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Acrolein (CASRN 107-02-8)

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Note: A TOXICOLOGICAL REVIEW is available for this chemical in Adobe PDF Format (106 Pages, 853 Kbytes). Similar documents can be found in the List of Available IRIS Toxicological Reviews.

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0364

Acrolein; CASRN 107-02-8

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 Acrolein

File First On-Line 09/07/1988

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	06/03/2003
Inhalation RfC Assessment (I.B.)	on-line	06/03/2003
Carcinogenicity Assessment (II.)	on-line	06/03/2003

_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — Acrolein
CASRN — 107-28-8
Last Revised — 06/03/2003

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.

An RfD for acrolein was not previously available on IRIS.

__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased survival Chronic gavage rat study Parent et al., 1992a	NOAEL: 0.05 mg/kg-day FEL*: 0.5 mg/kg-day	100	1	5×10^{-4} mg/kg-day

* FEL — frank effect level (an objective, clinically evident effect)

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

Parent et al. (1992a) administered acrolein in water daily via gavage to Sprague-Dawley rats, 70/sex/group, at dose levels of 0, 0.05, 0.5, and 2.5 mg/kg BW. Dosing volume was 10 ml/kg. Ten animals from each group were sacrificed after one year and the remainder after two years. An extensive array of tissues was examined microscopically, including stomach tissue. Although it was not explicitly stated that both the glandular stomach and forestomach were examined, it is unlikely that both parts of the stomach were not examined. Daily observations were made and various clinical, hematological and urinary parameters were measured after 3, 6, 12, and 18 months of treatment and immediately prior to sacrifice. There were no statistically significant increased incidences of microscopic lesions in the treated rats, whether neoplastic or non-neoplastic. Food consumption and body weights were unaffected by treatment. With the exception of a statistically significant depression of creatinine phosphokinase (creatine kinase) at all dose levels and at most time intervals (except 12 months), clinical chemistry parameters, hematology and urinalysis measurements were unaffected by treatment.

The most definitive responses reported were treatment-related increases in early cumulative mortality. Data were provided in the form of survival curves. Among high-dose males, survival was significantly reduced after one year ($p<0.05$), and marginally reduced among mid-dose males (p value not reported). Among high-dose males, a trend test for survival during the first year indicated a highly statistically significant ($p=0.003$) decrease; however, the statistical differences

are nullified when the survival data for two years are included in the analysis. Survival among females during the first year corresponded closely to those obtained for males. A statistically significant decrease in survival ($p<0.05$) was reported in the high-dose group, while a decrease in survival in the mid-dose group was marginally significant (p value not reported). Unlike responses in males, the significant associations between dosing and survival persisted in females through the end of the study. After two years, a statistically significant reduction in survival was noted based on four different statistical tests for the mid-dose group and in three of four statistical tests in the high-dose group (p values not reported). Although the differences in survival were statistically significant in females after two years, it should be noted that the differences were relatively small. No differences in survival compared to controls were seen in either the male or female low-dose groups (0.05 mg/kg/day). Thus, 0.5 mg/kg/day is considered a frank effect level (FEL) for the rat, and 0.05 mg/kg/day the no-observed-adverse-effect level (NOAEL). The FEL is defined as "a level of exposure or dose which produces irreversible, adverse effects at a statistically or biologically significant increase in frequency or severity between those exposed and those not exposed" (IRIS, 2003).

Other studies support the findings of reduced survival in laboratory animals exposed to acrolein as reported by Parent et al. (1992a). In a study designed to evaluate the potential carcinogenicity of acrolein (Parent et al., 1991), Swiss albino CD-1 mice (70-75/sex/group) were dosed via gavage (acrolein in distilled water and stabilized with hydroquinone) with 0, 0.5, 2.0 or 4.5 mg/kg/day for 18 months. The primary effect was increased mortality only in high-dose males of the 4.5 mg/kg/day group; mortality in the mid- and low-dose groups was less than control. There were no dose-related adverse histopathological or clinical findings.

In a 13-week daily gavage study of acrolein (in 0.5% methyl cellulose) in F344 rats and B6C3F1 mice conducted for the National Toxicology Program (NTP, 1995), 10 rats/sex/dose were administered 0, 0.75, 1.25, 2.5, 5.0, and 10 mg acrolein/kg; 10 mice/sex/dose received 0, 1.25, 2.5, 5.0, 10 and 20 mg/kg. Dose volume was 5 ml/kg for rats and 10 ml/kg for mice. Treatment resulted in similar dose-related effects in both sexes of both species: hemorrhage and necrosis and other lesions of the forestomach and glandular stomach and secondary changes associated with acrolein-induced mortality in high-dose animals (NTP, 1995; Pathology Working Group Review, 1997). Abnormal breathing and nasal/eye discharge were among the clinical findings in high-dose rats. Nearly all high-dose animals died or were removed from study because of gastrointestinal toxicity. The NOAEL was 0.75 mg/kg for female rats and 1.25 mg/kg for males, based on forestomach squamous epithelial hyperplasia in the 1.25 mg/kg group and 2.5 mg/kg group, respectively. There were no clinical signs of toxicity in mice. The forestomach lesions in mice were similar to those in the rat. Glandular stomach lesions were only seen in the 10 and 20 mg/kg males and in the 20 mg/kg females. Statistically significant increases in absolute and relative liver weights were seen in male mice at 10 mg/kg without attendant hepatic histopathology. There was no NOAEL for the male mouse (i.e., one male had squamous epithelial hyperplasia at the lowest dose of 1.25 mg/kg). The NOAEL for female mice was 1.25 mg/kg. Reasons for no reported observations of stomach lesions in Sprague-Dawley female rats at the highest dose (2.5 mg/kg) of the Parent et al. (1992a) study compared with forestomach squamous epithelial hyperplasia observed in female F344 rats in the NTP study at 1.25 mg/kg/day are not readily apparent, but may relate to differences in strain sensitivity or vehicle. The vehicle dose volume was 5 ml/kg in the NTP (1995) study and 10 ml/kg in the Parent et al. (1992a) study for rats, and there may have been a reduced local gastric mucosal irritation and pathology by virtue of dilution. There were also differences in the vehicle solution and, possibly, the stability of the dosing solutions. Parent et al. (1992a) conducted stability studies on acrolein in water, and monitored the stability of their dosing solutions (reporting losses of less than 10% for 3 hours at room temperature). They used a stabilizing agent, 0.25% hydroquinone, in the stock solution, and prepared dosing solutions daily. The NTP study used a dose vehicle of 0.5% methylcellulose in deionized water, and no information was available on stability or stabilizing agents.

For the mouse results, there is a similar divergence between the absence of reported forestomach lesions in the CD-1 mice at 4.5 mg/kg in the Parent et al. (1991) study compared with effects observed in female B6C3F1 at 2.5 mg/kg in the NTP study. Species differences and dose volume again may have accounted for observed differences in response. Dose volume in the NTP study for mice was 10 ml/kg, and was unspecified in the Parent et al. (1991) study.

A benchmark dose approach was unsuitable for RfD development because the data in the Parent et al. (1992a) study were presented graphically, with statistical evaluation at one and two-year time points, but no numerical values. Moreover, the NOAEL derived from the Parent et al. study and used as the basis for the RfD is from a statistically significant increase in mortality, a frank effect. A benchmark dose analysis would not be appropriate when the dose-response is for early cumulative mortality.

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

UF = 100.

A default UF_A of 10 was applied to account for interspecies differences between laboratory animals and humans. No information was available to support a change from the default.

A default UF_H of 10 was applied for intraspecies uncertainty to account for human variability and sensitive subpopulations, i.e., to account for human variability in the severity or range of response from any given acrolein exposure amongst different individuals.

A UF_D was not applied because the database for acrolein was considered complete. The available oral database includes chronic toxicity studies in the rat and mouse, an oral reproductive toxicity study in Sprague-Dawley rats and an oral developmental toxicity study in New Zealand white rabbits. The findings from the oral reproductive and developmental toxicity studies are supported by an inhalation reproductive toxicity study of acrolein in Fisher 344 rats that revealed no reproductive or developmental effects. Acrolein's high reactivity at the point of contact and the evidence for minimal systemic distribution of acrolein obviates the need for additional repeat dose studies.

The RfD is based on a NOAEL from a chronic study, which obviates the need for an uncertainty factor for LOAEL to NOAEL extrapolation or for subchronic to chronic extrapolation.

MF = 1.

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

Administration of acrolein in water by oral gavage at 0.05, 0.5, and 5.0 mg/kg to male and female Sprague-Dawley rats (30/sex/group) daily, 5 days per week for 13 weeks did not produce any significant adverse effects on mortality, on clinical, hematological, or urinalysis parameters, or on histopathology (Bioassay Systems Corp., 1981). This study was a precursor to Parent et al. (1992a), identified as the principal study.

In a range-finding gavage study in artificially inseminated New Zealand white rabbits (3-4/group), acrolein (0, 0.5, 1.0, 2.0, 4.0, and 6.0 mg/kg/day) produced high incidences of maternal mortality, spontaneous abortion, resorption, clinical signs, gastric ulceration, and/or sloughing of the gastric mucosa. The dose-response curve for mortality was steep. A factor of 2 in dose (from 2 to 4 mg/kg) resulted in 25% mortality in the high-dose animals compared to 0% in lower-dose animals (Parent et al., 1993). Mortality was 100% at 6 mg/kg.

In a two-generation reproductive toxicity study, four groups of 30 male and 30 female Sprague-Dawley rats were gavaged with 70 daily doses of acrolein at levels of 0, 1, 3, or 6 mg/kg in a dosing volume of 5 ml/kg (Parent, 1992b). Rats within each dosing group (F_0 generation) were then assigned to a 21-day period of cohabitation. Dosing continued for females through cohabitation, gestation, and lactation. A similar regime was carried out for F_1 generation offspring, resulting in F_2 generation pups. Mortality was significant (at 6 mg/kg) in both males and female of the F_0 and F_1 generations with the pattern continuing with F1 mid-dose animals, the latter showing signs of respiratory distress and histopathological lesions in the lungs and stomach. Reproductive parameters (i.e., mating performance and fertility indices) were unaffected. No treatment-related gross or microscopic effects were observed in the reproductive tissues of the F_0 or F_1 animals, and no gross abnormalities were observed in F_2 generation pups. The data provide evidence that acrolein is not a selective reproductive toxicant but does produce toxicological effects at doses as low as 3 mg/kg/day.

Arumugam et al. (1999) exposed male Wistar rats, 5 animals/group, daily to acrolein via intubation (2.5 mg/kg BW) for 45 days. The incidence of mortality, if any, was not reported in this study. This study clearly showed damage to mitochondria (through the loss of mitochondrial lamellae of the cristae), a decrease in the availability of reduced glutathione (a substrate for glutathione peroxidase), and a 30-56% decrease in activities of citric acid cycle enzymes, resulting in decreased energy production in liver cells. These results indicate that at least some uptake occurs from the oral route; however, the stomach was not examined by light microscopy.

Because of the highly reactive nature of acrolein, the concentration of a dose administered by gavage can affect the time course and degree of severity of toxicity at the point of entry and the relevance of the gavage bolus dose to human exposure. Rats have both a forestomach and a glandular stomach, while humans have only a glandular stomach. The glandular stomach is more resistant than the forestomach to pH changes and irritation. The residence time in the forestomach (of approximately 2 hours) is sufficiently long compared to the reaction time for toxicity with airway tissue observed in inhalation studies (i.e., microseconds) so that the dose to the glandular stomach may be much lower than that to the forestomach (TERA, 1998). The dog is a better model for glandular stomach toxicity than the rat, however, Parent et al. (1992c) administered acrolein (0.1% aqueous) in gelatin capsules to beagle dogs, so the dose concentration to the glandular tissue is not known. In lieu of studies that provide data on glandular stomach toxicity, the Parent et al. (1992a) study in the rat remains the most suitable choice for the principal study.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

__I.A.5. Confidence in the Oral RfD

Study — Medium
Database — High
RfD — Medium to High

The overall confidence in this RfD assessment is medium to high. Confidence in the principal study is medium. Several supporting studies involving other species also indicated that mortality increases sharply with elevated dose. The research demonstrating acrolein's high reactivity, low systemic distribution, toxicity at the point of entry, pronounced decreases in serum creatinine phosphokinase (creatine kinase), citric acid cycle enzymes and liver GSH, and increased mitochondrial damage in the Wistar rat suggest interference with normal metabolic processes or possibly the absorption of essential nutrients sufficient to lead to early mortality. Further

research is needed, however, to support a definitive mode of action. In the NTP (1995) study, glandular stomach and forestomach lesions were reported at higher doses and likely played a role in the observed mortality. Confidence in the database is judged high with chronic exposure studies in 2 species. Moreover, two studies (Parent et al., 1992b; Parent et al., 1993) provide evidence that reproductive and developmental effects are not critical endpoints although only one species was tested for reproductive effects (rat) and for developmental effects (rabbit). While the possibility of some transport of acrolein or a metabolite of acrolein to systemic sites remains, the critical target sites (discussed further in the Toxicological Review of Acrolein) are at the point of contact, e.g., the respiratory system, the gastrointestinal tract, mucous membranes, and skin. The high reactivity of acrolein and the lack of significant systemic distribution obviates the need to examine reproductive/developmental effects in a second species. The overall confidence in this RfD assessment is medium-to-high; a variety of studies across different durations of exposure and in several different laboratory animal species has been consistent in demonstrating that in the absence of mortality there are no clear indications of adverse effects.

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 Oral RfD

Source Document - U.S. EPA (2003)

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of the IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Acrolein (U.S. EPA, 2003). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review Comments and Disposition (PDF)***.

Agency Consensus Date - 05/16/2003

__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 (email address).

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

Substance Name — Acrolein
CASRN — 107-02-8
Last Revised — 06/03/2003

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 generally 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.

The revised RfC is the same value as the previous RfC of 2 x 10^{-5} mg/m^3 entered on IRIS 10/01/1991; however, this new RfC is based on an updated interpretation of the database.

__I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
Nasal lesions	NOAEL: none	1,000	1	2 x 10^{-5} mg/m^3
Subchronic rat inhalation study	LOAEL: 0.4 ppm (0.9 mg/m^3)			
Feron et al., 1978	LOAEL (ADJ): 0.16 mg/m^3			
	LOAEL (HEC): 0.02 mg/m^3			

*Conversion Factors and Assumptions: MW = 56.06 (HSDB, 2003). Assuming 25ºC and 760 mm Hg, the LOAEL of 0.4 ppm (0.9 mg/m^3) was adjusted to a continuous exposure as follows: LOAEL (ADJ) = 0.9 mg/m^3 x 6/24 x 5/7 = 0.16 mg/m^3. The LOAEL(HEC) was calculated for a Category 1 gas:respiratory effect in the extra-thoracic region by multiplying the LOAEL (ADJ) by the Regional Gas Dosimetry Ratio (RGDR(ET)), to derive a comparable human exposure (U.S. EPA, 1994). The calculation for the RGDR(ET) = (MVa/SAa) / (MVh/SAh) where MVa = 0.20 m^3/day, MVh = 20 m^3/day, SAa(ET) = 15.0 cm^2, SAh(ET) = 200 cm^2 RGDR(ET) = (0.20/15)/(20/200) = 0.14. The LOAEL(HEC) = LOAEL(ADJ) x RGDR(ET) = 0.16 mg/m^3 x 0.14 = 0.02 mg/m^3. Derivation of the RGDR is further described in the Toxicological Review for Acrolein.

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

Feron et al. (1978) exposed 6 Wistar rats/sex/concentration, 10 Syrian golden hamsters/sex/concentration, and 2 Dutch rabbits/sex/concentration for 6 hr/day, 5 days/week for 13 weeks to 0, 0.4, 1.4, or 4.9 ppm (0, 0.9, 3.2, or 11 mg/m^3) acrolein in a whole-body exposure chamber. Incidence data were not reported, but histopathological changes in the nasal cavity, lung, larynx, and trachea were graded as slightly, moderately, or severely affected. In rats, hematological parameters were unaffected by acrolein. Body weight gain was significantly inhibited at the high dose in rats, and less so at the intermediate concentration, but food consumption appeared to be decreased in these groups as well. At the intermediate concentration, both male and female rats showed significantly retarded weight gain ($p<0.05$). Three male and 3 female rats died during exposure at the highest dose. No other deaths considered to be treatment-related were reported in any of the species or exposure groups.

Histopathologic changes described as "slightly affected" were found in the nasal cavity of 1 of 12 rats exposed to 0.4 ppm (0.9 mg/m^3). Severity increased at the higher levels of exposure. No nasal lesions were reported in other species at 0.4 ppm (0.9 mg/m^3). The severity of nasal lesions was concentration-related in all 3 species, most clearly so in the rat. In the 4.9 ppm (11 mg/m^3) groups of all 3 species, slightly to markedly increased lesions were reported in the nasal cavity and trachea; moderate to marked effects were seen in the bronchi and lungs of rats and rabbits (but not hamsters). Based upon the concentration-related severity of lesions, the rat is clearly the most sensitive species, with hamsters and rabbits intermediate in sensitivity.

Although the Feron et al. (1978) study was adequately designed, the incidence of nasal lesions

for treated groups was not reported. However, histopathological grading allowed the determination of NOAELs, LOAELs and FELs for the 3 species, identification of the critical target site, and a comparison of sensitivities among the 3 species tested. Other limitations of this study include an exposure duration of 3 months rather than lifetime, histopathological examination of only 3 sections of the nasal cavity, lack of characterization of the type of nasal lesions by sex, and only 6 rats/sex exposed.

A more recent study, Cassee et al. (1996) examined the nasal effects of inhalation exposure of formaldehyde, acetaldehyde, and acrolein on male Wistar rats (5-6/group) exposed 6 hr/day, for 3 consecutive days, in a nose-only exposure chamber to acrolein at concentrations of 0, 0.25, 0.67, or 1.4 ppm (0, 0.6, 1.5, or 3.2 mg/m^3). The Cassee et al. (1996) study was designed to evaluate the severity of effects from mixtures versus single chemical exposure, and analyzed six levels of the nasal tract for histopathological and biochemical changes immediately after the last exposure. After one 6-hour exposure, no treatment-related histopathological lesions were found in any of the treatment groups. Only the histopathology of the 0.25 and 0.67 ppm (0.6 or 1.5 mg/m^3) groups were reported following 3 days of exposure; effects at 1.4 ppm (3.2 mg/m^3) were not reported. After 3 days, slight to moderate effects were observed from acrolein exposure in two of the four histopathology categories evaluated. In the category for disarrangement, necrosis, thickening and desquamation in the respiratory/transitional epithelium, 4/5 animals exposed to 0.25 ppm (0.6 mg/m^3) were observed to have slight effects (characterized as mainly disarrangement) and 1/5 developed a moderate level of effect. In the 0.67 ppm (1.5 mg/m^3) group, 3/6 were classified as slightly affected and 3/6 rats developed a moderate degree of response. For rhinitis, 1/5 of the 0.25 ppm (0.6 mg/m^3) rats developed a moderate response, and only 1/6 of the 0.67 ppm (1.5 mg/m^3) rats had a response and it was scored as a slight response. For the other two categories, single cell necrosis or atrophy of the olfactory epithelium, no effects were observed in either the 0.25 ppm (0.6 mg/m^3) or 0.67 ppm (1.5 mg/m^3) group. After one 6-hr exposure, no treatment-related proliferative response (defined as basal cell proliferation and/or an increased number of mitotic figures in respiratory/transitional epithelium) was found in any of the treatment groups. After 3 days, 3/5 rats at 0.25 ppm (0.6 mg/m^3) developed a slight focal proliferative response, and all rats in the 0.67 ppm (1.5 mg/m^3) group developed a slight or moderate response. Proliferative effects were not reported for the 1.4 ppm (3.2 mg/m^3) exposure group. Among biotransformation enzymes measured in homogenates of nasal tissue, glutathione S-transferase activity was significantly depressed in the 1.4 ppm (3.2 mg/m^3) exposure group ($p<0.01$) while formaldehyde dehydrogenase and aldehyde dehydrogenase activities was significantly increased ($p<0.05$). No changes were reported in the lower dose groups, or for glutathione peroxidase activity in any of the dose groups. Non-protein sulfhydryl (NPSH) depletion was not observed in this study. No biochemical effects were observed in olfactory tissue. The LOAEL in this study was 0.25 ppm (0.6 mg/m^3).

The occurrence of lesions at lower doses in the Cassee et al. (1996) study than used in the Feron et al. (1978) study may be: (1) a consequence of nose-only exposure where, unlike whole-body exposure, the animals cannot minimize exposure by burying their noses in their fur, so that animals receive a full and uninterrupted dose; or (2) due to a higher resolution evaluation from the use of extended sectioning (6 sections) of the nasal tract compared to only 3 in the Feron et al. (1978) study.

Cassee et al. (1996) do not discuss the persistence or reversibility of the observed histopathological changes in the low-dose group with exposures greater than 3 days (e.g., adaptive response). An adaptive response in nonprotein sulfhydryl levels after 3 days of exposure was observed and is discussed. Because the Feron et al. (1978) study was much longer in

duration, it is possible that some adaptation to the irritant effects of acrolein occurred with increasing duration, or that cessation of exposure for 2 days each week provided a period during which partial recovery from nasal effects might have occurred.

The rationale for choosing the Feron et al. (1978) study over the Cassee et al. (1996) study includes: (1) the higher number of test animals [12 (6/sex) vs. 6 male only]; (2) the longer duration [5 days/week for 13 weeks vs. 3 days]; (3) the testing of multiple species and both sexes in the Feron et al. study; and 4) the better characterization of multiple endpoints and the dose-response. Feron et al. evaluated many different end points and demonstrated dose response for all 3 dose groups in all 3 species tested. The Feron et al. study also evaluated a dose response over a 12-fold increase in dose from low to high dose. The Cassee et al. study used about a 6-fold increase in dose level from low to high.

A benchmark dose approach for derivation of the RfC was not possible because nasal pathology incidence data were not provided. Therefore, the approach used to derive the RfC was the determination of a LOAEL as the point of departure and application of uncertainty factors.

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

UF = 1,000.

A UF_A of 3 ($10^{1/2}$) was used for interspecies extrapolation, since this factor embodies two areas of uncertainty: pharmacokinetics and pharmacodynamics. In this assessment, the pharmacokinetic component was addressed by the calculation of the human equivalent concentration (HEC) according to the procedures in the RfC methodology (U.S. EPA, 1994b). Accordingly, only the pharmacodynamic area of uncertainty remains as a partial factor for interspecies uncertainty ($10^{1/2}$ or approximately 3).

A default UF_H of 10 was applied for intraspecies uncertainty to account for human variability and sensitive subpopulations, i.e., to account for human variability in the severity or range of response from any given acrolein exposure amongst different individuals.

A UF_S of 10 was applied for adjustment from subchronic to chronic duration because the principal study involved a 13-week dosing period and because there are insufficient inhalation data to preclude an increase in severity (or incidence) with an increase in exposure duration from subchronic to chronic.

A UF_L of 3 ($10^{1/2}$) was applied for use of a minimal LOAEL of 0.4 ppm (0.9 mg/m^3) in lieu of a NOAEL. Although the severity of the nasal effect at the 0.4 ppm level was minimal and in only 1 of 12 animals in the Feron et al. (1978) study, a 3-day study in the male Wistar rat by Cassee et al. (1996) also reported slight nasal effects in the respiratory/transitional epithelium from nose-only inhalation exposure at 0.25 ppm (0.6 mg/m^3). An exposure concentration of 0.4 ppm (0.9 mg/m^3) was designated a minimal LOAEL instead of a NOAEL, considering the Cassee et al. (1996) results and the observed increase in the severity of the effects with increasing dose in the Feron et al. (1978) study.

A UF_D was not applied because the database for acrolein was considered complete. The available inhalation database includes subchronic toxicity studies in multiple species, and an inhalation reproductive toxicity study of acrolein in Fisher 344 rats that revealed no reproductive or developmental effects. Acrolein's high reactivity at the point of contact and the evidence for minimal systemic distribution of acrolein obviates the need for additional studies of repeat-dose

toxicity or reproductive/developmental toxicity.

MF = 1.

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

Studies by Kutzman (1981), Kutzman et al. (1985) and Costa et al. (1986) support the Feron et al. (1978) results with additional evidence of lung deficits from exposure to acrolein. The Kutzman studies were cited as co-principal studies in the assessment previously on IRIS. Male F344 rats exposed to 0, 0.4, 1.4, or 4.0 ppm (0, 0.9, 3.2, or 9.2 mg/m^3) 6 hr/day, for a total of 62 exposure days over a duration of 12.4 weeks were examined on the sixth day post-exposure (to minimize acute effects) (Kutzman, 1981; Kutzman et al., 1985). Mortality (32/57) was observed only in males at the highest concentration, with many displaying severe acute bronchopneumonia. The changes in the nasal region consisted of only minimal evidence of submucosal lymphoid aggregates at 0.4 ppm (0.9 mg/m^3); although degree of involvement increased to moderate at higher concentrations, more extensive damage to the nasal epithelium was not observed. Lungs from the 0.4 or 1.4 ppm (0.9 or 3.2 mg/m^3) groups did not display treatment-related histopathological changes. At 4.0 ppm (9.2 mg/m^3) the surviving animals demonstrated bronchiolar epithelial necrosis and sloughing, bronchiolar edema with macrophages, and focal pulmonary edema.

Support for acrolein's respiratory effects and association with increased mortality is provided by Kutzman et al. (1984). Dahl rats (derived from the Sprague-Dawley rat) that were either susceptible (DS) or resistant (DR) to salt-induced hypertension were exposed in whole body inhalation chambers to 0.4, 1.4, and 4.0 ppm (0.9, 3.2, and 9.2 mg/m^3) acrolein; increased mortality (100% and 40% in DS and DR rats, respectively) was reported at 4.0 ppm (9.2 mg/m^3). Dose-response increases in the severity of epithelial lesions occurred in both species with the DS rats being more sensitive, and demonstrating a different pathological response at the high dose.

A continuous 90-day inhalation study involving exposure of dogs, guinea pigs, rats and monkeys to acrolein did not include an examination of the nasal tract by light microscopy (Lyon et al., 1970). Exposure concentrations were 0.22, 1.0 and 1.8 ppm (0.5, 2.3, and 4.1 mg/m^3). There was no mention of the use of control animals in the report although Lyon (2001) indicated that controls (not concurrent) were used. Two of the four dogs exposed to 0.22 ppm (0.5 mg/m^3) acrolein in this study showed moderate emphysema, acute congestion and occasionally some degree of constriction of the bronchioles. Monkeys also showed some apparent inflammatory effects at this concentration. It is uncertain if the effects seen at this concentration were directly related to exposure given the absence of control results. No histopathologic effects were reported for rats or guinea pigs at 0.22 ppm (0.5 mg/m^3).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF).

__I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Low to Medium
RfC — Medium

The overall confidence in this RfC assessment is medium. The confidence in the principal study is

medium. Although the principal study (3 species) was adequately designed and examined a wide range of endpoints, it had several shortcomings: (1) only 3 sections of the nasal cavity were examined, (2) there was low sample size, and (3) a lack of incidence data. Support for the minimal LOAEL is provided by subchronic studies in 2 other species (rabbit and hamster) and a 3-day study (Cassee et al., 1996) in the rat in which nasal lesions of similar type and severity were observed. The primary limitation in the database is the lack of a chronic inhalation study and the attendant uncertainty relating to the incidence/severity of nasal lesions at subchronic/chronic exposure levels lower than 0.4 ppm (0.9 mg/m^3). The high reactivity of acrolein at the point of contact, the lack of significant systemic distribution demonstrated in studies with the dog and rat, and the lack of effects in oral studies lessens the priority for an evaluation of reproductive/developmental endpoints in a two-generation inhalation study. Additional evaluation of immunological endpoints is warranted especially focusing on potential contribution to asthma or compromise in respiratory response. Thus, confidence in the database is judged low to medium. The confidence in the RfC is judged medium.

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 Inhalation RfC

Source Document — U.S. EPA (2003)

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Acrolein (U.S. EPA, 2003). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review Comments and Disposition (PDF)***.

Agency Consensus Date — 05/16/2003

__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 — Acrolein
CASRN — 107-02-8
Last Revised — 06/03/2003

Section II 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 exposure and inhalation exposure. Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS is described in the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999. Guidelines for carcinogen risk assessment. Review Draft, NCEA-F-0644, July. Risk Assessment Forum http://www.epa.gov/cancerguidelines/draft-guidelines-carcinogen-ra-1999.htm). The

quantitative risk estimates result from application of a low-dose extrapolation procedure, and both the central estimate and upper bound estimate of risk per unit of exposure are presented. The quantitative risk estimates are presented in three ways to facilitate their use. The oral slope factor is the 95% upper bound on the estimate of risk per (mg/kg)/day of oral exposure. The unit risk is the 95% upper bound on the estimate of risk, either per µg/L drinking water or per µg/cu.m air breathed. The third form in which risk is presented is the 95% lower bound on the estimated concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000.

_II.A. Evidence for Human Carcinogenicity

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

Under the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999), the potential carcinogenicity of acrolein cannot be determined because the existing "data are inadequate for an assessment of human carcinogenic potential for either the oral or inhalation route of exposure."

There are no adequate human studies of the carcinogenic potential of acrolein. Collectively, experimental studies provide inadequate evidence that acrolein causes cancer in laboratory animals. Specifically, two inhalation bioassays in laboratory animals are inadequate to make a determination because of protocol limitations. Two gavage bioassays failed to show an acrolein-induced tumor response in 2 species of laboratory animals. Suggestive evidence of an extra-thoracic tumorigenic response in a drinking water study in female rats was not supported in the reanalysis of data by an independently-convened pathology working group. Questions were also raised about the accuracy of the reported levels of acrolein in the drinking water from this study. A skin tumor initiation-promotion study was negative, and the findings from an intraperitoneal injection study were of uncertain significance. Although acrolein has been shown to be capable of inducing sister chromatid exchange, DNA cross-linking and mutations under certain conditions, its highly reactive nature and the lack of tumor induction at portals of entry make it unlikely that acrolein reaches systemic sites at biologically-significant exposure levels. The observations of positive mutagenic results in bacterial systems occurred at high concentrations near the lethal dose.

This evaluation replaces the cancer assessment for acrolein added to the IRIS database in 1988. Under the Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) applied at that time, acrolein was classified as a possible human carcinogen (Category C). The 1988 classification for acrolein was based on the increased incidence of adrenal cortical adenomas in female rats and carcinogenic potential of an acrolein metabolite, its mutagenicity in bacteria, and its structural relationship to probable or known human carcinogens. The updated cancer characterization considered new study results and reevaluated previous studies.

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 4.8 (PDF).

__II.A.2. Human Carcinogenicity Data

No data are available on carcinogenicity in humans exposed solely to acrolein. The only study relating to cancer was a nested case control study by Ott et al. (1989), in which individuals were classified as having been exposed to one of a large number of chemicals in the work environment.

The study investigators reported non-Hodgkin's lymphoma (52 cases), multiple myeloma (20 cases), nonlymphocytic leukemia (39 cases), and lymphocytic leukemia (18 cases) within a cohort of employed men from two chemical manufacturing facilities and a research and development center. Exposure odds ratios were examined in relation to 111 work areas, 21 specific chemicals, and 52 chemical activity groups. Odds ratios of 2.6 (2 cases) for non-Hodgkin's lymphoma, 1.7 (1 case) for multiple myeloma, and 2.6 (3 cases) for nonlymphocytic leukemia were reported for workers exposed to acrolein. None of the lower 95% confidence limits exceeded 1.0. Because of a lack of a statistically significant increase in the cancer endpoints and the likelihood of confounding by concomitant exposure to other chemicals in the workplace, the results must be considered equivocal.

__II.A.3. Animal Carcinogenicity Data

Feron and Kryusse (1977) reported negative findings for lung cancer induction in Syrian golden hamsters exposed 35 hours/week for 52 weeks to 4.0 ppm (9.2 mg/m^3) acrolein via inhalation, followed by sacrifice at 81 weeks. Le Bouffant et al. (1980) exposed 20 female Sprague-Dawley rats to 8 ppm (18 mg/m^3) acrolein, 5 hours/week for 10 or 18 months, with negative results. These findings, while negative, nevertheless fail to provide conclusive evidence that acrolein is not carcinogenic by the inhalation route. Both the rat and hamster studies were (1) less than lifetime, (2) the maximum tolerated dose may not have been achieved, and (3) only one concentration was used.

Negative results for carcinogenicity were reported for Sprague-Dawley rats, 70/sex/group, exposed via gavage to acrolein at doses of 0.0, 0.05, 0.5 and 2.5 mg/kg BW for 24 months (Parent et al., 1992a). Parent et al. (1991) also reported negative results in Swiss albino mice, 70-75/sex/group, administered acrolein via gavage at doses of 0.2, 2.0 and 4.5 mg/kg/day for 18 months.

The only suggestive evidence for carcinogenicity of acrolein was marginally significant increases in adrenal cortical tumors in a drinking water study reported by Lijinsky and Reuber (1987), and weak evidence for tumor initiating ability of acrolein reported by Cohen et al. (1992). Because no increase in adrenal cortical tumors was noted for either species in the Parent et al. (1991, 1992a) studies, an independent pathology working group (PWG) was convened to reevaluate the adrenocortical tumors reported by Lijinsky and Reuber (1987). According to the PWG (cited in Parent et al., 1992a), the "slightly elevated incidence of pheochromocytomas (3/20; 15%) in the treated females were well within limits for historical controls (3/34; 9%) and were of no biological significance (*sic*)." Parent et al. (1992a) further suggested that acrolein at a high dose may not have been as stable as assumed in the Lijinsky and Reuber study. Based on some assumptions about water intake and rat weight, Parent et al. estimated that the daily dose at the highest concentration administered by Lijinsky and Reuber would have exceeded the LD50 for rats. These questions concerning the stability of acrolein in high dose solutions and the rate of intake render the results of the Lijinsky and Reuber study less certain. Moreover, concurrent controls were not used in the Lijinsky and Reuber study.

Cohen et al. (1992) administered acrolein via intraperitoneal injection, 2 mg/kg/twice weekly to male Fischer 344 rats, 30/group, for either 53 weeks or for six weeks followed by an additional 47 weeks without treatment. Because of extreme toxicity, the animals were sacrificed after 53 weeks, rather than two years as originally planned. No increases in tumor incidences were reported. In an additional group administered acrolein for six weeks followed by tumor promotion with 3% uracil in the drinking water for 20 weeks, urinary bladder papillomas were reported in 18 of 30 and carcinoma in 1 of 30 rats, compared with papillomas in 8 of 30 and carcinoma in 1 of 30 rats treated with uracil alone ($p<0.05$). While it appears that acrolein may have some tumor initiating capability, when the incidence of nodular hyperplasias (considered precursors to

papillomas) and papillomas were combined, there were no significant differences between the two groups. Acrolein was too toxic to evaluate its tumor promoting potential, and the impact of its cytotoxicity on conclusions about its tumor initiating potential cannot be determined from this study alone.

No sarcomas were reported in a group of 15 female albino mice administered 0.2 mg acrolein by subcutaneous injection, weekly for 24 weeks, then held for a lifetime (Steiner et al., 1943). No evidence for skin tumor initiating capability was reported in S strain mice administered acrolein dermally in ten weekly applications for a total dose of 12.6 mg/animal, followed by treatment with the tumor promoter croton oil (Salaman and Roe, 1956).

__II.A.4. Supporting Data for Carcinogenicity

In vitro, acrolein has been shown to induce DNA adducts in a variety of cell types as well as mutagenesis in *Drosophila* and microorganisms under certain conditions, but there is only limited information regarding the ability of acrolein to induce mutations in normal mammalian cells. In mammalian cell *in vitro* assays, acrolein has been shown to induce sister chromatid exchange, DNA cross-linking, and binding to DNA polymerase. Even in the *in vitro* assays, acrolein is so reactive that special techniques must generally be employed to reduce cytotoxicity and induce positive effects. While mutagenic activity has occasionally been shown, positive results generally occurred only in a narrow, near lethal, dose range.

There have been conflicting results reported in the literature for *in vitro* mutagenicity. In a series of Ames assays, Parent et al. (1996b) proposed an explanation for the conflicting data by considering the presence or absence of non-DNA nucleophiles from the S9 activation mixture, in the test chemical solution, or in the plating solutions. Parent et al. suggest that in the presence of non-DNA nucleophiles, acrolein will rapidly and indiscriminately react with any available species and not reach the DNA target.

According to Beauchamp et al. (1985), acrolein administered by the inhalation route is retained primarily in the upper respiratory tract because of its reactivity. Some evidence for systemic uptake following oral exposure was noted by Draminski et al. (1983); however, the large doses used (10 mg/kg) would be expected to induce cellular damage, which may allow for some absorption. Tissues at the site of contact are, therefore, expected to be most highly exposed, and no evidence of tumor induction in the respiratory tract, skin or gastrointestinal tract has been reported. Studies by Parent et al. (1996a, 1998) indicate little systemic distribution to tissues.

The highly reactive nature of acrolein and studies supporting the lack of systemic distribution of acrolein suggest that acrolein is not likely to reach potential target sites at a sufficient concentration to initiate a carcinogenic process in mammalian species.

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

Not applicable.

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

Not applicable.

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

__II.D.1. EPA Documentation

Source Document — U.S. EPA (2003).

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of Acrolein (U.S. EPA, 2003). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review Comments and Disposition (PDF)***.

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 05/16/2003

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

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 — Acrolein
CASRN — 107-02-8
Last Revised — 06/03/2003

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_VII. Revision History

Substance Name — Acrolein
CASRN — 107-02-8

Date	Section	Description
09/07/1988	II.	Carcinogen summary on-line
04/01/1989	V.	Supplementary data on-line
07/01/1989	I.B.	Inhalation RfD now under review
03/01/1990	II.A.4.	Citations clarified (3rd paragraph)
03/01/1990	VI.	Bibliography on-line
05/01/1990	VI.C.	Hemminki et al., 1980 citation corrected
10/01/1991	I.B.	Inhalation RfC summary on-line
10/01/1991	I.B.	Inhalation RfC references added
01/01/1992	IV.	Regulatory Action section on-line
07/01/1993	I.B.1.	LOAEL(ADJ) corrected
02/01/1994	II.D.3.	Secondary contact's phone number changed
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
01/12/2000	I., II.	This chemical is being reassessed under the IRIS Program.
06/03/2003	I., II., VI.	RfD, RfC and cancer sections updated
12/2/2004	Toxicological Review	Technical correction to Toxicological Review describing units for ambient exposure levels (section 2) and acute exposure regimen in Weber-Tschopp et al. (1977)

_VIII. Synonyms

Substance Name — Acrolein
CASRN — 107-02-8
Last Revised — 06/03/2003

- 107-02-8
- acralaldehyde
- acrylaldehyde
- allyl aldehyde
- ethylene aldehyde
- propenal
- prop-2-en-l-al

- 2-propenal