Substance Code 0364
Substance name: Acrolein, CASRN 107-02-8; 00/00/00

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Acrolein

File First On Line 00/00/0000

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	On-line	00/00/0000
Inhalation RfC Assessment (I.B.)	On-line	00/00/0000
Carcinogenicity Assessment (II.)	On-line	00/00/0000

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name
CASRN 107-28-8
Last Revised –00/00/0000

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.I. 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	–	5×10^{-4} (mg/kg-day)

____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 (including the stomach although it was not clear if both the glandular and forestomach were evaluated) was examined microscopically. 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 termination. There were no significantly 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 at all dose levels and at most time intervals (except 12 months), clinical chemistry parameters, hematology and urinalysis measurements were unaffected by treatment. The significance of this depression is uncertain.

The most definitive responses reported were treatment-related increases in early cumulative mortality. Data was 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 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 an FEL for the rat.

In a similar study (Parent et al., 1991) designed to evaluate the potential carcinogenicity of acrolein in Swiss Albino CD-1 mice, 70/sex were dosed via gavage (acrolein in distilled water and stabilized with hydroquinone) with 0, 0.5, or 2.0 mg/kg/day for 18 months. A separate group (75/sex) was similarly dosed at 4.5 mg/kg/day. All animals were sacrificed at 18 months. The primary effect was increased mortality only in high-dose males, indicating that the NOAEL, based on survival, is 0.5 mg/kg/day. The FEL for the mouse is 2 mg/kg/day. 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), 10 rats/sex/dose were administered 0, 0.75, 1.25, 2.5, 5.0, and 10 mg acrolein/kg with 10 mice/sex/dose receiving 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, but there were no clinical signs of toxicity in mice. Nearly all high-dose animals died or were removed from study because of gastrointestinal toxicity. The no-observed-effect level (NOEL) for rats was 0.75 mg/kg, based on forestomach squamous epithelial hyperplasia in the 1.25 mg/kg group of females. There was no NOEL for the mouse.

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 two in dose (from 2 to 4 mg/kg) resulted in 25% mortality in the high-dose does compared to 0% in lower-dose animals (Parent et al., 1993). Mortality was 100% at 6 mg/kg.

Four groups of 30 male and 30 female Sprague-Dawley rats were gavaged daily with 70 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 F_1 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 any of the F_0 or F_1 animals. 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. This study clearly showed damage to mitochondria, (through loss of mitochondrial lamellae), a decrease in the availability of reduced glutathione (a substrate for glutathione peroxidase), and a decrease in activities of citric acid cycle enzymes, resulting in decreased energy production in liver cells. The study was well designed and showed definitive effects. While the duration of the study was less than subchronic in duration and

included only a single dose level, it provides support and a plausible explanation for the mortality increases reported in the Parent et al. (1992a) study. It also indicates that at least a portion of an oral dose is absorbed and reaches the liver. Incidence of mortality, if any, was not reported in this study.

Decreased survival was a feature in both the NTP and Parent et al. studies with rats and mice. However, only the rat/mouse study performed for the NTP resulted in stomach (forestomach and glandular) lesions. The absence of stomach lesions in the Parent et al. (1991; 1992a) studies involving rats and mice is not inconsistent with the positive findings for this organ in the NTP study. Reasons for the apparent dichotomy in results are unclear although it could relate to (1) the strength of the daily dosing solution, (2) strain and vehicle differences (methyl cellulose vs water) or (3) differences in reactivity of acrolein in the two vehicles. In any event, the administration of acrolein in water is a more environmentally-relevant mode of exposure than the gavage administration employed by the NTP.

____I.A.3 UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. An uncertainty factor of 10 was employed for interspecies variability in sensitivity and 10 for intraspecies variability in sensitivity. Based on gavage studies in rats and rabbits, it does not appear that acrolein causes reproductive or teratogenic effects. No additional uncertainty factors are required.

MF = 1

____I.A.4. ADDITIONAL STUDIES/COMMENTS (ORAL RfD)

A benchmark dose approach was unsuitable for RfC development because the data were presented graphically, with statistical evaluation at one and two-year time points, but with no numerical values.

____I.A.5.CONFIDENCE IN THE ORAL RfD

Study: High
Data Base: High
RfD: High

Confidence in the principal study is high; several supporting studies involving other species also indicated that mortality increases sharply with elevated dose. Two studies (Parent et al., 1992b; Parent et al., 1993) provide evidence that reproductive and developmental effects are not critical endpoints. The overall confidence in this RfD assessment is 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.

____I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document – U.S. EPA (2002) Toxicological review of acrolein in support of summary information on the Integrated Risk Information System (IRIS).

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 in Support of Summary Information (a PDF document) on the Integrated Risk Information System (IRIS) (US EPA, 2002).

____I.A.7 EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX), or HOTLINE.IRIS@EPAMAIL.EPA.GOV (email address).

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name Acrolein
CASRN – 107-02-8
Last Revised -- 00/00/0000

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/m^3. 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.

This RfC replaces the previous RfC of 2E-5 mg/m^3 entered on IRIS 7/01/1993. This new RfC is based on a more recent interpretation of the database.

__I.B.1. INHALATION RfC SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfC
nasal lesions	LOAEL: 0.4 ppm (0.9 mg/m^3)	1,000	1	3E-5 mg/m^3
Subchronic rat inhalation study	LOAEL (ADJ): 0.16 mg/m^3			
Feron et al., 1978	LOAEL (HEC): 0.03 mg/m^3			

*Conversion Factors and Assumptions – The LOAEL of 0.4 ppm (0.9 mg/m^3) was adjusted to continuous exposure by 0.9 mg/m^3 x 6/24 hours/day x 5/7 days/week to equal 0.16 mg/m^3. Applying a regional gas dose ratio (RGDR) of 0.18 for the extrathoracic region of the rat (EPA, 1994), an equivalent human concentration of 0.03 mg/m^3 is derived to which uncertainty factors are applied. Derivation of the RDGR is described in the Toxicological Review.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES (INHALATION RfC)

Chronic inhalation studies designed to evaluate the toxicological effects of acrolein are unavailable. The most suitable study for development of an RfC was reported by Feron et al. (1978). In this study, ten Syrian golden hamsters/sex, six Wistar rats/sex, and two Dutch rabbits/sex/dose were exposed 6 hours/day, 5 days/week for 13 weeks to 0, 0.4, 1.4, or 4.9 ppm (0.9, 3.2, or 11.2 mg/m^3) acrolein. Histopathology was performed on all major organs/tissues, including three transverse sections of the nasal cavity. Body weight gain was significantly inhibited at the high dose in all groups. At the intermediate dose, only male and female rats showed significantly retarded weight gain ($p<0.05$). Three male and three 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 dose groups. Histopathological changes were graded as minimal, moderate or marked. Minimal histopathologic changes were found in the nasal cavity of one male rat exposed to 0.4 ppm, but none were reported in other species at this concentration. The 1.4 ppm level induced moderate histopathology in the nasal cavity of rats and minimal histopathology in the nasal cavity of hamsters. At 4.9 ppm marked histopathology was reported in the nasal cavity (necrotizing rhinitis), trachea (nodules of granulation), bronchi, and lungs, with moderate effects in the larynx of rats. Marked histopathologic effects were noted in the nasal cavity of hamsters exposed to 4.9 ppm acrolein, as well as moderate effects in the trachea and minimal effects in the larynx. Moderate histopathologic effects were seen in the nasal cavity, bronchi and lungs with minimal effects in the larynx of rabbits exposed to the high concentration. Based on the severity of respiratory tract lesions in the rat compared to diminished responses in the rabbit and hamster in the 4.9 ppm groups, the rat is considered the most sensitive species of the three with a minimal LOAEL for nasal lesions of 0.4 ppm. Although only 1/12 rats at this concentration demonstrated minimal metaplastic and inflammatory changes, these effects were

consistent with the pathology demonstrated at the higher concentrations in which severity was increased.

The study was well designed and results were adequately reported. Grading of histopathology allowed determination of NOAELs, LOAELs, and FELs for the three species, determination of the critical target site, and a comparison of sensitivity among the 3 species tested.

Male F344 rats were examined by Kutzman et al. (1981, 1985) and 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. The principal limitation was that histopathology was not performed until the sixth day post-exposure. In addition, lungs from the 0.4 or 1.4 ppm groups did not display treatment-related histopathological changes. However, restrictive lung changes (enhanced air flow and an increase in tissue density) were observed at 0.4 ppm, but not at 1.4 ppm, presumably canceled by obstructive lesions that became apparent at 4 ppm (Costa et al., 1986). While exposure levels in this study were similar to those used by Feron et al. (1978), the duration was shorter (62 days) and the animals were examined six days from the end of exposure, rather than immediately post-exposure. For these reasons, this study was not selected as co-principal with the Feron et al. (1978) study.

A more recent study by Feron and colleagues (Cassee et al., 1996) examined the nasal effects of inhalation exposure of formaldehyde, acetaldehyde, and acrolein on male Wistar rats. Rats (5-6/group) were 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 1.40 ppm (0, 0.57, 1.5, or 3.2 mg/m^3). Six levels of the nasal tract were examined immediately after the last exposure. After one day of exposure, no treatment-related histopathological lesions were found. After three days, disarrangement, necrosis, thickening and desquamation of respiratory/transitional epithelium of a slight degree were reported in 4 of 5 animals exposed to 0.25 ppm and in 3/6 at 0.67 ppm. Slight changes were noted in 3/6 rats and moderate changes in the other 3 exposed to 0.67 ppm acrolein. Atrophy of the olfactory epithelium was not observed. These lesions are consistent with those found by Feron et al. (1978) and suggest that levels of 0.25 ppm and perhaps lower would cause adverse nasal effects at subchronic and chronic durations. Cassee et al. (1996) examined six levels of the nasal tract compared to only three by Feron et al. (1978); this protocol difference may explain the differences in incidences in the two studies.

___I.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF = 1,000. Uncertainty factors of 3 ($10^{1/2}$) each are employed for use of a LOAEL and for interspecies variability in sensitivity, and a 10 for intraspecies variability in sensitivity and a 10 for extrapolation from a subchronic to a chronic exposure duration. A three ($10^{1/2}$) was selected for interspecies variability in sensitivity based on application of the RfC methodology; since the rat was shown to be more sensitive to nasal pathology than either hamsters or rabbits in the Feron et al. (1978) study, a larger UF is not required. The 10 for intraspecies is considered adequate considering possible human differences in sensitivity and for the concentration-

response nasal differences in the 3-day (Cassee et al., 1996) and 13-week (Feron et al., 1978) studies in the Wistar rat. Two uncertainty factors of 3 coalesce to a 10. No uncertainty factor for the lack of adequate reproductive and developmental studies was adopted because (1) oral studies (Parent et al., 1992; 1993) indicated that acrolein is unlikely to be a reproductive or teratogenic agent and (2) acrolein does not appear to cause effects beyond the point of contact. Thus, the total UF of 1,000 when applied to the LOAEL is considered to be protective with regard to deeper regions of the respiratory tract.

MF = 1

___I.B.4. ADDITIONAL STUDIES/COMMENTS (INHALATION RfC)

The Lyon et al. (1970) continuous 90-day inhalation study (dogs, guinea pigs, rats and monkeys) did not examine the nasal tract by light microscopy. Exposure concentrations were 0.22, 1.0 and 1.8 ppm (0.50, 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 (beagles) exposed to 0.22 ppm 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 clearly related to exposure given the lack of acknowledgment in the published report of control results. No histopathologic effects were reported for rats or guinea pigs at 0.22 ppm.

The high degree of reactivity of acrolein increases the likelihood that its critical effects are at a site of contact. The experimental data support this supposition. There is no evidence that acrolein induces reproductive/developmental or other systemic toxic effects at the LOAEL for lung pathology. While the primary study is of medium quality (only three sections of the nasal cavity were sectioned), the principal limitation of the database is the lack of chronic exposures.

___I.B.5. CONFIDENCE IN THE INHALATION RfC

Study –medium
Data Base -- Medium
RfC -- Medium

The overall confidence in this RfC assessment is medium. The RfC was based on a well-designed subchronic study in three species, for which a wide range of endpoints were measured and reported. The principal limitation in this study was sectioning of only three sections of the nasal cavity. Support for the LOAEL is provided by subchronic studies in two other species and a three-day study 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 incidence/severity of nasal lesions at exposure levels lower than 0.4 ppm. In both

chronic and subchronic oral studies with mice (Parent et al., 1991b; NTP, 1995) and rats (Parent et al., 1992c; NTP, 1995), treatment-related mortality that shows evidence of dose-, strain- and/or sex-dependence should provide a basis for further study.

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document – U.S. EPA (2002) Toxicological review of acrolein in support of summary information on the Integrated Risk Information System (IRIS).

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 in Support of Summary Information (a PDF document) on the Integrated Risk Information System (IRIS) (US EPA, 2002).

Agency Consensus Date -- __/__/__

___I.B.7. EPA CONTACTS (INHALATION RfC)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone),(301)345-2876(FAX), or HOTLINE.IRIS@EPAMAIL.EPA.GOV (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name
CASRN – 107-02-8
Last Revised -- 00/00/0000

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 from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/cu.m air breathed. The third form in which risk is presented is a 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. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-

87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996) or Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999. Guidelines for carcinogen risk assessment. Review Draft, NCEA-F-0644, July 1999. Risk Assessment Forum) also refer to those guidelines where indicated. Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Applying the criteria outlined in the guidelines for carcinogen risk assessment (U.S. EPA, 1986) for evaluating the overall weight-of-evidence for carcinogenicity, acrolein is most appropriately classified into Group D, inadequate evidence for carcinogenicity. Applying the criteria outlined in the draft revised guidelines for carcinogen risk assessment (U.S. EPA, 1999), the data are inadequate for an assessment of human carcinogenic potential by either the inhalation or oral routes of exposure.

Collectively, there is a lack of evidence for human carcinogenicity and inadequate evidence that acrolein causes cancer in laboratory animals. No data for humans exposed to acrolein alone are available. Results were negative in rats and mice administered acrolein by gavage for 24 months and 18 months, respectively (Parent et al., 1991;1992). An inhalation study (Le Bouffant et al., 1980) reported negative results in rats exposed over 18 months to only one concentration; however, a maximum tolerated dose was not achieved. Results were negative in mice injected subcutaneously with 0.2 mg/kg acrolein for 24 weeks (Steiner et al., 1943) and in a 10-week dermal initiation-promotion study (Salaman and Roe, 1956).

The only suggestive evidence for carcinogenicity of acrolein were 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). The marginally significant data reported by Lijinsky and Reuber (1987) are rendered even less certain because of (1) a reevaluation questioning their findings, (2) the possibility that the doses were less than reported (Parent et al., 1992), (3) concurrent controls were not used, and (4) the tumor incidence did not exceed that of historical controls (from the Frederick Cancer Research Center Archives) when the histopathology for exposed groups was reevaluated. Because of the difference in findings between the 2 studies, an independent pathology working group (PWG) had been convened to reevaluate the adrenocortical tumors reported by Lijinsky and Reuber. According to the PWG (cited in Parent et al., 1992), the "slightly elevated incidence of pheochromocytomas in the treated females were (*sic*) "well within limits for historical controls and were of no biological significance." In the study reported by Cohen et al. (1992), six weeks treatment with acrolein followed by treatment with uracil resulted in a larger increase in tumor incidence than did the treatment with uracil alone; however, the incidence of papillary nodular hyperplasia was lower with acrolein followed by uracil than with uracil alone.

Based upon the negative findings in two gavage studies and a skin tumor initiation-promotion study, inadequate studies via inhalation, findings of uncertain significance from an

intraperitoneal injection study, and questionable results in a drinking water study, the animal carcinogenicity data must be considered to be inadequate for an assessment of human carcinogenic potential. While acrolein has been shown to be capable of inducing sister chromatid exchange, DNA crosslinking and mutagenesis under certain conditions, because of its highly reactive nature it is considered unlikely to reach systemic sites at environmentally-relevant exposure levels and did not induce tumors at portals of entry.

___II.A.2. HUMAN CARCINOGENICITY DATA

Ott et al. (1989) reported an odds ratio of 2.6 for nonlymphocytic leukemia and non-Hodgkin's lymphoma for workers employed at facilities with potential exposure to acrolein. However, the 95% lower bounds of the odds ratio did not exceed 1.0 for either of the two endpoints. Furthermore, the study was confounded by the likely concomitant exposure to other potential carcinogenic agents.

___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 for noncarcinogenicity of acrolein by the inhalation route. Both the rat and hamster studies were (1) less than lifetime, the maximum tolerated dose may not have been achieved, and (2) only one concentration was used.

Lijinsky and Reuber (1987) administered acrolein to Fischer 344 rats, 20/sex/group at concentrations of 100, 250 and 625 mg/ml in drinking water. The length of exposure was described as 104-124 weeks since high-dose animals stopped drinking the solution earlier than others. Average daily doses of 0, 1.9, 5.0, or 12.5 mg/day were cited. The maximum tolerated dose was not determined. A marginally significant increase in adrenal cortical adenomas ($p=0.091$) in high-dose female rats (5/20 versus 1/20 in controls), but not in males (0/20 versus 1/20 in controls), was reported. The difference from controls (Parent et al., 1992c reported that the controls used were started 10 months after the treated animals) in females was statistically significant ($p<0.05$) when adrenal cortical tumors and neoplastic nodules were combined, although the number of nodules was not reported. Significant increases in adrenal cortical tumors were not seen at the lower doses or in males at any of the dose levels**.** Parent et al. (1992c) speculated that acrolein at high dose may not have been as stable as purported; they estimated that the daily dose at the highest concentration administered by Lijinsky and Reuber would have exceeded the LD_{50} for rats.

Negative results for carcinogenicity were reported for Sprague Dawley rats, 50/sex/group, exposed via gavage to acrolein at doses of 0.05, 0.5 and 2.5 mg/kg bw for 24 months (Parent et al., 1992). 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. Because no increase in adrenal cortical tumors was noted for either species, a

pathology working group was convened to reevaluate the cortical tumors reported by Lijinsky and Reuber (1987) for high-dose females. According to Parent et al. (1992), the incidences of adrenocortical tumors found by this working group was well within those of historical controls, although the actual numbers were not reported. Also, Parent and colleagues called into question the stability of the acrolein in the high dose solutions used by Lijinsky and Reuber, rendering the results of the latter even less certain.

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 eight papillomas and one carcinoma among rats treated with uracil alone ($p<0.05$). While it appears that acrolein may have some tumor initiating capability, it should be noted that the incidence of papillomas and nodular hyperplasias combined was significantly greater in the uracil only group compared with the group initiated with acrolein ($p<0.05$). Nodular hyperplasias are considered to be precursors to papillomas.

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

Acrolein is capable of inducing sister chromatid exchange, DNA crosslinking and mutations under certain conditions. *In vitro* assays with bacterial or mammalian cells either deficient in DNA repair or treated to deplete glutathione were quite sensitive to the mutagenic and toxic effects of acrolein. However, according to Beauchamp et al. (1985), acrolein administered by the inhalation route is retained primarily in the upper respiratory tract because of its reactivity. While some evidence for systemic uptake following oral exposure was noted by Draminski et al. (1983), the large doses used (10 mg/kg) would be expected to induce cellular damage which may allow some absorption. While tissues at the site of contact are therefore expected to be most highly exposed, no evidence for tumor induction in the respiratory tract, skin or gastrointestinal tract has been reported.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document – U.S. EPA (2002) Toxicological review of acrolein in support of summary information on the Integrated Risk Information System (IRIS).

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 in Support of Summary Information (a PDF document) on the Integrated Risk Information System (IRIS) (U.S. EPA, 2002).

___II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Consensus Date -- __/__/__

___II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (301)345-2870 (phone), (301)345-2876 (FAX), or HOTLINE.IRIS@EPAMAIL.EPA.GOV (email address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. BIBLIOGRAPHY

Substance Name – Acrolein
CASRN – 107-02-8
Last Revised -- 00/00/000

__VI.A. ORAL RfD REFERENCES

Arumugam, VS; Sivakumar, V; Thanislass, J; et al. (1999) Acute pulmonary toxicity of acrolein in rats-underlying mechanism. Toxicol Lett 104(3):189-194

NTP (National Toxicology Program). (1995) 13-week gavage toxicity studies of allyl acetate, allyl alcohol, and acrolein in Fischer 344 rats and B6C3F1 mice. Abstract with tables.

Parent, RA; Caravello, HE; Long, JE. (1991) Oncogenicity study of acrolein in mice. J Am Coll Toxicol 10(6): 647-659.

Parent, RA; Caravello, HE; Long, JE. (1992a) Two-year toxicity and carcinogenicity study of acrolein in rats. J Appl Toxicol 12(2):131-139.

Parent, RA; Caravello, HE; Hoberman, AM. (1992b) Reproductive study of acrolein on two generations of rats. Fundam Appl Toxicol 19(2):228-237.

Parent, RA, Caravello, HE; Christian, MS; et al. (1993) Developmental toxicity of acrolein in New Zealand white rabbits. Fundam Appl Toxicol 20(2):248-256.

Pathology Working Group (1997) Chairperson's report, Pathology Working Group review of acrolein 13-week subchronic gavage study in F344 rats and B6C3F1 mice conducted at Battelle-Columbus.

U.S. EPA. (2002) Toxicological Review of Acrolein in Support of Summary Information on Integrated Risk Information System (IRIS) National Center for Environmental Assessment, Washington, DC. Available on line from: http://www.epa.gov/iris.

__VI.B. INHALATION RfC REFERENCES

Bouley, G; Dubreuil, A; Godin, J; et al. (1975) Effects of a small dose of acrolein constantly inhaled by rats. Eur J Toxicol Environ Hyg 8(5):291-297.

Bouley G; Dubreuil, A; Godin, J; et al. (1976) Phenomena of adaptation in rats continuously exposed to low concentrations of acrolein. Ann Occup Hyg 19(1):27-32.

Cassee, FR; Groton, JP; Feron, VJ. (1996) Changes in the nasal epithelium of rats exposed by inhalation to mixtures of formaldehyde, acetaldehyde, and acrolein. Fundam Appl Toxicol 29:208-218.

Feron , VJ; Kryusse, A; Til, HP; et al. (1978) Repeated exposure to acrolein vapor: subacute studies in hamsters, rats and rabbits. Toxicology 9:47-57.

Kutzman, RS. (1981) A subchronic inhalation study of Fischer 344 rats exposed to 0, 0.4 1.4, or 4.0 ppm acrolein. Brookhaven National Laboratory, Upton, NY. Conducted for the National Toxicology Program: Interagency Agreement No. 222-Y01-ES-9-0043.

Kutzman, RS; Popenoe, EA; Schmaeler, M; et al. (1985) Changes in rat lung structure and composition as a result of subchronic exposure to acrolein. Toxicology 34(2):139-151.

Lyon, JP; Jenkins, LJ, Jr; Jones, RA; et al. (1970) Repeated and continuous exposure of laboratory animals to acrolein. Toxicol Appl Pharmacol 17(3):726-732.

Lyon, JP. (2001) Personal communication with Mark Greenberg, USEPA.

Parent, RA; Caravello, HE; Hoberman, AM (1992) Reproductive study of acrolein on two generations of rats. Fundam Appl Toxicol 19(2):228-237.

Parent, RA, Caravello, HE; Christian, MS; et al. (1993) Developmental toxicity of acrolein in New Zealand white rabbits. Fundam Appl Toxicol 20(2):248-256.

U.S. EPA (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. EPA/600/8-90/066F.

U.S. EPA. (2002) Toxicological Review of Acrolein in Support of Summary Information on Integrated Risk Information System (IRIS) National Center for Environmental Assessment, Washington, DC. Available on line from : http://www.epa.gov/iris.

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Beauchamp, RO, Jr; Andjelkovich, DA; Kligerman, AD; et al. (1985) A critical review of the literature on acrolein toxicity. CRC Crit Rev Toxicol 14:309-378.

Cohen, SM; Garland, EM; St John, M; et al. (1992) Acrolein initiates rat urinary bladder carcinogenesis. Cancer Res 52 (13):3577-3581.

Draminski, W; Eder, E; Henschler, D. (1983) A new pathway of acrolein metabolism in rats (Short communication). Arch Toxicol 52(3):243-247.

Feron, VJ; Kryusse, A. (1977) Effects of exposure to acrolein vapor in hamsters simultaneously treated with benzo(a)pyrene or diethylnitrosamine. J Toxicol Environ Health 3:379-394.

Le Bouffant, L; Martin, JC; Daniel, H; et al. (1980) Actions of intensive cigarette smoke inhalations on the rat lung. Role of particulate and gaseous cofactors. J. Natl Cancer Inst 64(2):273-281.

Lijinsky, W; Reuber, MD. (1987) Chronic carcinogenesis studies of acrolein and related compounds. Toxicol Ind Health 3(3):337-345.

Ott, MG; Teta, J; Greenberg, HL. (1989) Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. Am J Ind Med 16:631-643.

Parent, RA; Caravello, HE; Long, JE. (1991) Oncogenicity study of acrolein in mice. J Am Coll Toxicol 11:91-95.

Parent, RA; Caravello, HE; Long, JE (1992) Two-year toxicity and carcinogenicity study of acrolein in rats. J Appl Toxicol 12(2):131-139.

Salaman, MH; Roe, FJC. (1956) Further tests for tumour initiating activity: *N*,*N*-di(2-chloroethyl)-*p*-aminophenylbutyric acid (CB1348) as an initiator of skin tumour formation in the mouse. Br J Cancer 10:363-378.

Steiner, PE; Steele, R; Koch, FC. (1943) The possible carcinogenicity of overcooked meats, heated cholesterol, acrolein and heated sesame oil. Cancer Res 3:100-143.

U.S. EPA. (1986) Guidelines for carcinogen risk assessment. Federal Register 51(185):33992-34003

U.S. EPA (1999) Review draft guidelines for carcinogen risk assessment. NCEA-F-0644, July, 1999, Washington, DC.

U.S. EPA. (200) Toxicological review of acrolein in support of summary information on Integrated Risk Information System (IRIS) National Center for Environmental Assessment, Washington, DC. Available on line from : http://www.epa.gov/iris.

_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	IB.	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
10/01/1990	I.B.	Inhalation RfC summary on-line
10/01/1990	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.
00/00/000	I.A.	New RfD on-line
00/00/0000	I.B.	Revised RfC on-line
00/00/0000	II.B.	Revised carcinogenicity assessment on-line

_VIII. SYNONYMS

Substance Name – Acrolein
CASRN -- 107-02-8
Last Revised -- 00/00/0000

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

.