TERA

Critical Review/Update of Carcinogenic Polycyclic Aromatic Hydrocarbons (PAHs) Potency Equivalence Factors (PEFs)

Presented to
Health Canada

Presented by
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Introduction

Toxicology Excellence for Risk Assessment is pleased to provide this cost estimate for the update of Potency Equivalence Factors (PEFs) for carcinogenic Polycyclic Aromatic Hydrocarbons (PAHs). This work is well within TERA's mission to support the protection of public health through the best use of toxicity data. TERA has extensive expertise in the technical approaches involved and will provide a highly efficient and technically sound approach to address the relevant issues.

Approach

Task 1 – Extraction of Data, Modeling, and Preparation of Tables

Task 1 will be carried out according to the approach described in the SOW. Specifically, the following steps will be carried out.

a) We will review the US EPA IRIS draft scientific review of PEF approach for PAH mixtures (US EPA 2010) and the USEPA SAB report (USEPA 2011a) with particular attention to the SAB's suggestions for revision. We will also take note of the US EPA response to the SAB comments (US EPA 2011b). Based on these reports, we will develop a final approach to the SOW, in consultation with Health Canada.
b) We will conduct a literature search from 2004 forward to identify additional studies for the carcinogenicity of the chemicals in Table 6-6 of the CCME document (i.e., the chemicals in Table A1 of the SOW, with the exception of benzo[a]pyrene - BaP). The literature searching will include Pubmed and Toxline. Other databases and the overall search strategy can be discussed with Health Canada. Based on the SAB criteria, the literature search will be screened to identify in vivo studies that evaluated tumors following dosing via a physiological route. All relevant studies will be retrieved and screened additionally to identify studies that also evaluated tumorigenicity of BaP or another PAH for which a high-quality PEF exists.
c) Based on the information in the US EPA (2010) report, an EXCEL spreadsheet will be prepared that contains the following information for each chemical and study: Route, short citation (to aid in internal tracking), number of data sets. This table will allow cross-checking with the US EPA report to ensure that all studies are captured, before studies are eliminated because they do not meet the SAB criteria. After the cross-checking is completed, the same information will be added for the additional retrieved studies.
d) Only studies based on the oral, inhalation or dermal routes will be investigated further. (i.e., studies via routes such as lung implantation will not be further considered)
e) PAHs without any studies via a physiological route will be noted as such and will not be further investigated.
f) For the remaining studies, the following information will be extracted: number of doses of the PAH tested; Benzo[a]pyrene (BaP) tested? If yes, how many doses? If BaP not tested, what other PAHs were tested? Was response noted, or only tumor multiplicity? Studies where only one dose of the PAH of interest and/or of BaP was tested will be

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flagged for attention as to whether the dose tested was in the high or low response region.

g) Particular attention will be paid to (1) PAHs for which only one study remains after studies via nonphysiological routes are removed, and (2) studies including only one dose of target PAH or of BaP. Studies not appropriate for inclusion will be removed, after discussion of criteria for removal with Health Canada. Conditions for inclusion of studies that include PAHs other than B[a]P as potential alternative benchmarks will be discussed with Health Canada.
h) Based on the completed summary table, PAHs that do and do not meet the criteria for inclusion will be identified
i) For those PAHs that continue to meet the criteria for inclusion, the relevant studies will be examined in greater detail, and detailed study information will be extracted, either based on the original study, or from the summary tables in US EPA (2010). The specific list of information extracted will be determined in consultation with Health Canada, but may include: Reference, study type, test chemical purity, number of animals/dose, species, tumor type, PAH, dose of PAH, dose units, mortality prior to tumor development, number of animals with tumors, number of animals in group, % tumor bearing animals; mean tumors/animal (if available); comments. This information matches that of Table C-1 of US EPA (2010), supplemented with information identified by SAB as additionally important for evaluation of study quality. Based on the extracted information, each study will be rated as low, medium or high quality, using criteria agreed upon with Health Canada.
j) For each study/species/sex/target, the PEF will be determined, either using the PEF/relative potency factor (RPF) determined by US EPA (2010), when available, or calculated for this project using benchmark dose modeling, following the approach used by US EPA (2010) and the additional recommendations of US EPA (2011a). It is assumed that <20 additional data sets will need to be modeled. The modeling output and graphs will be compiled as an appendix for the draft report, and the modeling results will be documented in a manner similar to that in Table E-1 of the US EPA (2010) report.
k) Summary information (range, summary statistics as appropriate) on the range of PEF values will be prepared for all of the PAHs that met the criteria for inclusion.

Task 2 – Draft Report

The draft report will include text documenting the approach used, the results obtained, and the conclusions reached, as well as supporting tables.

a) The data available for each PAH (excluding BaP) in Table A1 of the SOW will be described in a manner similar to that done in the EPA (2010) report. This will include the route, study type, species and sex tested, and other relevant information on study quality. If the only available studies are via a nonphysiological route, only limited additional study details will be provided. Based on this information, the reason for including or excluding the PAH for PEF calculation will be provided. If a chemical other than BaP was used as the index chemical, that chemical will be identified and a rationale provided.
b) Any PAHs for which the range of PEFs calculated is wide will be identified, and the validity of using central tendency statistics will be discussed, in light of comments in US

EPA (2011a).

c) The procedures and applicability of applying the age-dependent adjustment factor (ADAF) under the US EPA (2005) guidelines will be discussed.
d) Summary tables of PEFs will be prepared. Specifically, the following information will be included in a final table: chemical, range in potency relative to BaP; number of studies, and IARC carcinogenic classification (IARC 2010). Values for average and median potency, and any other central tendency approaches agreed to with Health Canada (e.g., a weighted geometric mean) will also be provided.
e) The draft report will also include summary tables similar to Table 1, 7-3 and 8-2 of US EPA (2010), and an update of Table 6-6 from the CCME report that includes only suitable PAHs, a recommended PEF for each PAH, and footnotes indicating how each potency value was calculated (e.g., mean, median, etc.).
f) All cited references will be included in the report text.

Task 3 – Final Report

Based on the Health Canada comments on the draft report, TERA will modify and finalize the report. If needed, we will have a teleconference with Health Canada to discuss the comments.

References

CCME (Canadian Council of Ministers of the Environment). 2010. Canadian Soil Quality Guidelines for Carcinogenic and Other Polycyclic Aromatic Hydrocarbons (Environmental and Human Health Effects). Scientific Criteria Document (revised). Soil Quality Guidelines Task Group, CCME, Winnipeg, MB.

IARC (International Agency for Research on Cancer). 2010. World Health Organization. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 92. Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures. Available at: [HYPERLINK "http://monographs.iarc.fr/ENG/Monographs/vol92/index.php"]

US EPA 2005. Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens.EPA/630/R-03/003F, March 2005.

US EPA. 2010. Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures. In Support of Summary Information on the Integrated Risk Information System (IRIS). External Review Draft. *EPA/635/R-08/012A*. U.S. Environmental Protection Agency, Washington, DC. Available at: [HYPERLINK "http://yosemite.epa.gov/sab/sabproduct.nsf/0/E65D909C98520C1D85257501005E46AE/$File/IRIS_PAH_RPF_ERD_Feb+2010.pdf"]

US EPA. 2011a. SAB Review of EPA's "Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures (February 2010 Draft). SCIENCE ADVISORY BOARD. EPA-SAB-11-004. Available at: [HYPERLINK "http://yosemite.epa.gov/sab/sabproduct.nsf/0/F24FBBBACA6EEABA852578570040C547/$Fil

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e/EPA-SAB-11-004-unsigned.pdf"]

US EPA. 2011b. EPA response letter to SAB review of EPA's "Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures (February 2010 Draft). Available at: [HYPERLINK "http://yosemite.epa.gov/sab/sabproduct.nsf/0/F24FBBBACA6EEABA852578570040C547/$File/EPA-SAB-11-004_Response_05-17-2011.pdf"]

Table A.1 from Statement of Work

Table A1. List of carcinogenic PAHs POTENCY EQUIVALENCE FACTORS (PEFs) FROM CCME (2010A)

CARCINOGENIC PAHS LISTED IN CCME (2010A)	PEF RELATIVE TO B[A]P
Benzo[a]pyrene	1
Benzo[a]anthracene	0.1
Benzo[b]fluoranthene	0.1
Benzo[j]fluoranthene	0.1
Benzo[k]fluoranthene	0.1
Benzo[g,h,i]perylene	0.01
Chrysene	0.01
Dibenzo[a,h]anthracene	1
Indeno[1,2,3-cd]pyrene	0.1

Notes:

1. Scope of work does not include Benzo[a]pyrene .
2. CCME uses one potency for Benzo[b]fluoranthene + Benzo[j]fluoranthene + Benzo[k]fluoranthene