



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
RESEARCH AND DEVELOPMENT

February 4, 2008

MEMORANDUM

SUBJECT: Request for SAB review of the Draft IRIS Assessment for Acrylamide

FROM: Ila Cote, Ph.D., Acting Director
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Office of Research and Development

TO: Sue Shallal, Ph.D.
Designated Federal Officer
EPA Science Advisory Board Staff Office (1400F)

This is to request a review by the Science Advisory Board of the draft document entitled "Toxicological Review of Acrylamide (CAS No. 79-06-1)" in support of summary information on the Integrated Risk Information System (IRIS). This document is an assessment of the potential for cancer and noncancer effects following exposure to acrylamide. The Toxicological Review of Acrylamide was prepared by the National Center for Environmental Assessment (NCEA), which is the health risk assessment program in the Office of Research and Development. The document has been made available for public comment on the Agency's NCEA web site at the following URL:

<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=187729>

The Toxicological Review of Acrylamide broadly supports activities authorized in the 1990 Clean Air Act and is applicable to the information and regulatory needs of all program Offices and Regions in evaluating the cancer and noncancer effects following exposure to acrylamide. EPA last published an assessment of the potential hazardous effect of acrylamide in 1988. The current assessment reviews more recent data and applies more recent methodology for deriving toxicity values.

Attached are the charge questions to the Science Advisory Board that provide background information as well as the questions and issues that are to be the focus of the Science Advisory Board's consultation on this assessment.

Attachment: Charge for EPA's Science Advisory Board (SAB) - IRIS Toxicological Review of Acrylamide

CHARGE FOR EPA'S SCIENCE ADVISORY BOARD (SAB)
IRIS Toxicological Review of Acrylamide

The U.S. Environmental Protection Agency (EPA) is releasing an external review draft of the revised IRIS Toxicological Review of Acrylamide that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). This revised version will replace the previous version of the IRIS Toxicological Review of Acrylamide that was posted in 1988. Science Advisory Board (SAB) review of this assessment is considered vital to the external review process. The IRIS Toxicological Review(s) is a compilation and summary of the available information on the potential for cancer and noncancer hazardous effects in humans from exposure to acrylamide. If information is sufficient to develop a quantitative characterization of the dose-response relationship for sensitive endpoints, toxicity values are derived that can be used for risk assessment including values for an oral reference dose (RfD), inhalation reference concentration (RfC), cancer oral slope factor, and inhalation unit risk.

In reviewing each of the chapters in the IRIS Toxicological Review of Acrylamide, the SAB is asked to comment on (1) whether the document is logical, clear and concise, (2) if the discussion is objectively and transparently represented, and (3) if it presents an accurate synthesis of the scientific evidence for noncancer and cancer hazard. The SAB is also asked to identify any additional relevant studies that should be included in the evaluation of the noncancer or cancer health effects of acrylamide, or in derivation of toxicity values. In addition, the SAB is asked to provide advice on the following specific charge questions related to the derivation of a proposed oral reference dose (RfD), and inhalation reference concentration (RfC) for non-cancer endpoints; cancer descriptor, oral slope factor, and inhalation unit risk for acrylamide.

Selection of Studies and Endpoints for the Oral Reference Dose (RfD)

In the draft assessment, the proposed most sensitive noncancer effect from exposure to acrylamide is neurotoxicity. This endpoint is based on an extensive database of animal and human studies. The next most sensitive effect is reproductive toxicity, which was in the 3-5 fold higher exposure range for a no effect response in animal studies. No human data were identified for acrylamide related reproductive effects. Heritable germ cell effects, a potentially serious noncancer effect, have been observed in male mice, however, the lowest dose levels tested are considerably higher (two orders of magnitude) than the doses where neurotoxicity were observed, and there is uncertainty about the shape of the low-dose-response relationship.

1. Please comment on the selection of neurotoxicity as the most appropriate choice for the most sensitive endpoint (in contrast to reproductive toxicity, heritable germ cell effects, or other endpoint) based upon the available animal and human data.
2. Please comment on the discussion of mode of action for acrylamide-induced neurotoxicity. Is the discussion clear, transparently and objectively described, and accurately reflective of the current scientific understanding?
3. Please comment on the qualitative discussion of acrylamide's heritable germ cell effects and whether the discussion is clear, transparently and objectively described, and reflective of the current science.

Derivation of the Reference Dose (RfD)

The proposed RfD (0.003 mg/kg-day) for acrylamide is based on a benchmark dose analysis of the dose-response relationship for neurotoxicity in two chronic drinking water exposure bioassays using Fischer 344 rats. Uncertainty factors and a PBPK model are used to extrapolate the animal dose-response to a human equivalent dose-response in the derivation of the RfD.

4. Please comment on whether the selection of the Friedman et al., (1995) and Johnson et al., (1986) studies as co-principal studies has been scientifically justified. Although EPA considers Friedman et al. and Johnson et al. to be co-principal studies, the final quantitative RfD value is derived only from the Johnson study. Please comment on this aspect of EPA's approach. Please also comment on whether this choice is transparently and objectively described in the document. Please identify and provide the rationale for any other studies that should be selected as the principal study(s).
5. Please comment on the benchmark dose methods and the choice of response level used in the derivation of the RfD, and whether this approach is accurately and clearly presented. Do these choices represent the most scientifically justifiable approach for modeling the slope of the dose-response for neurotoxicity? Are there other response levels or methodologies that EPA should consider? Please provide a rationale for alternative approaches that should be considered or preferred to the approach presented in the document.
6. Please comment on the selection of the uncertainty factors (other than the interspecies uncertainty factor) applied to the point of departure (POD) for the derivation of the RfD. For instance, are they scientifically justified and transparently and objectively described in the

document? [Note: This question does not apply to the interspecies uncertainty factor which is addressed in the questions on the use of the PBPK model (see PBPK model questions below)]

7. Please provide any other comments on the derivation of the RfD and on the discussion of uncertainties in the RfD.

Use of a PBPK Model in the Derivation of the RfD and the Inhalation Reference Concentration (RfC)

A physiologically-based toxicokinetic (PBTK) model originally developed by Kirman et al. (2003), and recalibrated by EPA with more recent kinetic and hemoglobin binding data in rats, mice, and humans (Boettcher et al., 2005; Doerge et al., 2005a, b; Fennell et al., 2005) was used in the derivation of the RfD to extrapolate from the animal dose-response relationship (observed in the co-principal oral exposure studies for neurotoxicity) to derive a human equivalent concentration (HEC). The HEC is the external acrylamide exposure level that would produce the same internal level of parent acrylamide (in this case the area under the curve [AUC] of acrylamide in the blood) that was estimated to occur in the rat following an external exposure to acrylamide at the level of the proposed point of departure, and related to a response level of 5% (i.e., the BMDL₅). The model results were used in lieu of the default interspecies uncertainty factor for toxicokinetics differences of 10^{1/2}, which left a factor of 10^{1/2} (which is rounded to 3) for interspecies differences in toxicodynamics.

With respect to the RfC, there are presently insufficient human or animal data to directly derive an RfC for acrylamide. The PBPK model was thus used to conduct a route-to-route extrapolation (oral-to-inhalation) to derive an RfC based on the dose-response relationship observed in the co-principal oral exposure studies for neurotoxicity. In this case, the HEC was based on a continuous inhalation exposure to acrylamide in the air that would yield the same AUC for the parent acrylamide in the blood as that estimated for the rat following an external oral exposure to acrylamide at the level of the proposed point of departure (i.e., the BMDL₅).

8. Please comment on whether the documentation for the recalibrated Kirman et al. (2003) PBTK model development, evaluation, and use in the assessment is sufficient to determine if the model was adequately developed and adequate for its intended use in the assessment. Please comment on the use of the PBTK model in the assessment, e.g., are the model structure and parameter estimates scientifically supportable? Is the dose metric of area-under-the-curve (AUC) for acrylamide in the blood the best choice based upon what is known about the mode of action for neurotoxicity and the available kinetic data? Please provide a rationale for alternative approaches that should be considered or preferred to the approach presented in the document.
9. Is the Young et al. (2007) PBTK model adequately discussed in the assessment with respect to model structure, parameter values, and data sets used to develop the model? Do you agree with the conclusion (and supporting rationale) that the recalibrated Kirman et al. (2003) model (model structure and parameter values presented in the Toxicological Review) currently represents the best model to use in the derivation of the toxicity values?
10. According to US EPA's RfC Methodology (1994), the use of PBTK models is assumed to account for uncertainty associated with the toxicokinetic component of the interspecies uncertainty factor across routes of administration. Does the use of the PBTK model for acrylamide objectively predict internal dose differences between the F344 rat and humans, is the use of the model scientifically justified, and does the use of the PBTK reduce the overall uncertainty in this estimate compared to the use of the default factor? Are there sufficient scientific data and support for use of this PBTK model to estimate interspecies toxicokinetic differences and to replace the default interspecies factor for toxicokinetic differences (i.e., $10^{1/2}$)? Is the remaining uncertainty factor for toxicodynamic differences scientifically justified, appropriate and correctly used?
11. Please comment on whether the PBTK model is adequate for use to conduct a route-to-route extrapolation for acrylamide to derive an RfC in the absence of adequate inhalation animal or human dose-response data to derive the RfC directly. Was the extrapolation correctly performed and sufficiently well documented?
12. Please provide any other comments on the derivation of the RfC and on the discussion of uncertainties in the RfC.

Margin of Exposure (MOE) Analysis

IRIS assessments do not include exposure assessments, which precludes the ability to conduct a Margin of Exposure (MOE) analysis. It has been suggested, however, that the acrylamide assessment include a Table that lists points of departure for various endpoints to facilitate a MOE evaluation by EPA's Regional or Program offices, or by other end users of the assessment.

13. Would you suggest that EPA include a Table that lists points of departure (e.g., NOAELs, BMDs, etc.) for various endpoints that could be used, in conjunction with exposure assessments, to conduct a MOE analysis?

Quantitating Heritable Germ Cell Effects

The Toxicological Review includes a discussion of methods to quantitate the risk for heritable germ cell effects (Section 5.4). The questions below address the uncertainty and utility of the quantitative results.

14. Please comment on the discussion of methods to quantitate the dose-response for heritable germ cell effects as to whether it is appropriate, clear and objective, and reflective of the current science. Has the uncertainty in the quantitative characterization of the heritable germ cell effects been accurately and objectively described?
15. Please comment on the scientific support for the hypothesis that heritable germ cell effects are likely to occur at doses lower than those seen for neurotoxicity? What on-going or future research might help resolve this issue?
16. The risks of heritable germ cell effects (i.e., number of induced genetic diseases per million offspring) for some estimated exposure in workers and the population are presented in Table 5-11, and are based on the quantitative methods and parameter estimates discussed in Section 5.4 of the Toxicological Review. Please comment on whether or not the quantitation of heritable germ effects should be conducted, the level of uncertainty in the results, if Table 5-11 is useful for risk assessment purposes, and if the RfD should be included in the Table as one of the exposure levels.
17. Do you know of any additional data or analyses that would improve the quantitative characterization of the dose-response for acrylamide-induced heritable germ cell effects? Would these data also support the quantitative characterization of "total" male-mediated reproduction risks to offspring (i.e., lethality + heritable defect)? If data are not available, do you have any recommendations for specific needed studies?

Carcinogenicity of Acrylamide

In accordance with EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), acrylamide is described as *likely to be carcinogenic to humans* based on: (1) significant increased incidences of thyroid tumors in male and female rats, scrotal sac mesotheliomas in male rats, and mammary gland tumors in female rats in two drinking water bioassays; (2) initiation of skin tumors following oral, intraperitoneal, or dermal exposure to acrylamide and the tumor promoter, TPA, in two strains of mice; and (3) increased incidence of lung adenomas in another mouse strain following intraperitoneal injection of acrylamide. Evidence from available human studies is judged to be limited to inadequate.

The mechanisms by which acrylamide may cause cancer are poorly understood, but EPA has determined that the weight of the available evidence supports a mutagenic mode of carcinogenic action, primarily for the acrylamide epoxide metabolite, glycidamide (GA). Other mode(s) of action (MOA) have been proposed for the carcinogenicity of acrylamide, but there is less support.

18. Have the rationale and justification for the cancer designation for acrylamide been clearly described? Is the conclusion that acrylamide is a likely human carcinogen scientifically supportable?
19. Do you agree that weight of the available evidence supports a mutagenic mode of carcinogenic action, primarily for the acrylamide epoxide metabolite, glycidamide (GA)? Has the rationale for this MOA been clearly and objectively presented, and is it reflective of the current science?
20. Are there other MOAs that should be considered? Is there significant biological support for alternative MOAs for tumor formation, or for alternative MOAs to be considered to occur in conjunction with a mutagenic MOA? Please specifically comment on the support for hormonal pathway disruption. Are data available on alternate MOAs sufficient to quantitate a dose-response relationship?
21. Two chronic drinking water exposure bioassays in Fischer 344 rats (Friedman et al., 1995; Johnson et al., 1986) were used to derive the oral slope factor, and to identify the tumors of interest for the MOA discussion. Are the choices for the studies, tumors, and methods to quantify risk transparent, objective, and reflective of the current science? Do you have any

- suggestions that would improve the presentation or further reduce the uncertainty in the derived values?
22. The cancer slope factor (CSF) derivation includes an adjustment for early mortality (i.e., time-to-tumor analysis). Is this adjustment scientifically supported in estimating the risk from the 2-year bioassay data for increased incidence of tumors in the rats?
 23. The dose metric used in the PBTK model analysis to derive the human equivalent concentration was area under the curve (AUC) in the blood for the putative genotoxic metabolite, glycidamide. Please comment on whether AUC for glycidamide is the best choice of the dose metric in estimating the human equivalent concentration to derive the oral slope factor. If other dose metrics are preferable, please provide the scientific rationale for their selection.
 24. As with the RfC, there were insufficient cancer inhalation data to derive an inhalation unit risk (IUR). The PBTK model was used in a route-to-route extrapolation of the dose-response relationship from the oral data, and to estimate the human equivalent concentration for inhalation exposure to acrylamide. Please comment on whether this extrapolation to derive the inhalation unit risk was correctly performed and sufficiently well documented.
 25. The recommendation to use the age-dependent adjustment factors (ADAFs) is based on the determination of a mutagenic MOA for carcinogenicity. Is this recommendation scientifically justifiable and transparently and objectively described
 26. Please provide any other comments on the CSF or IUR, and on the discussion of uncertainties in the cancer assessment.