Acrylamide; CASRN 79-06-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Acrylamide

File First On-Line 09/26/1988

Note: Hyperlinks to the reference citations throughout this document will take you to the NCEA HERO database (Health and Environmental Research Online) at http://epa.gov/hero. HERO is a database of scientific literature used by U.S. EPA in the process of developing science assessments such as the Integrated Science Assessments (ISA) and the Integrated Risk Information System (IRIS).

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	03/22/2010
Inhalation RfC (I.B.)	yes	03/22/2010
Carcinogenicity Assessment (II.)	yes	03/22/2010

I. Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose (RfD) for Chronic Oral Exposure

Substance Name — Acrylamide
CASRN — 79-06-1
Section I.A. Last Revised — 03/22/2010

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral

exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

The value presented here replaces the previous RfD for acrylamide (AA) posted on the IRIS database in 1988. In the previous IRIS assessment, the RfD of 0.0002 mg/kg-day was based on nerve damage observed in a rat subchronic drinking water study (Burek et al., 1980, 061311) with a reported no observed adverse effect level (NOAEL) of 0.2 mg/kg-day. The previous RfD was derived by dividing the NOAEL by a combined uncertainty factor (UF) of 1,000: 10 for uncertainty in extrapolating from animals to humans, 10 for intrahuman variability, and 10 for uncertainty in extrapolating from a subchronic to a chronic exposure. The new RfD is based on more recent chronic exposure studies (Friedman et al., 1995, 224307; Johnson et al., 1986, 061340), as well as current methodology for characterizing the dose-response curve, for determining the POD (i.e., the BMDL), and for deriving a human equivalent dose.

I.A.1. Chronic Oral RfD Summary

Critical Effect	Point of Departure*	UF	Chronic RfD
Degenerative nerve changes **Chronic rat study** **Johnson et al. (1986, 061340)**	HED_{BMDL} 0.053 mg/kg-day	30	0.002 mg/kg-day

*The HED_{BMDL} is the human equivalent dose to the rat $BMDL_5$ of 0.27 mg/kg-day (i.e., the POD). Details of the methods used are presented in Section 5.1.3 of the Toxicological Review of Acrylamide (U.S. EPA, 2010, 597278)

I.A.2. Principal and Supporting Studies (Oral RfD)

The Toxicological Review of Acrylamide (AA) reviews and summarizes the results of comprehensive histologic examinations of all major organs and tissues in the available chronic and subchronic animal bioassays (see Table 5-1 in U.S. EPA (2010, 597278)). The most sensitive observed adverse effect was identified as persistent microscopically-detected AA-induced degenerative nerve changes from lifetime exposures based on reproducible NOAELs of 0.5 mg/kg-day and LOAELs of 2 mg/kg-day in F344 male rats (Friedman et al., 1995, 224307; Johnson et al., 1986, 061340). There were no NOAELs for other exposure-related nonneoplastic lesions that were below 5 mg/kg-day.

Two chronic (2-year) drinking water studies (Friedman et al., 1995, 224307; Johnson et al., 1986, 061340) reported degenerative nerve changes in F344 rats, and were selected as co-principal studies to derive the RfD. Data from both studies were evaluated for dose-response characterization, and the final quantitative RfD value was based on the dose-response data from only the Johnson (1986, 061340) study.

Johnson et al. (1986, 061340) conducted a chronic toxicity and carcinogenicity study in which groups of F344 rats (90/sex/treatment group) were administered AA in the drinking water at concentrations calculated to provide AA doses of 0, 0.01, 0.1, 0.5, or 2.0 mg/kg-day for up to 2 years. Ten rats of each sex per treatment group were randomly selected for interim sacrifices after 6, 12, or 18 months of treatment. Complete postmortem gross pathologic examinations were performed on all rats in the study. Organ-to-body weight ratios were calculated for brain, heart, liver, kidneys, and testes. Representative sections from all major organs and tissues were stained with hematoxylin and eosin and subjected to histopathologic examination. Light microscopic examinations were performed on sections of three separate peripheral nerves (tibial nerve and two unspecified nerves), three locations of the spinal cord, and six sections through the brain and olfactory bulbs that had been stained with hematoxylin and eosin.

Light microscopic examination of peripheral nerve section revealed degenerative changes that consisted of focal swelling of individual nerve fibers with fragmentation of the myelin and axon and formation of vacuoles containing small round eosinophilic globules and macrophages. The study authors graded nerve degeneration as very slight, slight, moderate, or severe but did not further characterize the grading scheme. "Minimal" tibial nerve degeneration was observed in control and all treated groups beginning at the 12-month necropsy. Although the report indicated that 12-month assessment revealed increases in both incidence and degree of degeneration in the 2.0 mg/kg-day group, particularly the males, the actual data were not presented, precluding an independent analysis of the findings. Incidences of nerve degeneration increased in controls and treated groups alike throughout the remainder of the treatment period. There were no indications of significant effects on incidence of very slight or slight degeneration in control or treated males

or females. There was a statistically significant trend towards increased moderate and severe degeneration in tibial nerves of male rats up to the 2.0 mg/kg-day dose level, although the increase for the pooled moderate-to-severe data at the high dose was not statistically different from controls. There was a statistically significant increase in pooled incidence of slight-to-moderate degeneration in tibial nerves for female rats at 2.0 mg/kg-day.

Electron microscopic examinations of peripheral nerve sections from rats in the groups destined for independent neuropathologic assessment revealed slightly increased incidences of axolemma invaginations in 2 mg/kg-day male (but not female) rats, relative to controls, at 3- and 6-month interim sacrifices. There were no indications of treatment-related degenerative effects at lower treatment levels. At 12-month interim examination, degenerative myelin and axonal changes were observed in controls as well as all treatment groups and were considered to be the result of aging. High background incidences of degenerative changes at 18 and 24 months precluded the usefulness of electron microscopic analysis to detect differences between control and exposed groups. Thus, the most significant noncancer chronic effects observed by Johnson et al. (1986, 061340) in F344 rats exposed to AA in the drinking water for 2 years were increased incidences of axolemma invaginations (observed by electron microscopy) in the tibial branch of the sciatic nerve of male rats following 3 and 6 months of treatment and increased prevalence of "moderate" to "severe" degeneration (observed by light microscopy) in both males and females following 2 years of treatment. A NOAEL for these neurological effects was identified at 0.5 mg/kg-day, and a LOAEL was identified at the 2.0 mg/kg-day dose level.

Friedman et al. (1995, 224307) conducted a second chronic bioassay in F344 rats exposed to AA in drinking water that was designed to further evaluate and resolve questions concerning the observed tumor responses observed in the Johnson et al. (1986, 061340). Friedman et al. (1995, 224307) exposed male rats to 0, 0.1., 0.5, and 2.0 mg/kg-day, and female rats to 0, 1, and 3 mg/kg-day. Friedman et al. (1995, 224307) included 204 male rats in the 0.1 mg/kg-day group to increase the statistical power sufficient to detect a 5% increase in incidence of scrotal sac mesotheliomas over an expected background incidence of this tumor for F344 rats of about 1%. The study also had different dose group spacing for female rats to improve the characterization of the tumor dose-response relationships. Water consumption was measured weekly throughout the study. Body weight and food consumption were recorded for each animal prior to the start of treatment, weekly for the initial 16 weeks of treatment, and every 4 weeks thereafter. All animals were observed twice daily for mortality, morbidity, and obvious clinical signs of toxicity. Physical examinations were performed weekly for the first 16 weeks, every 4 weeks for the ensuing 24 weeks, and biweekly for the remainder of the study. Complete postmortem gross pathologic examinations were performed on all rats in the study.

There were only minor dose-related increases in cumulative mortality observed among the male rat groups during the first 60 weeks of treatment, after which mortality increased in high dose

males compared with all other groups, increasing by the end of the study to 75% vs. 53 and 44% in control groups 1 and 2, respectively. Differences in mortality among the male control groups were greater than differences among either control groups and the low- or mid-dose-treated males at study end. There were only minor differences in female rat mortality within the first 23 months; however, by study end, mortality rates in controls 1 and 2 and the 1.0 and 3.0 mg/kg-day treatment groups were 40, 28, 35, and 49%, respectively. With respect to nonneoplastic effects, at the level of behavioral and clinical observation performed in this bioassay protocol, no clinical signs of neurotoxicity were reported in any treated rats. Peripheral nerve degeneration was observed based on light microscopic examination (electron microscopy was not conducted) in F344 rats exposed to AA in drinking water for 2 years. Peripheral nerve degeneration was the most sensitive nonneoplastic effect observed in the Friedman et al. (1995, 224307) study with a NOAEL of 0.5 mg/kg-day and 1 mg/kg-day identified for male and female rats, respectively, and a LOAEL of 2 mg/kg-day for male rats.

Benchmark dose (BMD) models were used to characterize the dose-response relationship and to determine the point of departure (POD) used to derive the RfD. All available models in the EPA Benchmark Dose Software (BMDS version 1.3.1) were fit to the incidence data for microscopically-detected degenerative nerve changes in male and female F344 rats from the two 2-year drinking water studies (Friedman et al., 1995, 224307; Johnson et al., 1986, 061340). The results are discussed in detail in Section 5.1.2 in the Toxicological Review of Acrylamide (U.S. EPA, 2010, 597278).

The male rat data from the Johnson et al. (1986, 061340) study resulted in the lowest BMD. All models provided adequate fits to the data for changes in tibial nerves of male and female rats in, as assessed by a χ^2 goodness-of-fit test. Based on the Akaike's Information Criterion (AIC) diagnostic, however, the log-logistic model was the best fitting model for the male rat data. The log-logistic model was thus selected to estimate a BMD from the Johnson et al. (1986, 061340) data. The benchmark response (BMR) predicted to affect 5% of the population, BMR_5, was selected for the POD. A BMR of 5% extra risk was selected for the following reasons: (1) this effect level is considered to be a minimal biologically significant change given the critical effect of degenerative nerve changes; (2) the $BMDL_5$ remained near the range of observation; and (3) the 5% extra risk level is supportable given the relatively large number of animals used in the principal studies.

For male rats, the BMD_5 is 0.58 mg/kg-day, and the $BMDL_5$ is 0.27 mg/kg-day. The $BMDL_5$ is the lower 95% confidence limit for the 5% extra risk. For the female rats, the BMD_5 is 0.67 mg/kg-day, and the $BMDL_5$ is 0.49 mg/kg-day. The $BMDL_5$ of 0.27 mg/kg-day for male rats in the Johnson et al. (1986, 061340) study was thus chosen as the POD to derive the RfD.

An internal dose in the rat (area under a time-concentration curve, AUC) of AA and glycidamide (GA) can be derived from the external exposure to the $BMDL_5$ of 0.27 mg/kg-day based upon methods and data that characterize the relationships between hemoglobin (Hb) adducts, serum levels, and administered dose as reported in a number of studies in rats (Doerge et al., 2005, 224344; Doerge et al., 2005, 224348; Doerge et al., 2005, 224355; Tareke et al., 2006, 224387) and humans (Bergmark et al., 1993, 224424; Fennell et al., 2005, 224299). These studies were used to estimate the internal dose in rats, to extrapolate that dose to an internal dose in humans, and then to estimate the daily human intake of acrylamide needed to produce that internal human dose comparable to what would be produced in rats at the POD. This resulted in an estimate of the human equivalent dose (HED_{BMDL}) to the rat $BMDL_5$. The HED_{BMDL} is further reduced with uncertainty factors to account for uncertainties in going from animal to human estimates of risk, and for variability within the human population to derive the RfD. A detailed discussion of these methods and estimates is presented in Section 5.1.3 in the Toxicological Review of Acrylamide (U.S. EPA, 2010, 597278).

Based on a choice of the parent AA as the putative neurotoxin, and using the in vivo adduct formation rates to derive an AA-AUC conversion factor of 27.4 µM-hr per mg AA/kg bw, the estimated F344 male rat $AA\text{-}AUC_{BMDL}$ from exposure to a $BMDL_5$ of 0.27 mg/kg-day is 7.39 µM-hr. This internal level of AA was then used to estimate the HED_{BMDL} of 0.053 mg/kg-day based on a conversion factor of 140.1 µM AA-hr per mg AA/kg bw (see Section 5.1.3 in U.S. EPA, (2010, 597278) for details on the choice of conversion factor and the HED derivation). The HED_{BMDL} (i.e., the POD) of 0.053 mg/kg-day was then divided by a total uncertainty factor (UF) of 30 to derive an RfD of 0.002 mg/kg-day. The total UF of 30 was comprised of 3 for extrapolation for interspecies toxicodynamic differences ($UF_{A\text{-}TD}$: animal to human) and 10 for consideration of intraspecies variation (UF_H: human variability).

The RfD for AA was calculated as follows:

$$RfD = HED_{BMDL} \div UF$$
$$= 0.053 \text{ mg/kg-day} \div 30$$
$$= 0.002 \text{ mg/kg-day (rounded to one significant digit)}$$

I.A.3. Uncertainty Factors

Total UF = 30

$$= 3\ (UF_{A\text{-}TD}) \times 1\ (UF_{A\text{-}TK}) \times 10\ (UF_H) \times 1\ (UF_S) \times 1\ (UF_L) \times 1\ (UF_D)$$

A UF of 3 ($10^{1/2} = 3.16$, rounded to 3) was selected to account for uncertainties in extrapolating from rats to humans for toxicodynamic differences ($UF_{A\text{-}TD}$). It is reasonable to assume that the neuropathic effects observed in rats are relevant to humans since peripheral neuropathy in

humans has been widely associated with occupational (inhalation and dermal) exposure to AA, and cases of peripheral neuropathy associated with oral exposure have been reported. Available information is inadequate to quantify potential differences between rats and humans in the toxicodynamics of orally administered AA. The lack of a mechanistic basis or any quantitative information on toxicodynamic differences between rats and humans provides support for the $UF_{A\text{-}TD}$ of 3. The equivalent AUC method was used to account for intraspecies toxicokinetic differences, and thus the $UF_{A\text{-}TK} = 1$ instead of the default value of 3.16 ($10^{1/2}$).

A UF of 10 was used to account for interindividual variability in toxicokinetics and toxicodynamics to protect potentially sensitive populations and lifestages (UF_H). Although male rats appear to be slightly more sensitive than female rats to AA-induced neurotoxicity and were the basis of the POD for the RfD, the extent of variation in sensitivity to AA within the human population is unknown. In the absence of this information, the default value of 10 was selected.

A UF for extrapolating from a subchronic exposure duration to a chronic exposure duration (UF_S) was not needed, because the point of departure was derived from a study with chronic exposure (i.e., the $UF_S = 1$).

A UF to account for the extrapolation from a LOAEL to a NOAEL (UF_L) was not applied because the current approach is to address this extrapolation as one of the considerations in selecting a BMR for BMD modeling (i.e., $UF_L = 1$). In this case, EPA concluded a 5% increase in response is appropriate for use in deriving the RfD under the assumption that it represents a minimal biologically significant change.

A UF to account for database deficiency is not necessary (i.e., $UF_D = 1$). The oral toxicity database for laboratory animals repeatedly exposed to AA is robust and contains two 2 year carcinogenicity/toxicology drinking water studies in F344 rats and numerous shorter-term oral toxicity studies in animals; two two-generation reproductive toxicity studies, one in F344 rats and one in CD-1 mice; several single-generation reproductive toxicity studies involving prolonged prebreeding drinking water exposure of Long-Evans rats and ddY mice; and several developmental toxicity studies involving gestational exposure of Sprague-Dawley and Wistar rats and CD-1 mice. The database identifies nerve degeneration as the critical effect from chronic oral exposure. There are unresolved issues that warrant further research including the MOA of AA-induced neurotoxicity, the potential for behavioral or functional adverse effects not detected in the assays to date, and the uncertainty that heritable germ cell effects may occur at doses comparable to those inducing degenerative nerve lesions with chronic oral exposure. These issues, however, do not warrant applying an UF for database deficiencies.

I.A.4. Additional Studies/Comments

Neurological impairment (including peripheral neuropathy involving nerve tissue damage) has been repeatedly observed in case reports, and health surveillance studies, as well as extensive laboratory animal studies clearly establishing this endpoint as a potential human health hazard associated with acute and repeated occupational exposure via inhalation of airborne AA or dermal contact with AA-containing materials.

Functional neurotoxic deficits have been observed in both animal and human studies, and at least two MOA precursor events have been proposed (i.e., central nerve terminal damage or reduction in fast axonal transport). Either of these precursor events might result in other serious behavioral or functional neurological deficits that were not detected in the two co-principal chronic bioassays. More research is needed to further evaluate potentially more subtle irreversible adverse behavioral or functional effects in humans and laboratory animals.

As discussed in Section 4.4 in the Toxicological Review of Acrylamide (U.S. EPA, 2010, 597278), the magnitude of response at low doses, and the shape of the low dose-response curve for potentially serious heritable germ cell effects, is also a research need.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.9 (PDF).

I.A.5. Confidence in the Chronic Oral RfD

Study — Medium/High
Data Base — Medium/High
RfD — Medium/High

The overall confidence in this RfD assessment is medium to high based on medium-to-high confidence in the studies and medium-to-high confidence in the database. The animal database is robust. Although no data were available to characterize the neurotoxic dose-response relationships from chronic oral exposure in humans, neurotoxicity from inhaled or dermal occupational exposures to AA are well documented. Two co-principal studies provide adequate characterization of the dose-response relationship for degenerative nerve lesions from a chronic-duration oral exposure, and for neurotoxicity as the most sensitive endpoint. There might be behavioral or functional effects that were not evaluated in these bioassays, and that would result in lower LOAELs than those for the histological effects used to derive the RfD. There is also uncertainty as to the dose-response relationship for heritable germ cell effects. These two uncertainties lower the overall confidence in the RfD from high to medium-to-high. There are ongoing studies sponsored by the NTP and FDA that may address these data needs.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA Documentation and Review of the Chronic Oral RfD

Source Document — U.S. EPA (2010, 597278)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the Toxicological Review of Acrylamide (U.S. EPA, 2010, 597278). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF).***

Agency Completion Date — 03/22/2010

I.A.7. EPA Contacts

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. Reference Concentration (RfC) for Chronic Inhalation Exposure

Substance Name — Acrylamide
CASRN — 79-06-1
Section I.B. Last Revised — 03/22/2010

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994, 006488). Because

RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

The previous IRIS assessment did not derive an RfC for acrylamide.

I.B.1. Chronic Inhalation RfC Summary

Critical Effect	Point of Departure*	UF	Chronic RfC
Degenerative nerve changes **Chronic rat study** **Johnson et al. (1986, 061340)**	HEC_{BMDL} 0.18 mg/m^3	30	0.006 mg/m^3

*The HEC_{BMDL} is the human equivalent air concentration, and is based on the oral HED_{BMDL} of 0.053 mg/kg-day (i.e., the human equivalent dose to a rat $BMDL_5$ of 0.27 mg/kg-day). The HEC_{BMDL} was calculated from the HED_{BMDL} based on a 70 kg person who breathes 20 m^3 of air daily. See Section 5.2.2 in the Toxicological Review of Acrylamide (U.S. EPA, 2010, 597278) for a detailed discussion of these derivations.

I.B.2. Principal and Supporting Studies

The RfC was derived from a route-to-route extrapolation estimate of the HEC_{BMDL} from the HED_{BMDL} that was based on the degenerative nerve changes observed in the Johnson et al. (1986, 061340) oral exposure study. The justification for deriving an RfC directly from the oral exposure POD includes: (1) a well characterized dose-response and identification of the most sensitive noncancer endpoint from an adequate database of oral exposure studies; (2) considerable evidence from occupational experience that dermal and inhalation exposures to AA induce peripheral neuropathies, including development of the types of degenerative lesions observed in nerves of rats exposed via drinking water; (3) evidence of rapid, nearly complete absorption from the oral route and rapid distribution throughout the body (Kadry et al., 1999, 224596; Miller et al., 1982, 061351); (4) evidence that the elimination kinetics of radioactivity from oral or i.v. administration of radiolabeled AA in rats is similar (Miller et al., 1982, 061351); (5) similar flux of AA through metabolic pathways following either single dose oral or single 6 hr inhalation exposures in rats (Sumner et al., 2003, 224347); (6) some route-to-route differences

in the relative amounts of AA to GA, however, the differences are within two fold of each other; and (7) lack of support for portal of entry effects.

In the only animal inhalation kinetic study (i.e., no human inhalation kinetic information is available) Sumner et al. (2003, 224347) report a statistically significantly larger percentage of urinary metabolites associated with GA formation following an inhalation exposure compared with an i.p. and gavage exposure. GAVal levels are also higher and AAVal levels lower (as indicators of serum AUCs), following the single 6 hr inhalation exposures versus the single gavage dose in rats, however, statistical significance was not reported for the adduct level differences, and the numbers are within two fold of each other. Doerge et al. (2005, 224348; 2005, 224355) report an increased percentage of GA formation observed in mice and F344 rats from a gavage or dietary exposure compared to an i.v. exposure that, in conjunction with the Sumner et al. (2003, 224347) results, indicate that there is first pass metabolism in the lungs following an inhalation exposure similar to the first pass metabolism in the liver from an oral exposure, but apparently the lungs may have a larger percent of oxidative metabolism of AA to GA.

Although there appear to be some route-to-route differences in the relative amounts of AA to GA in the one animal inhalation kinetic study (Sumner et al., 2003, 224347), the differences are within two fold of each other, and the metabolic paths and total disposition are similar, supporting the derivation of the RfC based upon the oral POD that was used as the basis for the RfD.

The level of AA in the air that would result in a comparable intake to the oral exposure POD is based on a 70 kg person who breathes 20 m^3 of air/day. The benchmark response BMR_5 was selected for the following reasons: (1) this effect level is considered to be a minimal biologically significant change given the critical effect of degenerative nerve changes; (2) the $BMDL_5$ remained near the range of observation; and (3) the 5% extra risk level is supportable given the relatively large number of animals used in the principal studies.

The $BMDL_5$ for degenerative nerve lesions in male rats exposed to AA in drinking water for 2 years is the POD for deriving the RfC. The internal dose metric remains the AA-AUC in male rat blood. The human equivalent daily oral intake required to produce that same AA-AUC value in human blood (i.e., the HED_{BMDL}) is 0.053 mg/kg-day. The human equivalent concentration in air (the HEC_{BMDL}) that would result in that same internal AA-AUC in male rat blood is 0.18 mg/m^3 for a 70 kg person who breathes 20 m^3 of air daily.

This HEC_{BMDL} for a continuous inhalation exposure of 0.18 mg/m^3 (as the POD) is divided by a total UF of 30 to derive the RfC: 3 for extrapolation for interspecies toxicodynamic differences

(UF_{A-TD}: animal to human) and 10 for consideration of intraspecies variation (UF_H: human variability).

The RfC for AA is calculated as follows:

$RfC = HEC_{BMDL} \div UF$
$= 0.18\ mg/m^3 \div 30$
$= 0.006\ mg/m^3$ (rounded to one significant digit)

I.B.3. Uncertainty Factors

Total UF = 30
$= 3\ (UF_{A-TD}) \times 1\ (UF_{A-TK}) \times 10\ (UF_H) \times 1\ (UF_S) \times 1\ (UF_L) \times 1\ (UF_D)$

A UF of 3 ($10^{1/2} = 3.16$, rounded to 3) was selected to account for uncertainties in extrapolating from rats to humans for toxicodynamic differences (UF_{A-TD}). It is reasonable to assume that the neuropathic effects observed in rats are relevant to humans since peripheral neuropathy in humans has been widely associated with occupational (inhalation and dermal) exposure to AA, and cases of peripheral neuropathy associated with oral exposure have been reported. Available information is inadequate to quantify potential differences between rats and humans in toxicodynamics of orally administered AA. The lack of a mechanistic basis or any quantitative information on toxicodynamic differences between rats and humans provides support for the UF_{A-TD} of 3. The equivalent AUC method was used to account for intraspecies toxicokinetic differences, and thus the $UF_{A-TK} = 1$ instead of the default value of 3.16 ($10^{1/2}$).

A UF of 10 was used to account for interindividual variability in toxicokinetics and toxicodynamics to protect potentially sensitive populations and lifestages (UF_H). Although male rats appear to be slightly more sensitive than female rats to AA neurotoxicity and were the basis of the POD for the RfD, the extent of variation in sensitivity to AA within the human population is unknown. In the absence of this information, the default value of 10 was selected.

A UF for extrapolating from a subchronic exposure duration to a chronic exposure duration (UF_S) was not needed because the point of departure was derived from a chronic exposure study (i.e., the $UF_S = 1$).

A UF to account for the extrapolation from a LOAEL to a NOAEL (UF_L) was not applied because the current approach is to address this extrapolation as one of the considerations in selecting a BMR for BMD modeling (i.e., $UF_L = 1$). In this case, EPA concluded a 5% increase in response, is appropriate for use in deriving the RfD under the assumption that it represents a minimal biologically significant change.

A UF to account for database deficiency is not necessary for this derivation (i.e., $UF_D = 1$) because an AUC equivalence method was used to conduct the route-to-route extrapolation based on an oral POD, and the oral POD was based on an adequate database. The oral toxicity database for laboratory animals repeatedly exposed to AA is robust and contains two 2-year carcinogenicity/toxicology drinking water studies in F344 rats and numerous shorter-term oral toxicity studies in animals; two two-generation reproductive toxicity studies, one in F344 rats and one in CD-1 mice; several single-generation reproductive toxicity studies involving prolonged prebreeding drinking water exposure of Long-Evans rats and ddY mice; and several developmental toxicity studies involving gestational exposure of Sprague-Dawley and Wistar rats and CD-1 mice. The database identifies nerve degeneration as the critical effect from chronic oral exposure. There are unresolved issues that warrant further research, including the MOA of AA neurotoxicity, the potential for behavioral or functional adverse effects not detected in the assays to date, and the uncertainty that heritable germ cell effects may occur at lower than previously reported doses. These issues, however, do not warrant applying an UF for database deficiencies.

I.B.4. Additional Studies/Comments

Neurological impairment is a well-established human health hazard associated with acute and repeated occupational exposure involving inhalation of airborne AA and dermal contact with AA-containing materials. Studies describing reliable relationships, however, between exposure concentrations and neurological responses in humans or animals are not available. Two cross-sectional health surveillance studies of AA-exposed workers describe correlative relationships between hemoglobin adduct levels of AA (an internal measure of dose) and changes in a neurotoxicity index based on self-reported symptoms and clinical measures of neurological impairment (Calleman et al., 1994, 202900) or increased incidences in self-reported symptoms of neurological impairment and eye and respiratory irritation (Hagmar et al., 2001, 224453). These studies, however, provide limited information on dose-response relationships for chronic inhalation exposure to AA, because they involved mixed inhalation and dermal exposure (in both groups of workers, dermal exposure was thought to have been substantial), the duration of exposure was less than chronic, workers in both studies were exposed to confounding chemicals (acrylonitrile in the first study and NMA in the second), and the internal measure of dose (N terminal valine adducts of hemoglobin) is not specific for AA alone (i.e., NMA can form the same adduct).

Although the Calleman et al. (1994, 202900) data are limited, EPA derived an RfC from the Calleman et al (1994, 202900) data for comparison purposes (see Section Appendix F in the Toxicological Review of Acrylamide (U.S. EPA, 2010, 597278)).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.9 (PDF).

I.B.5. Confidence in the Chronic Inhalation RfC

Study — Medium/High
Data Base — Low/Medium
RfC — Medium

The overall confidence in this RfC assessment is medium. Since the RfC is based on a route-to-route extrapolation of the oral exposure data using the same AUC method to develop an inhalation HEC, the overall confidence in the RfC study is similar to that for the RfD, with additional uncertainty in the toxicokinetics for an inhalation exposure. Specifically, there is additional uncertainty concerning different internal disposition of AA and GA due to qualitatively similar but possibly quantitatively different first pass effects in lung versus the liver. On the other hand, a similar RfC derived from the Calleman et al. (1994, 202900) data provides some additional confidence in this RfC. Additional kinetic data (e.g., serum data) or improved estimates of the AA-AUC and GA-AUC from different exposure routes in humans or test animals based on hemoglobin adduct levels would improve the confidence in the RfC based on the oral HED. There is low-to-medium confidence in the database because inhalation studies are lacking. The overall confidence in the RfC is medium, i.e., less than the confidence in the RfD.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA Documentation and Review of the Chronic Inhalation RfC

Source Document — U.S. EPA (2010, 597278)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the Toxicological Review of Acrylamide (U.S. EPA, 2010, 597278). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

Agency Completion Date — 03/22/2010

I.B.7. EPA Contacts

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Acrylamide
CASRN — 79-06-1
Section II. Last Revised — 03/22/2010

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005, 086237) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005, 088823). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

A previous cancer assessment for AA was previously entered into the IRIS database in 1988. Using the EPA cancer classifications at that time, AA was classified as Group B2, a probable human carcinogen, based on inadequate human data and sufficient evidence of carcinogenicity in animals (significantly increased incidences of benign and/or malignant tumors at multiple sites in both sexes of rats and carcinogenic effects in a series of 1-year limited bioassays in mice by several routes of exposure). The classification was supported by positive genotoxicity data, adduct formation activity, and structure-activity relationships to vinyl carbamate and acrylonitrile. An oral slope factor of 4.5 $(mg/kg\text{-}day)^{-1}$ and a drinking water unit risk of 1.3×10^{-4} $(\mu g/L)^{-1}$ were derived using a linearized multistage procedural analysis (extra risk) of combined incidence data for tumors in the CNS, mammary and thyroid glands, uterus, and oral cavity in

female F344 rats exposed to AA in drinking water for 2 years (Johnson et al., 1986, 061340), with the external AA exposure as the dose metric.

The previous inhalation unit risk of 1.3×10^{-3} $(\mu g/m^3)^{-1}$ was calculated from the oral data and an external exposure level of AA, based on the assumption that the tissue distribution of AA appeared to be quantitatively the same regardless of route of exposure (Dearfield et al., 1988, 224308). This assumption was supported by the data on the distribution of AA following oral or i.v. administration in rats (Miller et al., 1982, 061351).

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

In accordance with the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005, 086237), acrylamide (AA) is characterized as "likely to be carcinogenic to humans." This characterization is based on the following findings: (1) chronic oral exposure of F344 rats to AA in drinking water induced statistically significant increased incidences of thyroid follicular cell tumors (adenomas and carcinomas combined in both sexes), scrotal sac mesotheliomas (males), and mammary gland fibroadenomas (females) in two bioassays; (2) oral, i.p., or dermal exposure to AA initiated skin tumors that were promoted by TPA in SENCAR and Swiss-ICR mice; (3) i.p. injections of AA induced lung adenomas in strain A/J mice. In addition, CNS tumors were found in both of the chronic F344 rat bioassays; and (4) ample evidence for the ability of AA (primarily associated with its metabolite GA) to induce a variety of genotoxic effects in mammalian cells.

There are no animal data on the carcinogenicity of chronic inhalation exposure to AA. EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005, 086237) indicate that for tumors occurring at a site other than the initial point of contact, the weight of evidence for carcinogenic potential may apply to all routes of exposure that have not been adequately tested at sufficient doses. In the case of AA, there is evidence of rapid, nearly complete absorption from the oral route and rapid distribution throughout the body (Kadry et al., 1999, 224596; Miller et al., 1982, 061351) and evidence that the elimination kinetics of radioactivity from oral or i.v. administration of radiolabeled AA in rats is similar(Miller et al., 1982, 061351). In addition, there is similar flux of AA through metabolic pathways following either single dose oral or single 6 hr inhalation exposures in rats (Sumner et al., 2003, 224347) and while there are some route-to-route differences in the relative amounts of AA to GA, the differences are within two fold of each other. For these reasons, acrylamide is considered likely to be carcinogenic to humans by all routes of exposure.

The mechanisms by which AA induces cancer in animals are not fully understood, however, the weight of the scientific evidence strongly supports a mutagenic MOA (see Section 4.8.3.1 in the

Toxicological Review of Acrylamide, U.S. EPA (2010, 597278)). An alternative MOA has been proposed for the development of AA-induced thyroid follicular cell tumors, scrotal sac mesotheliomas, and mammary gland tumors in rats, however, the available evidence in support of these hypotheses is judged to be inadequate. Therefore, the cancer dose-response relationships for tumors with statistically significantly elevated incidences in both of the available rat bioassays (thyroid tumors in both sexes, mammary gland tumors in females and tunica vaginalis mesotheliomas in males) are the best available basis for deriving an oral cancer slope factor and inhalation unit risk for AA.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.9 (PDF).

II.A.2. Human Carcinogenicity Data

Human studies provide very limited evidence to assess the carcinogenicity of AA (see Sections 4.1, 4.8.1, and 4.8.2 in the Toxicological Review of Acrylamide, U.S. EPA (2010, 597278)). No statistically significant increased risks for cancer-related deaths were consistently found in the cohort mortality studies of AA workers (Marsh et al., 2007, 224578; Swaen et al., 2007, 224357). In most case-control studies and prospective studies, no statistically significant associations were found between frequent consumption of foods with high or moderate levels of AA and cancer incidence for large bowel, bladder, kidney, renal cell, breast, colorectal, oral, pharyngeal, esophageal, laryngeal, ovarian, or prostate cancer. One case-control study reported a slightly increased risk of breast cancer later in life associated with the consumption of French fries during preschool (Michels et al., 2006, 224586), but there is considerable uncertainty in the accuracy of the exposure assessment methods. Increased risks of postmenopausal endometrial and ovarian cancer (Hogervorst et al., 2007, 224520) and renal cell cancer (Hogervorst et al., 2008, 224521) with increasing dietary AA intake were reported in prospective studies of a Dutch population, but estimations of dietary AA levels in foods on the market at baseline in 1986 were based on food samples analyzed since 2001 and questionnaires did not include details regarding specifics of food preparation. Olesen et al. (2008, 224303) reported a significant positive association between AA-Hb adduct levels in red blood cells and ER+ breast cancer after adjusting for smoking, but this study is limited by the relatively small number of subjects (374 cases and 374 controls) and uncertainty regarding extrapolation to lifetime exposure from AA exposure as assessed by a few months of AA-Hb adduct measurements.

II.A.3. Animal Carcinogenicity Data

Two chronic bioassays with F344 rats orally exposed to AA provide appropriate data to describe dose-response relationships for induced tumors (Friedman et al., 1995, 224307; Johnson et al., 1986, 061340). Strengths in both assays include sufficient numbers of animals in control and multiple exposure groups for statistical analysis of dose-response relationships, histological examinations of most tissues, and sufficient reporting of experimental details and results. Johnson et al. (1986, 061340) reported increased tumor incidences at sites in females (CNS, oral cavity, uterus, and pituitary) and males (adrenals), which were reported to not be elevated in the Friedman et al. (1995, 224307) bioassay. However, the Johnson et al. (1986, 061340) study had abnormally high CNS and oral cavity tumors in control males and possible confounding effects from a viral infection. The Friedman et al. (1995, 224307) study was designed to include different dose spacings to support better characterization of dose-response relationships in the low-dose region and substantially larger control (n = 204) and 0.1 mg/kg-day male rat (n = 204) groups to increase the statistical power in the study to detect significantly increased tumor incidence. Although glial tumors of brain and spinal cord were reported by Friedman et al. (1995, 224307) not to be increased, not all of the brains and spinal cords in the test animals were examined, and seven cases of a morphologically distinctive category of primary brain tumor described as "malignant reticulosis" were reported but excluded from the Friedman et al. (1995, 224307) analysis of the data. In addition, incidences of oral cavity tumors, clitoral gland adenomas and uterine adenomas were reported not to be increased, but the number of these tumors was not reported.

II.A.4. Supporting Data for Carcinogenicity

Other evidence of AA induced carcinogenicity includes: (1) increased incidences of skin tumors in SENCAR and Swiss-ICR mice given oral, i.p., or dermal initiating doses of AA followed by tumor-promoting doses of TPA (Bull et al., 1984, 202896; Bull et al., 1984, 202897); (2) increased incidences of lung tumors in strain A/J mice following i.p. injection of AA (Bull et al., 1984, 202896); and (3) ample evidence for the ability of AA (primarily associated with its metabolite GA) to induce a variety of genotoxic effects in mammalian cells (Adler et al., 1994, 224314; Besaratinia and Pfeifer, 2007, 224436; Dearfield et al., 1995, 224315; Doerge et al., 2005, 224344; Ehling and Neuhäuser-Klaus, 1992, 224391; Gamboa da Costa et al., 2003, 194572; Generoso et al., 1996, 224346; Ghanayem et al., 2005, 224351; Knaap et al., 1988, 224547; Moore et al., 1987, 224589; Rice, 2005, 224393; Russell et al., 1991, 224406; Segerbäck et al., 1995, 224485).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

II.B.1. Summary of Risk Estimates

II.B.1.1. Oral Slope Factor --

EPA has concluded, by a weight of evidence evaluation, that acrylamide is carcinogenic by a mutagenic mode of action. According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (Supplemental Guidance)* (U.S. EPA, 2005, 088823) those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for acrylamide are not sufficient to develop separate risk estimates for childhood exposure. The oral slope factor of 5×10^{-1} per mg/kg-day, calculated from data from adult exposure, does not reflect presumed early-life susceptibility for this chemical and age dependent adjustment factors (ADAFs) should be applied based on specific exposure data when assessing cancer risks. Example evaluations of cancer risks based on age at exposure are given in Section 6 of the *Supplemental Guidance*.

Risk Assessment Considerations: The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005, 088823). The 10 fold and 3 fold adjustments in slope factor are to be combined with age specific exposure estimates when estimating cancer risks from early life (<16 years age) exposure to AA. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/. In estimating risk, EPA recommends using age-specific values for both exposure and cancer potency; for acrylamide, age-specific values for cancer potency are calculated using the appropriate ADAFs. A cancer risk is derived for each age group, and these are summed across age groups to obtain the total risk for the exposure period of interest (see Section 6 of the *Supplemental Guidance*). Please see Section 5.4.6 of the Toxicological Review of Acrylamide (U.S. EPA, 2010, 597278) for example calculations of the application of ADAFs to the acrylamide oral slope factor.

The derivation of the oral slope factor of 0.5 $(\text{mg/kg-day})^{-1}$ is based on the summed risks for increased incidence of thyroid tumors and tunica vaginalis mesotheliomas in male F344 rats exposed to AA in drinking water for 2 years (Johnson et al., 1986, 061340). The dose metric used in the current estimation of the HED is GA-AUC rather than the external AA exposure. GA is considered to be the putative toxin for the hypothesized mutagenic MOA leading to carcinogenicity, and thus a better internal dose metric to correlate to response than the internal (or external) level of AA. The rat $BMDL_{10}$ of 1.5×10^{-1} mg/kg-day represents the POD used as the basis for the HED_{BMDL} of 1.94×10^{-1} mg/kg-day.

HED_{BMDL}, lower 95% bound (summed tumor incidence) on exposure at 10% extra risk - 1.94×10^{-1} mg/kg-day

HED_{BMDL}, central estimate (summed tumor incidence) on exposure at 10% extra risk - 3.08×10^{-1} mg/kg-day

The human oral slope factor is derived by linear extrapolation from the HED_{BMDL} of 1.94×10^{-1} mg/kg to the origin, corrected for background, and is calculated as the response rate (10^{-1}) divided by the HED_{BMDL} resulting in a value of 0.51 $[mg/kg\text{-}day]^{-1}$ (response rate of 0.1 / HED_{BMDL} of 1.94×10^{-1} mg/kg-day = 0.51 $[mg/kg\text{-}day]^{-1}$).

With rounding to one significant figure, the human oral slope factor based on the HED_{BMDL} for a BMR of 10^{-1} is 0.5 per mg/kg-day.

The slope factor for acrylamide should not be used with exposures exceeding the point of departure (HED_{BMDL}), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of acrylamide. Additionally, age dependent adjustment factors (ADAFs) should be applied to this slope factor when assessing cancer risks to individuals <16 years old as discussed above (U.S. EPA, 2005, 088823).

II.B.1.2. Drinking Water Unit Risk

Drinking water unit risks are not provided for acrylamide. Since acrylamide is carcinogenic by a mutagenic mode of action and increased susceptibility is assumed for early-life exposures (<16 years of age), the unit risk and concentrations at a specified risk levels will change based on the age of the individuals in the exposed group. Risk assessors should use the oral slope factor and current EPA guidance to assess risk based on site-specific populations and exposure conditions. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/.

II.B.1.3. Extrapolation Method

The Friedman et al. (1995, 224307) female data were fit with the multistage model to estimate the BMD and BMDL Male rats in the highest dose group in the Friedman et al. (1995, 224307) study showed early mortalities, and these data were fit with a multistage-Weibull model that adjusted for early mortality. The raw data from the Johnson et al. (1986, 061340) study were not available for a time to tumor analysis, and were fit with the multistage model. Both sets of data were evaluated for increased risks of developing individual tumors types, as well as the summed risks of developing more than one type of tumor. The summed risks were ranked, and one was selected to calculate the POD.

II.B.2. Dose-Response Data

Tumor type - thyroid tumors and tunica vaginalis mesotheliomas
Test Species - Rat/Fischer 344, males
Route - Oral, drinking water
References - Friedman et al., 1995, 224307; Johnson et al., 1986, 061340

Oral slope factors were calculated based on summed risks for increased incidence of multiple tumor types, focusing on those types that were reproducibly and (statistically) significantly increased in both of the F344 rat bioassays (e.g., mammary or thyroid tumors in females and TVM and thyroid tumors in males). The resulting slope factors were all within a four fold range across studies, and within a two fold range within studies.

Bioassay/sex/tumor sites	Oral slope factor based on rat BMDL (risk level/BMDL) (per mg/kg-day)
Friedman/female/mammary or thyroid	0.21
Johnson/female/mammary or thyroid	0.38
Johnson/female/mammary, thyroid, or CNS	0.44
Johnson/female/mammary, thyroid, CNS, or oral cavity	0.50
Friedman/male/TVM or thyroid	0.32
Johnson/male/TVM or thyroid	0.67
Johnson/male/TVM, thyroid, or adrenal	0.71

Note: Oral slope factors (= risk level/BMDL) are used to compare summed risks because the BMDLs in the summed risk analysis did not all have the same BMR (i.e., it is difficult to readily rank order BMDLs with different BMRs).

II.B.3. Additional Comments

The equivalent AUC method was an important approach in estimating the oral human equivalent concentration in the CSF derivation because the putative toxin was the AA metabolite, glycidamide. The default uncertainty factor for interspecies toxicokinetic differences would not account for differences in the internal levels of GA, while the AUC method did. Additional human serum data, however, are needed to better characterize the human in vivo adduct formation rate, and to further reduce uncertainty in the estimate of the human GA AUC per intake of AA.

II.B.4. Discussion of Confidence

The principal 2-year studies (Friedman et al., 1995, 224307; Johnson et al., 1986, 061340) provided corroborative results for most, but not all, tumor types. There remain some uncertainties concerning the differences between the two study tumor types and incidence data, in particular for the CNS tumors, and in the histopathological interpretation of the male TVMs. The database is also incomplete with only one animal species tested, and little human data to support AA's carcinogenic potential in humans. At this time, the preponderance of evidence supports a mutagenic MOA. Although an alternate MOA has been proposed involving hormonal pathway disruption for tumors specific to F344 rats, supporting data are limited or nonexistent. Additional MOA datawould be required to determine whether multiple MOAs are operational.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

II.C.1. Summary of Risk Estimates

II.C.1.1. Inhalation Unit Risk

EPA has concluded, by a weight of evidence evaluation, that acrylamide is carcinogenic by a mutagenic mode of action. According to the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens (Supplemental Guidance)* (U.S. EPA, 2005, 088823) those exposed to carcinogens with a mutagenic mode of action are assumed to have increased early-life susceptibility. Data for acrylamide are not sufficient to develop separate risk estimates for childhood exposure. The inhalation unit risk of 1×10^{-4} per $\mu g/m^3$, calculated from data from adult exposure, does not reflect presumed early-life susceptibility for this chemical and age dependent adjustment factors (ADAFs) should be applied based on specific exposure data to this unit risk when assessing cancer risks. Example evaluations of cancer risks based on age at exposure are given in Section 6 of the *Supplemental Guidance*.

Risk Assessment Considerations: The *Supplemental Guidance* establishes ADAFs for three specific age groups. The current ADAFs and their age groupings are 10 for <2 years, 3 for 2 to <16 years, and 1 for 16 years and above (U.S. EPA, 2005, 088823). The 10-fold and 3-fold adjustments in unit risk are to be combined with age specific exposure estimates when estimating cancer risks from early life (<16 years age) exposure to acrylamide. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/. In estimating risk, EPA recommends using age-specific values for both exposure and cancer potency; for acrylamide, age-specific values for cancer potency are calculated using the appropriate ADAFs. A cancer risk is derived for each age group, and these are summed across age groups to obtain the total risk for the exposure period of interest (see Section 6 of the *Supplemental Guidance*).

The inhalation unit risk is based on EPA's methodology for inhalation dosimetry (U.S. EPA, 1994, 006488). The inhalation unit risk for AA is based on adult exposures and is derived by dividing the risk (as a fraction) by the $BMDL_x$ which is the 95% lower bound on the exposure associated with an "x" extra cancer risk.

No human or animal inhalation cancer dose-response data were available for acrylamide to directly derive an inhalation unit risk. Animal toxicokinetic studies on AA and GA disposition following different routes of exposure indicate sufficient similar internal disposition of GA or AA to support a route-to-route extrapolation. The IUR was thus derived in a route-to-route extrapolation of the dose-response relationship (oral-to-inhalation exposure) by converting the oral daily intake POD (i.e., the HED_{BMDL}) developed to a human equivalent air concentration (HEC_{BMDL}). The oral HED_{BMDL} of 1.94×10^{-1} mg/kg-day is based on the Johnson et al. (1986, 061340) study results (see II.B.1 above). The HED_{BMD} (i.e., the central estimate) is 3.08×10^{-1} mg/kg-day.

The calculation used to derive the HEC_{BMDL} from the HED_{BMDL} is straightforward as shown below, and assumes a continuous 24-hour inhalation exposure for a 70 kg person who breathes 20 m^3/day air. The HEC_{BMDL} is 6.8×10^{-1} mg/m^3, and the HEC_{BMDL} is 1.1 mg/m^3.

$$HEC_{BMD} = Oral\ HED_{BMD} \times 70\,kg \div \frac{day}{20\,m^3}$$

$$= 3.08\,x10^{-1}\,mg/kg - day \times 70\,kg \div \frac{day}{20\,m^3} = 1.1\,mg/m^3$$

$$HEC_{BMDL} = Oral\ HED_{BMDL} \times 70\,kg \div \frac{day}{20\,m^3}$$

$$= 1.94\,x10^{-1}\,mg/kg - day \times 70\,kg \div \frac{day}{20\,m^3} = 6.8\,x10^{-1}\,mg/m^3$$

This HEC_{BMDL} is the lower 95% bound on exposure at a 10^{-1} response, and is used to derive an IUR of 1.47×10^{-4} $(\mu g/m^3)^{-1}$ as follows:

Inhalation unit risk based on the HEC_{BMDL} for a BMR of 10^{-1} in $(\mu g/m^3)^{-1}$ = $0.1/6.8 \times 10^{-1}$ mg/m^3= 1.47×10^{-4} $(\mu g/m^3)^{-1}$.

With rounding to one significant figure, the IUR is 1×10^{-4} per $\mu g/m^3$.

The unit risk for acrylamide should not be used with exposures exceeding the point of departure ($BDML_{10}$), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of acrylamide. Additionally, age dependent adjustment factors (ADAFs) should be applied to this slope factor when assessing cancer risks to individuals <16 years old as discussed above (U.S. EPA, 2005, 088823).

II.C.1.2. Air Concentrations at Specified Risk Levels

Air concentrations at specified risk levels are not provided for acrylamide. Since acrylamide is carcinogenic by a mutagenic mode of action and increased susceptibility is assumed for early-life exposures (<16 years of age), the concentrations at specified risk levels will change based on the age of the individuals in the exposed group. Risk assessors should use the unit risk and current EPA guidance to assess risk based on site-specific populations and exposure conditions. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines/.

II.C.1.3. Extrapolation Method

The unit risk was derived in a route-to-route extrapolation of the oral POD. See II.B.1.3. for extrapolation methods used to fit the oral data.

II.C.2. Dose-Response Data

The unit risk was derived in a route-to-route extrapolation of the oral POD. See II.B.2. for a discussion of the data used to characterize the dose-response.

II.C.3. Additional Comments

Support for use of the oral daily intake to derive an inhalation unit risk value comes from: (1) a characterized dose-response and identification of tumor types and incidence from two chronic oral bioasssays; (2) evidence of rapid, nearly complete absorption from the oral route and rapid distribution throughout the body (Kadry et al., 1999, 224596; Miller et al., 1982, 061351); (3) evidence that the elimination kinetics of radioactivity from oral or i.v. administration of radiolabeled AA in rats is similar (Miller et al., 1982, 061351); (4) similar flux of AA through metabolic pathways following either single dose oral or single 6 hr inhalation exposures in rats (Sumner et al., 2003, 224347); (5) some route-to-route differences in the relative amounts of AA to GA, however, the differences are within two fold of each other; and (6) lack of support for portal of entry effects.

In the only animal inhalation kinetic study (i.e., no human inhalation kinetic information is available) Sumner et al. (2003, 224347) report a statistically significantly larger percentage of urinary metabolites associated with GA formation following an inhalation exposure compared with an i.p. and gavage exposure. GAVal levels are also higher and AAVal levels lower (as indicators of serum AUCs), following the single 6 hr inhalation exposures versus the single gavage dose in rats, however, statistical significance was not reported for the adduct level differences, and the numbers are within two fold of each other. Doerge et al. (2005, 224348; 2005, 224355) report an increased percentage of GA formation observed in mice and F344 rats from a gavage or dietary exposure compared to an i.v. exposure that, in conjunction with the Sumner et al. (2003, 224347) results, indicate that there is first pass metabolism in the lungs following an inhalation exposure similar to the first pass metabolism in the liver from an oral exposure, but apparently the lungs may have a larger percent of oxidative metabolism of AA to GA. Although in this single study with inhalation kinetic data, there do appear to be some route-to-route differences in the relative amounts of AA to GA, the differences are within two fold of each other, and the metabolic paths and total disposition are similar, supporting the derivation of the inhalation unit risk based upon the oral POD (i.e., the BMDL).

II.C.4. Discussion of Confidence

See discussion in the Section II.B.4. In addition, there is uncertainty as to the impact that differences in first pass effects between an oral and an inhalation exposure (i.e., lung versus liver first pass effects) might have on overall disposition.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — U.S. EPA (2010, 597278)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the Toxicological Review of Acrylamide (U.S. EPA, 2010, 597278). ***To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition (PDF)***.

II.D.2. EPA Review

Agency Completion Date — 03/22/2010

II.D.3. EPA Contacts

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Acrylamide
CASRN — 79-06-1

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

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VII. Revision History

Substance Name — Acrylamide
CASRN — 79-06-1
File First On-Line — 09/26/1988

Date	Section	Description
09/26/1988	I.A.	Oral RfD summary on-line
09/26/1988	II.	Carcinogen summary on-line
10/01/1990	I.B.	Not verified; data inadequate
11/01/1990	I.B.	Inhalation RfC message on-line
03/22/2010	I., II., VI.	RfD and cancer assessment sections updated; RfC assessment added.

VIII. Synonyms

Substance Name — Acrylamide
CASRN — 79-06-1
Section VIII. Last Revised — 03/22/2010

- acrylic amide
- acrylic acid amide
- ethylenecarboxamide
- propenamide
- propenoic acid amide
- vinyl amide