

Draft Charge to External Reviewers for the IRIS Toxicological Review of Acrylonitrile January, 2010

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment of acrylonitrile that will appear on the Agency's online database, the Integrated Risk Information System (IRIS). IRIS is prepared and maintained by the EPA's National Center for Environmental Assessment (NCEA) within the Office of Research and Development (ORD).

The IRIS database currently contains an assessment for acrylonitrile that includes an inhalation reference concentration (RfC) (posted to the IRIS database in 1991), and an oral slope factor and inhalation unit risk (IUR) (posted to the IRIS database in 1987). The draft reassessment includes a reference dose (RfD), RfC, and carcinogenicity assessment. Below is a set of charge questions that address scientific issues in the assessment of acrylonitrile. Please provide detailed explanations for responses to the charge questions.

(A) General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA clearly synthesized the scientific evidence for noncancer and cancer hazard?
2. Please identify any additional studies that would have a significant effect on the outcome of the assessment of the noncancer and cancer health effects of acrylonitrile.

Chemical-Specific Charge Questions:

(B) Physiologically-based pharmacokinetic (PBPK) model for acrylonitrile

1. A PBPK model for acrylonitrile previously developed in rats (Kedderis et al., 1996) and extended to describe the dosimetry of both acrylonitrile and 2-cyanoethylene oxide (CEO) in humans (Sweeney et al., 2003) was modified in the assessment to include epoxide hydrolase (EH) activity in the rat model. Scientific support for this modification is based on the results of Guengerich et al. (1979) and de Waziers et al. (1990), which show the presence of EH, an enzyme that metabolized CEO, in *untreated* rat livers.

Since the previous rat model did not include EH, Sweeney et al. assumed that the *in vivo:in vitro* ratio for EH was the same as for P450. The EPA chose to scale EH based only on enzyme content (not using an activity adjustment factor). Please comment on whether the addition of EH to the rat model is justified and if the revised derivation of human parameters is appropriate.

2. CEO concentration in blood (AUC expressed on a 24-hour basis) was used as the internal dosimetric in PBPK modeling, although acrylonitrile concentration in blood (AUC expressed on a 24-hour basis) was also used for comparison. Please comment on whether the selection of CEO concentration in blood (AUC expressed on a 24-hour basis) as the internal dose metric is scientifically justified.

3. Has the PBPK modeling been appropriately conducted and clearly described?

(C) Oral reference dose (RfD) for acrylonitrile

1. An RfD for acrylonitrile has been derived from the two-year drinking water study in F344 rats (Johannsen and Levinkas, 2002; Biodynamics, 1992). Please comment on whether the selection of this study as the principal study is scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the principal study.
2. The incidence of forestomach lesions was selected as the critical effect for determination of the point of departure (POD). Please comment on whether the selection of this critical effect is scientifically justified. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.
3. The RfD has been derived based on benchmark dose (BMD) modeling of forestomach lesion incidence data in male F344 rats and PBPK modeling of CEO levels in blood (AUC/24 hours) of rats and humans assuming episodic exposure to acrylonitrile. Has the BMD modeling of CEO levels in rat blood been appropriately conducted? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., 5% extra risk) scientifically justified? Please identify and provide rationale for any alternative approaches (including the selection of BMR, model, etc.) for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.
4. Please comment on the rationale for the selection of the uncertainty factors applied to the POD for the derivation of the RfD. If changes to the selected uncertainty factors are proposed, please identify and provide a rationale.

(D) Inhalation reference concentration (RfC) for acrylonitrile

1. An RfC for acrylonitrile was derived from the epidemiologic study of neurobehavioral performance in acrylic fiber workers by Lu et al. (2005). Please comment on whether the selection of Lu et al. (2005) as the principal study is scientifically justified. Please identify and provide the rationale for any studies that should be selected as the principal study.
2. Neurobehavioral performance of exposed acrylic fiber workers was selected as the critical effect for determination of the POD. Please comment on whether the selection of this critical effect is scientifically justified. Please identify and provide the rationale for any other endpoints that should be considered in the selection of the critical effect.
3. The LOAEL of 0.24 mg/m³ for performance deficits in neurobehavioral tests from Lu et al. (2005) was selected as the POD for deriving the RfC. Has the POD been scientifically justified? Please identify and provide the rationale for any alternative approaches for the determination of the POD and discuss whether such approaches are preferred to EPA's approach.

4. EPA derived an alternative reference value from a chronic rat inhalation study (Quast, 1980) for purposes of comparison. Inflammatory and degenerative nasal lesions were selected as the critical effects. Please comment on whether the selection of these critical effects is scientifically justified.
5. BMD modeling of nasal lesion data from the rat inhalation study was conducted in order to determine the POD for the comparative reference value. Has the BMD modeling been appropriately conducted? Is the BMR selected for use in deriving the POD (i.e., 10% extra risk) scientifically justified?
6. Please comment on the rationale for the selection of the uncertainty factors applied to the POD for the derivation of the RfC. If changes to the selected uncertainty factors are proposed, please identify and provide a rationale(s).

(E) Carcinogenicity of acrylonitrile

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that acrylonitrile is *likely to be carcinogenic to humans* by all routes of exposure. Is the cancer weight of evidence characterization scientifically justified and adequately described?
2. Acrylonitrile was determined to be carcinogenic by a mutagenic mode of action. Please comment on whether the weight of the scientific evidence supports this conclusion.. Please comment on whether EPA has adequately described the data available for acrylonitrile that may support alternative modes of action.
3. An oral slope factor was derived using two-year drinking water studies in Sprague Dawley rats (Quast, 2002) and F344 rats (Johannsen and Levinskas, 2002). Please comment on whether the selection of these studies as the principal studies is scientifically justified. Please identify and provide the rationale for any other studies that should be selected as the principal study.
4. The oral slope factor was derived as a composite risk of several tumor types using a Bayesian approach. Has the modeling approach been appropriately conducted? Please identify and provide the rationale for any alternative approaches for the determination of the slope factor and discuss whether such approaches are preferred to EPA's approach.
5. The inhalation unit risk (IUR) was estimated from increased mortality from lung cancer from the Blair et al. (1998) occupational epidemiology study. The IUR was also estimated from a two-year inhalation study in Sprague-Dawley rats (Quast et al., 1980) for purposes of comparison.
 - Please comment on the selection of the Blair et al. (1998) study as the study used for quantification. Smoking data are available only for a random subset of the studied cohort. Please comment on the effect of this data limitation on the robustness of the risk estimate.

- The risk of death from lung cancer in acrylonitrile-exposed workers was characterized using a semi-parametric Cox regression model with a cumulative exposure metric (i.e., ppm-working years) as the only time-dependent covariate. The IUR estimate was derived by linear extrapolation from the LEC_{01} . Please comment on the application of this method [used in Starr et al. (2004)] to calculate the IUR.
6. Chemical-specific, data-derived early-life susceptibility factors were developed and recommended to be applied in assessing cancer risks associated with oral or inhalation exposures to acrylonitrile that begin in early-life.
- Please comment on the derivation of the early-life susceptibility adjustment factors, including the strength of the experimental evidence and the suitability of the quantification methods.
 - Please comment on the application of the adjustment factors, which were derived from an inhalation study, to oral acrylonitrile exposure.