Department of Defense Comments on the Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures					
Comments submitted by: Office of the Secretary of Defense Chemical and Material Risk Management Directorate			Organization: Department of Defense	Date Submitted: 28 October 2009	
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1		Global	By requiring that the experiments be performed *at the same time* in the same laboratory, EPA is excluding the highest quality data (absent data from human exposure), i.e., the whole animal cancer bioassays by the standard routes of exposure, i.e., ingestion or inhalation. A logical extension of this approach would be to conclude that it is not appropriate to compare the cancer potencies estimated from any of the NTP or other sets of bioassays, as most of them were not conducted concurrently. If such data were not appropriate to compare and combine, the procedures generally used by Federal regulatory agencies to compare cancer risks and estimate risks from exposure to more than one carcinogen would also not be appropriate. Moreover, as the document is trying to establish the relative cancer potency of the PAHs, it does not seem logical to exclude the cancer potency data for the individual chemicals when they are available. Finally, the relative potency estimates from the cancer bioassays could be compared to the relative potency estimates from other data, as a good indicator of whether the other data are producing reasonable estimates.	Exclusion of the whole animal cancer bioassay data might encourage stakeholders, e.g., industrial groups that have already filed other data quality challenges to do so in this case. Thus, it is recommended that the data selection criteria should be modified and the relative potency factors (RPFs) re-estimated. Alternatively, as this document only addresses the RPFs for carcinogenicity, the document could recommend that cancer potency factors based on bioassay data by the appropriate route of exposure be used whenever chemical-specific data are available, and that RPFs only be used in their absence. This approach has the advantage of making the document evergreen, as well as being one suggested by an expert review panel that discussed the related topic of TEFs for dioxin-like compounds (teleconference of 10/22/09 conducted by Versar on behalf of EPA's Risk Assessment Forum). Please also note, the cancer bioassays that were used to estimate the RPFs included those such as intraperitoneal and implantation that are known to differ in their estimate of cancer potency than those estimated from bioassay data from oral or inhalation routes of exposure.	S, M

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2		Global	The advisory report of EPA's Science Advisory Board (SAB, 2004; Review of EPA's Draft Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens - A Report by the Supplemental Guidance for Assessing Cancer Susceptibility Review Panel of the EPA SAB. At: http://yosemite.epa.gov/sab/sabproduct.nsf/WebReportsbyYearBOARD!OpenView&Start=1&Count=800&Expand=6#6) criticized the use of simple cancer potency ratios, i.e., as estimated by q1*, for relative potency estimates. In response, EPA developed a model for determining the relative potency of cancer data for its 2005 supplemental guidance to the cancer guidelines. This model is available on EPA's web site and was programmed in R, freeware also available on the internet. Use of this model would allow stakeholders to perform analyses that use different data, e.g., to see if use of the whole animals bioassays excluded from EPA's current analyses would change the RPFs.	Given the amount of analyses that went into this document, it would seem reasonable to use the more accurate relative potency estimate model already developed by EPA (At: http://epa.gov/cancerguidelines/data-analyses.htm). To quote from the SAB (2004) report: "Even assuming a full analysis as done by Halmes et al. (2000) is not used here, the computation of the relative slope coefficients for juveniles and adults could have been done on the **log-scale** rather than the **arithmetic** scale. Since most models for cumulative incidence for tumor onset assume a functional form that includes an exponentiated dose function, changes in the point-of-departure for a fixed risk would better be reflected by a comparison of log-transformed data. The math is as follows: P(dose)=1-[1-P(0)]exp(-slope*dose) [1] Hence {log[1-P(0)]-log[1-P(dose)]}/dose=slope [2] … For small P(dose) and small P(0), the EPA formula is approximately equal to [2]; for medium range P(dose) as we have here, the equations are not the same. **This**	S, M

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				transformation is nonlinear so the resulting ratios will be different [emphasis added]**.**"	
3		Global	While the points of departure (PODs) for many of the analyses are the ED10, as noted in the comments on Appendix E, some of the PODs from point estimates appear to use much higher response levels, i.e., above the ED50. If this is an accurate interpretation of the analysis, a linear extrapolation to low dose levels can not be used, as this is a response level below which a "low level linear" dose-response function can not be expected.	If this interpretation of the analyses is incorrect, the document should be edited to prevent this interpretation. If the interpretation is correct, the analyses should be changed, and the RPFs reestimated.	S, M
4	Executive Summary	Pg. iv Para. 1 See also comments for section 2.8	The actual requirements of using EPA's dose-additive model (as described in the 1986 guidelines; Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Risk Assessment Forum, Washington, DC, 1986, at: http://epa.gov/cancerguidelines/guidelines-carcinogen-risk-assessment-1986.htm) are that the chemicals have the **same** mechanism of action; that they act as lower concentrations of the index chemical; that they **do not** interact toxicologically; and that (for the mathematical derivation to work as presented) the **log(dose)-**response curves must be parallel. [The latter requirement also requires that the chemicals have the same efficacy, e.g., the same maximal response.] The guidelines allow for approximations,	The document should be corrected and/or state that these are approximations that are often used in lieu of the stringent biological and mathematical requirements of the model.	S

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			such as those stated in this document, but the actual requirements are more stringent. Please note: the assumption about dose-response curves is consistent with EPA's SAB's recommendation to perform the analysis using an exponentiated dose function.		
5	Executive Summary	Pg. iv Para. 1	These assumptions are not equivalent to additivity. When these conditions are present, additivity of various types may be used, but so may other models, including dose-additivity within the dose-response function to generate a dose-response surface (as mentioned in one reference in the text, but which is also recommended by a number of experts in the risk assessment of mixtures of chemicals).	The documents should be corrected to say that these approximations allow the assumption of dose additivity and the RPF model.	S
6	Executive Summary	Pg. iv Para. 1 See also comments for section 2.8	The assumption of lack of interaction at low levels is often made, but ignores the possibility of one of the chemicals being a strong antagonist. While this may be a reasonable regulatory assumption, its limitations have been demonstrated experimentally with mixtures of chemicals that are similar.	Change to state that it is a reasonable **regulatory** assumption to be health protective.	S
7	Executive Summary	Pg. v Para. 2 See also comments for section 2.8	Studies of defined PAH mixtures should not be excluded, as these will demonstrate the limitations of the method. In particular, such studies of similar chemicals often demonstrate that the dose-response curve of the mixture differs significantly from that of the index chemical, e.g., does not have the same slope and/or is not equally efficacious.	Available data on mixtures of known composition should be added and used to estimate uncertainty, quantitatively, if possible.	S

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8	Executive Summary	Pg. vi Para. 1st bullet See also comments on Appendix G	While simultaneous testing of BaP and other PAHs is preferable, excluding other assays, especially *in vivo* studies, seems excessively restrictive.	If no other data are available for that chemical for that endpoint, it would seem more reasonable to use the data with a qualifying notation that the estimate is likely to be less accurate. If the less reliable data is an outlier when all data are considered for the RPF, it can be discarded later.	S, M
9	Executive Summary	Pg. vi Para. 5th bullet and 3rd Paragraph See also comments on Appendix G	Even when tumor incidence is 90% or greater, it is not clear that multiplicity of tumors is informative. Though tempting to use such data (as dose-response assessment for such data is of questionable relevance), an increase in tumors with dose in a target organ is generally only used to increase the qualitative *weight of evidence* for carcinogenicity. These data should not be used quantitatively without further justification.	Use of multiplicity of tumors for quantitative dose-response estimates is not a conventional practice and should be justified. Otherwise, these data should not be used in the analysis.	S, M
10	2.4	Pg. 34 Fig 2-3	It is not clear whether this figure is proposing one mode of action that requires all of the key events in the figure, or several potential modes of action that may require one or more of the branches. If this is all one mode of action, does EPA anticipate that all pathways are active at all doses, or might different pathways be active at different dose levels (cf. discussion on pg 42 line 17 and following text)?	Please clarify these issues. PAHs may be assumed to have a mutagenic MOA as BaP was so named in EPA's supplemental guidance (U.S. EPA. Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. U.S. Environmental Protection Agency, Washington, DC, EPA/630/R-03/003F, 2005) and the other carcinogenic PAHs by EPA's implementation memos (Communication II: Performing Risk Assessments that include Carcinogens Described in the Supplemental Guidance as having a Mutagenic Mode of Action. At:	S

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				http://www.epa.gov/osa/spc/pdfs/cgiwg_communication_ii.pdf). In this case, however, the key events posited in Figure 2-3 can not be assumed and should be proven using the MOA framework in EPA's cancer guidelines.	
11	2.4	Pg. 39	Okey et al. (1994) is not in the reference list.	Add to reference list.	E
12	2.4	Pg. 40 Line 29	Please define "linear," as many mathematically accurate definitions exist, e.g., straight line, linearly proportional to, and each variable existing only once for each power in the reduced form of the equation (i.e., the Hill equation is inherently nonlinear by this last definition).	Please define "linear" here and, if used differently elsewhere, at all points where it is used. Alternatively, only use one definition of linear in the document and use other terms, e.g., a straight line, for other circumstances.	S
13	2.4	Pg. 42 Line 25	This paragraph asserts that there may be many MOAs for PAHs. While not questioning that conclusion, none of the MOAs are discussed using the framework in EPA's 2005 cancer guidelines (U.S. EPA. Guidelines for Carcinogen Risk Assessment (2005). U.S. Environmental Protection Agency, Washington, DC, EPA/630/P-03/001F, 2005) – or any other framework. As such, the MOAs can not be considered to have been determined or established, as recognized by the normal procedures. Simply asserting an MOA does not make it so. This is surprising, as the data are likely to exist to do so.	Use EPA's 2005 cancer guidelines section on determining a mode of action for carcinogenesis, and present the data in accord with their MOA framework.	S
14	2.4	Pg. 42	No logic or data are provided for selecting the "primary mode of carcinogenic action." Given the	Selection of a primary mode of action – for all or some exposure conditions – requires more	S, M

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		Line 26	previous paragraph, it is also likely that the MOA may change with dose. If this is the primary MOA, it is not clear whether it is for the rodent bioassay, the human exposures, all exposure levels and routes, or some other exposure(s). Determining an MOA is the primary step in choosing a linear or nonlinear extrapolation for lower doses. Moreover, if different MOAs primarily act at different levels of exposure, the logic for extrapolating from a high-dose MOA to a low-dose MOA should be presented, as the dose-response functions are likely to vary substantially.	than a simple assertion in one sentence. Please provide the data and logic behind this assertion, the conditions of exposure for which it is deemed appropriate should also be provided. The data and logic as to why the other potential MOAs are not considered primary should be discussed as well.	
15	2.4	Pg. 53 Line 4	The citation of USEPA 2009 is not in the reference list. The entry for BaP states that the last revision was 12/10/1998; for benz[a]anthracene, 04/01/1997. Nor is there any such action mentioned for 2009 at http://www.epa.gov/ncea/iris/recent.htm. EPA's Office of the Science Advisor issued an implementation memo on June 14, 2006 addressing the use of PAHs using the 1993 provisional guidance, which is cited in the document. The reference lists the citation as 2008, but a search of that year in the url above as well as a search of the 75 results for a search of the IRIS site for "Polycyclic Aromatic Hydrocarbons" also did not disclose this reference.	As such a document would be most useful for an analysis of this document, the correct citation, with a more specific url than that of the IRIS internet site, should be provided. Moreover, it would be useful to provide information on the authors and reviewers of this PAH document.	E
16	2.8	Global	Although the Executive Summary states that data from complex mixtures will not be used, the main document uses such data, e.g., in this section. References are also made throughout the document	Throughout the document, the text should be modified to state that mixtures will not be used to estimate the RPFs quantitatively. More importantly, the document should also cite	S

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			to studies where complex mixtures support their analyses, e.g., section 4.2 that includes epidemiological studies.	those studies of mixtures of chemicals with a similar mechanism of action where neither dose- nor response-additivity was observed.	
17	2.8	Pg. 46 Line 30	The sentence regarding dose additivity that begins at the end of this line is illogical. If binary mixtures of PAHs "can exhibit antagonism, synergism, or additivity…" more complex mixtures must also exhibit all of these interactions. Indeed there are examples of such in the literature. Dose additivity of PAHs is a reasonable, regulatory assumption as a screening method – but it is not accurate.	It is recommended that the independent clause that begins this sentence be modified. One suggestion is, "It is reasonable to assume that, for regulatory, screening assessments, risks of PAHs are additive,…"	
18	4.1	Pg. 60-61 Line 28 and following text	It is unclear why mutagenicity, and not AhR binding, is considered relevant for estimating RPFs when a previous section (2.6) discussed that the receptor binding correlated better than mutagenicity with the cancer bioassays. If the RPFs are to vary with dose, e.g., by using the dose-response surface model proposed, as mentioned on page 48, line 27, or if the document were to propose different RPFs for different MOAs that occur at different doses, the use of mutagenicity at lower doses might be able to be justified, after the MOAs were established and the approximate dose ranges for the MOAs estimated. Finally, it would appear that mutations would be an indicator of dose and should use dose additivity, rather than response additivity. Many of the attempts to relate mutagenic potency with carcinogenic potency have demonstrated that this is not a simple correlation.	Although mutagenicity is a cancer-related endpoint, its selection for combining or comparing directly with tumor data results in a logical inconsistency that should be resolved. There are several ways that this could be accomplished, e.g., by determining a function that relates mutagenic potency for PAHs to carcinogenic potency, and it is likely that the RPFs would need to be recalculated. Use of the AhR binding data would also likely require use of a nonlinear extrapolation, as standard receptor-binding data are inherently nonlinear (e.g., Simon et al., 2009 http://toxsci.oxfordjournals.org/cgi/reprint/kfp232). Finally, the logic for using response additivity rather than dose additivity for mutagenicity as a precursor to cancer should be justified, i.e., in contrast to the use of	S, M

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				mutagenicity as an endpoint by itself. In particular, if EPA believes that there are specific mutations required for the carcinogenicity, it would seem hard to assert that a stochastic process is occurring, which is one of the assumptions for response additivity.	
19	4.3	Pg. 89 Para. 1	Positive studies that did not follow the criteria for excluding negative studies should also be excluded from the quantitative analysis. The same reasoning used to exclude the negative studies for quantitative analysis should exclude the positive studies from use quantitatively. In particular, if the animals were observed for less than 6 month **and** were positive, the potency estimate from these studies is likely to vary from the potency estimate that would be estimated from a two-year bioassay, i.e., the tumor incidence would be expected to increase with increased exposure time. Even if a time-to-tumor analysis were used, the estimated potency from a longer study might produce a different cancer potency factor. Thus, such positive studies also should be only used for a weight of evidence determination, as they would be unlikely to fulfill the conditions for estimating a slope factor and therefore, the associated RPF.	Either clarify that these positive studies were not used quantitatively, or re-estimate the RPFs without them as one method for uncertainty analysis.	S, M

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20	5.1	Pg. 107 Line 5	Although use of number, i.e., multiplicity, of tumors is "discussed in Section 4.3," neither there nor here is the rationale for the use of these data (other than that they exist) explained or referenced. Indeed, the second paragraph (line 15) states that, in many cases, incidence and multiplicity were either not correlated or inversely correlated. Justification for the use of these data should be supplied.	Use of multiplicity or tumors for a quantitative analysis of potency is a non-standard procedure. As stated in this document, studies have generally shown multiplicity to be an unreliable estimate of potency. These data should not be used.	S, M
21	8.5	Pg. 209 2nd paragraph	Chemicals with a similar mode of action should be combined by dose additive methods according to EPA's mixtures guidelines and guidance. Use of response additivity for chemicals with similar modes of action seems contrary to the assumption in that model that the chemicals act independently.	The use of response addition for chemicals with a similar mode of action requires more explanation, especially with regard to EPA's guidelines and guidance on this subject. As the document assumes a linear, no-threshold model, the results are identical quantitatively. Nevertheless, the appropriate assumptions and models should be identified and justified.	S
22	8.5	Pg. 209 Last paragraph	No data will ever completely support the assumption of additivity, as it is a useful model that is sufficiently accurate for some purposes under some sets of conditions.	This paragraph should be rewritten to reflect the reality of models rather than posit an unrealistic ideal that may raise expectations that can not be met.	S
23	Appendix D	General	It appears that most of these runs were performed in 2005. The software has been modified since then. Would this make a difference in the result, especially with regard to whether the lower confidence limit is actually a two-sided, 95% confidence limit?	If the changes in the software might change the results, the data should be run again.	S, M

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24	Appendix E	Pg. E-2	Relative potency usually is defined as the ratio of the doses required to produce the same effect. Given that the analyses were such that a dose to produce an equivalent effect, e.g., a BMR of 0.1, was always estimated, the ratio of those doses can and should be used without further calculation.	Unnecessary conversions obfuscate the data and in this case, the results should be the same.	S
25	Appendix E	Pg. E-2	Hoffmann and Wynder and other such studies in the table should not be used. EPA's cancer guidelines allow the combination of cancers with papillomas, but papillomas alone are not considered a positive response for cancer.	Recommend deleting these data from the analysis. Given the wealth of data, there is no reason to use marginal data, e.g., Rice et al. on page E-3 where the type(s) of tumors were "unspecified".	S, M
26	Appendix E	Pg. E-2	LaVoie et al.: The same method should be used to calculate the doses for all of the chemicals in one analysis. In this case, three of the chemicals used a point estimate, and presumably the BMR for the fourth (which required dropping the highest dose to get this method to work) was also not a very good fit. Changing the method by which the doses are estimated within one study is likely to add unnecessary uncertainty. Also, the use of a linear extrapolation at low dose levels is violated in some of the estimates made in this document. These data appear to have been extrapolated from a greater than *80% response level*, a response level below which a "low level linear" dose-response function can not be expected.	We suggest changing the calculation for BjF. The RPF needs to be estimated at a lower response level. Using a straight line extrapolation to the origin can only be justified from low BMRs, e.g., 10% or less. Thus, the cancer slope factor, i.e., the potency, will be incorrectly estimated, as will the relative potency.	S, M

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27	Appendix E	Pg. E-5	As stated previously, multiplicity of tumors is **not** a standard method for quantifying cancer potency. Even if this were a standard method, the process for detecting the number of tumors would need to be vetted. Even for skin tumors, small tumors may be missed, or tumors that have grown together may be incorrectly counted. Again, as most of these tumors are only papillomas or unspecified, these data should not be used anyway. Moreover, it appears that some of the data, e.g., Cavalieri et al.,1983, appear to be used for both methods, thus double-counting and overweighting these data.	It is recommended that Table E-2 be eliminated, and the data not used for calculating RPFs.	S, M
28	Appendix F	Pg. "G-1"	The page number incorrect.	The page number should be changed to F-1	E
29	Appendix G	Pg. G-1 Line 28	By requiring that the experiments be performed at the same time in the same laboratory, EPA is excluding the highest quality data, i.e., the whole animal cancer bioassays. Moreover, a logical extension of this approach would be to state that it is not appropriate to compare the cancer potencies estimated from any of the NTP or other sets of bioassays as most of them were not conducted concurrently (as discussed in Comment #1).	This criterion for exclusion of data should be changed, at a minimum for the cancer bioassays. As suggested before, the RPF method should only be used as a substitute for chemical-specific potencies. When relevant, chemical-specific data are available, they are preferable to a model that, while useful, has more uncertainties and assumptions inherent in its use.	S, M

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30	Appendix G	Pg. G-3 Line 3	Data from newborn animals should not be used in estimating RPFs, as EPA's 2005 supplemental guidance demonstrates that newborns react to these chemicals differently than the adults. These data might be able to be used to estimate different cancer potency for exposures to younger animals, as stated in EPA's 2005 cancer guidelines and supplemental guidance.	It is recommended that such data be eliminated from the RPF calculations, or if no other data are available, the resulting RPFs should have an accompanying indicator.	S, M
31	Appendix G	Pg. G-6 Line 18 and text following	This statement is puzzling, given that a quick PubMed search turned up the following citation for heterocyclic amines (HAs): Bogen KT 1994. Food Chem Toxicol. 32(6):505-15. The abstract states, "Thus, in addition to 82 tumor-type-specific potencies estimated for these compounds, 24 additional estimates of aggregate potency (to induce one or more tumor types) were made, using different methods to scale estimated bioassay cancer potency to humans. The currently unknown potency of an additional cooked-food HA was estimated using linear regressions of log-carcinogenic on log-mutagenic potency for the other 10 HAs, some of which were highly significant (e.g. $r = 0.85$, $P < 0.004$)." Also missing are citations from several studies that found no or limited correlations between cancer potency and mutagenic potency, including one by the National Academies.	A more complete data search might be useful. Negative studies should also be cited.	S
32	G-2	Pg. G-6	This section could have been significantly reduced by consulting a special issue of Mutation Research (March 1992) that addressed it.		E