Acrylic acid (CASRN 79-10-7)

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 Acrylic acid

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	04/01/1994
Inhalation RfC (I.B.)	yes	04/01/1994
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Acrylic acid
CASRN — 79-10-7
Last Revised — 04/01/1994

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of

substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this 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.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Reduced pup weight **Rat Reproductive Study** **BASF, 1993**	NOAEL: 53 mg/kg-day (500 ppm in water) LOAEL: 240 mg/kg-day (2500 ppm in water)	100	1	5E-1 mg/kg-day

*Conversion Factors and Assumptions — Dose in mg/kg-day was reported based on measurements of actual drinking water concentrations and water consumption.

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

Note: The RfD for acrylic acid was originally verified in August 1985. The RfD was revised because of the availability of new information, including a two-generation reproductive study in rats, a chronic drinking water study in rats, developmental studies by the inhalation route in rats and rabbits, and a bioavailability study in rats and mice.

BASF (Badische Anilin- und Sodafabrik). 1993. Reproduction toxicity study with acrylic acid in rats: Continuous administration in the drinking water over 2 generations (1 litter in the first and 1 litter in the second generation). Project No. 71R0114/92011. BASF Aktiengesellschaft, Dept. of Toxicology, Rhein, FRG.

In a two-generation reproductive study in rats (BASF, 1993) acrylic acid was administered in drinking water at concentrations of 0, 500, 2500, and 5000 ppm to groups of 25 male and 25 female Wistar rats (35 days old at the beginning of treatment). After at least 70 days of treatment, the F0 parental generation animals were mated within the dose groups to produce one litter. Litters were culled to eight pups at day 4 postparturition, and groups of 25 male and female F1 pups were selected for the F1 parental generation and were mated after at least 98 days of treatment. F2 litters were culled to eight pups and were raised to day 21 postpartum. Acrylic acid

treatment was continuous throughout the premating, gestational, and lactational periods. Pups from both generations were necropsied at day 4 and 21 postpartum. In addition to body weight, food and water consumption, and general reproductive parameters, pups were monitored for behavior and developmental milestones and some pups were examined for visceral and skeletal abnormalities. The acrylic acid doses were estimated to be 53, 240, and 460 mg/kg-day in the animals receiving 500, 2500, and 5000 ppm in drinking water, respectively. A consistent finding throughout the study was decreased water consumption, possibly due to taste aversion, and reduced body weight gains were observed in some of the groups dosed with 240 and 460 mg/kg-day. Water consumption was reduced 11-14% at 460 mg/kg-day in the F0 parental animals compared with controls throughout premating, gestation, and lactation, but was not reduced in F0 animals at 240 mg/kg-day. The F1 parental animals had water intake reduced by 18-27% throughout the study at 460 mg/kg-day and by 6-13% at 240 mg/kg-day. Reductions in body weight were reported that appear to parallel the reductions in water intake and were more severe in the pups. In the F0 parental generation exposed to 460 mg/kg-day, the males showed decreased body weight to 91% of controls, but not until the postmating period (12-21 weeks), but females were not affected. In the F1 pups exposed to 460 mg/kg-day, significantly lower body weights were observed at day 21 of the lactation period (65% of controls). Pup weights in the 240-mg/kg-day group were reduced to 89% of controls at day 21 of gestation. The F1 parental animals had reduced food consumption during the premating period (87-92% of controls) and also showed lower body weights than controls in the 460-mg/kg-day-dose group. Because the F1 pups were so much lower in weight in the high-dose group, the F1 parental generation in the high-dose group weighed 75% of the controls at 14 weeks prior to mating. This difference was 85-89% of controls at the time of mating. Thus, although the body weights were significantly lower in the high-dose F1 parental generation, the overall weight gain was similar in the F1 parental animals, suggesting that the effect resulted primarily from the reduced weight during the preweaning period. In the animals exposed to 240 and 460 mg/kg-day, body weights were reduced in the F2 pups to 88 and 68% of controls, respectively, and were associated with reduced maternal water consumption, compared with controls. Reduced weight was not observed in the parental generations exposed to 240 mg/kg-day. No changes in water consumption or body weight were observed in the animals exposed to 53 mg/kg- day. The reduced weight gain in the F0 generation was less than 10% of controls in males and is not considered adverse, and the decreased body weight in the F1 parental generation was greatest at the earliest recorded time and likely reflects preweaning and early postweaning effects. Reduced body weight in the F1 and F2 pups was observed at 240 and 460 mg/kg-day. Although these changes occurred at the end of the period of active nursing and are associated with decreases in maternal water consumption, it is not clear that the reduced weight compared with controls can be attributed only to reduced maternal water intake.

Other endpoints recorded in the two-generation reproductive study included nesting, littering and lactation behavior, gripping reflex, hearing startle reflex, pupillary reflex, pinna unfolding,

auditory canal opening, and eye opening. Slight reductions in the number of pups with eye opening or auditory canal opening on time were statistically significant in some groups, but are not considered to be adverse. There were no adverse treatment-related effects on reproductive function. The only clearly treatment-related adverse effects were histopathological lesions in the forestomach and glandular stomach in animals exposed to 460 mg/kg-day. Hyperkeratosis of the limiting ridge of the forestomach and edema of the submucosa of the glandular stomach were observed in males and females. These lesions were observed in both the F0 and F1 parental generations at 460 mg/kg-day but not at 53 or 240 mg/kg-day. No reproductive effects were found in the highest dose tested, 460 mg/kg-day. The NOAEL for reproductive effects is 460 mg/kg-day, and the NOAEL for histological changes in the stomach is 240 mg/kg-day. The effects on pup weights are considered to be treatment related and adverse, and this study identifies a LOAEL of 240 mg/kg-day and a NOAEL of 53 mg/kg-day for this effect.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — The uncertainty factor of 100 includes a factor of 10 for interspecies extrapolation and a factor of 10 to protect sensitive individuals. An uncertainty factor for an inadequate database due to the lack of a chronic study in a second species was not considered to be necessary due to the results of the bioavailability study showing no difference between rats and mice in the rapid rate of elimination of acrylic acid from oral and intravenous routes.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

In a chronic study (Hellwig et al., 1993; BASF, 1989) acrylic acid was administered in drinking water to groups of 50 male and female Wistar rats at concentrations of 0, 120, 400, or 1200 ppm. Drinking water consumption and body weights were determined regularly throughout the study, which ran for 26 months for males and 28 months for females. Blood samples for hematological evaluations were taken at 12, 18, and 24 months and at termination, and complete gross and histopathological examinations were conducted at the terminal sacrifice. Based on measurements of drinking water concentration and consumption the doses were estimated to be 0, 8, 27, and 78 mg/kg-day. Drinking water consumption was slightly reduced at 78 mg/kg-day, but the difference was not significant. This result is consistent with the BASF (1993) study that showed no effect on water consumption in rats exposed to 53 mg/kg-day acrylic acid in drinking water. No clinical signs of toxicity or changes in body weights were observed in treated animals. No exposure related changes were seen in the hematological measurements. Histopathological examinations also showed no clear indications of target organ pathology. Hyperkeratosis of the forestomach was reported in a small number of animals, but the change is not clearly exposure related because of the occurrence of this lesion in the control and low-dose groups. This lesion

also was observed at 460 mg/kg-day by BASF (1993) in the parental animals, but not at 240 or 53 mg/kg-day acrylic acid in drinking water. A slight increase in liver fatty change in the high-dose group also was observed and may be treatment related, but is not considered adverse because liver effects were not observed in other drinking water studies at much higher doses. The high-dose group in this study establishes a NOAEL at the highest dose tested, 78 mg/kg-day, which supports the NOAEL identified in the critical study.

In a preliminary study to the chronic study (Hellwig et al., 1993; BASF, 1988) acrylic acid was administered in drinking water to groups of 30 male and female Wistar rats for 3 months (10/sex/group) or 12 months (20/sex/group). Acrylic acid concentration in drinking water was 0, 120, 800, 2000, and 5000 ppm. Food and drinking water consumption, body weight, hematology, blood chemistry, and urinalysis were measured periodically throughout the study. At termination of dosing, histopathological examination was carried out on tissues from the control and 2000- and 5000-ppm groups (10 tissues at 3 months and about 40 tissues at 12 months). The estimated doses were 9, 61, 140, and 331 mg/kg-day in the groups exposed to 120, 800, 2000, and 5000 ppm, respectively. In the 12-month study, drinking water consumption was reduced in males by 15-20% relative to controls in the 331-mg/kg-day group during most of the study, and 10% relative to controls in the 140-mg/kg-day group during the first 14 weeks. Female drinking water consumption was minimally affected. Body weight in males was reduced to 93% of controls at the end of the 3-month study. In the 12-month study, male body weights were reduced to 94% of controls at 91 days and to 91-92% of controls in males dosed with 140 or 331 mg/kg-day. There was no effect on body weight in females in the 3- or 12- month studies. There were no clearly treatment-related effects on blood chemistry, hematology, or urinalysis parameters. There were also no gross or histological changes detected in any of the tissues examined. In particular, the lack of effect in the 331-mg/kg-day-dose group in the stomach contrasts with the finding of mild histological lesions in the two-generation reproductive study in the same species at the same drinking water concentration. This may be explained in part by the higher dose estimated for the two studies (460 mg/kg-day in the reproductive study vs. 331 mg/kg-day in the chronic study). This difference in effect also may be explained by the increase in drinking water consumption in females during lactation and by the fact that males in the reproductive study were exposed for up to 20 weeks. These studies suggest that doses in the 300-500-mg/kg range are near the threshold for histological effects in the stomach in the subchronic study. Body weight changes were observed in males at 3 and 12 months but were not more than 10% of control weight and are not considered adverse. Both the subchronic and the 12-month studies identify a NOAEL for body weight changes at 331 mg/kg-day (5000 ppm in water), and no specific target organ effects were observed at this dose.

In contrast to the subchronic drinking water study, Hellwig et al. (1993; also BASF, 1987) reported a gavage study in which Wistar rats (10/sex/group) were dosed by gavage with 150 or 375 mg/kg-day in water. When delivered as a bolus dose at approximately the same doses used

in the subchronic drinking water study, acrylic acid caused death in 10/20 animals at the low dose and 15/20 animals at the high dose (males and females combined). Marked gross and microscopic effects, as well as some respiratory tract effects, were observed in the gastrointestinal tract and kidneys.

DePass et al. (1983) reported a subchronic drinking water study in which Fischer 344 rats (15/sex/group) were administered doses of 0, 83, 250, or 750 mg/kg-day. Urinalysis, blood chemistry, and hematology were assessed during the study, and, at study termination, histological examination of tissues from the control and high-dose groups was performed. A dose-related decrease in water consumption was observed that was significant in all dose groups in males and in the 250- and 750-mg/kg-day group females. In males and females at 750 mg/kg-day, food consumption was decreased and body weight was reduced to 81 and 84% of controls in males and females, respectively, as were several organ weights. These effects were not seen in males at 250 mg/kg-day. In females at 250 mg/kg-day, a significant effect on body weight gain was reported, but the final body weight was 95% of the controls. There were no effects noted on histological examination of the high-dose animals. A NOAEL for changes in body weight and organ weight is identified at 250 mg/kg-day, and there was no specific target organ pathology observed at 750 mg/kg-day. It is not clear whether the forestomach was examined in this study.

A single generation reproductive study was conducted in which 10 male and 20 female rats were administered acrylic acid in drinking water at concentrations resulting in doses of 83, 250, and 750 mg/kg-day for 3 months (DePass et al., 1983). After the exposure period, the animals were mated within exposure groups and exposure was continued throughout gestation and lactation. Water consumption was reduced to 95, 83, and 61% of controls in the 83-, 250-, and 750-mg/kg-day groups, respectively, in males and 97, 83, and 58% of controls in females. Decreases in food consumption and body weight (79% of controls in males and females) were statistically significant only at the highest dose in males and at the two higher doses in females. There were no histological changes observed in high-dose animals in 26 tissues, including respiratory tract, stomach, liver, and kidneys. An apparent decrease in the fertility of females and a reduction in gestation index, number of live pups per litter, and percentage of pups weaned in animals at the highest dose were observed, but these differences were not statistically significant compared with the control group. The unusually low fertility in the control group makes interpretation difficult. At the highest dose, there was a statistically significant decrease in body weight of the male and female pups. The males also exhibited significant decreases in absolute and relative liver weights and absolute kidney and heart weights at 0.75 g/kg/day. The females showed a significant decrease in absolute and relative spleen weight and absolute liver weight at the highest dose. There was an increase in relative brain weight in both sexes at this dose. This study identifies a NOAEL for maternal and fetal toxicity and possibly for reproductive effects at 250 mg/kg-day.

Developmental toxicity studies of inhaled acrylic acid in Sprague-Dawley rats (Klimisch and Hellwig, 1991) and rabbits (Chun et al., 1993; Neeper- Bradley and Kubena, 1993) have been reported. These studies are described in detail in the inhalation RfC (U.S. EPA, 1994). These studies did not show adverse developmental effects. The rat study identifies a NOAEL for developmental effects at 360 ppm (1060 mg/cu.m). The NOAEL for effects on body weight in rats was 40 ppm (120 mg/cu.m). In the rabbit study, the NOAEL for developmental effects was 225 ppm (663 mg/cu.m).

Studies of the bioavailability of acrylic acid in mice and rats evaluated the disposition after administration by the inhalation, oral, dermal, and i.v. doses (Frantz and Beskitt, 1993; Black, 1993; Kutzman et al., 1982). These studies are described in detail in the inhalation RfC (U.S. EPA, 1994). These studies show that acrylic acid administered by various routes is highly bioavailable and is fairly rapidly metabolized and excreted. The metabolism and elimination do not appear to be so fast as to prevent widespread circulation of unchanged acrylic acid to the body. However, the bioavailability studies have not attempted to measure acrylic acid at less than 1 hour after exposure. The half-time for elimination in the in vivo studies was on the order of 20-40 minutes.

Both in vitro and in vivo studies of acrylic acid metabolism have produced strong evidence that the metabolism proceeds by a mitochondrial biochemical pathway for propionic acid metabolism, which normally functions in the body in the final stages of the breakdown of fatty acids and in the production of intermediates for the tricarboxylic acid cycle (Black et al., 1993; DeBethizy et al., 1987; Winter and Sipes, 1993; Finch and Frederick, 1992). Metabolism by this route was most active in the liver and kidney (DeBethizy et al., 1987). This route of metabolism would explain the rapid rate of elimination as carbon dioxde and the presence of 3-hydroxypropionate in vitro and in vivo after administration of acrylic acid. The limited reactivity of acrylic acid in the body was suggested by the observation that acrylic acid does not react with glutathione in vitro, nor does it deplete nonprotein sulfhydryls in blood in vitro (Miller et al., 1981). After an oral dose of 400 or 1000 mg/kg, nonprotein sulfhydryls (NPSH) were depleted in the forestomach of rats, and a lower dose of 40 mg/kg also caused a reduction in NPSH in the glandular stomach (DeBethizy et al., 1987), but no changes in NPSH were seen in blood or liver. A theoretical analysis of the potential reactivity of acrylic acid anion (the predominant form at physiological pH) concluded that there would be very limited potential for reaction of acrylic acid with cellular nucleophiles, such as sulfhydryl and amino groups (Frederick and Reynolds, 1989).

The oral and inhalation toxicity studies show portal-of-entry effects but no indication of specific target organ toxicity at other sites. Mechanistic and kinetic studies show limited reactivity and rapid detoxification, but no accumulation of the dose. The rapid detoxification and the limited reactivity in the body are consistent with low systemic toxicity. The portal-of-entry effects may

result from high local concentrations that lead to greater tissue reactivity or changes in pH. The available evidence from both oral and inhalation routes of exposure suggests that the portal-of-entry effects are true sentinel effects in that they occur at much lower exposures than systemic (non-portal-of-entry) effects. In addition, disposition studies using radiolabeled acrylic acid administered by several routes show that nearly all of the acrylic acid is absorbed and is metabolized to carbon dioxide, with very little radioactivity excreted in the urine or feces. This similarity suggests that it is reasonable to use the developmental toxicity studies from the inhalation route to support the database requirements of the oral RfD. Because the dose of acrylic acid is distributed fairly rapidly and metabolized similarly for several routes of exposure, a crude extrapolation of the inhalation developmental studies to the oral route is reasonable. Based on default values for rat and rabbit respiration rates and body weights, the NOAELs for developmental effects in the inhalation studies (in the presence of respiratory tract effects) are 1140 and 250 mg/kg-day in the rat and rabbit studies, respectively. This is based on a crude route extrapolation and is done for the purpose of comparison only. It is concluded that developmental effects are not critical to the RfD derivation.

I.A.5. Confidence in the Oral RfD

Study — High
Database — High
RfD — High

The confidence in the principal studies is high because a sufficient number of animals were used and all relevant endpoints were reported thoroughly. The database contains two developmental studies and two chronic studies of good quality, all of which are consistent in identifying the critical effect, resulting in high confidence. High confidence in the RfD follows.

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

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1984

Agency Work Group Review — 08/19/1985, 02/17/1994

Verification Date — 02/17/1994

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for acrylic acid conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new

studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

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 (internet address).

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

Substance Name — Acrylic acid
CASRN — 79-10-7
Last Revised — 04/01/1994

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this 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.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Degeneration of the nasal olfactory epithelium **Mouse Subchronic Inhalation Study** **Miller et al., 1981a**	NOAEL: None LOAEL: 14.94 mg/cu.m LOAEL(ADJ): 2.67 mg/cu.m LOAEL(HEC): 0.33 mg/cu.m	300	1	1E-3 mg/cu.m

*Conversion Factors and Assumptions — MW = 72.06. At 21.1 degrees C and assuming 760 mmHg, LOAEL(mg/cu.m) = 5 ppm x 72.06/24.12 = 14.94. LOAEL(ADJ) = 14.9mg/cu.m x 6 hours/24 hours x 5 days/7 days = 2.67. The LOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.04 cu.m, MVh = 20 cu.m, Sa(ET) = 2.9 sq.cm, Sh(ET) = 177 sq.cm. RGDR(ET) = (MVa/Sa)/(MVh/Sh) = 0.122. LOAEL(HEC) = LOAEL(ADJ) x RGDR = 0.33 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Note: The RfC for acrylic acid was originally verified in August 1990. The RfC was revised because of the availability of new information, including a two-generation reproductive study in rats, a developmental study in rabbits, and a bioavailability study in rats and mice. The uncertainty factor used previously for the incomplete database was reduced based on the new data.

Miller, R.R., J.A. Ayres, G.C. Jersey, and M.J. McKenna. 1981a. Inhalation toxicity of acrylic acid. Fund. Appl. Toxicol. 1(3): 271-277.

Fifteen Fischer 344 rats and 15 B6C3F1 mice of each sex/group were exposed to actual concentrations measured by infrared analysis of 0, 5, 25, or 75 ppm acrylic acid (0, 14.9, 74.7, or 224 mg/cu.m) (Miller et al., 1979b, 1981a). The exposure was 6 hours/day, 5 days/week for 13 weeks (duration-adjusted concentrations of 0, 2.66, 13.3, or 40.0 mg/cu.m). Animals were observed twice per day. Parameters monitored for 10 animals of each sex from each exposure group included body weight, organ weights, organ-to-body weight ratios, hematologic parameters (packed-cell volume, erythrocyte count, hemoglobin concentration, and differential leukocyte counts), clinical chemistry parameters (urea nitrogen, glucose, SGPT, alkaline

phosphatase), and urinalysis (rats only). All rats and mice in the control and 75-ppm exposure groups were examined for gross pathology and histopathology of major tissues, including lung, trachea, and nasal turbinates; the other exposure groups were examined when positive results were obtained at the highest dose level. There were no treatment-related deaths of rats or mice during the study period; three mice died, however, apparently from traumatic injury due to handling. There were no significant differences in organ weights, organ-to-body weight ratios, clinical chemistry parameters, urinalysis parameters, or gross pathology that could clearly be related to exposure. In mice only, mean hemoglobin was significantly decreased relative to controls in the 25- and 75- ppm exposure groups for males and in the 75-ppm exposure group for females; however, the values were within normal limits for this strain of mice. Focal degeneration of the olfactory epithelium was observed in 1/10, 2/10, 11/11, and 10/10 male mice and in 0/10, 4/10, 9/10, and 12/12 female mice in the control and 5-, 25-, and 75-ppm exposure groups, respectively. The LOAEL is therefore 5 ppm [LOAEL(HEC) = 0.33 mg/cu.m] for effects in the nasal olfactory epithelium. The severity as well as the incidence of the lesion increased with exposure concentration. A NOAEL in mice was not determined in this study. No effects were observed in the lungs, trachea, larynx, or GI tract. Rats first demonstrated lesions of the nasal olfactory epithelium at 75 ppm; there were no effects at 25 ppm [NOAEL(HEC) = 1.43 mg/cu.m].

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — A factor of 10 is used for protection of sensitive human subpopulations. A factor of 3 is used for extrapolation from subchronic to chronic duration due to limited progression between short-term and subchronic exposures and due to rapid metabolism. A factor of 10 is applied to account for both interspecies extrapolation, because dosimetric adjustments were applied, and use of a LOAEL because the effect is considered mild.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

In a 2-week subacute inhalation study (Miller et al., 1979a), rats and mice (5/sex/group) were exposed to actual concentrations of 0, 25, 74, or 223 ppm (0, 75, 220, or 666 mg/cu.m) acrylic acid for 6 hours/day, 5 days/week (duration-adjusted concentrations of 13, 40, or 119 mg/cu.m). Significant decreases in body weight gain were seen in exposed groups at 223 ppm. Decreased body weight gains in male mice at 25 and 74 ppm are not considered exposure related because of the low initial weights and unusually large weight gains in the controls. A decrease in adipose tissue was observed in female rats at 223 ppm. Rats had lesions of the nasal mucosa at 223 ppm. Mice had dose-related lesions of the nasal mucosa, with lesions increasing in size, severity, and incidence from 25 to 223 ppm. Comparison of the degenerative lesions observed at the 25-ppm

exposure in the 2-week and subchronic studies (Miller et al., 1981a) reveals that there is an increase in incidence (6/10 at 2 weeks vs. 19/20 subchronic; males and females combined) and limited progression in severity. For this reason, the likelihood of progression of the lesion with further exposure may be limited as well, and the uncertainty in extrapolating from the subchronic study to the chronic scenario is reduced. This study identifies a NOAEL in rats for body weight changes at 74 ppm [NOAEL(HEC) = 40 mg/cu.m for extrarespiratory effect assuming lambda(a)/lambda(h) = 1 and periodicity attained] and a LOAEL for nasal effects in rats at 74 ppm [LOAEL(HEC) = 4.2 mg/cu.m]. The LOAEL for extrathoracic respiratory effects in mice is 25 ppm [LOAEL(HEC) = 1.6 mg/cu.m]. No effects on lung or trachea were observed in rats or mice.

Alderly Park rats were exposed to several concentrations of acrylic acid for different durations to determine the acute and subacute toxicity of the chemical (Gage, 1970). One 5-hour exposure to an atmosphere saturated with acrylic acid [6000 ppm (17,700 mg/cu.m)] produced nose and eye irritation, respiratory difficulty, and unresponsiveness in four rats (two males and two females). One rat died. Eight rats (four males and four females) exposed to 1500 ppm for 6 hours/day for 4 days showed nasal discharge, lethargy, and weight loss. Exposure to 80 or 300 ppm for 6 hours/day, 5 days/week, for 4 weeks produced some nose irritation, lethargy, retarded weight gain in eight rats at the higher dose. Histopathology showed all organs were normal in both groups, and no signs of toxicity were observed at the lower dose; but limited information is reported. This study suggests that concentrations much higher than those used in the principal study are required to produce overt systemic toxicity.

Rats exposed for 1 hour to acrylic acid concentrations of 100, 300, or 500 ppm exhibited dose-dependent decreases in both respiratory frequency and minute volume (Silver et al., 1981). Buckley et al. (1984) reported concentrations resulting in a 50% decrease in respiratory rate of 685 ppm in B6C3F1 mice and 513 ppm in Fischer 344 rats. Respiratory irritation and reduced ventilation therefore are not expected at the concentrations used in the principal study.

A developmental toxicity study of inhaled acrylic acid in Sprague-Dawley rats was reported by Klimisch and Hellwig (1991). In a preliminary study, groups of five pregnant animals were exposed to 0, 225, or 450 ppm acrylic acid for 6 hours/day on days 6-15 of gestation. Signs of nasal and eye irritation were observed in both exposed groups during exposure, and, at necropsy on day 20 of gestation, degeneration of the olfactory epithelium of the nose with metaplasia of the respiratory epithelium were observed in all exposed animals. Body weight gain was reduced throughout exposure at 450 ppm. Assessment of developmental endpoints was not done in the preliminary study. In the definitive study, groups of 30 pregnant Sprague-Dawley rats were exposed to 0, 40, 120, or 360 ppm acrylic acid (0, 120, 350, or 1060 mg/cu.m) for 10 days during days 6-15 of gestation. Maternal toxicity was evident in animals exposed to 120 and 360 ppm because body weight was reduced in the 360- ppm group on days 15 and 20, and body weight

minus uterus weight was reduced in animals exposed to 120 or 360 ppm on day 20. Signs of irritation were observed throughout the exposure in the 360-ppm group, but not at 40 or 120 ppm. Histopathological examination was not performed in the dams. No exposure-related adverse effects were observed on implantations, live implantations, resorptions, preimplantation loss, fetal length or weight, or on morphological abnormalities (skeletal or soft tissue). This study identifies a NOAEL for developmental effects at 360 ppm [NOAEL(HEC) = 1060 mg/cu.m] and a LOAEL for maternal body weight effects at 120 ppm [LOAEL(HEC) = 88 mg/cu.m].

An inhalation developmental study was also reported in rabbits. In the range-finding study (Chun et al., 1993), groups of eight pregnant New Zealand white rabbits were exposed to 0, 30, 60, 125, or 250 ppm acrylic acid on days 10-23 of gestation. Three animals per group were necropsied on day 23 of gestation, and the remaining animals were examined on day 29. Exposure- related maternal toxicity in the 125- and 250-ppm groups was observed, including signs of nasal irritation and reduced body weight. Final body weight was reduced to a lesser degree in animals exposed to 30 and 60 ppm. Histopathological examination of a single section of the nose showed adverse effects in the olfactory epithelium. The lesions included squamous metaplasia, epithelial erosion, and ulceration of the epithelium and increased in severity with increasing exposure concentration, with the effect first appearing in the 30-ppm group at day 23 and in the 60-ppm group at day 29. In the definitive developmental study (Neeper-Bradley and Kubena, 1993), groups of 16 pregnant rabbits were exposed to 0, 25, 75, or 225 ppm acrylic acid on gestation days 6-18. Maternal toxicity was evident in groups exposed to 225 or 75 ppm, but not to 25 ppm. Signs of nasal irritation including perinasal wetness and nasal congestion were observed. Significant decrements in food consumption and body weight gain were observed occasionally during exposure, but the body weights at the end of the exposure were not significantly affected. Histological examination of maternal tissues was not performed. No exposure-related adverse effects were observed in the number of corpora lutea and total, viable, or nonviable implantations; preimplantation loss; fetal length or weight; or on morphological abnormalities (skeletal or soft tissue). This study identifies a NOAEL for developmental effects at 225 ppm [NOAEL(HEC) = 663 mg/cu.m].

In a two-generation reproductive study in rats (BASF, 1993) acrylic acid was administered in drinking water at concentrations of 0, 500, 2500, and 5000 ppm to groups of 25 male and 25 female Wistar rats (35 days old at the beginning of treatment). This study is described in more detail in the oral RfD (U.S. EPA, 1994). A consistent finding throughout the study was decreased water consumption and body weight gain in some of the groups dosed with 240 and 460 mg/kg-day. Reduction in body weights paralleling the reductions in water intake were more severe in the pups. The effect on pup weights are considered to be treatment related and adverse, and this study identifies a LOAEL of 240 mg/kg-day and a NOAEL of 53 mg/kg-day for this effect.

A single-generation reproductive study was conducted by the oral route of exposure in which 10 male and 20 female rats were administered acrylic acid in drinking water at concentrations resulting in doses of 83, 250, and 750 mg/kg-day for 3 months (DePass et al. 1983). This study is described in more detail in the oral RfD (U.S. EPA, 1994). Decreases in food consumption and body weight gain were statistically significant only at the highest dose in males and at the two higher doses in females. This study identifies a LOAEL for maternal and fetal toxicity and possibly for reproductive effects at 750 mg/kg-day.

A study of the bioavailability of acrylic acid in mice and rats evaluated the disposition of oral, dermal, and i.v. doses (Frantz and Beskitt, 1993). Carbon-14-labeled acrylic acid (carboxyl carbon) was administered at 10 mg/kg i.v., 40 or 150 mg/kg orally, or 10 or 40 mg/kg dermally, and expired air, urine, feces, and tissues were analyzed for radioactivity at various times after dosing. Regardless of route, the majority (more than 75%) of the recovered radioactivity was eliminated as exhaled carbon dioxide within the first 24 hours after exposure. Most of the i.v. dose was exhaled within the first hour. After oral dosing, most of the dose was exhaled as carbon dioxide during the first hour, but a significant amount remained in the gut 1 hour after dosing. Analysis of the chemical form of the radioactivity measured in this study was reported (Black, 1993). One hour after dosing with 150 mg/kg, a very small amount of unchanged acrylic acid were found in the liver and urine but was undetectable in the plasma. Unchanged acrylic acid was not detected after 40 mg/kg. In contrast, 3-hydroxypropionate, a product of acrylic acid metabolism, was found in plasma and tissues after oral administration. In a study of acrylic acid disposition after inhalation exposure, Kutzman et al (1982) exposed rats to carbon-1-labeled acrylic acid for 1 minute. At 1.5 minutes following exposure, most of the radioactivity was associated with the head, suggesting a high degree of nasal deposition. By 65 minutes after exposure, most of the acrylic acid had been expired as carbon dioxide. These studies show that acrylic acid administered by various routes is highly bioavailable and is fairly rapidly metabolized and excreted. The metabolism and elimination do not appear to be so fast as to prevent widespread circulation of unchanged acrylic acid to the body. The half-time for elimination in the in vivo studies was on the order of 20-40 minutes.

Both in vitro and in vivo studies of acrylic acid metabolism have produced strong evidence that the metabolism proceeds by a mitochondrial biochemical pathway for propionic acid metabolism that normally functions in the body in the final stages of the breakdown of fatty acids and the production of intermediates for the tricarboxylic acid cycle (Black et al., 1993; DeBethizy et al., 1987; Winter and Sipes, 1993; Finch and Frederick, 1992). This route of metabolism would explain the rapid rate of elimination as carbon dioxide and the presence of 3-hydroxypropionate in vitro and in vivo after administration of acrylic acid. The limited reactivity of acrylic acid in the body was suggested by the observation that acrylic acid does not react with glutathione in vitro nor does it deplete nonprotein sulfhydryls in blood in vitro (Miller et al., 1981b). After an oral dose of 400 or 1000 mg/kg, nonprotein sulfhydryls (NPSH) were depleted in the

forestomach of rats (88 or 54% of control, respectively), and a lower dose of 40 mg/kg also caused a reduction in NPSH in the glandular stomach (77% of control; 64 and 25% of control at 400 and 1000 mg/kg, respectively) (DeBethizy et al., 1987), but no changes in NPSH were seen in blood or liver. In these studies, increases in dose were achieved by increases in gavage solution concentrations (0.8, 8, and 20% solutions were used). A theoretical analysis of the potential reactivity of acrylic acid anion (the predominant form at physiological pH) concluded that very limited potential exists for reaction of acrylic acid with cellular nucleophiles, such as sulfhydryl and amino groups (Frederick and Reynolds, 1989).

The oral and inhalation toxicity studies show portal-of-entry effects and no indication of specific target organ toxicity at other sites. Mechanistic and kinetic studies show limited reactivity, rapid detoxification, and no accumulation of the dose. The rapid detoxification and the limited reactivity in the body are consistent with low systemic toxicity. The portal-of-entry effects may result from high local concentrations that lead to greater tissue reactivity or changes in local pH. The available evidence from both oral and inhalation routes of exposure suggest that the portal-of-entry effects are true sentinel effects in that they occur at much lower exposures than systemic (non-portal-of-entry) effects. In addition, disposition studies using radiolabeled acrylic acid administered by several routes show that nearly all of the acrylic acid is absorbed and is metabolized to carbon dioxide, with very little excreted in the urine or feces. This similarity suggests that it is reasonable to use the reproductive toxicity study from the oral route to support the database requirements of the RfC. Because the dose of acrylic acid is distributed fairly rapidly and metabolized similarly for several routes of exposure, a crude extrapolation of the oral reproductive studies to the inhalation route is reasonable. Based on default values for rat respiration rates and body weight, the NOAEL for reproductive toxicity is much greater than the NOAEL for nasal effects. This is based on a crude route extrapolation and is done for purpose of comparison only. It is concluded that reproductive effects are not critical to the RfC derivation.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

The study by Miller et al. (1981a) was well conducted and identified a LOAEL for a mild occurence of the most sensitive effect. The confidence in the study was determined to be medium because a NOAEL was not identified, a small number of animals was used, and there is limited description of the nasal lesion reported. Although a subchronic inhalation study in a second species, two inhalation developmental studies in different species, and a two- generation reproductive study by the oral route support the principal study, the confidence in the database is medium due to lack of chronic data. The confidence in the RfC is medium.

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

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1984

Agency Work Group Review — 08/23/1990, 02/17/1994

Verification Date — 02/17/1994

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for acrylic acid conducted in August 2003 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

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 (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Acrylic acid
CASRN — 79-10-7

Not available at this time.

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

VI. Bibliography

Substance Name — Acrylic acid
CASRN — 79-10-7
VI.A. Oral RfD References

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VI.B. Inhalation RfC References

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VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Acrylic acid
CASRN — 79-10-7

Date	Section	Description
10/01/1990	I.B.	Inhalation RfC summary on-line
03/01/1994	I.A.	Withdrawn; new oral RfD verified (in preparation)
03/01/1994	I.B.	Withdrawn; new inhalation RfC verified (in preparation)
04/01/1994	I.A.	Oral RfD summary replaced; new RfD
04/01/1994	I.B.	Inhalation RfC summary replaced; new RfC
10/28/2003	I.A.6., I.B.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Acrylic acid
CASRN — 79-10-7
Last Revised — 01/31/1987

- 79-10-7
- Acroleic acid
- Acrylic Acid
- Acrylic acid, glacial
- Ethylenecarboxylic acid
- Propene acid
- Propenoic acid
- 2-Propenoic acid
- RCRA waste number U008
- UN 2218