IRIS SUMMARY

0290
Acetaldehyde; CASRN 75-07-0; 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 ACETALDEHYDE

File First On-Line __/__/__

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

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

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

Acetaldehyde
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The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable

risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Histologic alterations in the gastrointestinal tract	NOAEL: 125 mg/kg-day		3000	1	4E-2 mg/kg-day
4-week rat drinking water study.	LOAEL: 625 mg/kg-day			
Til et al. (1988)				
Histologic alterations in the gastrointestinal tract				
8-month rat drinking water study.	LOAEL: 324 mg/kg-day			
Homann et al. (1997)				

*Conversion Factors and Assumptions -- None. The study authors (Til et al., 1988; Homann et al., 1997) estimated doses using body weight and water consumption data.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Homann, N; Kärkkäinen, P; Koivisto, T; Nosova, T; Jokelainen, K; Salaspuro, M. (1997) Effects of acetaldehyde on cell regeneration and differentiation of the upper gastrointestinal tract mucosa. J. Natl. Cancer Inst. 89:1692-1697.

Til, HP; Woutersen, RA; Feron, VJ; Clary, JJ. (1988) Evaluation of the oral toxicity of acetaldehyde and formaldehyde in a 4-week drinking-water study in rats. Fd. Chem. Toxicol. 26(5):447-452.

Til et al. (1988) exposed groups of 10 male and 10 female (20 male and 20 female for the unexposed group) Wistar rats to 0, 25, 125, or 625 mg/kg-day in drinking water for 4 weeks. To account for potential effects of decreased water consumption in treated animals, an additional group of 10 male and 10 female rats was given drinking water in an amount equal to the amount of liquid consumed by the group given the highest dose. Endpoints examined included food and water intake, body weight, daily observations for condition and behavior, organ weights, hematologic and clinical chemistry parameters, urinalysis, and gross and histologic pathology. Acetaldehyde exposure resulted in no decrease in body weight or food consumption, but did lead to a decrease in liquid intake for both males and females at the highest dose only. There were no changes in hematology among the groups. In the 625 mg/kg-day male rats, the plasma level of urea was significantly increased and that of bilirubin was significantly decreased, while plasma alkaline phosphatase and alanine aminotransferase activities were significantly decreased in females exposed to 625 mg/kg-day. The relative weights of the kidneys were slightly, but significantly, increased in males, but not females, in the 625 mg/kg-day group; absolute weights were not reported. No change in the relative weights of the gonads, brain, heart, or liver were observed following acetaldehyde treatment. A slight (in 6/10 males and 6/10 females) or moderate (in 2/10 males and 2/10 females) focal hyperkeratosis of the stomach was observed in animals exposed to 625 mg/kg-day, but not in any of the other exposure levels. This study established a NOAEL of 125 mg/kg-day and a LOAEL of 625 mg/kg-day for histologic alterations of the gastrointestinal tract in male and female Wistar rats.

In another study reporting similar findings, Homann et al. (1997) exposed groups of 10 male Wistar rats to 0 or 120 mM acetaldehyde in drinking water for 8 months. Exposure levels for the acetaldehyde-exposed rats were calculated by the researchers to be 324 ± 24 mg/kg-day. No significant changes in fluid intake or body weight were observed between groups, and no cancerous or dysplastic lesions were located in the upper gastrointestinal tract of rats from either group. The epithelial thickness of the tongue, epiglottis, and forestomach was increased in acetaldehyde-treated rats relative to controls, and was accompanied by a significant increase in the expression of Ki67, a marker of cellular proliferation. This study established a LOAEL of 324 mg/kg-day for histologic alterations of the gastrointestinal tract in male Wistar rats.

Evidence of gastrointestinal irritation has also been demonstrated in dogs. Following a single gavage exposure of 6 male dogs to 600 mg/kg of acetaldehyde in distilled water, Booze and Oehme (1986) reported vomiting in all six dogs, which continued for several hours and was often bloody. Two of the six dogs so exposed, the two with the highest plasma levels of acetaldehyde, developed slight tremors, which were transient. Upon gross examination, the stomachs of all acetaldehyde-treated dogs presented extensive hemorrhagic areas on the mucosa, suggestive of a severe irritation.

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

UF = 3000. (10 for interspecies variation, 10 for human variability, 10 for use of a subchronic study, and 3 for database insufficiencies) The database insufficiencies include a lack of a developmental toxicity study in a second species and a multi-generation reproductive toxicity study. A full factor of 10 was not considered necessary because (1) there is no evidence to suggest that acetaldehyde accumulates in the body, (2) a substantial first-pass effect is seen

following oral acetaldehyde exposure, and (3) the high reactivity of the acetaldehyde molecule suggests that the portal of entry effects will be the most sensitive toxic endpoints.

MF = 1.

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

Other studies examining oral administration have not examined alterations of the gastrointestinal tract. HoLownia et al. (1992) exposed groups of 15 male Wistar rats daily by gavage to 0 or 800 mg/kg of acetaldehyde for 4 weeks. Following sacrifice, the livers were homogenized and the activity of superoxide dismutase (SOD), glutathione peroxidase, and catalase were measured. Acetaldehyde significantly reduced the level of SOD activity, but not of the other enzymes examined, in treated rats. Acetaldehyde treatment also significantly reduced the total level of sulfhydral compounds in the liver, which the authors attributed to a decrease in glutathione levels.

The effect of long-term oral exposure to acetaldehyde on collagen biosynthesis in the liver of rats was examined (Pawlicka et al., 1991; Bankowski et al., 1993). Groups of 10 male Wistar rats were exposed to 0.05% acetaldehyde in the drinking water for up to 6 months (~75 mg/kg-day, based on subchronic reference values for water intake and body weight from U.S. EPA, 1988). Acetaldehyde exposure resulted in a progressive increase of 5-^{3}H-proline incorporation into collagen synthesized by the liver, but no change in noncollagen protein synthesis. Collagen content in the liver did not change significantly at early (up to 4 months) time points, but was significantly increased by 6 months of exposure. No differences in the types of collagen synthesized were noted.

I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- Medium
Data Base -- Low
RfD -- Low

Confidence in the co-principal studies is medium, as the studies examined a sufficient number of endpoints in a sufficient number of animals at several doses (Til et al., 1988 only). Confidence in the database is low, owing to the lack of chronic oral data, lack of subchronic or chronic data in species outside the rat, and lack of adequate reproductive toxicity data. Low confidence in the RfD results.

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

Source Document -- _____

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 _____.

Other EPA Documentation -- _____

Agency Consensus Date -- __/__/__

I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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

Acetaldehyde
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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.

I.B.1. INHALATION RfC SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfC
Degeneration of olfactory epithelium	NOAEL: 702 mg/m^3 (390 ppm) NOAEL(ADJ): 125 mg/m^3 NOAEL(HEC): 5.45 mg/m^3	1000	1	5E-3 mg/m^3
Subchronic hamster inhalation study Kruysse et al., 1975	LOAEL: 2412 mg/m^3 (1340 ppm) LOAEL(ADJ): 431 mg/m^3 LOAEL(HEC): 18.8 mg/m^3			

*Conversion Factors and Assumptions -- MW = 44.05
Kruysse et al., 1975: Assuming 25°C and 760 mmHg, NOAEL(mg/m^3) = 390 ppm x 44.05/24.45 = 702. NOAEL(ADJ) = 702 mg/m^3 x 6 hours/day x 5 days/7 days = 125 mg/m^3. The NOAEL(HEC) was calculated for a gas:respiratory effect in the ExtraThoracic region. MVa = 0.061 m^3/day, MVh = 20 m^3/day, Sa(ET) = 14 cm^2, Sh(ET) = 200 cm^2. RGDR(ET) = (MVa/Sa) / (MVh/Sh) = 0.0436. NOAEL(HEC) = NOAEL(ADJ) x RGDR = 5.45 mg/m^3. Similarly, LOAEL(mg/m^3)=1340 ppm x 44.05/24.45 = 2412. LOAEL(ADJ) = 2412 mg/m^3 x 6 hours/day x 5 days/7 days = 431 mg/m^3. LOAEL(HEC) = LOAEL(ADJ) x RGDR = 18.8 mg/m^3.

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

Kruysse, A.; Feron, VJ; Til, HP. (1975) Repeated exposure to acetaldehyde vapor. Arch. Environ. Health. 30:449-452.

Kruysse et al. (1975) conducted a 90-day inhalation study in Syrian golden hamsters (10/sex/concentration). The hamsters were exposed to acetaldehyde vapor at concentrations of 0, 390, 1340, or 4560 ppm (0, 702, 2412 or 8200 mg/m^3, respectively), for 6 hours/day, 5 days/week for 90 days. At the highest concentration (4560 ppm), profound effects were observed. Body weights were significantly decreased (~25% reduction) relative to controls, and the relative weights of the heart, kidneys, brain, testicles, and lungs were significantly increased. In the nasal cavity, rhinitis, necrosis, rarefaction of turbinate bones, and metaplasia of respiratory and olfactory epithelium were noted, as well as a disappearance of subepithelial glands and thickening of the submucosa by an increased amount of fibrous tissue. In the larynx, the normal respiratory epithelium was replaced by a stratified squamous epithelium which was often keratinized, especially in the region caudad to the vocal cords. Likewise, large areas of the tracheas of high-dose hamsters were covered with a stratified squamous epithelium, often with heavy keratinization and inflammatory changes. Similar changes were evident to a lesser extent in the main stem bronchi. At the 1340 ppm exposure level, relative kidney weights in male hamsters were elevated, and some animals (4 male, 2 female) showed focal metaplastic responses of the

tracheal epithelium, with small areas of stratified epithelium present. No treatment-related alterations were observed in animals exposed to 390 ppm of acetaldehyde. This study established a NOAEL of 390 ppm and a LOAEL of 1340 ppm, based on histopathologic alterations of the tracheal epithelium of hamsters. These values correspond to a NOAEL(HEC) of 5.45 mg/m^3 and a LOAEL(HEC) of 18.8 mg/m^3.

Appelman et al. (1986) exposed groups of 10 male Wistar rats for 6 hours/day, 5 days/week for 4 weeks to 0, 110/150, or 500 ppm (0, 200/273, or 910 mg/m^3, respectively) of acetaldehyde. At each exposure concentration, three groups were examined. One group was exposed without interruption (150 or 500 ppm), a second group was interrupted for 1.5 hours between the first and second 3-hour period (150 or 500 ppm), and a third group (110 or 500 ppm) was interrupted as described with a superimposed peak exposure profile of 4 peaks at 6-fold the basic concentration (660 or 3000 ppm) per 3-hour period. Urine samples were collected from all rats, and lung lavage was performed on 4-5 per group at the end of the experiment. Cell density, viability, number of phagocytosing cells, and phagocytic index were determined on the lavage fluid. Microscopic examination was performed on the nasal cavity, larynx, trachea with bifurcation and pulmonary lobes of all rats of all groups. Continuous and interrupted exposure to 500 ppm did not induce any visible effect on general condition or behavior, but animals exposed to 500 ppm with peak exposures of 3000 ppm showed signs of irritation. Mean body weights of the groups exposed to 500 ppm with interruption and with peak exposures were statistically significantly lower than those of the controls. Body weights were similar to controls in the other exposure groups. Mean lavage cell density and cell viability were significantly decreased in the groups exposed to 500 ppm with interruption, either with or without peak exposures. The mean percentage of phagocytosing cells and the phagocytic index were significantly lower than controls in all groups exposed to 500 ppm, particularly in the group with peak exposures. Histopathological changes attributable to exposure were found only in the nasal cavity, where degeneration of the olfactory epithelium was observed in all groups of rats exposed to 500 ppm. Interruption of the exposure or interruption combined with peak exposure did not appear to influence this adverse effect. No compound-related effects were observed in rats exposed to 150 ppm of acetaldehyde during the 4-week exposure period. This study established a NOAEL in rats of 150 ppm and a LOAEL of 500 ppm, based on histologic alterations of the nasal epithelium. These values correspond to a NOAEL(HEC) of 7.46 mg/m^3 and a LOAEL(HEC) of 24.6 mg/m^3.

Appelman et al. (1982) exposed groups of 10 male and 10 female Wistar rats to acetaldehyde for 6 hours/day, 5 days/week for 4 weeks at nominal concentrations of 0, 400, 1000, 2200, or 5000 ppm. Measured mean exposure concentrations were 0, 401, 941, 2217, or 4975 ppm (0, 730, 1713, 4035, or 9055 mg/m^3, respectively). Growth retardation occurred in males of the 3 highest dose groups and in females of the highest dose group only. There were statistically significant differences in several blood chemistry parameters between the exposure groups and the control group, but none of them were concentration-related. Statistically significant changes in relative organ weight occurred only in the 5000 ppm group, and included decreased liver weights in both male and female rats and increased lung weights in male rats. Males exposed to 5000 ppm produced less urine, but it was of higher density. Compound-related histopathological changes

were observed only in the respiratory system. The nasal cavity was most severely affected, with the anterior portions generally less affected than the posterior portions. Alterations in the nasal region demonstrated a concentration-response relationship. In the 400 ppm exposure group, a loss of microvilli accompanied by thinning and disarrangement of the epithelium in the dorsal part of the nose was observed in 9/10 of the males and 7/10 of the females. In animals exposed at the 1000 or 2200 ppm levels, more severe degenerative changes were observed, with hyperplastic and metaplastic changes in the olfactory and respiratory epithelium of the nasal cavities of all rats exposed to 2200 ppm. At 5000 ppm, the changes included severe degenerative hyperplastic and metaplastic changes, with a thickening of the submucosal region. The vocal cord region of the larynx of rats exposed to 2200 or 5000 ppm showed hyperplastic and metaplastic alterations, characterized by slightly keratinized stratified squamous epithelium. In the tracheal region, degeneration with hyperplasia and metaplasia occurred in the laryngeal and tracheal epithelium at the 2200 or 5000 ppm exposure levels; nearly all rats in the 5000 ppm group demonstrated a metaplasia of the respiratory epithelium, manifested by flat, elongated superficial cells and large basal cells containing huge, bizarre nuclei with large nucleoli. Tracheal changes were more severe in the upper trachea than in the lower trachea. Minor changes in the alveolar region of the lung were occasionally seen in animals of the high-dose group, but not in other groups. This study established a LOAEL of 400 ppm, based on histologic alterations of the nasal epithelium in Wistar rats; no NOAEL was established. This value corresponds to a LOAEL(HEC) of 19.7 mg/m^3.

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

UF -- 1000 (3 for interspecies extrapolation using dosimetric adjustments, 10 for human variability, 10 for the use of a less than chronic study, and 3 for database insufficiencies) A partial UF of 3 was used for database insufficiencies because data on the developmental and reproductive effects of acetaldehyde following inhalation exposure are not available. A full factor of 10 was not considered necessary because pharmacokinetic data suggest that because of the rapid metabolism of acetaldehyde and a lack of substantial accumulation in the body following inhalation exposure, portal of entry effects, specifically nasal lesions, are likely to be the most sensitive endpoint.

MF -- 1.

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

Nasal lesions similar to those described by Kruysse et al. (1975) have been seen in a number of inhalation carcinogenicity studies of acetaldehyde (Feron et al., 1982; Woutersen et al., 1985, 1986; Woutersen and Feron, 1987). These studies were not selected as critical studies because they utilized higher exposure levels than the Kruysse et al. (1975) study, and none established a NOAEL.

I.B.5. CONFIDENCE IN THE INHALATION RfC

Study -- Medium
Data Base -- Low
RfC -- Low

Confidence in the principal study is medium, as the study was conducted in both sexes of animals, examined endpoints seen in chronic inhalation studies, and established an exposure-response relationship. However, the study was only performed in one species, though studies in other species have shown similar effects. Confidence in the database is low due to the lack of chronic data establishing NOAELs and due to the lack of reproductive and developmental toxicity data following inhalation exposure. Low confidence in the RfC results.

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

Source Document -- _____

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 _____.

Other EPA Documentation -- _____

Agency Consensus Date -- __/__/__

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

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II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Acetaldehyde
CASRN -- 75-07-0
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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 $\mu g/m^3$ 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). 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

Under the 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a), acetaldehyde is classified as Group B2 (Probable Human Carcinogen), based on insufficient data on the carcinogenicity of acetaldehyde in humans and sufficient evidence of carcinogenicity in animals, as evidenced by increased incidence of upper respiratory tract tumors in male and female rats and male hamsters following inhalation exposure. Under the proposed cancer guidelines (U.S. EPA, 1996a, 1999), acetaldehyde is considered likely to be carcinogenic to humans.

While available human studies have weakly suggested a possible association between risk of various types of cancer and acetaldehyde exposure (Bittersohl, 1974; Ott et al., 1989a, 1989b), limitations of the studies, including inability to control for concurrent exposures to other chemicals, make them inadequate for assessing the carcinogenic potential of acetaldehyde. Available chronic animal studies have demonstrated the carcinogenic potential of inhaled acetaldehyde in male and female rats, as well as in male hamsters (Feron et al., 1982; Woutersen and Appelman, 1984; Woutersen et al., 1985, 1986; Woutersen and Feron, 1987). Acetaldehyde-induced tumors in both rats and hamsters were only located in the upper respiratory tract, with the posterior nasal regions being the most prevalent site for increased tumor incidence. No studies suitable for evaluation of the oral carcinogenic potential of acetaldehyde were located.

There is evidence that acetaldehyde exposure is capable of eliciting genotoxic effects. While evaluations for mutagenic effects in bacteria have generally yielded negative results, tests for sister-chromatid exchanges, unscheduled DNA synthesis, and mutations in human and animal cells have demonstrated potentially genotoxic effects of acetaldehyde. *In vitro* treatment with acetaldehyde has also resulted in increased micronucleus formation in human lymphocytes and an

increased incidence of DNA-protein cross-links and DNA adducts. *In vivo* exposure to acetaldehyde has resulted in increased incidence of DNA-protein crosslinks, sister-chromatid exchange, and micronucleus formation.

The exact mechanism of acetaldehyde-induced carcinogenic effects in animals is not known. Acetaldehyde is chemically reactive, and inhalation exposure to acetaldehyde results in substantial toxic effects in the nasal epithelium, including hyperplastic and metaplastic changes. It is possible that the carcinogenic effects seen following acetaldehyde inhalation are a result of this enhanced proliferation, a response to the substantial cytotoxic effects seen in chronic studies. However, acetaldehyde has also been shown to have mutagenic effects in mammalian cells, is capable of binding to protein, lipid, and DNA molecules, and causes increased levels of protein-DNA adducts in nasal tissues following inhalation exposure. Thus, a direct genotoxic effect of acetaldehyde cannot be ruled out. The carcinogenic effects are most likely the result of a combination of the two mechanisms, whereby cytotoxicity-induced proliferative changes render the cells more susceptible to genotoxic effects, resulting in increased mutation frequency, which may lead to both additional cytotoxicity, enhancing the effect, or tumor formation. Animals exposed by inhalation for 52 weeks and allowed to recover for up to 52 weeks showed similar tumor incidence rates as animals exposed for their entire lifetime, suggesting that once the initial carcinogenic insult occurs, additional exposure is not necessary for progression of the lesion.

II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. Only one cohort study regarding acetaldehyde exposure and incidence of cancer has been reported. Bittersohl (1974) examined a cohort of 220 individuals who were actively employed in an acetaldol and aliphatic aldehyde factory in the German Democratic Republic between 1967 and 1972, approximately 150 of whom were employed for more than 20 years in the factory. The numbers of male and female cohort members were not specified. Only workers actively employed during the study time were included in the study cohort. Acetaldehyde concentrations in workplace air were found to range from 1 to 7 mg/m^3 (0.55-3.9 ppm). Nine cases of cancer (five squamous cell carcinomas of the bronchi, two squamous cell carcinomas of the mouth cavity, one adenocarcinoma of the stomach, and one adenocarcinoma of the cecum) were identified among males in the cohort. Of these, eight were reported to have smoked 5-10 cigarettes per day. The ninth smoked more than 30 cigarettes daily. Two female cancer cases were excluded from analysis because the author felt that the latency period for these cases was too short for their cancers to have been the result of industrial chemical exposure. A cancer incidence rate of 6000 per 100,000 population was calculated for this study cohort, compared to 1200 per 100,000 in the general German Democratic Republic population. Because the incidence rates were not age adjusted, and because this study has several other major methodological limitations (concurrent exposure to acetaldol, butyraldehyde, crotonaldehyde, “large” condensed aldehydes, and acrolein; smoking history [all patients with cancer reported having smoked]; and small number of subjects; lack of followup of workers who terminated employment before the

study was begun; lack of information on subject selection, age and sex distribution), the data are considered inadequate to evaluate the carcinogenicity of acetaldehyde.

A cohort study of 29,139 men employed at any of three chemical manufacturing facilities in West Virginia over a 39-year period identified an increase in deaths caused by both cancers of the liver and lymphatic and hematopoietic tissue cancer (Rinsky et al. 1988). These findings led to the initiation of a case-control study by Ott et al. (1989a, 1989b), examining 129 cases of hematopoietic tissue malignancies taken from the larger cohort, with a detailed analysis of exposure classifications published in a separate report (Ott et al. 1989c). Co-exposure to other chemicals (e.g., acrylonitrile, alkyl sulfates, epichlorohydrin, metal salts, vinyl chloride) was common throughout exposure categories. In particular, job categories exposed to acetaldehyde were also co-exposed to acrylonitrile. The study revealed nonsignificant increases (95% lower confidence interval of the OR did not exceed 1.0) in odds ratios (OR) for acetaldehyde exposure when non-Hodgkins lymphoma (7 cases, OR 2.3), multiple myeloma (3 cases, OR 2.3), and non-lymphocytic leukemia (3 cases, OR 1.3) were examined. Therefore, a definitive association between acetaldehyde exposure and these cancers could not be made from these data.

II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. Feron (1979) exposed groups of 35 male Syrian golden hamsters to airborne concentrations of 0 or 1500 ppm of acetaldehyde for 7 hours/day, 5 days/week for 52 weeks. Five animals were killed and autopsied immediately following cessation of exposure, and the remaining animals were observed for an additional 26 weeks. Immediately following 52 weeks of exposure, acetaldehyde-exposed animals showed marked lesions in the nasal cavity, including hyperplasia and metaplasia of the olfactory and respiratory epithelium and a slight to moderate rhinitis. In the trachea, slight focal hyper- and metaplastic changes of the lining epithelium were observed in nearly all animals that were exposed to acetaldehyde. Following 26 weeks of recovery, these lesions had lessened in severity, but were still present. The larynx, trachea, bronchi, and bronchioli and alveoli were examined for increased tumor incidence. Acetaldehyde exposure did not result in increased incidence of tumors in these tissues at any time point examined.

In the second part of the study, groups of 35 male and 35 female Syrian golden hamsters were intratracheally instilled once weekly for 52 weeks with 0.2 ml of a 2 or 4% acetaldehyde solution (4 or 8 µl, respectively), and observed for an additional 52 weeks. Extensive peribronchiolar adenomatoid lesions, often accompanied by inflammatory changes, were observed in many animals. Following 52 weeks of observation (study week 104), the inflammatory changes had reduced in severity, but the epithelial changes remained unaltered, though they had not progressed to a neoplastic state.

In a later study, Feron et al. (1982) exposed groups of 18 male and 18 female Syrian golden hamsters for 7 hours/day, 5 days/week for 52 weeks to a time-weighted average (TWA)

concentration of 0 or 2028 ppm (3650mg/m^3). The TWA concentration reflects an initial concentration of 2500 ppm that was lowered throughout the study to a final level of 1650 ppm to avoid early mortality) of acetaldehyde. After 52 weeks of exposure, animals were observed for an additional 29 weeks (81 weeks total study duration). Hamsters exposed to acetaldehyde had significantly lower body weights than those of controls from week 4 and onwards. Mortality was slightly higher in acetaldehyde-exposed hamsters than in control animals. There were no significant differences in hematological and biochemical findings between air-exposed and acetaldehyde-exposed hamsters, with the exception of an increase in alkaline phosphatase in exposed females. The relative weights of kidneys and lungs were higher in acetaldehyde-exposed hamsters than in controls, but were only statistically significantly elevated in females. Acetaldehyde-exposed animals killed at the end of exposure showed pathological changes in the nose, larynx, and trachea. Nasal alterations included rhinitis, thinning of the olfactory epithelium, and hyper- and metaplasia, often with heavy keratinization. In both the larynx and trachea, slight to moderate focal hyper- and metaplasia of the epithelium were found. Similar lesions were still found in the nose, larynx, and trachea at the end of the recovery period. Increased incidence of tumors of the larynx was noted following exposure to acetaldehyde, but was only statistically significant in males (6/29 in exposed compared to 0/30 for controls).

A lifetime carcinogenicity study of acetaldehyde vapor in rats was conducted by Woutersen et al. (1985, 1986). Groups of 75 male and 75 female Wistar rats were exposed to 0, 750, 1500, or 3000 ppm (0, 1350, 2700, or 5400 mg/m^3) acetaldehyde for 6 hours/day, 5 days/week for 28 months. Because of signs of severe toxicity in the 3000 ppm group, the concentration was gradually decreased to a final concentration of 1000 ppm in week 52 and onwards. The mean (TWA for high-dose) of the measured concentrations throughout the study were 0, 727, 1438, and 1592 ppm for the control, low-, mid-, and high-dose groups, respectively. Interim sacrifices occurred at weeks 13 (5 rats/sex), 26 (5 rats/sex), and 52 (10 rats/sex). Acetaldehyde exposure resulted in an increase in mortality in all exposed groups, compared to the controls, in a concentration-related manner (22, 11, 9, or 0 male rats survived to the end of the study in the 0, 750, 1500, and 3000 ppm groups, respectively; 28, 17, 11 or 0 female rats survived to the end of the study in the 0, 750, 1500, and 3000 ppm groups, respectively). All of the male and female rats exposed to the highest exposure concentration died by day 715 of the study. Statistically significant retardations of growth occurred in males of each dose group (~8, 17, or 22% for 750, 1500, or 3000 ppm groups) and in the 1500 ppm (~14%) and 3000 ppm (~11%) females at study day 560. Significantly increased tumor incidences were limited to the nasal region, consisting primarily of adenocarcinomas and squamous cell carcinomas, with other respiratory tract tumors limited to a single laryngeal carcinoma and one pulmonary adenocarcinoma. In the nose, only one benign tumor was reported; all other nasal tumors were malignant. Total respiratory tract tumor incidences were 1/55, 17/54, 40/55, or 31/53 for control, 750, 1500, or 3000 ppm male rats, respectively, and 0/54, 8/55, 36/55, or 39/55 for control, 750, 1500, or 3000 ppm female rats, respectively. Nasal degeneration occurred in all dose groups, beginning as early as 52 weeks of exposure. It was characterized by basal cell hyperplasia in the 750 and 1500 ppm groups and squamous metaplasia, with slight to severe hyperkeratosis, in 1500

and 3000 ppm rats, beginning as early as week 13. The authors concluded that acetaldehyde vapor can cause severe nasal cytotoxicity, as well as carcinogenic effects in nasal tissues.

In a concurrent study (Woutersen and Appelman, 1984; Woutersen and Feron, 1987), groups of 30 male and female rats were exposed as described above for the carcinogenicity study, with exposure durations of 52 weeks followed by observation for up to 52 weeks of air exposure as a "recovery" period. Nonneoplastic nasal lesions observed in rats following 52 weeks of exposure had partially regressed following 52 weeks of recovery. Regenerative changes including small nerve bundles, groups of sensory cells, and groups of epithelial cells resembling acinar cells of the Bowman's glands were evident after both 26 and 52 weeks of recovery. However, tumor incidence rates were similar to those in animals exposed throughout their lifetimes, indicating that after 52 weeks of exposure to acetaldehyde, proliferative epithelial lesions of the nose may develop into tumors even without continued exposure.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Acetaldehyde has tested negative for reverse mutation in *Salmonella typhimurium*, both with and without S-9 activating mixture (Litton Bionetics, Inc, 1979; Dellarco, 1988; Aeschbacher et al., 1989; Kato et al., 1989; Dillon et al., 1998), though its high volatility makes testing difficult. Evaluation of acetaldehyde in the SOS/*umu* test was also negative (Reifferscheid and Heil, 1996). Acetaldehyde has tested positive for mutations in the *E. coli* polA system (Leifer et al., 1981), but negative in the *E. coli* K-12 *uvrB/recA* DNA repair host-mediated assay (Kato et al., 1989; Hellmér and Bolcsfoldi, 1992). Exposure of *Saccharomyces cerevisiae* to acetaldehyde resulted in chromosomal damage, including both single-strand and double-strand breaks (Ristow et al., 1995).

Olin et al. (1996) reported a concentration-related increase in DNA-protein cross links in Chinese hamster ovary cells exposed to acetaldehyde, but not in human fibroblasts. Lower concentrations were not directly clastogenic in Chinese hamster ovary cells, but potentiated the clastogenic effects of several other DNA-damaging agents (Lin et al., 1989). Primary rat hepatocytes treated with 100 µM acetaldehyde for 3 hours showed an increase in unscheduled DNA synthesis (Stevens et al., 1991). Acetaldehyde tested positive for induction of forward mutations in L5178Y mouse lymphoma cells (Wangenheim and Bolcsfoldi, 1988). Acetaldehyde exposure of up to 100 mM in freshly isolated human lymphocytes resulted in a dose-related increase in single-strand and double-strand DNA breaks, which the cells appeared to be unable to repair within 2 hours post-exposure (Singh and Khan, 1995). Exposure of human lymphocytes at acetaldehyde levels of up to 400 µM resulted in an increased frequency of sister-chromatid exchanges, which was potentiated by the addition of an aldehyde dehydrogenase inhibitor (Helander and Lindahl-Kiessling, 1991). Acetaldehyde exposure resulted in a dose-related increase in micronucleus formation in human lymphocytes (Migliore and Nieri, 1991). Human lymphocytes exposed to acetaldehyde have shown an increased frequency of mutations at the HPRT locus (He and Lambert, 1990; Lambert et al., 1994). Acetaldehyde is capable of

producing DNA-protein cross-links in human lymphoma cells (Costa et al., 1997). Vaca et al. (1998) demonstrated a dose-related formation of DNA adducts in human buccal epithelial cells exposed to up to 100 mM acetaldehyde *in vitro*.

Acetaldehyde induces dominant lethal effects in *Drosophila* following injection, but not following oral exposure (Woodruff et al., 1985). Chromosomal translocations in *Drosophila* have not been observed following injection of acetaldehyde (Woodruff et al., 1985), nor have acetaldehyde-related effects on X chromosome segregation been observed following oral exposure of *Drosophila* females (Rey et al., 1994). Acetaldehyde has tested positive in the *Drosophila* wing spot test (Graf et al., 1989). A concentration-dependent increase in DNA-protein crosslinks was found in the nasal mucosa of rats exposed by inhalation to 0, 100, 300, 1000, or 3000 ppm of acetaldehyde for 6 hours, which was increased in animals exposed to 1000 ppm for 5 consecutive days (Lam et al., 1986). Chinese hamsters exposed to 0.5 mg/kg by intraperitoneal injection, but not those exposed to 0.01 or 0.1 mg/kg, showed an increased frequency of sister-chromatid exchanges in bone marrow cells (Korte and Obe, 1981). CD-1 mice exposed by intraperitoneal injection to up to 380 mg/kg of acetaldehyde showed an increase in micronucleated polychromatic erythrocytes in a dose-related manner (Morita et al., 1997). Hybrid male mice exposed by intraperitoneal injection to up to 250 mg/kg of acetaldehyde daily for 5 days showed no alterations in sperm morphology or production (Lähdetie, 1988).

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

No data on the long-term carcinogenic effects of oral exposure to acetaldehyde in humans or animals were located. Because the tumors seen following inhalation exposure to acetaldehyde are located in the respiratory tract, a route-to-route extrapolation from the available inhalation data was not attempted.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1. SUMMARY OF RISK ESTIMATES

Inhalation Unit Risk – 1.3E-5 per ($\mu g/m^3$)

Extrapolation Method – Linear extrapolation from point of departure (LEC_{10}, extra risk)

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	8E+0 $\mu g/m^3$
E-5 (1 in 100,000)	8E-1 $\mu g/m^3$
E-6 (1 in 1,000,000)	8E-2 $\mu g/m^3$

II.C.2. DOSE-RESPONSE DATA FOR CARCINOGENICITY, INHALATION EXPOSURE

Tumor Type – combined upper respiratory tract tumors
Test Animals – rat/SPF Wistar, male

Route – inhalation
Reference – Woutersen et al. (1985, 1986)

--------Dose --------
Lifetime Average Exposure

Administered (ppm)	Human Equivalent (mg/m^3)	Tumor Incidence
0	0	1/55
727	36	17/52
1439	71	40/54
1592	78	31/41

II.C.3. ADDITIONAL COMMENTS (CARCINOGENICITY, INHALATION EXPOSURE)

Because the exposure concentration of the highest exposure level was varied throughout the study, a variant of the Armitige-Doll multistage model with a time-dependent dose pattern was also used (Crump and Howe, 1984). This model utilizes the exact time-dependent dose pattern rather than a single measure, such as a time-weighted average. Because data correlating individual animal tumor incidence with time-to-tumor data, such as is required by this model, were not available, the reported mortality data, tumor incidences at monitored timepoints, and variations in exposure levels (converted to HEC in mg/m^3) were used to generate a data set suitable for use in the model. The model returned an LEC_{10} value of 5.08 mg/m^3, from which an inhalation unit risk of 2.0E-5 per ($\mu g/m^3$) can be calculated. Because of the similarity of this value to the one derived by a standard polynomial fit of the data, and owing to the uncertainty involved in the generation of a suitable data set, the unit risk derived utilizing the time-weighted average concentration and a standard polynomial curve fit is recommended.

II.C.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, INHALATION EXPOSURE)

An adequate number of animals was observed in a lifetime study. Increases in nasal tumors were observed in both male and female rats, and similar unit risks were obtained using these data. Similar tumors have also been observed in hamsters following inhalation of acetaldehyde.

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

II.D.1. EPA DOCUMENTATION

Source Document -- _____

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 _____.

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 (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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

VI. BIBLIOGRAPHY

Acetaldehyde
CASRN -- 75-07-0
Last Revised -- 00/00/00

VI.A. ORAL RfD REFERENCES

Bankowski, E; Pawlicka, E; Sobolewski, K. (1993) Liver collagen of rats submitted to chronic intoxication with acetaldehyde. Mol. Cell Biochem. 121(1):37-43.

Booze TF; Oehme FW. (1986) An investigation of metaldehyde and acetaldehyde toxicities in dogs. Fundam. Appl. Toxicol. 6(3):440-6.

HoLownia, A., M. Chwiecko, D. PawLowska and R. Farbiszewski. (1992) The diminution of liver glutathione content and changes in activities of antioxidant enzymes in long-term acetaldehyde poisoning. Rocz. Akad. Med. Bialystok. 37: 18-23.

Homann, N; Kärkkäinen, P; Koivisto, T; Nosova, T; Jokelainen, K; Salaspuro, M. (1997) Effects of acetaldehyde on cell regeneration and differentiation of the upper gastrointestinal tract mucosa. J. Natl. Cancer Inst. 89:1692-1697.

Pawlicka, E; Bankowski, E; Sobolewski, K. (1991) Chronic intoxication with acetaldehyde stimulates collagen biosynthesis in rat liver. Arch. Toxicol. 65(8):678-680.

Til, HP; Woutersen, RA; Feron, VJ; Clary, JJ. (1988) Evaluation of the oral toxicity of acetaldehyde and formaldehyde in a 4-week drinking-water study in rats. Fd. Chem. Toxicol. 26(5):447-452.

VI.B. INHALATION RfC REFERENCES

Appelman, LM; Woutersen, RA; Feron, VJ. (1982) Inhalation toxicity of acetaldehyde in rats. I. Acute and subacute studies. Toxicology. 23:293-307.

Appelman, LM; Woutersen, RA; Feron, VJ; Hooftman, RN; Notten, WRF. (1986) Effect of variable versus fixed exposure levels on the toxicity of acetaldehyde in rats. J. Appl. Toxicol. 6(5):331-336.

Feron, VJ; Kruysse, A; Woutersen, RA. (1982) Respiratory tract tumours in hamsters exposed to acetaldehyde vapour alone or simultaneously to benzo(a)pyrene or diethylnitrosamine. Eur. J. Cancer Clin. Oncol. 18:13-31.

Kruysse, A.; Feron, VJ; Til, HP. (1975) Repeated exposure to acetaldehyde vapor. Arch. Environ. Health. 30:449-452.

Woutersen, R; van Garderen-Hoetmer, A; LM Appelman. (1985) Lifespan (27 months) inhalation carcinogenicity study of acetaldehyde in rats. Report No. V85.145/190172. CIVO-Institutes TNO, The Netherlands.

Woutersen, RA; Appelman, LM; van Garderen-Hoetmer, A.; Ferron, VJ. (1986) Inhalation toxicity of acetaldehyde in rats. III. Carcinogenicity study. Toxicology 41(2):213-232.

Woutersen, RA; Ferron, VJ. (1987) Inhalation toxicity of acetaldehyde in rats. IV. Progression and regression of nasal lesions after discontinuation of exposure. Toxicology 47(3):295-306.

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Aeschbacher, HU; Wolleb, U; Löliger, J; Spadone, JC; Liardon, R. (1989) Contribution of coffee aroma constituents to the mutagenicity of coffee. Fd. Chem. Toxic. 27(4):227-232.

Bittersohl, G. (1974) Epidemiologic investigations on cancer incidence in workers contacted by acetaldol and other aliphatic aldehydes. Arch. Geschwulstforsch 43:172-176.

Costa, M; Zhitkovich, A; Harris, M; Paustenbach, D; Gargas, M. (1997) DNA-protein cross-links produced by various chemicals in cultured human lymphoma cells. J. Toxicol. Environ. Health. 50:433-449.

Crump, KS; Howe, RB. (1984) The multistage model with a time-dependent dose pattern: applications to carcinogenic risk assessment. Risk Analysis. 4(3):163-176.

Dellarco, VL. (1988) A mutagenicity assessment of acetaldehyde. Mutat. Res. 195(1):1-20.

Dillon, D; Combes, R; Zeiger, E. (1998) The effectiveness of Salmonella strains TA100, TA102 and TA104 for detecting mutagenicity of some aldehydes and peroxides. Mutagenesis. 13(1):19-26.

Feron, VJ. (1979) Effects of exposure to acetaldehyde in Syrian hamsters simultaneously treated with benzo(a)pyrene or diethylnitrosamine. Prog. Exp. Tumor Res. 24:162-176.

Feron, VJ; Kruysse, A; Woutersen, RA. (1982) Respiratory tract tumours in hamsters exposed to acetaldehyde vapour alone or simultaneously to benzo(a)pyrene or diethylnitrosamine. Eur. J. Cancer Clin. Oncol. 18:13-31.

Graf, U; Frei, H; Kägi, A; Katz, AJ; Würgler, FE. (1989) Thirty compounds tested in the Drosophila wing spot test. Mutat. Res. 222:359-373.

He, S-M; Lambert, B. (1990) Acetaldehyde-induced mutation at the *hprt* locus in human lymphocytes in vitro. Environ. Mol. Mutagen. 16(2):57-63.

Helander, A; Lindahl-Kiessling, K. (1991) Increased frequency of acetaldehyde-induced sister-chromatid exchanges in human lymphocytes treated with an aldehyde dehydrogenase inhibitor. Mutat. Res. 264(3):103-107.

Hellmér, L; Bolcsfoldi, G. (1992) An evaluation of the *E. coli* K-12 *uvrB/recA* DNA repair host-mediated assay. I. In vitro sensitivity of the bacteria to 61 compounds. Mutat. Res. 272:145-160.

Kato, F; Araki, A; Nozaki, K; Matsushima, T. (1989) Mutagenicity of aldehydes and diketones. Mutat. Res. 216:366-367.

Korte, A; Obe, G. (1981) Influence of chronic ethanol uptake and acute acetaldehyde treatment on the chromosomes of bone-marrow cells and peripheral lymphocytes of Chinese hamsters. Mutat. Res. 88:389-395.

Lähdetie, J. (1988) Effects of vinyl acetate and acetaldehyde on sperm morphology and meiotic micronuclei in mice. Mutat. Res. 202:171-178.

Lam, C-W; Casanova, M; Heck, HD. (1986) Decreased extractability of DNA from proteins in the rat nasal mucosa after acetaldehyde exposure. Fundam. Appl. Toxicol. 6(3):541-550.

Lambert, B; Andersson, B; Bastlova, T; Hou, S-M; Hellgren, D; Kolman, A. Mutations induced in the hypoxanthine phosphoribosyl transferase gene by three urban air pollutants: acetaldehyde, benzo(a)pyrene diolepoxide, and ethylene oxide. Environ. Health Persp. 102(suppl 4):135-138.

Leifer, Z; Kada, T; Mandel, M; Zeiger, E; Stafford, R; Rosenkranz, HS. (1981) An evaluation of tests using DNA repair-deficient bacteria for predicting genotoxicity and carcinogenicity. Mutat. Res. 87:211-297.

Lin, Y-C; Ho, I-C; Lee, T-C. (1989) Ethanol and acetaldehyde potentiate the clastogenicity of ultraviolet light, methyl methanesulfonate, mitomycin C and bleomycin in Chinese hamster ovary cells. Mutat. Res. 216:93-99.

Litton Bionetics, Inc. (1979) Mutagenicity Evaluation of C-54 (Acetaldehyde) in the Ames Salmonella/Microsome Plate Test (Final Report) with Cover Letter. U.S. EPA/OPTS Public Files, Fiche #OTS0534477.

Migliore, L; Nieri, M. (1991) Evaluation of twelve potential aneuploidogenic chemicals by the *in vitro* human lymphocyte micronucleus assay. Toxic. *In Vitro*. 5(4):325-336.

Morita, T; Asano, N; Awogi, T; Sasaki, YF; Sato, S; Shimada, H; Sutou, S; Suzuki, T; Wakata, A; Sofuni, T; Hayashi, M. (1997) Evaluation of the rodent micronucleus assay in the screening of IARC carcinogens (groups 1, 2A and 2B). The summary report of the 6th collaborative study by SCGMT/JEMS MMS. Collaborative Study of the Micronucleus Group Test. Mammalian Mutagenicity Study Group. Mutat. Res. 389(1):3-122.

Olin, KL; Cherr, GN; Rifkin, E; Keen, CL. (1996) The effects of some redox-active metals and reactive aldehydes on DNA-protein cross-links *in vitro*. Toxicology. 110(1-3):1-8.

Ott, MG; Teta, MJ; Greenberg, HL. (1989a) Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment with attached tables and cover letter. U.S. EPA/OPTS Public Files, Fiche #OTS0513414-2.

Ott, MG; Teta, MJ; Greenberg, HL. (1989b) Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. Am. J. Ind. Med. 16(6):631-643.

Ott, MG; Teta, MF; Greenberg, HL. (1989c) Assessment of exposure to chemicals in a complex work environment. Am J. Ind. Med. 16:617-630.

Reifferscheid, G; Heil, J. (1996) Validation of the SOS/*umu* test using test results of 486 chemicals and comparison with the Ames test and carcinogenicity data. Mutat. Res. 369:129-145.

Rey, M; Palermo, AM; Muñoz, ER. (1994) Lack of effect of acute acetaldehyde treatment on X chromosome segregation in *Drosophila melanogaster* females. Mutat. Res. 320:1-7.

Rinsky, RA; Ott, MG; Ward, E; Greenberg, HL; Halperin, W; Leet, T. (1988) Study of mortality among chemical workers in the Kanawha Valley of West Virginia. Am. J. Ind. Med. 13:429-438.

Ristow, H; Seyfarth, A; Lochmann, E-R. (1995) Chromosomal damages by ethanol and acetaldehyde in *Saccharomyces cerevisiae* as studied by pulsed field gel electrophoresis. Mutat. Res. 326:165-170.

Singh, NP; Khan, A. (1995) Acetaldehyde: genotoxicity and cytotoxicity in human lymphocytes. Mutat. Res. 337:9-17.

Stevens, G; Rank, K; Sauer, J; Stapleton, S; Ginsberg, LC. (1991) Evaluation of unscheduled DNA synthesis induced in acetaldehyde treated primary rat hepatocytes. Environ. Mol. Mutagen. 17(Suppl 19):71.

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

U.S. EPA. (1996) Proposed guidelines for carcinogen risk assessment. Washington, DC: National Center for Environmental Assessment. EPA/600/P-92/003C.

U.S. EPA. (1999) Guidelines for Carcinogen Risk Assessment. Preliminary Draft. NCEA-F-0644.

Vaca, CE; Nilsson, JA; Fang, J-L; Grafström, RC. (1998) Formation of DNA adducts in human buccal epithelial cells exposed to acetaldehyde and methylglyoxal *in vitro*. Chem. Biol. Interact. 108:197-208.

Wangenheim, J; Bolcsfoldi, G. (1988) Mouse lymphoma L5178Y thymidine kinase locus assay of 50 compounds. Mutagenesis. 3(3):193-205.

Woodruff, RC; Mason, JM; Valencia, R; Zimmering, S. (1985) Chemical mutagenesis testing in *Drosophila*. V. Results of 53 coded compounds tested for the National Toxicology Program. Environ. Mutagen. 7(5):677-702.

Woutersen, RA; LM Appelman. (1984) Lifespan inhalation carcinogenicity study of acetaldehyde in rats. III. Recovery after 52 weeks of exposure. Report No. V84.288/190172. CIVO-Institutes TNO, The Netherlands.

Woutersen, R; van Garderen-Hoetmer, A; LM Appelman. (1985) Lifespan (27 months) inhalation carcinogenicity study of acetaldehyde in rats. Report No. V85.145/190172. CIVO-Institutes TNO, The Netherlands.

Woutersen, RA; Appelman, LM; van Garderen-Hoetmer, A.; Ferron, VJ. (1986) Inhalation toxicity of acetaldehyde in rats. III. Carcinogenicity study. Toxicology 41(2):213-231.

Woutersen, RA; Ferron, VJ. (1987) Inhalation toxicity of acetaldehyde in rats. IV. Progression and regression of nasal lesions after discontinuation of exposure. Toxicology 47(3):295-305.

VII. REVISION HISTORY

Acetaldehyde
CASRN -- 75-07-0

Date	Section	Description
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__/__/__		
__/__/__		

VIII. SYNONYMS

Acetaldehyde
CASRN -- 75-07-0
Last Revised -- __/__/__

75-07-0
Acetaldehyde
Acetic aldehyde
Acetic ethanol
Acetylaldehyde
AI3-31167
CCRIS 1396
CTFA 00005
EINECS 200-836-8
Ethanal
Ethyl aldehyde
FEMA No. 2003
HSDB 230
NCI-C56326
NSC 7594
RCRA waste no. U001
UN1089