issues. Recommend adding a discussion regarding potential impact of bolus dosing protocols on cancer risk calculations.	S
44	2.5.4.	2-37	DoD greatly appreciates the qualifying statement "Note that the dermal slope factor should only be used with lifetime human exposures <20 µg/day, the human equivalent of the PODM, because above this level, the dose-response relationship may not be proportional to the mass of benzo[a]pyrene applied."	None required.	S

45	2.6	2-40	Rather than using default procedures, EPA needs to show these data (Vesselinovitch et al., 1975), since they appear to be a solid basis for the ADAF. Note that these data may be useful to explore different ADAFs with the different tumor types.	Please show the comparative data between adults and children. In the absence of convincing data, revise ADAF discussion to be consistent with EPA cancer guidelines by incorporating specific data that indicates that an ADAF for oral cavity tumors is not needed. Such an ADAF may be needed for other tumors.	S
46	Appendix A, Table A-1	A-1	We noted that the only state values reported are those from CalEPA. As other states also provide toxicity values for chemicals, it seems that those should be listed as well.	We suggest that either all available state values be presented or none; or that the listing of only those from CalEPA be justified.	S
47	Appendix B	B-1, line 23 to B-4 line 27	In our earlier comment, we indicated that the discussion regarding AhR's role in BaP-mediated carcinogenesis is poorly written and inadequate. BaP-specific information needs to be clearly distinguished from general AhR biology and from evidence from PAH mixture studies. Figure B-3 can be dramatically improved with more sophisticated and BaP-specific information. There are numerous sentences that are not clear within this section. AhR may be involved in regulating BaP metabolism AND/OR involved in the upregulation of genes involved in cell cycle and differentiation. These two distinct roles of AhR are not clearly described nor	Recommend significant edits to improve the evaluation of BaP-mediated AhR activation, as it relates to both tumor initiation and promotion.	S

			evaluated. Our comments were ignored.		
48	Appendix B	General	The numbering in this appendix starts over to B-1 several times.	Page numbering needs correction.	E
49	Appendix B	B-3, line 24; B-6, line 8	The number and extent of typographical errors has been improved compared to previous IASD draft Tox Reviews. We appreciate this extra round of editing. Unfortunately, a few always slip though.	Fix minor typographical errors	E
50	Appendix B	B-86, lines 5-8	EPA has not been consistent in reporting NOAELs or LOAELs in the text. For example, for the Wu et al. (2003), NOAEL or LOAEL has not been called out but these effect levels were reported for the Archibong et al. (2001) study. This lack of consistency permeates the text.	Recommend being consistent in reporting effect levels (NOAELs, LOAELs, BMDLs) for all studies for which such levels can be identified.	S

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Comments submitted by: Chemical Material Risk Management Program	Organization: Department of Defense	Date Submitted: 7/16/2012

*Comment categories: Science or methods (S); Editorial, grammar/spelling, clarifications needed (E); or Other (O). Also please indicate if Major i.e. affects the outcome, conclusions or implementation of the assessment.

Comment No.	Section	Pages	Comment	Suggested Action, Revision and References (if necessary)	*Category
1	General		See action.	We suggest that any charge question that involves clarity or completeness of the analysis also request that the reviewers opine on the accuracy of the analysis.	S/M
2	Oral Reference Dose, #4		We would like to know the panel's opinion regarding the validity of developmental RfDs representing an overall chronic RfD.	Please add "..is appropriate for development of a chronic RfD, is scientifically defensible.." at the end of the question.	S/M
3	Inhalation Reference Concentration, #4		We would like to know the panel's opinion regarding the validity of a developmental RfC representing and being applied as a chronic RfC.	Please add "...is appropriate for development of a chronic RfC..." prior to "scientifically supported".	S/M
4	Oral Slope Factor		We believe the high mortality in two of the key studies should be addressed.	Please add a new question #2 such as: ”Does the high and early mortality suggest that the maximum tolerated dose was exceeded? If the MTD was exceeded, should these data be used for estimating the cancer potency?"	S/M
5	Oral Slope		Since there are no human studies reporting an	Please add "...relevant for human exposures to	S/M

	Factor, #2		association between alimentary canal tumors and PAH or B[a]P exposure and the fact that humans do not have a forestomach, the question of the selected study's relevance to humans is important.	B{a}P.." after scientifically supported in the second sentence.	
6	Oral Slope Factor, #3		We have not seen a composite slope factor developed in an IRIS assessment and believe the panel should address it specifically.	Please add include a question addressing development of the composite oral slope factor. Some suggested language: "Part of the OSF development used a method involving the assumption that the variability in the candidate slope factors for females and males could characterized by a normal distribution which resulted in a composite slope factor. Is the composite slope factor scientifically supported and accurately developed?"	S/M
7	Oral Slope Factor, #2		Since there are no human studies reporting an association between alimentary canal tumors and PAH or B[a]P exposure and the fact that humans do not have a forestomach, the question of the selected study's relevance to humans is important.	Please add "...relevant for human exposures to B{a}P.." after scientifically supported in the second sentence.	S/M
8	Summary and Evaluation	#2	We would like the experts to be asked to provide their opinion on whether BaP is a point of contact carcinogen.	Create a question 2b, something like "Given that BaP causes GI tumors when ingested and lung tumors when inhaled and given that BaP causes tumors primarily at high doses, do the data support a mode of action that BaP is not a systemic carcinogen but causes tumors via high doses at a location of contact or concentration (e.g., forestomach by ingestion).	S/M