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# Provisional Peer Reviewed Toxicity Values for

# Acrolein
(CASRN 107-02-8)

Derivation of an Oral Slope Factor

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

## Acronyms and Abbreviations

| | |
|---|---|
| bw | body weight |
| cc | cubic centimeters |
| CD | Caesarean Delivered |
| CERCLA | Comprehensive Environmental Response, Compensation and Liability Act of 1980 |
| CNS | central nervous system |
| cu.m | cubic meter |
| DWEL | Drinking Water Equivalent Level |
| FEL | frank-effect level |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| g | grams |
| GI | gastrointestinal |
| HEC | human equivalent concentration |
| Hgb | hemoglobin |
| i.m. | intramuscular |
| i.p. | intraperitoneal |
| IRIS | Integrated Risk Information System |
| IUR | inhalation unit risk |
| i.v. | intravenous |
| kg | kilogram |
| L | liter |
| LEL | lowest-effect level |
| LOAEL | lowest-observed-adverse-effect level |
| LOAEL(ADJ) | LOAEL adjusted to continuous exposure duration |
| LOAEL(HEC) | LOAEL adjusted for dosimetric differences across species to a human |
| m | meter |
| MCL | maximum contaminant level |
| MCLG | maximum contaminant level goal |
| MF | modifying factor |
| mg | milligram |
| mg/kg | milligrams per kilogram |
| mg/L | milligrams per liter |
| MRL | minimal risk level |
| MTD | maximum tolerated dose |
| MTL | median threshold limit |
| NAAQS | National Ambient Air Quality Standards |
| NOAEL | no-observed-adverse-effect level |
| NOAEL(ADJ) | NOAEL adjusted to continuous exposure duration |
| NOAEL(HEC) | NOAEL adjusted for dosimetric differences across species to a human |
| NOEL | no-observed-effect level |
| OSF | oral slope factor |
| p-IUR | provisional inhalation unit risk |
| p-OSF | provisional oral slope factor |
| p-RfC | provisional inhalation reference concentration |

| | |
|---|---|
| p-RfD | provisional oral reference dose |
| PBPK | physiologically based pharmacokinetic |
| ppb | parts per billion |
| ppm | parts per million |
| PPRTV | Provisional Peer Reviewed Toxicity Value |
| RBC | red blood cell(s) |
| RCRA | Resource Conservation and Recovery Act |
| RDDR | Regional deposited dose ratio (for the indicated lung region) |
| REL | relative exposure level |
| RfC | inhalation reference concentration |
| RfD | oral reference dose |
| RGDR | Regional gas dose ratio (for the indicated lung region) |
| s.c. | subcutaneous |
| SCE | sister chromatid exchange |
| SDWA | Safe Drinking Water Act |
| sq.cm. | square centimeters |
| TSCA | Toxic Substances Control Act |
| UF | uncertainty factor |
| µg | microgram |
| µmol | micromoles |
| VOC | volatile organic compound |

# PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR ACROLEIN (CASRN 107-02-8) Derivation of an Oral Slope Factor

## Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

## Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional

Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

**Questions Regarding PPRTVs**

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

## INTRODUCTION

The CRAVE workgroup (U.S. EPA, 1992) assigned acrolein to weight-of-evidence Group C, possible human carcinogen, on the basis of no evidence in humans and limited evidence in animals (increased incidence of adrenal cortical adenomas in female rats in an oral study, but no increased tumors in inadequate inhalation, skin painting, and subcutaneous injection studies). Supporting evidence included the carcinogenic potential of an acrolein metabolite, the mutagenicity of acrolein in bacteria, and the structural relationship of acrolein to probable or known human carcinogens. This assessment is listed on IRIS (U.S. EPA, 2001). No oral slope factor for acrolein is listed on IRIS (U.S. EPA, 2001), in the HEAST (U.S. EPA, 1997), or in the Drinking Water and Health Advisories list (U.S. EPA, 2000). Source documents for the IRIS assessment were a Health Assessment Document (HAD) (U.S. EPA, 1986) and a Health Effects Assessment (HEA) for acrolein (U.S. EPA, 1987). The CARA list (U.S. EPA, 1991, 1994) also includes a Health and Environmental Effects Profile (HEEP) on acrolein (U.S. EPA, 1985). IARC (1979, 1985, 1995) assigned acrolein to Group 3, not classifiable as to human carcinogenicity because of inadequate evidence in humans and animals. A Toxicological Profile for acrolein (ATSDR, 1990), an Environmental Health Criteria document on acrolein (WHO, 1992), a carcinogenicity review of low-molecular-weight aldehydes (NIOSH, 1991), and a toxicity review on aldehydes (Morandi and Maberti, 2001) were consulted for relevant information. The NTP (2001) health and safety report for acrolein was also examined. These resources contained no additional studies of acrolein itself. However, a metabolite of acrolein,

glycidaldehyde, yielded positive results for carcinogenicity in skin painting assays in mice and subcutaneous injection assays in mice and rats. In addition, the reviews note that acrolein is a metabolite of cyclophosphamide, an immunosuppressive drug that is associated with an increase in bladder cancer in humans. The reviews report both positive and negative results for acrolein in genotoxicity tests. Literature searches were conducted from 1988 to April 2001 for studies relevant to the derivation of an oral slope factor for acrolein. The databases searched were: TOXLINE, MEDLINE, CANCERLIT, RTECS, GENETOX, HSDB, CCRIS, TSCATS, EMIC/EMICBACK, and DART/ETICBACK.

## REVIEW OF THE PERTINENT LITERATURE

### Human Studies

Reviews by the U.S. EPA (1985, 1986, 1987) and other agencies (ATSDR, 1990; NIOSH, 1991; WHO, 1992; IARC, 1979, 1985, 1995) reported that no relevant data were available regarding carcinogenicity of acrolein in humans following oral exposure. No relevant human studies were located in the literature search.

### Animal Studies

Reviews by the U.S. EPA (1985, 1986, 1987) and other agencies (ATSDR, 1990; WHO, 1992; IARC, 1979, 1985, 1995) reported that the data regarding carcinogenicity in animals following oral exposure to acrolein were limited. The cancer assessment on IRIS (U.S. EPA, 2001) is based on the increased incidence of adrenal cortical adenomas (5/20 vs 0/20 controls) observed in female rats exposed to 625 ppm of acrolein in drinking water for 100 weeks (Lijinsky and Reuber, 1987). The literature search located two additional oral carcinogenicity assays for acrolein in rodents.

No increased tumor incidence was reported in rats exposed to acrolein by gavage for 2 years, but the complete tumor incidence data were not available for evaluation (Parent et al., 1992). Groups of Sprague-Dawley rats (70 per sex per group) were gavaged with acrolein (94.9-98.5% pure, stabilized with 0.25% hydroquinone) at doses of 0, 0.05, 0.5 or 2.5 mg/kg-day for 2 years. Rats were checked twice daily for signs of toxicity, morbidity and mortality. Detailed physical examinations were carried out daily for the first 4 weeks and weekly thereafter; animals were palpated weekly for masses. Body weight and food consumption were recorded weekly for the first 14 weeks and once every 4 weeks thereafter. At 13 weeks, 5 animals of each sex in the high-dose group were sacrificed and necropsied; only the stomach was examined for histopathology. Ten rats of each group sacrificed at 1 year and all surviving rats at termination were necropsied and organ weights were recorded. In the control and high-dose groups, 42 tissues and any gross lesions were examined by histopathological examination. In the low- and mid-dose groups, the lungs, liver, kidneys and any gross lesions were examined microscopically; additional organs were examined if lesions occurred in the high-dose rats. The frequency of clinical signs (including masses; data not shown) was elevated in a dose-related manner in mid- and high-dose rats. Treatment caused no significant effect on body weight. There were

significant dose-related trends for increased mortality in high-dose males during the first year and in mid- and high-dose females throughout the study. Nevertheless, survival was adequate to allow for late-developing tumors in all groups. The incidence of tumors in the adrenal gland did not exhibit any dose-relationship. Since no tumor incidence data were reported for any other organ, there is no basis for evaluating the authors' statements that tumor incidences were within historical control values and occurred independently of dose. One source of uncertainty is that several of the references for historical control data are several decades out-of-date and are, therefore, not an appropriate basis for evaluating background levels for tumor incidences. Another source of uncertainty centers on the authors' definition of 'dose-related effects.' In the context of the frequency of clinical signs, the authors stated that no dose-related effects were observed, despite finding a dose-effect at the mid- and high-doses; in this instance, low-dose animals showed fewer clinical signs than controls. Thus, it is not clear whether the authors may have discounted significant tumor frequencies at higher doses if the incidences in the control group were higher than in the low exposure group.

No increase in tumor incidence was observed in CD-1 mice that were gavaged daily with acrolein at doses of $\leq$4.5 mg/kg-day for 18 months (Parent et al., 1991). Groups of CD-1 mice (70-75 per sex per group) were gavaged with 0, 0.5, 2.0, or 4.5 mg/kg-day of acrolein (94.9-98.5% pure, stabilized with 0.25% hydroquinone) daily for 18 months. Mice were checked twice daily for signs of toxicity, morbidity and mortality. Detailed physical examinations were carried out daily for the first 4 weeks and weekly thereafter; animals were palpated weekly for masses. Body weight and food consumption were recorded weekly for the first 14 weeks and once every 4 weeks thereafter. At termination, all mice were subjected to gross necropsy, during which absolute and relative organ weights of liver, kidneys, brain, and testes were recorded. Gross lesions from all animals were examined for histopathology; in addition, 44 tissues in the control and high dose groups, and the lungs, liver, and kidneys of low and mid-dose groups, were also examined microscopically. Survival was significantly reduced in high-dose males throughout the study due to an excess of mortality during the first 50 days of exposure. Nevertheless, survival was adequate to allow for late-developing tumors in all groups. Body weights were significantly reduced in high-dose males after week 20 and in high- and mid-dose females after week 30. There was no increase in the incidence of neoplastic lesions in the liver or lung in mice treated with acrolein compared to controls; no tumor incidence data were presented for other organs.

**Other Studies**

Recent studies by other routes provide negative or only suggestive evidence for the carcinogenicity of acrolein in animals. When doses of 1-2 mg/kg were administered by i.p. injection into male F344 rats once or twice a week for 6 weeks, acrolein initiated urinary bladder carcinogenesis promoted by dietary uracil, doubling the incidence of papilloma compared to uracil treatment alone (Cohen et al., 1992). Papillary/nodular hyperplasia of the bladder developed in a few rats treated with acrolein alone for 26 weeks, but no tumors developed. In an acute study by Roemer et al. (1993), groups of 3-5 male Sprague Dawley rats were exposed (head only) by inhalation to 0, 0.2 or 0.6 ppm of acrolein vapor for 6 hours/day for 1 or 3 successive days. Exposure to acrolein significantly increased cell proliferation in the trachea and

lung at ≥0.2 ppm and in the nose at 0.6 ppm. However, the effect of 3 days of exposure was less than in rats exposed a single time, which the authors considered an adaptive response.

The review documents cited above reported positive and negative results for acrolein in genotoxicity assays. Varied results were also reported in the additional genotoxicity studies located in the literature search. With or without metabolic activation with S9, acrolein was mutagenic in *Salmonella typhimurium* strains TA100, TA2638, and TA98, and was not mutagenic in strains TA102, TA104, TA1535, TA1537, or TA1538 (Parent et al., 1996; Eder et al., 1990; Jung et al., 1992; Kato et al., 1989; Müller et al., 1993; Watanabe et al., 1998). Acrolein was mutagenic in the *Bacillus subtilis* rec-assay without, but not with, S9 activation (Matsui et al., 1989), was not mutagenic in *Escherichia coli* WP2/pKM101 or WP2 *uvrA*/pKM101 without activation (Watanabe et al., 1998), but was marginally mutagenic to strain WP2 *uvrA*, with or without activation (Parent et al., 1996). Mutagenicity of acrolein to *E. coli* was increased in a strain that was deficient in glutathione (Nunoshiba and Yamamoto, 1999). Acrolein did not induce the expression of SOS-regulated genes in *S. typhimurium* TA1535/pSK1002 (Benamira and Marnett, 1992) and *E. coli* strain PQ37 (Eder et al., 1993).

The formation of acrolein-DNA adducts has been reviewed (Marnett, 1994; Chung et al., 1999). Endogenous acrolein-derived exocyclic adducts (1,$N^2$-propanodeoxyguanosine adducts) have been identified as common DNA lesions in human and rat liver (Nath and Chung, 1994; Nath et al., 1996), and human lung and colon (Yang et al., 1999). Acrolein-DNA adducts have been generated following reactions with deoxynucleotides (Chenna et al., 1992; Chenna and Iden, 1993), purified eukaryotic DNA (Maccubbin et al., 1990, 1992; Kuchenmeister et al., 1998), or bacterial cells (Hoffman et al., 1989). Acrolein has induced DNA cross-links in plasmids (Kawanishi et al., 1998), and DNA-protein cross-links in cultured human lymphoma cells (Costa et al., 1997), in mixtures of plasmid DNA and calf thymus histone (Kuykendall and Bogdanffy, 1992), and in SV40 virus (Permana and Snapka, 1994). Acrolein-modified DNA was identified in peripheral blood leukocytes of 6/12 cancer patients who were treated with cyclophosphamide, compared to 0/15 patients not treated with the drug (McDiarmid et al., 1991).

In studies on cultured human bronchial cells (reviewed in Grafström, 1990), acrolein reduced colony forming efficiency, clonal growth rate, and cellular levels of glutathione, and increased the frequency of DNA single-strand breaks, DNA-protein cross-links, and the percent of cells synthesizing cross-linked envelopes. Acrolein induced single-strand breaks in DNA in human skin fibroblasts (Dypbukt et al., 1993), in a human lymphoblastoid cell line (Eisenbrand et al., 1995), and, at high cytotoxic doses (1 mmol), in *Salmonella typhimurium* (Eder et al., 1993).

## DERIVATION OF A PROVISIONAL ORAL SLOPE FACTOR FOR ACROLEIN

The cancer bioassays by Parent et al. (1991, 1992) provide no evidence for increased tumor incidence in rats or mice following chronic oral exposure to acrolein. In both studies, an

adequate number of animals of both sexes was tested and evaluated comprehensively, and survival was long enough for tumors to have been detected. Based on survival and/or body weight effects at the highest doses, the dosing levels appear to have been adequate for both species. A limitation of both studies is that reporting of tumor incidence data was restricted to the adrenals for rats and the lung and liver for mice. Thus, the complete data sets were not available for evaluation. Older studies provided at best marginal evidence of acrolein carcinogenicity and were not considered suitable for derivation of an oral slope factor in prior assessments (U.S. EPA, 2001). On the basis of the available information, it is not possible to derive a provisional oral slope factor for acrolein.

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Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

## Acronyms and Abbreviations

| | |
|---|---|
| bw | body weight |
| cc | cubic centimeters |
| CD | Caesarean Delivered |
| CERCLA | Comprehensive Environmental Response, Compensation and Liability Act of 1980 |
| CNS | central nervous system |
| cu.m | cubic meter |
| DWEL | Drinking Water Equivalent Level |
| FEL | frank-effect level |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| g | grams |
| GI | gastrointestinal |
| HEC | human equivalent concentration |
| Hgb | hemoglobin |
| i.m. | intramuscular |
| i.p. | intraperitoneal |
| IRIS | Integrated Risk Information System |
| IUR | inhalation unit risk |
| i.v. | intravenous |
| kg | kilogram |
| L | liter |
| LEL | lowest-effect level |
| LOAEL | lowest-observed-adverse-effect level |
| LOAEL(ADJ) | LOAEL adjusted to continuous exposure duration |
| LOAEL(HEC) | LOAEL adjusted for dosimetric differences across species to a human |
| m | meter |
| MCL | maximum contaminant level |
| MCLG | maximum contaminant level goal |
| MF | modifying factor |
| mg | milligram |
| mg/kg | milligrams per kilogram |
| mg/L | milligrams per liter |
| MRL | minimal risk level |
| MTD | maximum tolerated dose |
| MTL | median threshold limit |
| NAAQS | National Ambient Air Quality Standards |
| NOAEL | no-observed-adverse-effect level |
| NOAEL(ADJ) | NOAEL adjusted to continuous exposure duration |
| NOAEL(HEC) | NOAEL adjusted for dosimetric differences across species to a human |
| NOEL | no-observed-effect level |
| OSF | oral slope factor |
| p-IUR | provisional inhalation unit risk |
| p-OSF | provisional oral slope factor |
| p-RfC | provisional inhalation reference concentration |

| | |
|---|---|
| p-RfD | provisional oral reference dose |
| PBPK | physiologically based pharmacokinetic |
| ppb | parts per billion |
| ppm | parts per million |
| PPRTV | Provisional Peer Reviewed Toxicity Value |
| RBC | red blood cell(s) |
| RCRA | Resource Conservation and Recovery Act |
| RDDR | Regional deposited dose ratio (for the indicated lung region) |
| REL | relative exposure level |
| RfC | inhalation reference concentration |
| RfD | oral reference dose |
| RGDR | Regional gas dose ratio (for the indicated lung region) |
| s.c. | subcutaneous |
| SCE | sister chromatid exchange |
| SDWA | Safe Drinking Water Act |
| sq.cm. | square centimeters |
| TSCA | Toxic Substances Control Act |
| UF | uncertainty factor |
| µg | microgram |
| µmol | micromoles |
| VOC | volatile organic compound |

# PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR ACROLEIN (CASRN 107-02-8) Derivation of an Inhalation Unit Risk

## Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

## Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional

Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

**Questions Regarding PPRTVs**

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

## INTRODUCTION

The CRAVE workgroup (U.S. EPA, 1992) assigned acrolein to weight-of-evidence Group C, possible human carcinogen, on the basis of no evidence in humans and limited evidence in animals (increased incidence of adrenal cortical adenomas in female rats in an oral study, but no increased tumors in inadequate inhalation, skin painting, and subcutaneous injection studies). Supporting evidence included the carcinogenic potential of an acrolein metabolite, the mutagenicity of acrolein in bacteria, and the structural relationship of acrolein to probable or known human carcinogens. This assessment is listed on IRIS (U.S. EPA, 2001). No inhalation unit risk factor for acrolein is listed on IRIS (U.S. EPA 2001) or in the HEAST (U.S. EPA, 1997). Source documents for the IRIS assessment were a Health Assessment Document (HAD) (U.S. EPA, 1986) and a Health Effects Assessment (HEA) for acrolein (U.S. EPA, 1987). The CARA list (U.S. EPA, 1991, 1994) also includes a Health and Environmental Effects Profile (HEEP) on acrolein (U.S. EPA, 1985). IARC (1979, 1985, 1995) assigned acrolein to Group 3, not classifiable as to human carcinogenicity because of inadequate evidence in humans and animals. ACGIH (1998, 2000) lists an A4 notation for acrolein, indicating its status as not classifiable as a human carcinogen. NIOSH (1991, 2001) notes that although carcinogenicity testing is not complete for acrolein, enough studies report chemical reactivity and mutagenicity to warrant efforts to reduce exposure. A Toxicological Profile for acrolein (ATSDR, 1990), an Environmental Health Criteria document on acrolein (WHO, 1992), a carcinogenicity review of low-molecular-weight aldehydes (NIOSH, 1991), and a toxicity review on aldehydes (Morandi

and Maberti, 2001) were consulted for relevant information. The NTP (2001) health and safety report for acrolein was also examined. These resources contained no additional studies of acrolein itself. However, a metabolite of acrolein, glycidaldehyde, yielded positive results for carcinogenicity in skin painting assays in mice and subcutaneous injection assays in mice and rats. In addition, the reviews note that acrolein is a metabolite of cyclophosphamide, an immunosuppressive drug that is associated with an increase in bladder cancer in humans. The reviews report both positive and negative results for acrolein in genotoxicity tests. Literature searches were conducted from 1988 to April 2001 for studies relevant to the derivation of an inhalation unit risk for acrolein. The databases searched were: TOXLINE, MEDLINE, CANCERLIT, RTECS, GENETOX, HSDB, CCRIS, TSCATS, EMIC/EMICBACK, and DART/ETICBACK.

## REVIEW OF THE PERTINENT LITERATURE

### Human Studies

Reviews by the U.S. EPA (1985, 1986, 1987) and other agencies (ATSDR, 1990; NIOSH, 1991; WHO, 1992; IARC, 1979, 1985, 1995) reported that no relevant data were available regarding carcinogenicity of acrolein in humans following inhalation exposure. The literature search uncovered a single case report in which acrolein was suggested as the cause of alveolar cell carcinoma in a non-smoking cook (Wardle, 1988). The author argued that the individual, who unavoidably inhaled the fumes of hot fat and oils in a confined space over many years, was likely to have been exposed to acrolein as a common constituent of smoke. However, exposure to acrolein was not established in this case, and in addition, the individual was likely to have been exposed to other potential carcinogens as well.

### Animal Studies

Reviews by the U.S. EPA (1985, 1986, 1987) and other agencies (ATSDR, 1990; WHO, 1992; IARC, 1979, 1985, 1995) report that the data regarding carcinogenicity in animals following inhalation exposure to acrolein is limited. No tumors were found in hamsters intermittently exposed to acrolein for one year, but the duration of the experiment was too short to allow for latency (Feron and Kruysse, 1977). No additional studies were located in the literature search regarding carcinogenicity in animals following chronic or subchronic inhalation exposure to acrolein. The cancer assessment on IRIS (U.S. EPA, 2001) is based on the increased incidence of adrenal cortical adenomas in female rats exposed to 625 ppm of acrolein in drinking water for 100 weeks (Lijinsky and Reuber, 1987). However, in more recent studies, acrolein administered by gavage did not increase the incidence of tumors in mice dosed with $\leq$4.5 mg/kg-day for 18 months (Parent et al., 1991) or in rats dosed with $\leq$2.5 mg/kg-day for 2 years (Parent et al., 1992).

**Other Studies**

Recent short-term studies in animals provide negative or only suggestive evidence of the carcinogenic potential of acrolein. When doses of 1-2 mg/kg were administered by i.p. injection into male F344 rats once or twice a week for 6 weeks, acrolein initiated urinary bladder carcinogenesis promoted by dietary uracil, doubling the incidence of papilloma compared to uracil treatment alone (Cohen et al., 1992). Papillary/nodular hyperplasia of the bladder developed in a few rats treated with acrolein alone for 26 weeks, but no tumors developed. In an acute study by Roemer et al. (1993), groups of 3-5 male Sprague Dawley rats were exposed (head only) by inhalation to 0, 0.2 or 0.6 ppm of acrolein vapor for 6 hours/day for 1 or 3 successive days. Exposure to acrolein significantly increased cell proliferation in the trachea and lung at $\geq$0.2 ppm and in the nose at 0.6 ppm. However, the effect of 3 days of exposure was less than in rats exposed a single time, which the authors considered an adaptive response.

The review documents cited above reported positive and negative results for acrolein in genotoxicity assays. Varied results were also reported in the additional genotoxicity studies located in the literature search. With or without metabolic activation with S9, acrolein was mutagenic in *Salmonella typhimurium* strains TA100, TA2638, and TA98, and was not mutagenic in strains TA102, TA104, TA1535, TA1537, or TA1538 (Parent et al., 1996; Eder et al., 1990; Jung et al., 1992; Kato et al., 1989; Müller et al., 1993; Watanabe et al., 1998). Acrolein was mutagenic in the *Bacillus subtilis* rec-assay without, but not with, S9 activation (Matsui et al., 1989), was not mutagenic in *Escherichia coli* WP2/pKM101 or WP2 *uvrA*/pKM101 without activation (Watanabe et al., 1998), but was marginally mutagenic to strain WP2 *uvrA*, with or without activation (Parent et al., 1996). Mutagenicity of acrolein to *E. coli* was increased in a strain that was deficient in glutathione (Nunoshiba and Yamamoto, 1999). Acrolein did not induce the expression of SOS-regulated genes in *S. typhimurium* TA1535/pSK1002 (Benamira and Marnett, 1992) and *E. coli* strain PQ37 (Eder et al., 1993).

The formation of acrolein-DNA adducts has been reviewed (Marnett, 1994; Chung et al., 1999). Endogenous acrolein-derived exocyclic adducts (1,$N^2$-propanodeoxyguanosine adducts) have been identified as common DNA lesions in human and rat liver (Nath and Chung, 1994; Nath et al., 1996), and human lung and colon (Yang et al., 1999). Acrolein-DNA adducts have been generated following reactions with deoxynucleotides (Chenna et al., 1992; Chenna and Iden, 1993), purified eukaryotic DNA (Maccubbin et al., 1990, 1992; Kuchenmeister et al., 1998), or bacterial cells (Hoffman et al., 1989). Acrolein has induced DNA cross-links in plasmids (Kawanishi et al., 1998), and DNA-protein crosslinks in cultured human lymphoma cells (Costa et al., 1997), in mixtures of plasmid DNA and calf thymus histone (Kuykendall and Bogdanffy, 1992), and in SV40 virus (Permana and Snapka, 1994). Acrolein-modified DNA was identified in peripheral blood leukocytes of 6/12 cancer patients who were treated with cyclophosphamide, compared to 0/15 patients not treated with the drug (McDiarmid et al., 1991).

In studies on cultured human bronchial cells (reviewed in Grafström, 1990), acrolein reduced colony forming efficiency, clonal growth rate, and cellular levels of glutathione, and increased the frequency of DNA single-strand breaks, DNA-protein cross-links, and the percent

of cells synthesizing cross-linked envelopes. Acrolein induced single-strand breaks in DNA in human skin fibroblasts (Dypbukt et al., 1993), in a human lymphoblastoid cell line (Eisenbrand et al., 1995), and, at high cytotoxic doses (1 mmol), in *Salmonella typhimurium* (Eder et al., 1993).

## FEASIBILITY OF DERIVING A PROVISIONAL INHALATION UNIT RISK FOR ACROLEIN

The literature search disclosed no new information regarding carcinogenicity of acrolein following inhalation exposure in humans or animals. Although acrolein is designated a possible human carcinogen (Group C) on IRIS (U.S. EPA, 2001), there are no inhalation data upon which to base an inhalation unit risk.

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