Charge to External Reviewers for the IRIS Toxicological Review of Acrylonitrile
June 2011

The U.S. Environmental Protection Agency (EPA) is seeking an external peer review of the scientific basis supporting the human health assessment for 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). An existing IRIS assessment for acrylonitrile includes an inhalation reference concentration (RfC), which was posted on IRIS in 1991, and an oral slope factor and inhalation unit risk (IUR), which were posted on IRIS in 1987.

The current draft health assessment includes an oral reference dose (RfD), inhalation RfC, and a 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 and any other significant scientific issues of concern, including recommendations for resolution. Please consider the accuracy, objectivity, and transparency of EPA's analyses and conclusions in your review.

General Charge Questions:

1. Is the Toxicological Review logical, clear and concise? Has EPA clearly presented and synthesized the scientific evidence for noncancer and cancer hazards?

2. Please identify any additional studies that would be likely to make a significant impact on the conclusions of the Toxicological Review.

Chemical-Specific Charge Questions:

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

1. PBPK modeling was used for calculating the internal dosimetry in the derivation of the RfD and in the cancer assessment. A PBPK model for acrylonitrile was previously developed in rats (Kedderis et al., 1996) and extended to describe the dosimetry of both acrylonitrile and the reactive metabolite, 2-cyanoethylene oxide (CEO), in humans (Sweeney et al., 2003). While the published human version of the model (Sweeney et al., 2003) included epoxide hydrolase (EH) activity, the rat model (Kedderis et al., 1996) did not. EPA chose to also include EH in the rat PBPK 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 in humans was the same as for CYP450. The approach used by EPA was to scale EH based only on enzyme content (not using an activity adjustment factor for either rats or humans) and then to re-fit the remaining metabolic parameters to the original data for rats. This parameter re-estimation in rats provided a revised value of the *in vivo:in vitro* adjustment factor for CYP450, which was then used along with human *in vitro* CYP450 data

(i.e., the same calculation as Sweeney et al. used but with a revised adjustment factor for CYP450) to estimate the corresponding human value.

a. Please comment on whether the addition of EH to the rat model is scientifically supported and clearly described.

b. Please comment on whether the approach used for deriving the rat and human parameters is scientifically supported and clearly described.

c. Does the PBPK model, modified by EPA, adequately represent the toxicokinetics of acrylonitrile? Was the PBPK modeling appropriately conducted and clearly described? Are the model assumptions and parameters scientifically supported and clearly described? Are the uncertainties in the model structure appropriately considered and discussed, and is the sensitivity analysis in Appendix D adequately and clearly presented?

2. CEO concentration in blood (AUC expressed on a 24-hour basis) was used as the internal dose metric in PBPK modeling. For purposes of comparison, acrylonitrile concentration in blood (AUC expressed on a 24-hour basis) was also evaluated. Please comment on whether the selection of CEO concentration in blood as the internal dose metric is scientifically supported and clearly described.

(B) Oral reference dose (RfD) for acrylonitrile

1. A two-year drinking water study of acrylonitrile in F344 rats (Johannsen and Levinskas, 2002; Biodynamics, 1992) was selected as the basis for the derivation of the RfD. Please comment on whether the selection of this study as the principal study is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. The incidence of forestomach lesions in male and female rats was selected as the critical effect for the RfD. Please comment on whether the selection of this critical effect is scientifically supported and clearly described. Please identify and provide the rationale for any other endpoints that should be selected as the critical effect.

3. Benchmark dose (BMD) modeling was applied to the forestomach lesion incidence data in male rats to derive the point of departure (POD) for the RfD. Has the BMD modeling been appropriately conducted and clearly described? Is the benchmark response (BMR) selected for use in deriving the POD (i.e., a 10% increase in the incidence of forestomach lesions) scientifically supported and clearly described?

4. Please comment on the rationale for the selection of the uncertainty factors (UFs) applied to the POD for the derivation of the RfD. Are the UFs scientifically supported and clearly described? If changes to the selected UFs are proposed, please identify and provide a rationale.

(C) Inhalation reference concentration (RfC) for acrylonitrile

1. An epidemiologic study of neurobehavioral performance in acrylic fiber workers exposed to acrylonitrile (Lu et al., 2005) was selected as the basis for the derivation of the RfC. Please comment on whether the selection of this study as the principal study is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be selected as the principal study.

2. Deficits in neurobehavioral performance of acrylonitrile-exposed workers was selected as the critical effect for the RfC. Please comment on whether the selection of this critical effect is scientifically supported and clearly described. Please identify and provide the rationale for any other endpoints that should be selected as the critical effect.

3. The NOAEL/LOAEL approach was used to derive the POD for the RfC. The LOAEL of 0.24 mg/m^3 for performance deficits in neurobehavioral tests from Lu et al. (2005) was selected as the POD. Please comment on whether this approach is scientifically supported and clearly described.

4. Please comment on the rationale for the selection of UFs applied to the POD for the derivation of the RfC. Are the UFs scientifically supported and clearly described? If changes to the selected UFs are proposed, please identify and provide a rationale.

(D) Carcinogenicity of acrylonitrile

1. Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgrd.html), acrylonitrile is *likely to be carcinogenic to humans* by all routes of exposure. Is the cancer weight of evidence characterization scientifically supported and clearly described?

2. A mutagenic mode of carcinogenic action is proposed for acrylonitrile. Please comment on whether this determination is scientifically supported and clearly described. Please comment on data available for acrylonitrile that may support alternative modes of action.

Quantitative cancer assessment – oral exposure

3. A two-year drinking water study of acrylonitrile in Sprague Dawley rats (Quast, 2002) was selected for the derivation of an oral slope factor. Please comment on whether the selection of this study for quantitation is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be selected.

4. The tumor data in rats (increased incidences of CNS, Zymbal gland, forestomach, tongue, and mammary gland tumors) reported by Quast et al. (1980a) were selected to serve as the basis for the oral slope factor. Please comment on whether this selection is scientifically supported and clearly described. Please identify and provide the rationale for any other endpoints that should be selected to serve as the basis for the quantitative oral cancer assessment.

5. The oral slope factor was derived using linear extrapolation following the estimation of the POD (i.e., the BMDL corresponding to the composite risk of the multiple tumor types) using a Markov chain Monte Carlo (MCMC) approach from the POD. Please comment on whether this approach is scientifically supported and clearly described. Has the modeling been appropriately conducted and clearly described?

Quantitative cancer assessment – inhalation exposure

6. The inhalation unit risk (IUR) was estimated based on increased mortality from lung cancer in acrylonitrile-exposed workers (Blair et al., 1998). For purposes of comparison, an IUR was also estimated from a two-year inhalation study in Sprague-Dawley rats (Quast et al., 1980).

    a. Please comment on whether the selection of the Blair et al. (1998) study for derivation of the IUR is scientifically supported and clearly described. Please identify and provide the rationale for any other studies that should be selected.

    b. 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 time-dependent covariate. The Cox regression model was used to estimate an acrylonitrile exposure concentration (EC) and its associated 95% lower confidence limit (LEC) associated with a 10^{-2} risk of dying from lung cancer at age 80. The IUR estimate was then derived by linear extrapolation from the LEC_{01}. Please comment on whether this approach for derivation of the IUR is scientifically supported and clearly described. Has the modeling been appropriately conducted and clearly described?

    c. Please identify and provide a rationale for any alternative approaches to IUR derivation that should be conducted and an explanation for why an alternative approach would be considered superior to the chosen approach.