Charge to Peer Reviewers

ATSDR Toxicological Profile for Acrylamide
Revised Minimal Risk Level Review

WRITTEN COMMENTS ARE DUE NO LATER THAN MARCH 30, 2012

Please review the Minimal Risk Levels (MRLs) that are derived for Acrylamide. Since the public comment period that ended on February 26, 2010, a PBPK model was published for acrylamide (Sweeney et al., 2010). The Sweeney et al. PBPK model was used by ATSDR to calculate internal dose of acrylamide. Thus, the acute and intermediate-duration oral MRLs presented are based on internal dose and hence are somewhat different from those that were presented in the draft toxicological profile for public comment. However, the principal study and the toxicological endpoints used for derivation of the acute and intermediate duration MRLs remain the same.   Also, an additional MRL for chronic duration has been derived utilizing the PBPK model.

Please review and provide your comments on the MRL sections specifically, the Rationale Statement, MRL Worksheets, the MRL discussion in Chapter 2.3., and the Chapter 2. Please address the following issues in your review:

1. The rationale, derivation, and clarity of presentation of each of the MRLs.
2. Appropriateness of the application of the PBPK model.
3. The study/endpoint selection for derivation of the chronic-duration oral MRL.
4. Your awareness of studies that would be more appropriate or impact the ATSDR proposed MRLs.
5. Your concurrence with the proposed MRLs.

A short summary of the revised MRLs follows:

SUMMARY OF MRLs

- **Acute-Duration Oral Exposure**

ATSDR has derived an MRL of **0.01 mg/kg/day** for acute-duration oral exposure (14 days or less) to acrylamide. The MRL is based on decreased fertility in rats (Sublet et al., 1989). A physiologically based pharmacokinetic (PBPK) rat model of acrylamide and glycidamide (Sweeney et al. 2010) was used to estimate dose metrics for blood time-weighted average (TWA) acrylamide and glycidamide (a readily-formed metabolite of acrylamide in aqueous environment) for each of the administered doses. All dichotomous models in the EPA Benchmark Dose Software (Version 2.1.2) were fit to the incidence data for unsuccessful impregnation (infertility)using the PBPK-modeled rat blood TWA acrylamide and glycidamide dose as the dose metric. The best-fitting model for each dose metric provided a $BMDL_{10}$ of 0.00177669 mM for rat blood TWA acrylamide and a $BMDL_{10}$ of 0.00220167 mM for rat blood TWA glycidamide. Using these BMDLs, the human PBPK model (Sweeney et al. 2010) predicted a human equivalent dose (HED) of 0.31 mg acrylamide/kg/day based on blood TWA acrylamide and a HED of 5.25 mg acrylamide/kg/day based on blood TWA glycidamide. Both acrylamide and glycidamide are widely distributed by the blood and both are reactive. However,

based on uncertainty regarding the proximal toxicant(s) responsible for acrylamide-induced reproductive toxicity in the male rat, a conservative public health approach was taken and the lowest HED of 0.31 mg acrylamide/kg/day (based on blood TWA acrylamide) was selected as the point of departure (POD). An uncertainty factor of 30 (3 for interspecies extrapolation using a PBPK model and 10 for human variability) was applied to the HED of 0.31 mg/kg/day to derive an MRL of 0.01 mg/kg/day.

- **Intermediate-Duration Oral Exposure**

    ATSDR has derived an MRL of **0.001 mg/kg/day** for intermediate-duration oral exposure (15– 364 days) to acrylamide. The MRL is based on degenerative nerve change (Burek et al. (1980). This was selected as the principal study because it identified the lowest lowest-observed-adverse-effect-level (LOAEL) for the critical effect. A NOAEL/LOAEL approach was selected because results of the ultrastructural evaluations included only 3 of 10 rats/group and were reported only as the total numbers of fields (per group) with ultrastructural changes as axolemma invaginations or Schwann cells without axons and/or with degenerating myelin. The distribution of fields exhibiting ultrastructural changes among the three rats within a particular dose group was not included in the study report. The lack of adequate quantitative data precludes the utilization of benchmark dose (BMD) analysis to derive an intermediate-duration oral MRL for acrylamide. A rat PBPK model for acrylamide and glycidamide (Sweeney et al. 2010) was used to predict the rat blood TWA acrylamide dose and TWA glycidamide dose associated with the rat NOAEL of 0.2 mg/kg/day. Based on PBPK model-predicted rat blood TWA acrylamide dose metric at the NOAEL of 0.2 mg acrylamide/kg/day, the HED is 0.038 mg acrylamide/kg/day. An uncertainty factor of 30 (3 for interspecies extrapolation using a PBPK model and 10 for human variability) was applied to the HED of 0.038 mg/kg/day to derive an MRL of 0.001 mg/kg/day.

- **Chronic-Duration Oral Exposure**

ATSDR has derived an MRL of **0.001 mg/kg/day** for chronic-duration oral exposure (365 days or more) to acrylamide. The MRL is based on degenerative sciatic nerve changes (Friedman et al. 1995). A PBPK rat model of acrylamide and glycidamide (Sweeney et al. 2010) was used to estimate blood TWA acrylamide and glycidamide dose metric for each of the administered acrylamide doses for male and female rats from chronic studies (Friedman et al. 1995; Johnson et al. 1986; NTP 2011b). All dichotomous models in the EPA Benchmark Dose Software (Version 2.1.2) were fit to the incidence data for degenerative peripheral nerve changes using PBPK-modeled rat blood TWA acrylamide and glycidamide as the dose metric. For the initial BMD modeling exercise, a benchmark response (BMR) of 10% extra risk was selected. Also, a BMR of 5% extra risk was used for each model considered to provide the best fit to the data from each of the three chronic studies, using TWA acrylamide and glycidamide as the dose metric. A human PBPK model (Sweeney et al. 2010) was used to predict the HED corresponding to the $BMDL_{10}$ and $BMDL_{05}$ values for rat blood TWA acrylamide and glycidamide from the best-fitting models for each of the three chronic studies. A BMR of 5% extra risk is justified because the chronic studies using light microscopy had sufficient numbers of animals (≥38 per dose group, with the exception of 20 animals in the 1.0 mg/kg/day dose group of female rats in the study of Friedman et al. 1995). The lowest PBPK model-predicted HED is 0.042 mg acrylamide/kg/day based on PBPK model-predicted blood TWA acrylamide for the male rats from the study of Friedman et al. (1995). This HED was selected as the POD for deriving a chronic-duration oral MRL for acrylamide because it represents the most public health protective POD. An uncertainty factor of 30 (3 for interspecies extrapolation using a PBPK model and 10 for human variability) was applied to the HED of 0.042 mg/kg/day to has derive an MRL of 0.001 mg/kg/day.