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TOXICOLOGICAL REVIEW

OF

PROPIONALDEHYDE

(CAS No. 123-38-6)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

September 2008

U.S. Environmental Protection Agency
Washington, DC

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ADJ	dosimetrically adjusted
AIC	Akaike Information Criterion
ALDH	aldehyde dehydrogenase
ATPase	adenosine triphosphatase
BMC	benchmark concentration
BMCL	95% lower confidence limit of the benchmark concentration
BMD	benchmark dose
BMDS	benchmark dose software
BMR	benchmark response
CASRN	Chemical Abstracts Service Registry Number
CHED	Chinese hamster embryonic diploid (cells)
CHO	Chinese hamster ovary (cells)
DPX	DNA protein cross-link
EC_{50}	median effective concentration
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
GD	gestation day
HEC	human equivalent concentration
HGPRT/HPRT	hypoxanthine-guanine phosporibosyltransferase
IC_{50}	median inhibitory concentration
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
i.v.	intravenous
KCl	potassium chloride
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
M, mM, μM	Molar (M), milli molar (10^{-3} M), micro molar (10^{-6} M)
MR	molecular reactivity
NLM	National Library of Medicine, Hazardous Substances Database
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
ppb, ppm	parts per billion, parts per million
PND	postnatal day
POD	point of departure
RD_{50}	concentration required to elicit a 50% decrease in respiratory rate.
RfC	reference concentration
RfD	reference dose
RGDR	regional gas dose ratio
S9	post mitochondrial microsomal liver fraction
SA	surface area
SCE	sister chromosome exchanges
SDS	sodium-dodecyl sulfate
UDS	unscheduled DNA synthesis
UF	uncertainty factor
V_E	ventilation rate
WHO/JECFA	World Health Organization/Joint Expert Committee on Food Additives

FOREWORD

The purpose of this Toxicological Review is to provide scientific support and rationale for the hazard and dose-response assessment in IRIS pertaining to chronic exposure to propionaldehyde. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of propionaldehyde.

The intent of Section 6, *Major Conclusions in the Characterization of Hazard and Dose Response*, is to present the major conclusions reached in the derivation of the reference dose, reference concentration and cancer assessment, where applicable, and to characterize the overall confidence in the quantitative and qualitative aspects of hazard and dose response by addressing the quality of data and related uncertainties. The discussion is intended to convey the limitations of the assessment and to aid and guide the risk assessor in the ensuing steps of the risk assessment process.

For other general information about this assessment or other questions relating to IRIS, the reader is referred to EPA's IRIS Hotline at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

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This document has been peer reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the Toxicological Review of Propionaldehyde.

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1. INTRODUCTION

This document presents background information and justification for the Integrated Risk Information System (IRIS) Summary of the hazard and dose-response assessment of propionaldehyde. IRIS Summaries may include oral reference dose (RfD) and inhalation reference concentration (RfC) values for chronic and other exposure durations, and a carcinogenicity assessment.

The RfD and RfC, if derived, provide quantitative information for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. The RfD (expressed in units of mg/kg-day) is defined as 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. The inhalation RfC (expressed in units of mg/m^3) is analogous to the oral RfD, but provides a continuous inhalation exposure estimate. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory or systemic effects). Reference values are generally derived for chronic exposures (up to a lifetime), but may also be derived for acute (≤24 hours), short-term (>24 hours up to 30 days), and subchronic (>30 days up to 10% of lifetime) exposure durations, all of which are derived based on an assumption of continuous exposure throughout the duration specified. Unless specified otherwise, the RfD and RfC are derived for chronic exposure duration.

The carcinogenicity assessment provides information on the carcinogenic hazard potential of the substance in question and quantitative estimates of risk from oral and inhalation exposure may be derived. The information includes a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen and the conditions under which the carcinogenic effects may be expressed. Quantitative risk estimates may be derived from the application of a low-dose extrapolation procedure. If derived, the oral slope factor is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, an inhalation unit risk is a plausible upper bound on the estimate of risk per $\mu g/m^3$ air breathed.

Development of these hazard identification and dose-response assessments for propionaldehyde has followed the general guidelines for risk assessment as set forth by the National Research Council (NRC) (1983). EPA Guidelines and Risk Assessment Forum Technical Panel Reports that may have been used in the development of this assessment include the following: *Guidelines for Mutagenicity Risk Assessment* (EPA, 1986b), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (EPA, 1988), *Guidelines for Developmental Toxicity Risk Assessment* (EPA, 1991), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (EPA, 1994), *Use of the Benchmark Dose Approach in Health Risk Assessment* (EPA, 1995), *Guidelines for Reproductive*

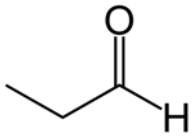
Toxicity Risk Assessment (EPA, 1996), *Guidelines for Neurotoxicity Risk Assessment* (EPA, 1998), *Science Policy Council Handbook*: *Risk Characterization* (EPA, 2000b), *Benchmark Dose Technical Guidance Document* (EPA, 2000c), *A Review of the Reference Dose and Reference Concentration Processes* (EPA, 2002), *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (EPA, 2005b), *Science Policy Council Handbook: Peer Review* (EPA, 2006b), and *A Framework for Assessing Health Risks of Environmental Exposures to Children* (EPA, 2006a).

The literature search strategy employed for this compound was based on the Chemical Abstracts Service Registry Number (CASRN) and at least one common name. Any pertinent scientific information submitted by the public to the IRIS Submission Desk was also considered in the development of this document. The relevant literature was reviewed through June 2008.

2. CHEMICAL AND PHYSICAL INFORMATION

Propionaldehyde is an aldehyde also known as propanal, propionic aldehyde, methylacetaldehyde, propyl aldehyde, propaldehyde, and propylic aldehyde. Some relevant chemical and physical properties are listed in Table 2-1.

Table 2-1. Chemical and physical properties of propionaldehyde

Propionaldehyde	
CAS registry number	123-38-6
Empirical formula	C_3H_6O
Molecular weight	58.08
Vapor pressure	317 mm Hg (at 25°C) (~400,000 ppm)
Vapor density	1.8 (at 100°F = 37.8°C)
Boiling point	49°C
Melting point	–81°C
Density/specific gravity	0.8657 (at 25°C)
Solubilities	Water = 3.06×10^5 mg/L at 25°C; soluble in chloroform; miscible with alcohol and ether
Viscosity	0.3167 cP (at 26.7°C)
Octanol/water partition coefficient (as log P)	0.59
Auto ignition temperature	207°C
Conversion factors (in air)	1 ppm = 2.38 mg/m^3; 1 mg/m^3 = 0.42 ppm

Sources: National Library of Medicine (NLM) (2004); International Programme on Chemical Safety (IPCS) (1993).

Propionaldehyde is a colorless liquid with a suffocating, fruity odor. It is used in the manufacturing of propionic acid and polyvinyl and other plastics, in the synthesis of rubber chemicals, and as a disinfectant and preservative. It is prepared by treating propyl alcohol with a bichromate oxidizing mixture or by passing propyl alcohol vapor over copper at a high temperature (NLM, 2004).

Propionaldehyde can form explosive peroxides and may polymerize with the addition of acids, bases, amines, and oxidants, resulting in a fire or explosion hazard. It decomposes on burning, producing toxic gases and irritating fumes (International Programme on Chemical Safety [IPCS], 1993).

The chemical is released to the environment primarily through the combustion of wood, gasoline, diesel fuel, and polyethylene (NLM, 2004). Propionaldehyde is also a component of both mainstream and sidestream cigarette smoke (Counts et al., 2005). Municipal waste incinerators can also release propionaldehyde to ambient air. In air, propionaldehyde is expected to exist solely as a vapor; it may be degraded in the atmosphere by reaction with photochemically produced hydroxyl radicals with a half-life of 19.6 hours for this reaction in air.

Studies have indicated that propionaldehyde is readily biodegradable in wastewater, and its potential for bioconcentration in aquatic organisms appears to be low (NLM, 2004).

Propionaldehyde has been detected in ambient and indoor air in several studies. Baez et al. (2003) measured the concentrations of propionaldehyde in indoor and outdoor air in Mexico to be 0.0002–0.018 mg/m^3 and 0.0002–0.016 mg/m^3, respectively. A North Carolina roadside study of 23 hydrocarbons and 10 aldehydes reported that propionaldehyde accounted for approximately 4% of the total aldehydes measured (Zweidinger et al., 1988). Propionaldehyde was detected at concentrations ≤14 parts per billion (ppb) (0.014 parts per million [ppm] or 0.033 mg/m^3) in Los Angeles air when measured during severe photochemical pollution episodes (Grosjean, 1982) and at concentrations ranging from 0.007–0.025 ppm (0.017–0.06 mg/m^3) in the exhaust from a jet airplane, measured at 50 meters behind the engine at an idle power setting (Miyamoto, 1986).

Propionaldehyde has also been approved by both the U.S. Food and Drug Administration (FDA) and World Health Organization/Joint Expert Committee on Food Additives (WHO/JECFA) as a synthetic flavoring ingredient for direct addition to food; the alcohol (propanol) and acid (propionic acid) are similarly approved (FDA, 2003; WHO, 1999; IPCS, 1998). Propionaldehyde was determined to pose no safety concern since its expected oral intake (140 µg/day) is below the threshold for human intake (1800 µg/day, as defined by WHO) and it is oxidized to propionic acid, which is metabolized via the citric acid cycle (WHO, 1999; IPCS, 1998).

Limited information is available on the occurrence of propionaldehyde in water. In the National Organics Reconnaissance Survey conducted in the 1970s, propionaldehyde was found to be one of the 18 organic chemicals detected most frequently in the drinking water of the 10 cities surveyed (Bedding et al., 1982).

3. TOXICOKINETICS

There are a limited number of published studies on the toxicokinetics of propionaldehyde. The absorption of propionaldehyde in the respiratory tract of dogs has been measured after inhalation exposure. The metabolism of propionaldehyde via aldehyde dehydrogenase (ALDH) (NADP- and NAD-dependent) has been investigated in rodent hepatoma cell lines. The distribution and localization of ALDH in rat respiratory tract tissues, and presence in human tissues, have also been examined. The urinary elimination of propionaldehyde formed via lipid peroxidation has been examined in rats.

3.1. ABSORPTION

3.1.1. ORAL

There are no studies available examining the absorption or the bioavailability of propionaldehyde via the oral route of exposure.

3.1.2. INHALATION

Egle (1972a) reported the regional retention levels (percent of amount inhaled) in the respiratory tract of mongrel dogs of both sexes after exposure to concentrations ranging from 0.4–0.6 µg/mL (403–604 mg/m^3 or 168–252 ppm) propionaldehyde via nasal inhalation through a fitted mask. Retention levels of propionaldehyde were measured for the total respiratory tract as well as for the surgically isolated upper and lower respiratory tracts. Ventilatory rates were varied, ranging from 6 to 20/minute. Neither detailed information on the inspiratory flow rates nor the time period of exposure were reported. Average retention levels were reported from 6–20 experiments, with at least four dogs per experiment exposed to propionaldehyde. The retention of propionaldehyde by the total respiratory tract was between 70 and 80%, and there was a significant inverse relationship between retention and ventilation rate ($p < 0.01$). Retention of propionaldehyde in the isolated upper respiratory tract under cyclic breathing conditions also averaged 70–80% with a significant effect of ventilation rate ($p < 0.01$). However, under unidirectional breathing conditions, retention in the isolated upper respiratory tract averaged approximately 63% over the range of ventilation rates. In the lower respiratory tract, propionaldehyde retention averaged between 65 and 75% with a significant inverse relationship between retention and ventilation rate ($p < 0.01$). No effect of exposure concentration on total respiratory tract retention was noted in animals exposed over a concentration range of 0.4–1.2 µg/mL (403–1,200 mg/m^3 or 168–500 ppm) propionaldehyde. Variation in tidal volume over a range of 100–200 ml was also without affect on propionaldehyde retention.

3.2. DISTRIBUTION

Based on its physical-chemical properties, propionaldehyde likely crosses biological membranes and thus could distribute throughout various bodily fluids. However, no specific studies are available that describe the distribution of propionaldehyde.

3.3. METABOLISM

Propionaldehyde is oxidized to its corresponding carboxylic acid (i.e., propionic acid) via ALDH (NADP- and NAD-dependent) (Bassi et al., 1997). The metabolisms of propionaldehyde and three other aldehydes (acetaldehyde, benzaldehyde, and valeraldehyde) were examined in two metabolically competent rodent hepatoma cell lines. Propionaldehyde, as well as the other aldehydes tested, was efficiently metabolized in the rat hepatoma cell line. In the mouse hepatoma cell line, low enzyme activities were observed. The authors concluded that the differences in the metabolic activities between these two cell lines could be attributed to greater oxidative activity in the rat cell line and greater reductive than oxidative activity in the mouse cell line.

Respiratory tract tissues of both rats and humans contain ALDH (Zhang et al., 2005; Stanek and Morris, 1999; Bogdanffy et al., 1998,1986; Morris, 1997; Casanova-Schmitz et al., 1984). Acetaldehyde metabolism rates have been measured directly in rat nasal tissue homogenates (Stanek and Morris, 1999; Morris, 1997; Casanova-Schmitz et al., 1984). These studies identified a low-affinity, high-capacity isozyme, as well as a high-affinity, low-capacity isozyme. In the rat, the distribution and localization of ALDH in the respiratory tract has been examined (Bogdanffy et al., 1986). ALDH activity examined qualitatively was detected principally in the nasal respiratory epithelium, while low activity was observed in the olfactory epithelium. Epithelial cells of the trachea also demonstrated little enzyme activity; however, the Clara cells of the bronchioles showed high enzyme activity. The authors noted that the pattern of lower enzyme activity and localization correlated with the pattern of lesion distribution observed after exposure to acetaldehyde, which is most notable in the olfactory epithelium. Bogdanffy et al. (1998) also compared the enzyme activities of ALDH and carboxyl esterase in rat and human nasal tissues for vinyl acetate. Enzyme activities were measured indirectly via the disappearance of vinyl acetate or acetaldehyde form the headspace of incubation vials containing nasal tissue. Rat respiratory epithelium ALDH activity was approximately twofold higher than that of humans but was equivalent in the olfactory epithelium. K_m values did not differ between species. In addition, the presence of ALDH in fetal and adult human nasal tissues has been confirmed by using gene expression analysis (Zhang et al., 2005).

Additionally, the Krebs (citric acid or tricarboxylic acid) cycle is thought to play a role in the metabolism of aldehydes after oxidation to their corresponding carboxylic acids. After oral intake, the Krebs cycle is expected to efficiently metabolize a number of aldehydes used as food

additive flavoring agents (WHO, 1999). For propionaldehyde, its metabolite, propionic acid, is also the end product of the metabolism of odd chain fatty acids via the β-oxidation pathway. Propionic acid reacts with coenzyme A to form propionyl-CoA, which enters the Krebs cycle after conversion to succinyl-CoA via methylmalonyl-CoA (Stipanuk, 2000; Voet and Voet, 1990). Succinyl-CoA is an intermediate in the Krebs cycle. In comparison, acetic acid, the metabolite of acetaldehyde, condenses with coenzyme A. This complex undergoes β-oxidation to form acetyl-CoA. Acetyl-CoA can enter the Krebs cycle directly or be used anabolically in fatty acid and cholesterol synthesis (Voet and Voet, 1990). The fate of formic acid, formed by the oxidation of formaldehyde via formaldehyde dehydrogenase, includes binding to tetrahydrofolic acid, which is used in transmethylation reactions and as a source of single carbon additions (Stipanuk, 2000; Voet and Voet, 1990).

Wang et al. (2002) performed a genotype analysis of the ALDH2 gene in the livers of human volunteers in order to investigate the metabolism of a variety of aldehydes. Of a total of 39 subjects, 8 were heterozygotes of the wild-type (ALDH2*1) and mutant (ALDH2*2) alleles, and the others were homozygotes of the wild-type allele. The ability of mitochondria to metabolize propionaldehyde was significantly ($p < 0.05$) lower (80% for propionaldehyde) in the heterozygotes (ALDH2*1/*2) compared to the homozygotes (ALDH2*1/*1), showing differences in metabolism between the two genotypes.

Oyama et al. (2007) evaluated the inhalation toxicity of acetaldehyde in ALDH2 knockout (KO) mice. Male C57BL/6 wild-type and KO mice were exposed to 0, 125, or 500 ppm acetaldehyde 24 hours/day for 14 days via whole body-inhalation. Although the average blood acetaldehyde concentration was greater in the KO mice compared to the wild-type, no differences in liver and lung effects between the two groups were noted. However, the incidence of erosion of the respiratory epithelium and subepithelial hemorrhage in the nasal cavity, and degeneration of the respiratory epithelium in the larynx, pharynx, and trachea were greater in the KO mice compared to the wild-type. These results indicate that the ALDH2 KO mice are more sensitive to acetaldehyde-induced effects.

3.4. ELIMINATION

No information specific to the elimination of administered propionaldehyde is available. De Tata et al. (2001) reported age-related effects in the urinary excretion of aldehydes formed via lipid peroxidation in male Sprague-Dawley rats fed either a normal ad libitum diet or kept on a restricted diet (every other day feeding, or 40% caloric restriction). The results showed that the urinary excretion of propionaldehyde increased with age between 6 and 27 months and was higher in animals on a restricted diet compared with animals fed ad libitum.

3.5. PHYSIOLOGICALLY BASED TOXICOKINETIC MODELS

No physiologically based toxicokinetic models were identified for propionaldehyde.

4. HAZARD IDENTIFICATION

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS

No studies in humans were identified for propionaldehyde.

4.2. SUBCHRONIC AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1. ORAL STUDIES

No subchronic or chronic oral studies were identified for propionaldehyde. However, the structurally-related aldehydes, formaldehyde and acetaldehyde, appear to be less hazardous by the oral route compared to the inhalation route (Morris et al., 1996).

4.2.2. INHALATION STUDIES

No subchronic or chronic inhalation studies were identified for propionaldehyde. In a short-term study, Gage (1970) exposed four male and four female Alderley-Park rats to 1300 ppm (3,094 mg/m^3) propionaldehyde for 6 hours/day for 6 days via whole-body inhalation. Urine was collected after the last exposure for analysis of pH, bilirubin, and protein. Blood was collected during sacrifice for analysis of hemoglobin concentration, blood differential counts, platelets, clotting function, and the concentration of urea, sodium, and potassium. The lungs, liver, kidneys, spleen, and adrenals; and occasionally, the heart, intestines, and thymus were collected for microscopic examination. No changes in body weight were noted. At autopsy, histological examination of all principal organs and tissues revealed liver cell vacuolation. No other findings were noted. Four male and four female rats were also exposed to 90 ppm (214 mg/m^3) for 6 hours/day for 20 days. All organs were reported to be normal at autopsy, and no clinical signs of toxicity were noted. Thus, a no-observed-effect level (NOEL) of 90 ppm can be derived from this study.

In a short duration inhalation study, Steinhagen and Barrow (1984) determined the concentration of propionaldehyde required to elicit a 50% decrease in respiratory rate (RD_{50}) as a measure of sensory irritation potential of propionaldehyde in B6C3F_1 and Swiss-Webster mice. Groups of three to four mice per strain were exposed via inhalation in a head-only exposure chamber for 10 minutes to varying concentrations of propionaldehyde. Respiratory rates were measured by a method in which animals were sealed in airtight plethysmographs and attached to a head-only exposure chamber, and concentration-response curves were constructed to determine the RD_{50}. In animals, sensory irritants produce a reflex decrease in respiratory rate characterized as a pause at the onset of expiration. The RD_{50} for propionaldehyde was calculated to be 2,078 ppm or 4,946 mg/m^3 in B6C3F_1 mice and 2,052 ppm or 4,884 mg/m^3 in Swiss-Webster mice.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES—INHALATION

Two short-term rat developmental inhalation studies were conducted by Union Carbide (1993, 1991).[1] In a range-finding study, young adult female CD rats (seven per group) were exposed to 0, 500, 1,000, 1,500, or 2,500 ppm (0, 1,190, 2,380, 3,570, or 5,950 mg/m^3) propionaldehyde for 6 hours/day via whole-body inhalation on gestation days (GDs) 0–20, following successful mating with naive males (Union Carbide, 1991). Clinical observations were made daily following the exposure, and maternal body weights were measured on GDs 0, 7, 14, and 21. Food consumption was measured weekly throughout the study. At sacrifice on GD 21, the dams were evaluated for liver and uterine weights, number of corpora lutea, and number and status of implantation sites. Fetuses were dissected from the uterus, weighed, and examined externally for malformations and variations. The pregnancy rate was equivalent among the groups. None of the groups displayed any exposure-related clinical signs. Maternal toxicity was noted as exposure-related differences in body weight gain, which were 82 and 72% (–28.9 and –43.3 g, respectively, $p < 0.01$) of control over the entire gestation period at exposure concentrations of 1,500 and 2,500 ppm. At 1,000 ppm, body weight gain was depressed only during the first week of exposure. However, these decreases in body weight gain were accompanied by statistically significant decreases in food consumption compared those of controls ($p < 0.05$) throughout the gestation period at 1,000, 1,500, and 2,500 ppm. The average food consumption ranged from 82–89% of control at these exposure concentrations. None of these effects were noted at 500 ppm. In addition, there were no exposure-related differences in gestational parameters, including total number of implants and the number of viable and nonviable implants. In the high exposure group, there was a significant reduction in fetal body weights of approximately 12% (−0.6 g) compared with controls ($p < 0.01$), but no other evidence of any treatment-related external malformations or variations was observed. The results of this study indicate a no-observed-adverse-effect level (NOAEL) for developmental toxicity of 1,500 ppm. Indications of maternal effects (i.e. changes in body weight gain) related to propionaldehyde exposure were most notable at 2,500 ppm.

In the second study, young adult male and female CD rats (15/sex/group) were exposed to 0, 150, 750, or 1,500 ppm (0, 357, 1,785, or 3,570 mg/m^3) propionaldehyde for 6 hours/day, 7 days/week via whole-body inhalation, during a 2-week premating period and a 14-day (maximum) mating phase (Union Carbide, 1993). The mated females were exposed daily through GD 20 only for a minimum of 35 days and a maximum of 48 days depending upon when they mated (average exposure period ~ 38 days). The females were then allowed to deliver their litters naturally and raise their offspring until postnatal day (PND) 4 both free of exposure to

[1] The Union Carbide studies (1991 and 1993) are unavailable in the peer-reviewed literature. These unpublished studies were submitted to EPA under the Toxic Substances Control Act. An external peer review was conducted to evaluate the accuracy of experimental procedures, results, and interpretation and discussion of the findings presented. See References for more information.

propionaldehyde. The males continued to be exposed for a total of 52 exposures until sacrifice in week 7. Clinical observations were made daily, following exposure, and body weight and food consumption were measured at regular intervals throughout the study. Offspring body weight, viability, and disposition were monitored from birth until PND 4. Following the last exposure, males were fasted and blood samples were obtained for clinical pathology analyses prior to necropsy. On PND 4, necropsies were performed on adult females, and a number of organs and tissues, including at least two sections of the nasal cavity (sectioning details not provided), were examined histologically. The offspring were examined externally and sacrificed without pathologic evaluation.

No exposure-related clinical signs were noted in the adult females. During the first week of exposure to 750 and 1,500 ppm, body weight gains were decreased to approximately 60 and 71% ($p < 0.01$), respectively, of controls, and food consumption was decreased by approximately 7% ($p < 0.05$) of controls at both concentrations. No differences were observed during the second week of exposure. During gestation, body weight (over GDs 0–14) and food consumption (over GDs 0–21) were decreased in the high exposure group compared with controls, but no significant differences in body weight gain were observed. At sacrifice, no gross lesions attributable to propionaldehyde exposure were found. However, microscopic examination of the nasal cavity revealed propionaldehyde-induced vacuolization of the olfactory epithelium in the 150 and 750 ppm exposure groups and atrophy of the olfactory epithelium in the 750 and 1,500 ppm exposure groups. These effects were noted to be localized to the dorsal anterior two sections of the nasal cavity. The incidence of atrophy was 0/15, 0/15, 2/15, and 15/15 at 0, 150, 750, and 1,500 ppm, respectively (see Table 4-1). The severity of this nasal lesion increased with exposure concentration being minimal to mild at 750 ppm and moderate to marked at 1,500 ppm. No evidence of squamous metaplasia was found in olfactory or respiratory epithelium. Low incidences of minimal to mild rhinitis involving the respiratory epithelium were also noted at 150, 750, and 1,500 ppm. No significant effects of exposure on any of the reproductive parameters assessed were found. Litter size and viability were similar among the groups. Pup body weights on the day of birth and PND 4 were not affected by exposure, although at the high concentration only body weight gain for that period was significantly depressed ($p < 0.05$, –0.8 g) compared with controls. The biological significance of this finding is difficult to assess since changes in absolute body weight were not demonstrated and the time period of observation was relatively short.

The adult males did not display any overt signs of toxicity at any time during the study. Body weight, weight gain, clinical observation, and food consumption were similar among all exposure groups and controls. Hematology and clinical chemistry analyses revealed elevated erythrocyte counts, with a corresponding increase in hemoglobin and hematocrit values and an increase in monocytes in the males exposed to 1,500 ppm. These effects were considered to be consistent with and indicative of dehydration. At necropsy (examination performed as per the

adult females), no gross lesions were found that could be attributable to propionaldehyde exposure. However, similar to effects in the females, microscopic examination revealed exposure-related effects in the olfactory epithelium of the nasal cavity that consisted of vacuolization and atrophy in the low, intermediate, and high exposure groups. These effects were also noted to be localized to the dorsal anterior two sections of the nasal cavity. The incidence of atrophy was 0/15, 2/15, 10/15, and 15/15 at 0, 150, 750, and 1,500 ppm, respectively (see Table 4-1).

Table 4-1. Summary of nasal lesion incidence data in female and male rats exposed to various concentrations of propionaldehyde

Group	Nasal lesion	Exposure concentration (ppm)			
		0	150	750	1,500
Females[a]	Vacuolization - Olfactory	0/15	15/15[b]	15/15[b]	0/15
	minimal	0	8	0	0
	mild	0	7	7	0
	moderate	0	0	8	0
	Atrophy - Olfactory	0/15	0/15	2/15	15/15[b]
	minimal	0	0	1	0
	mild	0	0	1	0
	moderate	0	0	0	6
	marked	0	0	0	9
	Necrosis - Respiratory	0/15	0/15	0/15	1/15
	moderate	0	0	0	1
	Rhinitis - Respiratory	0/15	1/15	6/15[c]	1/15
	minimal	0	1	0	0
	mild	0	0	6	1
Males[a]	Vacuolization - Olfactory	0/15	12/15[b]	14/15[b]	2/15
	minimal	0	6	2	0
	mild	0	4	3	0
	moderate	0	2	2	0
	marked	0	0	7	2
	Atrophy - Olfactory	0/15	2/15	10/15[b]	15/15[b]
	minimal	0	2	1	0
	mild	0	0	6	1
	moderate	0	0	3	8
	marked	0	0	0	6
	Squamous metaplasia - Respiratory	0/15	0/15	1/15	2/15
	mild	0	0	1	0
	moderate	0	0	0	2
	Rhinitis - Respiratory	0/15	0/15	7/15[b]	14/15[b]
	minimal	0	0	1	3
	mild	0	0	5	7
	moderate	0	0	1	4

[a]Females were exposed daily only until GD 20 and sacrificed on PND 4; males were exposed daily until sacrifice. See Section 4.3 for details
[b]Significantly different from control at $p < 0.01$.
[c]Significantly different from control at $p < 0.05$.

Source: Union Carbide (1993).

The severity of this nasal lesion increased with exposure concentration being minimal at 150 ppm, minimal to moderate at 750 ppm, and mild to marked at 1,500 ppm. Squamous metaplasia of the respiratory epithelium was reported in one male from the 750 ppm group and two males from the 1,500 ppm group. An increased incidence of minimal to moderate rhinitis involving the respiratory epithelium was also noted at 750 and 1,500 ppm. The results of this study indicate a lowest-observed-adverse-effect level (LOAEL) for portal-of-entry toxicity of 150 ppm as a result of olfactory atrophy graded by Union Carbide (1993) as being of minimal severity by the study authors and supported by the presence of vacuolization.

4.4. OTHER STUDIES

4.4.1. GENOTOXICITY

A number of other structurally related aldehydes, including acetaldehyde, formaldehyde, butyraldehyde (butanal), and isobutyraldehyde (isobutanal) were evaluated concurrently for their genotoxic potential. The results of these other aldehydes tested for similar genotoxic endpoints are included in the evaluation of propionaldehyde for comparative purposes where available. However, the results and comparisons presented for these aldehydes do not provide an examination of the aldehyde database as a whole. No in vivo studies examining the genotoxicity of propionaldehyde are available.

4.4.1.1. Bacteria

The mutagenicity test results for nonmammalian systems are summarized in Table 4-2. Propionaldehyde was found to be mutagenic in *Salmonella typhimurium* strain TA1534 at incubation concentrations ≥20 mM, but nonmutagenic in strains TA1950 and TA1952 at concentrations up to 50 mM (Sampson and Bobik, 2008). Propionaldehyde was found to be nonmutagenic in strains TA98, TA100, TA1535, and TA1537 when tested at concentrations up to 10 mg/plate in the preincubation procedure with or without rat or hamster liver postmitochondial microsonal liver fraction S9 (Aeschbacher et al., 1989; Mortelmans et al., 1986) or when tested in strains TA100, TA102, and TA104 in the presence or absence of rat or mouse liver S9 (Dillon et al., 1998; Aeschbacher et al., 1989). It was also nonmutagenic in strains TA100, TA102, and TA104, when tested as a vapor in a desiccator at concentrations up to 3.3% in air with or without rat or mouse liver S9 (Dillon et al., 1998). In a plate test procedure, propionaldehyde was not mutagenic in strain TA1535 at concentrations up to 2.5 µmol/plate (equivalent to 145 µg/plate) with or without rat liver S9 (Pool and Wiessler, 1981).

Acetaldehyde was also found to be nonmutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested at concentrations ≤10 mg/plate in a preincubation procedure with or without rat or hamster liver S9 (Mortelmans et al., 1986) or when tested in strains TA98, TA100, and TA102 at concentrations up to 1.7 mmol/plate with or without rat liver

S9 (Aeschbacher et al., 1989). It was nonmutagenic in strains TA100 and TA104 when tested at concentrations ≤1 mL/desiccator chamber with or without rat or mouse S9, but an equivocal response was seen in strain TA102 at 1 mL/desiccator chamber in the presence of rat liver S9 (Dillon et al., 1998). In a plate test procedure, acetaldehyde was not mutagenic in strain TA1535 when tested at concentrations up to 2.5 µmol/plate with or without rat liver S9 (Pool and Wiessler, 1981).

Table 4-2. Mutagenicity of various aldehydes in *Salmonella typhimurium*

Aldehyde	Strains	Protocol	S9, species	Result[a]	LED (HTD)[b]	Reference
Propionaldehyde	TA 1534	Preincubation	None	+	20 mM	(Sampson and Bobik, 2008)
Propionaldehyde	TA 1950	Preincubation	None	–	50 mM	(Sampson and Bobik, 2008)
Propionaldehyde	TA 1952	Preincubation	None	–	50 mM	(Sampson and Bobik, 2008)
Propionaldehyde	TA98, 100, 1535, 1537	Preincubation	None, rat, hamster	–	10 mg/plate	(Mortelmans et al., 1986)
Propionaldehyde	TA98, 100, 102	"Modified" preincubation	None, rat	–	0.13 mmol/plate (7.5 mg/plate)	(Aeschbacher et al., 1989)
Propionaldehyde	TA100, 102, 104	Preincubation	None, rat, mouse	–	10 mg/plate	(Dillon et al., 1998)
Propionaldehyde	TA100, 102, 104	Vapor in desiccator	None, rat, mouse	–	3.3% in air	(Dillon et al., 1998)
Propionaldehyde	TA1535	Plate test	None, rat	–	2.5 µmol/plate (145 µg/plate)	(Pool and Wiessler, 1981)
Acetaldehyde	TA98, 100, 1535, 1537	Preincubation	None, rat, hamster	–	10 mg/plate	(Mortelmans et al., 1986)
Acetaldehyde	TA98, 100, 102	"Modified" preincubation	None, rat	–	1.7 mmol/plate (75 mg/plate)	(Aeschbacher et al., 1989)
Acetaldehyde	TA100, 102, 104	Preincubation	None, rat, mouse	–	N/A (toxic level)	(Dillon et al., 1998)
Acetaldehyde	TA100, 104	Vapor in desiccator	None, rat, mouse	–	1.0 mL/ desiccator	(Dillon et al., 1998)
Acetaldehyde	TA102	Vapor in desiccator	Rat	?	1.0 mL/ desiccator	(Dillon et al., 1998)
Acetaldehyde	TA1535	Plate test	None, rat	–	2.5 µmol/plate (110 µg/plate)	(Pool and Wiessler, 1981)
Formaldehyde	TA100	Preincubation	None, rat, hamster	+	10 µg/plate	(Haworth et al., 1983)
Formaldehyde	TA98, 1535, 1537	Preincubation	None, rat, hamster	–	333 µg/plate	(Haworth et al., 1983)
Formaldehyde	TA100, 102, 104	Preincubation	None, rat, mouse	+	15 µg/plate	(Dillon et al., 1998)
Formaldehyde	TA1535	Plate test	None, rat	–	2.5 µmol/plate (75 µg/plate)	(Pool and Wiessler, 1981)

Aldehyde	Strains	Protocol	S9, species	Result[a]	LED (HTD)[b]	Reference
Butyraldehyde	TA98, 100, 1535, 1537	Preincubation	None, rat, hamster	–	3,333 µg/plate	(Mortelmans et al., 1986)
Butyraldehyde	TA100, 102, 104	Preincubation	None, rat, mouse	–	1000 µg/plate	(Dillon et al., 1998)
Butyraldehyde	TA1535	Plate test	None, rat	–	2.5 µmol/plate (180 µg/plate)	(Pool and Wiessler, 1981)
Isobutyraldehyde	TA98, 100, 1535, 1537	Preincubation	None, rat, hamster	–	10,000 µg/plate	(Mortelmans et al., 1986)
Isobutyraldehyde	TA100, 102, 104	Preincubation	None, rat, mouse	– / ?	5,000 µg/plate	(Dillon et al., 1998)

[a]Test results are either positive (+), negative (−), or equivocal (?).
[b]LED is the lowest effective concentration for positive test results; HTD is the highest tested concentration for negative or inconclusive results. N/A = not applicable.

Formaldehyde was mutagenic in *S. typhimurium* strain TA100 when preincubated with rat and hamster S9 at concentrations between 10 and 100 µg/plate and weakly mutagenic without S9 (Haworth et al., 1983). It was also found to be mutagenic in strains TA100, TA102, and TA104 when tested over a concentration range of 6.25–50 µg/plate with and without rat and mouse liver S9 (Dunnett's test; no statistical values nor effective concentrations reported) (Dillon et al., 1998). Formaldehyde was not mutagenic in strains TA98, TA1535, or TA1537 when tested at concentrations up to 333 µg/plate under the same conditions (Haworth et al., 1983) (no statistical evaluation). Formaldehyde was not mutagenic in strain TA1535 when tested at concentrations up to 2.5 µmol/plate (75 µg/plate) by using a plate test procedure with and without rat liver S9 (Pool and Wiessler, 1981).

Butyraldehyde was nonmutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested at concentrations up to 3,333 µg/plate with rat and hamster liver S9 in a preincubation procedure (Mortelmans et al., 1986). Butyraldehyde was also nonmutagenic in strains TA100, TA102, and TA104 when tested at concentrations ≤1,000 µg/plate in the presence and absence of rat or mouse liver S9 (Dillon et al., 1998). It was not mutagenic in TA1535 when tested up to 2.5 µmol/plate (180 µg/plate) with and without rat liver S9 and using a plate test procedure (Pool and Wiessler, 1981).

Similarly, isobutyraldehyde was nonmutagenic in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested at concentrations up to 10,000 µg/plate with rat and hamster liver S9 in a preincubation procedure (Mortelmans et al., 1986). Isobutyraldehyde produced equivocal responses in strains TA100, TA102, and TA104, but was judged to be nonmutagenic overall when tested at concentrations between 50-5,000 µg/plate in the presence and absence of rat or mouse liver S9 (Dillon et al., 1998).

4.4.1.2. Mammalian Cells In Vitro

4.4.1.2.1. *Mutagenicity.*

Propionaldehyde produced a concentration-related increase in HGPRT and ouabain

mutants in V79 hamster cells following a 60-minute exposure over a concentration range of 3–90 mM. The increase in HGPRT mutants was significant ($p < 0.01$ versus controls) at 30 and 90 mM, and the increase in ouabain mutants was significant at 10, 30, and 90 mM (equivalent to 0.58, 1.7, and 5.2 mg/mL) (Brambilla et al., 1989). However, these increases were associated with significant decreases in cell viability at ≥ 30 mM in hypoxanthine-guanine phosphoribosyl transferase (HGPRT) and at 90 mM in ouabain mutants. In a subsequent study, propionaldehyde was not mutagenic at the HGPRT locus in V79 hamster cells exposed to 1 or 2 μM (equivalent to 0.058 or 0.12 μg/mL) for 2 hours; toxicity was seen at 2 μM (Smith et al., 1990).

Acetaldehyde was found to induce mutations in the HPRT locus in cultured human lymphocytes (He and Lambert, 1990). Cells treated with 1.2–2.4 mM acetaldehyde for 24 hours or 0.2–0.6 mM acetaldehyde for 48 hours showed a 3- to 16-fold increase in mutant frequency. This effect was accompanied by a dose-dependent decrease in cell survival.Formaldehyde did not induce mutations at the hypoxanthine-guanine phosphoribosyltransferase (HPRT) locus in V79 hamster cells treated for 4 hours with concentrations ranging from 125–500 μM (Merk and Speit, 1999). Formaldehyde concentrations ≥250 μM produced significant decreases in cell survival. In Chinese hamster ovary cells (CHO K1), formaldehyde was found to induce a 4.7-fold increase in HPRT mutations following a 1 hour exposure to 1 mM (Graves et al., 1996).

Butyraldehyde also induced concentration-related increases in the frequencies of HGPRT and ouabain mutants in V79 hamster cells, following 60-minute exposures (Brambilla et al., 1989). Significant increases in HGPRT and oubain mutants ($p < 0.05–0.01$ versus controls) were observed at 10 and 30 mM. Similarly, the additional aldehydes tested, including pentanal, hexanal, and nonanal, all induced concentration-related increases in the frequencies of HGPRT and ouabain mutants in V79 hamster cells, following 60-minute exposures (Brambilla et al., 1989). Significant increases in HGPRT mutants ($p < 0.05–0.01$ versus controls) were observed at 10 and 30 mM for pentanal, 30 mM for hexanal, and 0.1 and 0.3 mM for nonanal. Significant increases in ouabain mutants ($p < 0.05–0.01$ versus controls) were observed at 10 and 30 mM for pentanal, 3 and 10 mM for hexanal, and 0.3 mM for nonanal. The majority of these increases were also associated with decreases in cell viability.

Isobutyraldehyde was found to be strongly mutagenic in the mouse lymphoma assay in the absence of S9 (NTP, 1999). In this study, L5178Y mouse lymphoma cells were treated with isobutyraldehyde for 4 hours at concentrations ranging from 62.5 to1000 μg/mL. Concentrations ≥125 μg/mL produced significant increases in mutations; 1000 μg/mL was found to be cytotoxic.

The results of the mutagenicity tests conducted in mammalian systems are compiled in Table 4-3.

Table 4-3. Mutagenicity of various aldehydes in mammalian cells

Aldehyde	Cells	Endpoint	Results[a]	LED (HTD)[b]	Reference
Propionaldehyde	V79	HGPRT	+	30 mM (1.7 mg/mL) [30 mM]	(Brambilla et al., 1989)
Propionaldehyde	V79	HGPRT	−	2 µM (0.12 µg/mL) [2 µM]	(Smith et al., 1990)
Propionaldehyde	V79	Ouabain	+	10 mM (581 µg/mL) [90 mM]	(Brambilla et al., 1989)
Acetaldehyde	Human lymphoctyes	HPRT	+	1.2 mM (53 µg/mL) [2.4 mM]	(He and Lambert, 1990)
Acetaldehyde	Human lymphoctyes	HPRT	+	0.2 mM (9 µg/mL) [0.4 mM]	(He and Lambert, 1990)
Formaldehyde	V79	HPRT	−	500 µM (15 µg/mL) [250 µM]	(Merk and Speit, 1999)
Formaldehyde	CHO K1	HPRT	+	1 mM (30 µg/mL)	(Graves et al., 1996)
Butyraldehyde	V79	HGPRT	+	10 mM (720 µg/mL) [30 mM]	(Brambilla et al., 1989)
Butyraldehyde	V79	Ouabain	+	10 mM (720 µg/mL)	(Brambilla et al., 1989)
Isobutyraldehyde	L5178Y	—	+	125 µg/mL [1000 µg/mL]	(NTP, 1999)
Pentanal	V79	HGPRT	+	10 mM (860 µg/mL) [30 mM]	(Brambilla et al., 1989)
Pentanal	V79	Ouabain	+	10 mM (860 µg/mL) [30 mM]	(Brambilla et al., 1989)
Hexanal	V79	HGPRT	+	30 mM (3.0 mg/mL) [10 mM]	(Brambilla et al., 1989)
Hexanal	V79	Ouabain	+	3 mM (300 µg/mL) [10 mM]	(Brambilla et al., 1989)
Nonanal	V79	HGPRT	+	100 µM (14 µg/mL) [300 µM]	(Brambilla et al., 1989)
Nonanal	V79	Ouabain	+	300 µM (43 µg/mL)	(Brambilla et al., 1989)

[a]Test results are either positive (+), negative (−), or equivocal (?).

[b]LED is the lowest effective concentration for positive test results; HTD is the highest tested concentration for negative or inconclusive results; [ ] is the test concentration that resulted in notable decreases in cell viability or toxicity.

4.4.1.2.2. *Chromosomal aberrations*. The results for chromosome damage in mammalian cells in vitro are summarized in Table 4-4. Propionaldehyde induced a concentration-related increase in chromosome aberrations in cultured Chinese hamster embryonic diploid (CHED) cells treated with concentrations of 5×10^{-4} (0.0005), 1×10^{-3} (0.001), and 2×10^{-3} (0.002) % (equivalent to 4.3, 8.7, and 17 µg/mL) for 1.5 hours (Furnus et al., 1990). Aneuploidy was induced at all three concentrations but not in a concentration-related manner. No increase in the proportions of polyploid cells was observed. An increase in lagging chromosome fragments, which is indicative of chromosome breaks, was observed in Chinese hamster ovary (CHO) cells treated with 2.5, 5.0, and 7.5×10^{-4} % propionaldehyde (equivalent to 2.2, 4.3, and 6.5 µg/mL) for 8 hours (Seoane and Dulout, 1994). Only the increase at the highest concentration tested (7.5×10^{-4}%) was statistically significant ($p < 0.05$ versus untreated controls). No other aldehydes were examined in this study.

Increases in chromosomal aberrations were induced in CHED cells treated with 4 and 6×10^{-3}%, but not 2×10^{-3}% acetaldehyde for 24 hours, and aneuploidy at all concentrations tested (Dulout and Furnus, 1988). Concentrated-related increases in SCE were induced in CHO cells treated with $2.5–15 \times 10^{-4}$% acetaldehyde for 24 hours (Obe and Beek, 1979).

Formaldehyde increased the frequency of sister chromatid exchanges (SCE) in a concentrated-related manner in V79 hamster cells treated for 4 hours with concentrations up to 125 µM (Merk and Speit, 1999). Concentrated-related increases in SCE were also induced in CHO cells treated with $1–4 \times 10^{-4}$% formaldehyde for 24 hours, and in human lymphocytes treated with $10^{-4}–10^{-3}$% formaldehyde for 24 or 48 hours (Obe and Beek, 1979).

Treatment of CHO cells with butyraldehyde at concentrations of 59, 90, and 135 µg/mL for up to 26 hours in the absence of S9 did not induce increases in chromosomal aberrations (Galloway et al., 1987). Butyraldehyde exposure did induce increases in SCE in CHO cells treated with 9 to 90 µg/mL for 25–29 hours in the absence of S–9 (Galloway et al., 1987), but not in human lymphocytes treated with 2×10^{-3}% butyraldehyde for 24 and 48 hours (Obe and Beek, 1979).

Isobutraldehyde was also tested for the induction of chromosomal aberrations and SCE in CHO cells (NTP, 1999). In cells treated with 16–4000 µg/mL without S–9 for 12 hours, isobutyraldehyde induced a concentration-related increase in chromosomal aberrations. Similarly, isobutyraldehyde treatment induced a concentration-related increase in SCE in cells treated for 26 hours over a concentration range of 5–500 µg/mL in the absence of S–9.

Table 4-4. Aldehyde-induced chromosome damage in mammalian cells in vitro

Aldehyde	Cells	Endpoint	Results[a]	LED (HTD)[b]	Reference
Propionaldehyde	CHED	Aberrations	+	5×10^{-4}% (4.3 µg/mL)	(Furnus et al., 1990)
Propionaldehyde	CHO	Fragments	+	0.75×10^{-5}% (0.64 µg/mL)	(Seoane and Dulout, 1994)
Propionaldehyde	CHED	Aneuploidy	+	5×10^{-4}% (4.3 µg/mL)	(Furnus et al., 1990)
Acetaldehyde	CHED	Aberrations	+	4×10^{-3}%	(Dulout and Furnus, 1988)
Acetaldehyde	CHED	Aneuploidy	+	2×10^{-3}%	(Dulout and Furnus, 1988)
Acetaldehyde	CHO	SCE	+	2.5×10^{-4}%	(Obe and Beek, 1979)
Formaldehyde	V79	SCE	+	125 µM	(Merk and Speit, 1999)
Formaldehyde	CHO	SCE	+	1×10^{-4} %	(Obe and Beek, 1979)
Formaldehyde	Human lymphocytes	SCE	+	1×10^{-4} %	(Obe and Beek, 1979)
Butyraldehyde	CHO	Aberrations	–	135 µg/mL	(Galloway et al., 1987)
Butyraldehyde	CHO	SCE	+	9 µg/mL	(Galloway et al., 1987)
Butyraldehyde	Human lymphocytes	SCE	–	2×10^{-3}%	(Obe and Beek, 1979)
Isobutyraldehyde	CHO	Aberrations	+	500 µg/mL	(NTP, 1999)
Isobutyraldehyde	CHO	SCE	+	5 µg/mL	(NTP, 1999)

4.4.1.2.3. ***DNA damage*****.** The results for DNA damage caused by propionaldehyde and other aldehydes are summarized in Table 4-5. Propionaldehyde induced a concentration-related increase in unscheduled DNA synthesis (UDS) in rat hepatocytes at concentrations of 10, 30, and 100 mM (equivalent to 0.58, 1.7, and 5.8 mg/mL) following a 20-hour exposure in vitro (Martelli, 1997; Martelli et al., 1994). UDS increases of 36–37% repair were statistically significant at 30 and 100 mM ($p < 0.001$ compared with controls). A parallel test conducted in human hepatocytes provided no evidence for UDS. Propionaldehyde concentrations of 300 mM (equivalent to 17.4 mg/mL) were toxic to both cell lines.

Table 4-5. Aldehyde-induced DNA damage in vitro

Aldehyde	Species	Cells	Endpoint	Results[a]	LED (HTD)[b]	Reference
Propionaldehyde	Human	Hepatocytes	UDS	–	100 mM (5.8 mg/mL) [300 mM]	(Martelli et al., 1994)
Propionaldehyde	Human	Lymphoma	Cross-links	+	75 mM (4.4 mg/mL)	(Costa et al., 1997)
Propionaldehyde	Rat	Hepatocytes	UDS	+	30 mM (1.7 mg/mL) [300 mM]	(Martelli et al., 1994)
Propionaldehyde	Hamster	CHO-K1	Strand breaks	+	4.5 mM (261µg/mL)	(Marinari et al., 1984)
Propionaldehyde	Hamster	CHO-K1	Cross-links	–	4.5 mM (261 µg/mL)	(Marinari et al., 1984)
Propionaldehyde	N/A[c]	Cell-free plasmid	Cross-links	+	295 mM (17.1 mg/mL)	(Kuykendall and Bogdanffy, 1992)
Acetaldehyde	Human	Lymphoma	Cross-links	+	17.5 mM (771 mg/mL)	(Costa et al., 1997)
Acetaldehyde	Hamster	CHO-K1	Strand breaks	–	4.5 mM (198 µg/mL)	(Marinari et al., 1984)
Acetaldehyde	Hamster	CHO-K1	Cross-links	+	4.5 mM (198 µg/mL)	(Marinari et al., 1984)
Acetaldehyde	N/A	Cell-free plasmid	Cross-links	+	115 mM (5.0 mg/mL)	(Kuykendall and Bogdanffy, 1992)
Formaldehyde	Hamster	CHO-K1	Strand breaks	–	4.5 mM (135.1 µg/mL)	(Marinari et al., 1984)
Formaldehyde	Hamster	CHO-K1	Cross-links	+	4.5 mM (135.1 µg/mL)	(Marinari et al., 1984)
Formaldehyde	N/A	Cell-free plasmid	Cross-links	+	1.5 µM (0.045 µg/mL)	(Kuykendall and Bogdanffy, 1992)
Butyraldehyde	Human	Hepatocytes	UDS	–	100 mM (7.2 mg/mL)	(Martelli et al., 1994)
Butyraldehyde	Rat	Hepatocytes	UDS	+	30 mM (2.2 mg/mL) [300 mM]	(Martelli et al., 1994)
Butyraldehyde	N/A	Cell-free plasmid	Cross-links	+	360 mM (26.0 mg/mL)	(Kuykendall and Bogdanffy, 1992)
Pentanal	Human	Hepatocytes	UDS	–	30 mM (2.6 mg/mL)	(Martelli et al., 1994)
Pentanal	Rat	Hepatocytes	UDS	+	3 mM (0.26 mg/mL) [100 mM]	(Martelli et al., 1994)
Hexanal	Human	Hepatocytes	UDS	–	30 mM (3.0 mg/mL)	(Martelli et al., 1994)
Hexanal	Rat	Hepatocytes	UDS	+	30 mM (3.0 mg/mL) [100 mM]	(Martelli et al., 1994)
Hexanal	Hamster	CHO-K1	Strand breaks	+	4.5 mM (0.45 mg/mL)	(Martelli et al., 1994)
Hexanal	Hamster	CHO-K1	Cross-links	–	4.5 mM (0.45 mg/mL)	(Martelli et al., 1994)

Aldehyde	Species	Cells	Endpoint	Results[a]	LED (HTD)[b]	Reference
Nonanal	Human	Hepatocytes	UDS	–	30 mM (4.3 mg/mL)	(Martelli et al., 1994)
Nonanal	Rat	Hepatocytes	UDS	–	30 mM (4.3 mg/mL) [100 mM]	(Martelli et al., 1994)

[a]Test results are either positive (+), negative (−), or equivocal (?).
[b]LED is the lowest effective concentration for positive test results; HTD is the highest tested concentration for negative or inconclusive results; [ ] is the test concentration that resulted in notable decreases in cell viability or toxicity.
[c]N/A = not applicable.

The aldehydes butanal, pentanal, and hexanal also induced concentration-related increases in UDS in rat hepatocytes, following a 20-hour exposure in vitro (Martelli, 1997; Martelli et al., 1994). Significant increases in UDS ($p < 0.001$ compared with controls) were observed at butanal concentrations of 30 and 100 mM (equivalent to 2.16 and 7.21 mg/mL), pentanal concentrations of 3, 10, and 30 mM (equivalent to 0.258, 0.86, and 2.58 mg/mL), and a hexanal concentration of 30 mM (equivalent to 3.0 mg/mL). The increases in UDS (20–30% repair) induced by these aldehydes were comparable in potency to those produced by propionaldehyde (36–37% repair). Nonanal did not induce UDS at the concentrations tested. No significant increase in UDS (0–9% repair) was seen in human hepatocytes treated under similar conditions with butanal, pentanal, hexanal, or nonanal at any of the concentrations tested.

Propionaldehyde produced a weak, concentration-related increase in DNA protein cross-links (DPXs) in cultured human lymphoma cells, following a 4-hour exposure to concentrations of 0.75, 3, 15, and 75 mM (equivalent to 0.044, 0.17, 0.87, and 4.4 mg/mL) (Costa et al., 1997). The increase in DPX formation was significant ($p < 0.05$ compared with controls) at 75 mM, a concentration that was toxic at a longer duration of exposure. Similar results were shown for acetaldehyde. Acetaldehyde produced a weak, concentration-related increase in DPXs in cultured human lymphoma cells, following a 4-hour exposure to concentrations of 0.035, 0.175, 0.875, 3.5, and 17.5 mM (equivalent to 0.0015, 0.008, 0.039, 0.154, and 0.77 mg/mL). The increase in DPX formation was significant ($p < 0.05$ compared with controls) at 17.5 mM, a concentration that was toxic at longer durations of exposure.

Treatment of CHO-K1 cells with 0.5, 1.5, and 4.5 mM (equivalent to 0.029, 0.087, and 0.26 mg/mL) propionaldehyde or hexanal (equivalent to 0.05, 0.15, and 0.45 mg/mL) for 90 minutes induced DNA single-strand breaks but not cross-links, based on concentration-dependent decreases in the relative retention of DNA as measured by alkaline elution (Marinari et al., 1984).

In contrast, treatment of CHO-K1 cells with formaldehyde and acetaldehyde produced DPXs but not single-strand breaks when tested at concentrations of 0.5, 1.5, and 4.5 mM (equivalent to 0.015, 0.045, 0.135, and 0.022, 0.066, 0.2 mg/mL, respectively). It was noted that formaldehyde produced minimal cytotoxicity in this study.

A filter-binding assay based on sodium dodecyl sulphate-potassium chloride (SDS-KCl) precipitation of protein and covalently attached DNA was used to study the kinetics of plasmid-histone cross-link formation with saturated and unsaturated aldehydes in vitro. In this study, 295 mM (equivalent to 17.1 mg/mL) propionaldehyde produced one cross-link per plasmid molecule (Kuykendall and Bogdanffy, 1992). In comparison, the other aldehydes tested, acetaldehyde, acrolein, formaldehyde, and butyraldehyde, produced one cross-link per plasmid molecule at concentrations of 116 mM, 170 µM, 1.6 µM, and 357 mM, respectively.

4.4.1.2.4. ***Non-DNA adduct formation*****.** Propionaldehyde (5 mM ≈ 290 µg/mL) has been shown to form protein adducts with adult human hemoglobin (1 mM) in vitro (Hoberman and San George, 1988). In another study, propionaldehyde (25 mM ≈ 1,450 µg/mL) did not form protein adducts with freshly prepared human hemoglobin (~ 150 mg Hb/mL) in the absence of an added arachidonic acid lipid peroxidation system (Kautiainen, 1992).

Acetaldehyde (5 mM ≈ 220 µg/mL) and butyraldehyde (5 mM ≈ 360 µg/mL) were also shown to form protein adducts with adult human hemoglobin (1 mM) in vitro. The efficiency of formation was noted to be inversely proportional to the aldehyde chain length (Hoberman and San George, 1988). No protein hemoglobin adducts were recovered following treatment of freshly prepared human hemoglobin (~ 150 mg Hb/mL) with pentanal (25 mM ≈ 2,150 µg/mL) or hexanal (25 mM ≈ 2,500 µg/mL) in the absence of a supplementary oxidizing system (Kautiainen, 1992). Low levels of adducts were seen when an arachidonic acid lipid peroxidation system was added.

4.4.1.3. Genotoxicity Summary

In summary, the genotoxicity of propionaldehyde has been studied in bacteria and a number of mammalian cells in vitro. Propionaldehyde was found to be mutagenic in *S. typhimurium* strain TA1534 (Sampson and Bobik, 2008), and nonmutagenic in all other strains tested (Dillon et al., 1998; Aeschbacher et al., 1989; Mortelmans et al., 1986). The positive mutagenic response was observed in a mutated strain in which a bacterial microcompartment thought to mitigate toxicity was inactivated (Sampson and Bobik, 2008). Propionaldehyde produced concentration-related increases in HGPRT and ouabain mutants in V79 hamster cells (Brambilla et al., 1989). These effects, however, were associated with decreases in cell viability in these test systems. Smith et al. (1990) determined that propionaldehyde was not mutagenic at the HGPRT locus in V79 hamster cells exposed to lower, noncytotoxic concentrations. Propionaldehyde produced a concentration-related increase in chromosome aberrations in Chinese hamster embryonic cells (Furnus et al., 1990) and chromosome breaks in CHO cells (Seoane and Dulout, 1994). In addition, propionaldehyde induced a concentration-related increase in unscheduled DNA synthesis in rat, but not human, hepatocytes (Martelli, 1997; Martelli et al., 1994) and a weak, concentration-related increase in DPXs in cultured human

lymphoma cells (Costa et al., 1997). Although the information provided in these in vitro studies suggests that propionaldehyde is DNA reactive, supportive information from in vivo animal bioassay studies is unavailable.

The relevance of the in vitro test doses and effects in these studies is unclear as a number of these results were associated with significant cellular toxicity. In addition, the relevance of the in vitro dose and effect to in vivo dose and effect is also difficult to ascertain. For example, increases in DPXs have been used as a tissue dose surrogate and serve as an important aspect in describing the dosimetry and the mode of action for formaldehyde-induced nasal lesions based on its correlation with cell replication at specific sites in the nose (Conolly et al., 2000; Casanova et al., 1994). However, studies measuring DPX formation in the nose in response to inspired acetaldehyde have been negative although DPX formation was detected in nasal tissue homogenates treated with acetaldehyde (Dorman et al., 2008; Stanek and Morris, 1999). Consequently, with respect to DPX formation, formaldehyde may represent a special case because of its highly focal deposition and toxicity in the nose as well as its greater potency to form cross-links compared to other aldehydes.

In general, this information indicates that the rank order of potency of aldehydes across similar genotoxic endpoints appears to be as follows: formaldehyde >> acetaldehyde ≈ propionaldehyde > butyraldehyde and isobutyraldehyde. For DPX, the rank order of potency is: formaldehyde >> acetaldehyde > propionaldehyde > butyraldehyde.

4.4.2. CARDIOVASCULAR EFFECTS

Egle (1972b) investigated the effects of propionaldehyde on arterial blood pressure and heart rate. Male Wistar rats were exposed to propionaldehyde concentrations ranging from 3.0–200 µg/mL (3,000–200,000 mg/m^3 or 1260–84,000 ppm) via inhalation for 1-minute intervals. Propionaldehyde-induced changes in blood pressure and heart rate (expressed as percent change ± SE) were compared with those in control rats (n = 93) exposed to clean air. The results are summarized in Table 4-6.

Table 4-6. Effects of inhalation of propionaldehyde on blood pressure and heart

Exposure concentration, µg/mL (mg/m^3)	Blood pressure (% change ± SE)[a]	Heart rate (% change ± SE)[a]
Control (air)	↓ 0.8 ± 0.7	↓ 0.9 ± 0.6
3.0 (3000)	↑ 3.2 ±1.0	↓ 3.3 ± 0.6
10.0 (10,000)	↑ 5.9 ± 1.13[b]	↑ 3.0 ± 1.2
20.0 (20,000)	↑ 10.6 ± 1.5[c]	↑ 6.1 ± 1.1[c]
30.0 (30,000)	↑ 20.8 ± 2.6[c]	↑ 5.0 ± 1.0[c]
50.0 (50,000)	↑ 20.6 ± 2.1[c]	↑ 1.6 ± 0.7
100.0 (100,000)	↑ 27.1 ± 6.3[c]	↑ 1.7 ± 2.2
150.0 (150,000)	↑ 41.6 ± 4.7[c]	↑ 3.4 ± 4.2
200.0 (200,000)	↑ 47.0 ± 4.9[c]	↓ 26.0 ± 9.1[c]

[a]Increase (↑); decrease (↓).
[b]Significantly different from control at $p < 0.05$.
[c]Significantly different from control at $p < 0.01$.

Source: Egle (1972b).

A slight but nonsignificant rise in blood pressure was seen at 3.0 µg/mL (3.2 ± 1.0%; n = 7), while exposure-related significant increases ($p < 0.05$) in blood pressure were seen at 10 µg/mL (5.9 ± 1.13%; n = 6), 20 µg/mL (10.6 ± 1.5%; n = 6), 30 µg/mL (20.8 ± 2.6%; n = 5), 50 µg/mL (20.6 ± 2.1%; n = 6), 100 µg/mL (27.1 ± 6.3%; n = 3), 150 µg/mL (41.6 ± 4.7%; n = 3), and 200 µg/mL (47.0 ± 4.9%; n = 3). The lowest exposure concentration (3.0 µg/mL; n = 7) was without effect on heart rate, while concentrations of 20 (6.1 ± 1.1%; n = 6) and 30 µg/mL (5.0 ± 1.0%; n = 5) produced significant increases in heart rate ($p < 0.01$ versus controls). No change in heart rate was seen in the 50–150 µg/mL exposure groups as compared with that in controls. However, exposure to 200 µg/mL propionaldehyde resulted in a significant decrease (–26.0 ± 9.1%; n = 3) ($p < 0.01$) in heart rate. Based on the data, 3,000 mg/m^3 (3 µg/mL) appears to be a NOEL for rat cardiac responses. However, the biological significance of these changes is uncertain as relatively high concentrations of propionaldehyde were required to produce effects, and thus limits the usefulness of these data.

In another study, Egle et al. (1973) examined the effects of intravenous (i.v.) administration of propionaldehyde on blood pressure and heart rate. Male Wistar rats (7–10/dose/treatment group) were administered propionaldehyde at dosing regimens of 5 mg/kg at 10-minute intervals and 10, 20, and 40 mg/kg at 20-minute intervals. A group of control animals (n = 9) received saline injections that were found to have no effect on resting blood pressure and heart rate. Results were expressed as the percent change ± SE from the initial resting blood pressure or heart rate in each dose/treatment group. Multiple observations were made in each dose/treatment group, and data were reported as the frequency of each response as a function of the number of observations (e.g., a dose/treatment group of seven rats may yield a frequency of response of 18 for 21 [18/21] total observations). After administration of 5 and 10 mg/kg propionaldehyde, pressor responses predominated as average increases in blood pressure of 10.5 ± 1.1% (17/17) and 12.4 ± 1.9% (18/21), respectively, were observed. Although pressor

responses were still evident, depressor responses predominated after administration of 20 and 40 mg/kg propionaldehyde as average decreases in blood pressure of 40.0 ± 8.1% (11/20) and 63.9 ± 7.2% (13/16), respectively, were observed. The pressor responses induced by propionaldehyde were partially inhibited by the adrenergic antagonists reserpine (a depletor of monoamine neurotransmitters) and phentolamine, and the depressor responses were reduced by the anticholinergic agent atropine as well as by bilateral vagotomy. Administration of 40 mg/kg propionaldehyde also induced a profound decrease in heart rate of 71 ± 6.1% (n = 16) from baseline. This response was partially attenuated by phentolamine and atropine and completely reversed by bilateral vagotomy. Based on the results of this study, the authors concluded that propionaldehyde exerts two opposing actions on the cardiovascular system at different dose levels—a sympathomimetic effect that results primarily from release of norepinephrine and produces vasoconstriction and an increase in blood pressure and a secondary reflex stimulation of the vagus nerve that results in bradycardia and hypotension.

The effect of propionaldehyde on isolated smooth muscle systems was studied (Beckner et al., 1974). In the first part of the study, isolated vas deferens from Wistar rats was treated with propionaldehyde and contractile responses and concentration-response relationships were examined. The isolated rat vas deferens was first exposed to ^{14}C-norepinephrine for 15 minutes, and the ability of the aldehydes to produce an increase in loss of radioactivity was then examined. Propionaldehyde ($p < 0.05$) significantly reduced ^{14}C-concentration in tissue. The contractile response produced by propionaldehyde was reversible and blocked by reserpine pretreatment. In the second part of the study, the effect of propionaldehyde on ^{45}Ca binding in the aorta isolated from New Zealand white rabbits was examined. Propionaldehyde significantly ($p < 0.05$) reduced calcium binding in isolated rabbit aorta at approximately 10^{-2} M after 30 minutes of exposure. The authors concluded that propionaldehyde can cause the release of endogenous catecholamines (e.g., norepinephrine) and may interact with tissue norepinephrine stores by inhibiting Na^+, K^+-dependent adenosine triphosphatase (ATPase) and affect nonspecific membrane calcium-binding sites. These results provide further support that the cardiovascular effects induced in animals after exposure to propionaldehyde appear to be due to their sympathomimetic activities.

4.4.3. IMMUNOTOXICITY

Poirier et al. (2002) assessed propionaldehyde as a chemical component of tobacco smoke for its effects on viability and proliferation of mouse lymphocytes in vitro. Propionaldehyde significantly inhibited T-lymphocyte and B-lymphocyte proliferation, with median inhibitory concentration (IC_{50}) values of approximately 3×10^{-5} M after 3 hours of exposure. Other chemical components that also inhibited T-lymphocyte and B-lymphocyte proliferation were formaldehyde, catechol, acrylonitrile, acrolein, crotonaldehyde, and hydroquinone with IC_{50} values in the range of 1.19×10^{-5} to 5.86×10^{-4} M. Based on their IC_{50}

values, propionaldehyde was determined to be more inhibitory than formaldehyde but less than acrolein and crotonaldehyde. Propionaldehyde did not affect lymphocyte cell viability since the IC_{50} for lymphocyte cell viability was in the same range as the control. Acrolein and crotonaldehyde were the only compounds shown to affect lymphocyte cell viability. These results suggest that propionaldehyde may have effects on important lymphocyte function.

4.4.4. CYTOTOXICITY

In a cytotoxicity study, Bombick and Doolittle (1995) used the neutral red uptake assay, which measures cellular membrane damage and cell viability, to investigate the cytotoxic potential and chemical structure of low molecular weight aldehydes, including propionaldehyde. CHO cells were treated with propionaldehyde for 24 hours, and the median effective concentration (EC_{50}) (the chemical concentration required to reduce the absorbance value by 50% after a 24-hour exposure) was determined. The EC_{50} for propionaldehyde was 17.2 mM.

In another cytotoxicity study, Koerker et al. (1976) treated the NBP_2 clone of C1300 mouse neuroblastoma cells in culture with propionaldehyde and investigated their effects on the inhibition of cell growth and viability, changes in the morphologic appearance of the cells, and increase in the percentage of cells sloughing into the medium. For propionaldehyde, the molar (M) concentrations producing a 50% change from control in each cytotoxic endpoint after 24 hours of exposure ranged from 2×10^{-4} to 1×10^{-2} M.

4.4.5. COMPARATIVE TOXICITY OF RELATED ALDEHYDES

Several studies that provide information on the comparative toxicity of various aldehydes were identified in the literature. The majority of these studies examined and compared the relative potencies of aldehydes in a variety of in vivo and in vitro systems. The studies discussed below are limited primarily to those studies in which a number of aldehydes were examined together and/or studies in which endpoints relevant to propionaldehyde were evaluated, allowing for more direct comparisons. The endpoints evaluated include respiratory and cardiac effects, effect on smooth muscle, and cellular cytotoxicity.

Guth (1996) reviewed and assessed the noncancer effects of propionaldehyde based on comparative toxicity with other low molecular weight aldehydes, such as formaldehyde, acrolein, and acetaldehyde. The effects of i.v. administration of acetaldehyde or propionaldehyde on blood pressure and heart rate in rats were very similar (Egle et al., 1973), and the effects from inhalation on blood pressure and heart rate showed that acetaldehyde and propionaldehyde also have similar potencies by this route of exposure (Egle, 1972b). Guth (1996) concluded that these results, taken together, suggest that acetaldehyde and propionaldehyde are absorbed and distributed similarly after inhalation exposure, since changes in heart rate and blood pressure are systemic effects. In a comparative kinetic study conducted in dogs, Egle (1972a) observed similar magnitudes of respiratory tract deposition after inhalation exposure for acetaldehyde,

acrolein, and propionaldehyde, with deposition averaging between 70 and 80%. In addition, propionaldehyde and acetaldehyde exhibit similar median lethal doses (LD_{50}) after oral exposure (1930 and 1410 mg/kg, respectively) and subcutaneous dosing (640 and 820 mg/kg). In comparing the RD_{50} values among various aldehydes, Steinhagen and Barrow (1984) observed that the unsaturated aldehydes and formaldehyde were approximately 2 orders of magnitude more potent than the longer-chain saturated aldehydes (e.g., propionaldehyde).

In a study designed to test general and portal-of-entry toxicity, the most sensitive noncancer effect identified in rats for acetaldehyde was degeneration of the olfactory nasal epithelium (Woutersen et al., 1986; Appelman et al., 1982;). Appelman et al. (1982) exposed male and female Wistar rats to 400, 1,000, 2,200, or 5000 ppm acetaldehyde 6 hours/day, 5 days/week for 4 weeks. Small reductions in weight gain were seen at exposure concentrations of 1000 ppm and greater. Degeneration of the nasal olfactory epithelium was observed at the lowest exposure concentration tested (400 ppm), and this effect increased in severity with increasing exposure concentration. Similar results were obtained by Appelman et al. (1986), when degeneration of the olfactory epithelium was observed in rats exposed to 500 ppm acetaldehyde 6 hours/day, 5 days/week for 4 weeks. Reductions in weight gain were not noted in these animals, and no compound-related effects were seen in animals exposed to 150 ppm acetaldehyde. In a recent study by Dorman et al. (2008), a similar pattern and progression of nasal olfactory lesions were observed in F344 rats exposed to acetaldehyde concentrations of 150, 500, and 1,500 ppm via whole-body inhalation for 6 hours/day, 5 days/week for up to 65 exposure days. Olfactory epithelial degeneration, noted as the most sensitive endpoint observed, increased in incidence and severity with both exposure concentration and duration. The presence of vacuolization was also noted, but the severity was not graded. In animals exposed to 50 ppm, no lesions were observed. The portal-of-entry effects of the structurally-related aldehyde isobutyraldehyde was also evaluated in a 2-year chronic toxicology and carcinogenicity study (NTP, 1999). In this study groups of male and female F344 rats were exposed to 0, 500, 1,000, or 2,000 ppm isobutyraldehyde by inhalation of 6 hours/day, 5 days/week for 105 weeks. No increases in neoplastic nasal lesions were observed in this study. Nonneoplastic lesions in the nose consisted of squamous metaplasia of the respiratory epithelium, degeneration of the olfactory epithelium, and suppurative inflammation. Incidences of minimal to mild squamous metaplasia in 1,000 and 2,000 ppm males and females and in 500 ppm females were significantly greater than those in the chamber controls. Another lesion associated with exposure was minimal to mild degeneration of the olfactory epithelium in 2,000 ppm males and females. The incidences of suppurative inflammation (rhinitis) in male and female rats exposed to 2,000 ppm were increased compared to the chamber controls.

Although studies of comparable design examining the effects of propionaldehyde on the nasal epithelium are unavailable, a similar pattern and progression of nasal olfactory lesions were reported in adult male and female CD rats in a propionaldehyde inhalation reproductive and

developmental study conducted by Union Carbide (1993, 1991) (see Sections 4.3 and 4.5.2). Increases in olfactory epithelium atrophy were observed at 150, 750, and 1,500 ppm propionaldehyde. In toto, these comparisons suggest that acetaldehyde and propionaldehyde produce similar respiratory and cardiac effects, and may produce nasal lesions at similar exposure concentrations.

Steinhagen and Barrow (1984) compared the RD_{50} values of 14 aldehydes in $B6C3F_1$ and Swiss-Webster mice as a measure of sensory irritation potential. Groups of three to four mice per strain were exposed via inhalation in a head-only exposure chamber for 10 minutes to varying concentrations (usually five) of the test aldehyde. Respiratory rates were measured by a method in which animals were sealed in airtight plethysmographs and attached to a head-only exposure chamber, and concentration-response curves were constructed to determine the RD_{50}. In animals, sensory irritants produce a reflex decrease in respiratory rate characterized as a pause at the onset of expiration. The RD_{50} values for propionaldehyde, acetaldehyde, formaldehyde, and acrolein for each mouse strain are shown in Table 4-7. Other aldehydes tested included crotonaldehyde, isovaleraldehyde, butyraldehyde, caproaldehyde, valeraldehyde, and isobutyraldehyde. Comparing the values for the aldehydes tested, the RD_{50} values spanned approximately 3.5 orders of magnitude. The α,β-unsaturated aliphatic aldehydes (acrolein and crotonaldehyde) and formaldehyde were approximately two orders of magnitude more potent than the saturated aliphatic aldehydes (propionaldehyde, isovaleraldehyde, butyraldehyde, caproaldehyde, valeraldehyde, acetaldehyde, and isobutyraldehyde) in producing a 50% decrease in respiration rate.

Table 4-7. RD_{50} values for propionaldehyde and selected, related aldehydes measured in $B6C3F_1$ and Swiss-Webster mice

Aldehyde	$B6C3F_1$[a]	Swiss-Webster
Propionaldehyde	2,078 ppm (1,803–2402) 4,946 mg/m^3 (4,291–5,717)	2,052 ppm (1,625–3,040) 4,884 mg/m^3 (3,868–7,235)
Isobutyraldehyde	3016 ppm (2568–3610)	4167 ppm (3258–5671)
Acetaldehyde	2,932 ppm (2,627–3,364)	2,845 ppm (1,967–3,954)
Formaldehyde	4.90 ppm (3.9–6.4)	3.2 ppm (2.1–4.7)
Acrolein	1.41 ppm (1.16–1.73)	1.03 ppm (0.70–1.52)

[a]Ranges for RD_{50} values shown in parentheses.

Source: Steinhagen and Barrow (1984).

The effects of propionaldehyde, acetaldehyde, formaldehyde, and acrolein on isolated smooth muscle systems were studied (Beckner et al., 1974). In the first part of the study, isolated vas deferens from Wistar rats was treated with the four aldehydes and contractile responses and concentration-response relationships were examined. The isolated rat vas deferens was first exposed to ^{14}C-norepinephrine for 15 minutes, and the ability of the aldehydes to produce an increase in loss of radioactivity was then examined. Propionaldehyde ($p < 0.05$) and

acetaldehyde ($p < 0.01$) at 10^{-2} M and formaldehyde ($p < 0.05$) and acrolein ($p < 0.01$) at 10^{-3} M significantly reduced ^{14}C-concentration in tissue. The contractile responses produced by propionaldehyde and acetaldehyde, but not formaldehyde and acrolein, were reversible and blocked by reserpine pretreatment. In the second part of the study, the effect of these aldehydes on ^{45}Ca binding in the aorta isolated from New Zealand white rabbits was examined. All four aldehydes significantly ($p < 0.05$) reduced calcium binding in isolated rabbit aorta in the same concentration range (10^{-2} M) after 30 minutes of exposure. The authors concluded that these results suggest that propionaldehyde and acetaldehyde can cause the release of endogenous catecholamines (e.g., norepinephrine), and all four aldehydes may interact with tissue norepinephrine stores by inhibiting Na^+, K^+-dependent ATPase and affect nonspecific membrane calcium-binding sites. These results provide further support that the cardiovascular effects induced in animals after exposure to propionaldehyde and other aldehydes appear to be due to their indirect sympathomimetic activities (see Egle et al., [1973] in Section 4.4.2).

Wang et al. (2002) performed a genotype analysis of the ALDH2 gene in the livers of human volunteers in order to investigate the metabolism of a variety of aldehydes. Of a total of 39 subjects, 8 were heterozygotes of the wild-type (ALDH2*1) and mutant (ALDH2*2) alleles, and the others were homozygotes of the wild-type allele. The ability of mitochondria to metabolize propionaldehyde, acetaldehyde, formaldehyde, n-butyraldehyde, capronaldehyde, and heptaldehyde was significantly lower ($p < 0.05$) (between 37 and 93%, depending on the aldehyde; 80% for propionaldehyde) in the heterozygotes (ALDH2*1/*2) compared to the homozygotes (ALDH2*1/*1), showing differences in metabolism between the two genotypes. However, the mitochondrial activity was not lower for octylaldehyde, decylaldehyde, retinaldehyde, benzaldehyde, 3-hydroxybenzaldehyde, 2,5-dihydroxybenzaldehyde, phenylacetaldehyde, and 3-phenylpropionaldehyde, showing similar metabolism between the two genotypes. Based on these results, the authors hypothesized that the polymorphisms of the ALDH2 gene may only alter the metabolism of the short aliphatic chain aldehydes.

In a cytotoxicity study, Bombick and Doolittle (1995) used the neutral red uptake assay, which measures cellular membrane damage and cell viability, to investigate the relationship between the cytotoxic potential and chemical structure of low molecular weight aldehydes. CHO cells were treated with formaldehyde, acetaldehyde, propionaldehyde, acrolein, pyridine, 2-vinyl pyridine, 4-vinyl pyridine, 4-picoline, butanol, and ammonium hydroxide for 24 hours, and the chemical concentrations required to reduce the absorbance value by 50% after a 24-hour exposure (EC_{50}) were determined. The EC_{50} values for the aldehydes were as follows: 0.009 mM for acrolein, 0.6 mM for formaldehyde, 2.3 mM for acetaldehyde, and 17.2 mM for propionaldehyde. Thus, formaldehyde was considered more toxic than acetaldehyde, which was more toxic than propionaldehyde, with the α-, β-unsaturated aldehyde, acrolein, being the most toxic compound by almost three orders of magnitude. Based on these results, the authors

concluded that cytotoxicity generally appears to decrease with increasing (saturated) aldehyde chain length.

In another cytotoxicity study, Koerker et al. (1976) treated the NBP_2 clone of C1300 mouse neuroblastoma cells in culture with propionaldehyde, acetaldehyde, and acrolein formaldehyde, and investigated their effects on the inhibition of cell growth and viability, changes in the morphologic appearance of the cells, and the increase in the percentage of cells sloughing into the medium. For each aldehyde, the molar concentrations producing a 50% change from control in each cytotoxic endpoint after 24 hours of exposure are shown in Table 4-8. Based on these results, the authors noted that toxicity increased with decreasing aldehyde chain length, perhaps reflecting the ease of cross-linking or the reactivity of the carbonyl group. For example, acrolein was considerably more toxic than propionaldehyde for each endpoint, illustrating the increased activity of the carbonyl group caused by the presence of the conjugated double bond.

Table 4-8. Concentration [M] of selected aldehydes required to produce a 50% change from control in each cytotoxic endpoint

Effect	Propionaldehyde	Acetaldehyde	Acrolein	Formaldehyde
Sloughed cells	2.2×10^{-3}	5.4×10^{-4}	1.0×10^{-6}	8.3×10^{-6}
Neurite formation	2.1×10^{-4}	7.9×10^{-4}	7.6×10^{-6}	2.0×10^{-6}
Viability of sloughed cells	1.0×10^{-3}	6.4×10^{-3}	5.3×10^{-6}	4.5×10^{-6}
Total cell number	1.0×10^{-2}	6.4×10^{-3}	5.8×10^{-4}	2.8×10^{-6}
Viability of harvested cells	4.8×10^{-3}	9.0×10^{-3}	3.0×10^{-5}	2.2×10^{-4}

Source: Koerker et al. (1976).

Egyud (1967) investigated the effects of a variety of chemical groups, including the aldehydes, on cell division in *Escherichia coli*. The chemicals were added to logarithmically growing bacteria, and the reaction was followed by measuring the increase in the optical density on a colorimeter. The concentration of the aliphatic aldehydes tested was 10^{-3} M. Formaldehyde and acetaldehyde completely and irreversibly inhibited cell division, while the other aldehydes, including propionaldehyde, produced a transient inhibitory effect.

The studies summarized above provide some insight in comparing the relative potencies of various aldehydes for the same endpoint(s) and in the same or similarly conducted studies. Whether the endpoint be portal-of-entry effects, decrease in respiration, or in vitro cytotoxicity, the rank order of potency appears to be acrolein > formaldehyde >> acetaldehyde ≈ propionaldehyde > isobutryaldehyde with potency further decreasing with increasing (saturated) aldehyde chain length.

4.5. SYNTHESIS AND EVALUATION OF MAJOR NONCANCER EFFECTS

4.5.1. ORAL

No human or animal studies are available on the oral effects of propionaldehyde.

4.5.2. INHALATION

The most notable propionaldehyde-induced effects reported in animal inhalation exposure studies are respiratory tract irritation, histopathology, and cardiovascular perturbations.

Two short-term reproductive/developmental inhalation studies were conducted by Union Carbide, one for 20 days (Union Carbide, 1991) and the second for a duration of 7–8 weeks (Union Carbide, 1993).

In a range-finding study, young adult female CD rats (seven per group) were exposed to 0, 500, 1,000, 1,500, or 2,500 ppm propionaldehyde for 6 hours/day, on GDs 0 through 20, following successful mating with naive males (Union Carbide, 1991). Maternal toxicity was noted as exposure-related decreases in body weight gain; however, these decreases in body weight gain were accompanied by decreases in food consumption throughout the gestation period. There were no exposure-related differences in gestational parameters, including total number of implants and the number of viable and nonviable implants. No other evidence of any treatment-related external malformations or variations was observed.

In the second study, young adult male and female CD rats (15/sex/group) were exposed to 0, 150, 750, or 1,500 ppm propionaldehyde for 6 hours/day, 7 days/week, during a 2-week premating period and a 14-day mating phase (Union Carbide, 1993). The mated females were exposed daily through GD 20 for a minimum of 35 days and a maximum of 48 days depending upon when they mated (average exposure period ~ 38 days). The females were then allowed to deliver their litters naturally and raise their offspring until day 4 of lactation, when they were sacrificed. The males continued to be exposed until sacrifice in week 7, for a total of 52 exposures.

In the adult females, no exposure-related clinical signs were noted. Body weight gains and food consumption were slightly decreased during the first week of exposure to 750 and 1,500 ppm. During gestation, body weight and food consumption were decreased in the high exposure group compared with controls, but no differences in body weight changes were observed. No significant effects of exposure on any of the reproductive parameters assessed were found. Litter size and viability were similar among the groups. At sacrifice, no gross lesions attributable to propionaldehyde exposure were found. However, microscopic examination of the nasal cavity revealed propionaldehyde-induced vacuolization of the olfactory epithelium in the 150 and 750 ppm exposure groups and atrophy of the olfactory epithelium in the 750 and 1,500 ppm exposure groups. These effects were noted to be localized to the dorsal anterior two sections of the nasal cavity. The incidence of atrophy was 0/15, 0/15, 2/15, and 15/15 at 0, 150, 750, and 1,500 ppm, respectively (see Table 4-1). The severity of this nasal lesion increased with exposure concentration being minimal to mild at 750 ppm and moderate to marked at 1,500 ppm. No evidence of squamous metaplasia was found in olfactory or respiratory epithelium. Low incidences of minimal to mild rhinitis involving the respiratory epithelium were also noted at 150, 750, and 1,500 ppm.

In the males, body weights, weight gains, clinical observations, and food consumption were similar among all exposure groups and controls. At necropsy, no gross lesions were found. However, similar to effects in the females, microscopic examination revealed exposure-related effects in the olfactory epithelium of the nasal cavity that consisted of vacuolization in the low and intermediate exposure groups and atrophy in the intermediate and high exposure groups. These effects were noted to be localized to the dorsal anterior two sections of the nasal cavity. The incidence of atrophy was 0/15, 2/15, 10/15, and 15/15 at 0, 150, 750, and 1,500 ppm, respectively. The severity of this nasal lesion increased with exposure concentration being minimal at 150 ppm, minimal to moderate at 750 ppm, and mild to marked at 1,500 ppm. Squamous metaplasia of the respiratory epithelium was reported in one male from the 750 ppm group and two males from the 1500 ppm group. An increased incidence of minimal to moderate rhinitis involving the respiratory epithelium was also noted at 750 and 1,500 ppm. The decrease in incidence and severity of the nasal lesions in females relative to males is likely to be attributable to the differences in exposure duration and approximate 6-day period between cessation of exposures after GD 20 and sacrifice on day 4 of lactation. This observation may also indicate that these effects are reversible and that repair and regeneration of the olfactory epithelium has been initiated. However, pathological indications (e.g., cell proliferation, hyperplasia) that these processes have started in the female rats were not noted. Consequently, although the incidence of olfactory epithelium atrophy was not the most sensitive effect observed after exposure to propionaldehyde, the U.S. EPA considers this endpoint to be a biologically significant effect (as discussed in Section 5.2.1).

The respiratory tract effects induced by propionaldehyde are consistent with the portal-of-entry effects reported for other aldehydes, such as acrolein, acetaldehyde, and formaldehyde, all of which deposit significantly in the upper respiratory tract. In addition, isobutyraldehyde produces a similar pattern of portal-of-entry effects; however, respiratory tract uptake information is lacking. Egle (1972a) demonstrated in dogs that approximately 70–80% of inhaled propionaldehyde is retained in the upper respiratory tract. In addition, when comparing the sensory irritation potential (i.e., RD_{50} values) among aldehydes, propionaldehyde was found to be two orders of magnitude less potent than acrolein and formaldehyde, slightly more potent than acetaldehyde, and approximately 1.5-fold more potent than isobutyraldehyde (Steinhagen and Barrow, 1984). This reflex decrease in respiratory rate is mediated via stimulation of nasal trigeminal nerves and is characterized as a pause at the onset of expiration. In studies examining the effects of propionaldehyde on blood pressure and heart rate in rats after both i.v. and inhalation exposure, propionaldehyde was shown to produce dose-related pressor (at low doses) and depressor (at high doses) responses (Egle et al., 1973; Egle, 1972b). The pressor responses induced by propionaldehyde were partially inhibited by the adrenergic antagonists reserpine and phentolamine, and the depressor responses were reduced by the anticholinergic agent atropine as well as by bilateral vagotomy. Administration of 40 mg/kg propionaldehyde i.v. also induced a

profound decrease in heart rate from baseline (a response also observed at the high inhalation exposure concentration). This response was partially attenuated by phentolamine and atropine and completely reversed by bilateral vagotomy. Based on the results of these studies, it can reasonably be surmised that propionaldehyde exerts two opposing actions on the cardiovascular system at different dose levels—a sympathomimetic effect that results primarily from release of norepinephrine and produces vasoconstriction and an increase in blood pressure and a secondary reflex stimulation of the vagus nerve that results in bradycardia and hypotension.

Similar results were observed when propionaldehyde, acetaldehyde, formaldehyde, and acrolein were tested in vitro on isolated smooth muscle systems (Beckner et al., 1974). In the first part of the study, the contractile responses produced by propionaldehyde and acetaldehyde, but not formaldehyde and acrolein, were reversible and blocked by reserpine pretreatment. In the second part of the study, all four aldehydes significantly reduced calcium binding in isolated rabbit aorta in the same concentration range. The authors concluded that taken together these results suggest that propionaldehyde and acetaldehyde can cause the release of endogenous catecholamines (e.g., norepinephrine), and all four aldehydes may interact with tissue norepinephrine stores by inhibiting Na^+, K^+-dependent ATPase and affect nonspecific membrane calcium-binding sites. In addition, these results provide support that the cardiovascular effects induced in animals after exposure to propionaldehyde and other aldehydes appear to be due to their sympathomimetic activity.

Gage (1970) exposed four male and four female Alderley-Park rats to 1,300 ppm propionaldehyde 6 hours/day for 6 days via whole-body inhalation. No changes in body weight were noted; however, microscopic examination revealed liver cell vacuolation. Four male and four female rats were also exposed to 90 ppm 6 hours/day for 20 exposures. All organs were reported to be normal at autopsy and no clinical signs of toxicity were noted.

4.6. WEIGHT-OF-EVIDENCE EVALUATION AND CANCER CHARACTERIZATION

4.6.1. SUMMARY OF OVERALL WEIGHT OF EVIDENCE

In accordance with the *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a), there is "inadequate information to assess the carcinogenic potential" for propionaldehyde. No human health effects data or chronic animal bioassay studies are available that assess the carcinogenic effects of propionaldehyde.

The genotoxicity of propionaldehyde has been studied in bacteria and a number of mammalian cells in vitro. Propionaldehyde was found to be mutagenic in *S. typhimurium* strain TA1534 (Sampson and Bobik, 2008) and nonmutagenic in all other strains tested (Dillon et al., 1998; Aeschbacher et al., 1989; Mortelmans et al., 1986), but produced concentration-related increases in HGPRT and ouabain mutants in V79 hamster cells (Brambilla et al., 1989). These effects, however, were associated with decreases in cell viability in these test systems. Smith

et al. (1990) determined that propionaldehyde was not mutagenic at the HGPRT locus in V79 hamster cells exposed to lower, noncytotoxic concentrations. Propionaldehyde produced a concentration-related increase in chromosome aberrations in Chinese hamster embryonic cells (Furnus et al., 1990) and chromosome breaks in CHO cells (Seoane and Dulout, 1994). In addition, propionaldehyde induced a concentration-related increase in UDS in rat, but not human, hepatocytes (Martelli, 1997; Martelli et al., 1994) and a weak, concentration-related increase in DPXs in cultured human lymphoma cells (Costa et al., 1997). For formaldehyde, increases in DPXs serve as an important aspect in describing the dosimetry and the carcinogenic mode of action for nasal tumors (Conolly et al., 2000; Casanova et al., 1994). Although the information provided in the in vitro studies suggests that propionaldehyde is DNA reactive, information from in vivo animal bioassay studies is unavailable. This overall lack of information represents a data gap and does not allow for either a quantitative or a qualitative assessment of the carcinogenic potential of propionaldehyde or a definitive statement concerning its mutagenic potential.

It is important to note that inhalation exposure to propionaldehyde produced a low incidence of respiratory epithelium squamous metaplasia in male rats in the intermediate and high exposure groups (Union Carbide, 1993). Although this alteration may be viewed as an adaptive response typical of nasal epithelial tissues in response to continued irritant insult, the lesion may become part of a progression from nasal tissue injury and toxicity (e.g., epithelial degeneration and atrophy) to hyperplasia to increased cell proliferation and lastly to nasal tumorigenesis (Renne et al., 2007; Boorman et al., 1990). Squamous metaplasia is also noted in studies examining the nasal effects of both acetaldehyde and formaldehyde in which marked to severe metaplasia and/or hyperplasia and increases in cell proliferation are observed prior to nasal tumor formation during chronic exposure (Monticello et al., 1996; Zwart et al., 1988; Woutersen et al., 1984; 1986; Appelman et al., 1982). A similar pattern of nasal lesions were also noted in a 2-year chronic study evaluating the toxicology and carcinogenesis of isobutyraldehyde, but no increases in neoplastic lesions were observed (NTP, 1999). In contrast, the exposure concentrations required to induce similar nasal effects were higher compared to formaldehyde and acetaldehyde. Thus, the pattern of nasal tissue effects and the carcinogenicity of related aldehydes raise concern. However, the more specific alterations observed for related aldehydes, such as squamous metaplasia with atypia and disorganization, concurrent hyperplasia, changes in cell proliferation, and tumor formation in nasal tissues, were not observed after exposure to propionaldehyde (Union Carbide, 1993). Therefore, as it relates to the effects observed after exposure to propionaldehyde, the presence of squamous metaplasia alone is considered to be a nonneoplastic lesion in nasal tissue and is of limited quantitative use in assessing cancer risk.

4.7. SUSCEPTIBLE POPULATIONS AND LIFE STAGES

4.7.1. POSSIBLE CHILDHOOD SUSCEPTIBILITY

No studies are available on possible childhood or other age group susceptibility to propionaldehyde. However, in general, children may represent a particularly sensitive population to the effects of airborne pollutants (Bateson and Schwartz, 2008). Their enhanced sensitivity is most likely a result of their higher ventilation rates and undeveloped lungs relative to adults which together may increase their exposure to toxicants and susceptibility to respiratory tract injury.

4.7.2. POSSIBLE GENDER DIFFERENCES

No studies investigating the possible gender differences in susceptibility specific to propionaldehyde are available**.**

4.7.3. POSSIBLE GENETIC DIFFERENCES

Wang et al. (2002) performed a genotype analysis of the ALDH2 gene in the livers of human volunteers in order to investigate the metabolism of a variety of aldehydes. Of a total of 39 subjects, 8 were heterozygotes of the wild-type (ALDH2*1) and mutant (ALDH2*2) alleles, and the others were homozygotes of the wild-type allele. The ability of mitochondria isolated from these livers to metabolize propionaldehyde, acetaldehyde, formaldehyde, *n*-butyraldehyde, capronaldehyde, and heptaldehyde was significantly ($p < 0.05$) lower (between 37 and 93%, depending on the aldehyde; 80% for propionaldehyde) in the heterozygotes (ALDH2*1/*2) compared to the homozygotes (ALDH2*1/*1), showing differences in metabolism between the two genotypes. However, the mitochondrial activity was not lower for octylaldehyde, decylaldehyde, retinaldehyde, benzaldehyde, 3-hydroxybenzaldehyde, 2,5-dihydroxybenzaldehyde, phenylacetaldehyde, and 3-phenylpropionaldehyde, showing similar metabolism between the two genotypes. Based on these results, the authors hypothesized that polymorphisms of the ALDH2 gene appear to exist in the human population, which may alter the metabolism of the short aliphatic chain aldehydes. It is not clear, however, if the potential increase to parent aldehyde exposure exists in vivo for heterozygotes.

4.7.4. POSSIBLE SENSITIVE SUBGROUPS - ASTHMATICS

Although no studies investigating the possible increased susceptibility of asthmatic specific to propionaldehyde are available, asthmatics represent another potential sensitive subgroup to inhaled irritant aldehydes (Singh and Busse, 2006; Leikauf, 2002). Asthmatics may have an increased susceptibility to lower concentrations of inhaled irritants which can augment symptoms in persons with asthma. Aggravation of underlying asthma can result from moderate exposures (Nowak, 2002). One possible mechanism by which inhaled irritants may exert their

effects is via airway sensory receptor-mediated reflex bronchoconstriction (Nowak, 2002). Specifically, formaldehyde might exacerbate asthma and induce bronchoconstriction via irritant mechanisms as well as via deregulation of the endogenous bronchodilator S-nitrosoglutathione (Thompson and Grafstrom, 2008).

5. DOSE-RESPONSE ASSESSMENTS

5.1. ORAL REFERENCE DOSE (RfD)

No human or animal oral studies for propionaldehyde were identified on which to base an oral RfD.

5.2. INHALATION REFERENCE CONCENTRATION (RFC)

5.2.1. CHOICE OF PRINCIPAL STUDY AND CRITICAL EFFECT

No human inhalation studies are available for propionaldehyde. No subchronic or chronic animal inhalation studies were identified for propionaldehyde. However, one short-term animal inhalation study (Gage, 1970) and two short-term reproductive/developmental animal inhalation studies were identified (Union Carbide, 1993, 1991). In addition, two acute animal studies were identified (Steinhagen and Barrow, 1984; Egle, 1972b). The database for propionaldehyde is further depicted in the Exposure-Response Array, Figure 5.1, and outlined in Table 5-1. The exposure-response array shows the low- and high-exposure concentrations, and if identified, the NOAEL and/or LOAEL (y-axis) for the respective study arranged by exposure duration, endpoint and species (x-axis). The database consists of 5 animal (rat and mouse) studies.

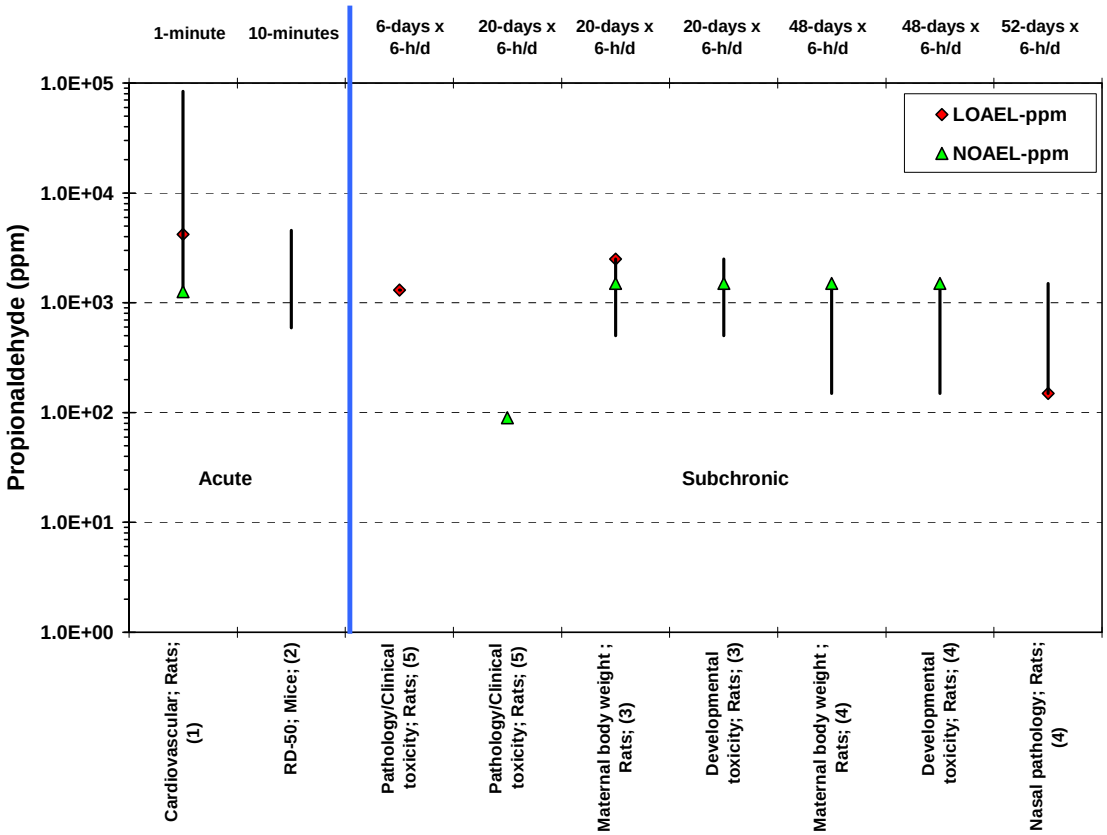


Figure 5-1. Exposure-Response Array for Propionaldehyde

Table 5-1. Propionaldehyde References for Exposure-Response Array

Array (#)	Endpoint	Species	Reference
1	Cardiovascular	Rats	Egle (1972b)
2	RD_{50}	Mice	Steinhagen and Barrow (1984)
3	Maternal body weight	Rats	Union Carbide (1991)
3	Developmental toxicity	Rats	Union Carbide (1991)
4	Maternal body weight	Rats	Union Carbide (1993)
4	Developmental toxicity	Rats	Union Carbide (1993)
4	Nasal pathology	Rats	Union Carbide (1993)
5	Pathology/Clinical toxicity	Rats	Gage (1970)
5	Pathology/Clinical toxicity	Rats	Gage (1970)

The Union Carbide (1993) study was selected as the principal study for derivation of the RfC. Based on the database available for propionaldehyde, this study provided the most adequate exposure concentration response and longest duration information for derivation of a reference value. The study was conducted over a range of exposure concentrations, included a control group, and demonstrated an exposure concentration-related effect more extensively than each of the reported liver and cardiac effects described in Section 4.5.2. In addition, the studies examining cardiac and liver effects were conducted over much shorter durations or required much higher exposure concentrations to produce observable effects (Egle et al., 1973; Egle, 1972b; Gage, 1970). The critical endpoint chosen for analysis from this study was the incidence of atrophy (diminished cell size and function) of the olfactory epithelium in male rats. This effect is considered biologically relevant effect, exhibited a concentration-response relationship, and was observed at the lowest exposure concentration tested (150 ppm). The atrophy observed at the lowest exposure concentration was of minimal severity and not noted in females, possibly as a result of the greater exposure duration of the male rats compared to the female rats in this study. The atrophy observed at the middle exposure concentration (750 ppm) was characterized as being of minimal to moderate severity. The induction of nasal lesions by propionaldehyde is consistent with the irritant properties and the portal-of-entry effects observed in studies conducted for other aldehydes (e.g., acetaldehyde, isobutyraldehyde and formaldehyde).

Along with an increased incidence of atrophy, an increased incidence of vacuolization of the olfactory epithelium was also noted in propionaldehyde-exposed rats (Union Carbide, 1993). Vacuolization (i.e., intracellular autophagy) is a normal cellular functional, homeostatic, and adaptive response (Robbins and Angell, 1976). It is a characteristic of and often accompanies cells/tissues undergoing atrophy (Kumar et al., 2004; Robbins and Angell, 1976). The presence of these effects may also include observable inflammation and hypertrophic/hyperplastic responses (Boorman et al., 1990). However, the qualitative and quantitative biological relationship between vacuolization and atrophy is unclear and unknown. In vitro studies conducted in nutrient depleted cells indicate that severe levels of vacuolization may also result in

cell death via apoptosis or autophagic cell death characterized by an accumulation of autophagic vacuoles (Gonzalez-Polo et al., 2005). Indications that either process occurred was not noted in the principal study. High incidence levels of vacuolization were observed at 150 and 750 ppm propionaldehyde. At 1,500 ppm, it appears that olfactory epithelium atrophy had progressed to the point where cellular function was sufficiently diminished so that vacuolization was not observed in this exposure group. In general, atrophied cells and tissues may have diminished function, but are not considered to be devoid of function. However, atrophy may progress to more severe cell injury and eventually cell death with continued exposure (Kumar et al., 2004). Atrophy was chosen from the principal study as the critical endpoint because it is considered to be an adverse effect and is observed, along with vacuolization, at the lowest exposure concentration. This does not imply that the vacuolization observed in the same nasal tissue is not relevant. Vacuolization is also considered to be a compound- related effect not noted in controls, and typically accompanies atrophy. Vacuolization was observed in male and female animals exposed at the lowest concentration. If vacuolization was a known precursor to atrophy, this endpoint would be considered the critical effect. However, as this effect is considered an autophagocytic response and accompanies the minimal atrophy at the lowest dose, atrophy was selected as the critical effect and is considered an effect that is on the continuum to severe cell injury and cell death.

The decrease in incidence and decreased severity of the nasal lesions in females relative to males is likely to be attributable to the differences in exposure duration and approximate 6-day period between cessation of exposures after GD 20 and sacrifice on PND 4. This observation may also indicate that these effects are reversible and that repair and regeneration of the olfactory epithelium has been initiated. Regeneration and repair of the olfactory epithelium are dynamic processes characterized initially by disorganized cell proliferation of basal cells, which may begin within 24 hours, but complete turnover of cells takes approximately 30 days (Harkema et al., 2006; Hardisty et al., 1999). However, pathological indications (e.g., cell proliferation, hyperplasia) that these processes were ongoing in the female rats were not noted.

Taken together, the nasal lesion data for propionaldehyde over the range of exposure concentrations tested show a progression in both severity and incidence from no effects in controls to manifestations of more definitive cellular injury, diminished cellular function, and nasal tissue toxicity (i.e., atrophy accompanied by vacuolization, necrosis, and squamous metaplasia). This progression was observed in both males and females. In addition, this pattern of nasal lesion progression is similar to that observed with exposure to acetaldehyde in animals (Woutersen et al., 1986; 1984; Appelman et al., 1982). In these studies, inhalation exposure to acetaldehyde over a period for up to 28 months produced olfactory degeneration/atrophy with and without hyperplasia/metaplasia at 4 weeks, followed by progression to focal basal cell hyperplasia of the olfactory epithelium and squamous metaplasia of the respiratory epithelium at 12–15 months and finally by squamous cell carcinomas and adenocarcinomas at 16–28 months.

The severity and incidence of these nasal effects were dependent on exposure concentration and duration. A similar pattern and progression of nasal olfactory lesions were observed in rats exposed to acetaldehyde for up to 65 exposure days (Dorman et al., 2008). Olfactory epithelial degeneration, noted as the most sensitive endpoint observed, increased in incidence and severity with both exposure concentration and duration. The presence of vacuolization was also noted, but the severity was not graded. In this study, olfactory degeneration was observed prior to the appearance of vacuolization upon interim sacrifice at each exposure concentration tested. Vacuolization was not observed at exposure concentrations that did not induce degeneration. In rats exposed chronically to isobutyraldehyde, nonneoplastic lesions in the nose consisted of squamous metaplasia of the respiratory epithelium at concentrations ≥500 ppm, degeneration of the olfactory epithelium at 2,000 ppm, and suppurative inflammation at 2,000 ppm (NTP, 1999). No increases in neoplastic nasal lesions were observed in this study. Exposure to formaldehyde for 13 weeks also produced similar effects in the nasal respiratory epithelium, consisting of epithelial hyperplasia, squamous metaplasia, and increases in cell proliferation at concentrations as low as 3 ppm (Zwart et al., 1988). Formaldehyde-induced nasal tumors are reported at concentrations ≥6 ppm after chronic exposure (Monticello et al., 1996).

5.2.2. METHODS OF ANALYSIS

A benchmark concentration (BMC) analysis was conducted on the incidence of atrophy of the olfactory epithelium in male rats as observed in the Union Carbide (1993) study. This nasal lesion in male rats was the most biologically and toxicologically relevant response identified, and the available concentration-response information supports the use of this analytical approach. The results from the BMC analysis and the model outputs are discussed in Section 5.2.3 and shown in Appendix B.

5.2.3. RFC DERIVATION—INCLUDING APPLICATION OF UNCERTAINTY FACTORS (UFS)

The benchmark dose (BMD) approach provides the BMC and its 95% lower confidence limit (BMCL) associated with a particular benchmark response (BMR). The BMCL is then used as the point of departure (POD) in determining the RfC. A BMR of 10% extra risk of olfactory atrophy was considered appropriate for derivation of the RfC under the assumption that it represents a minimally biologically significant response level, owing to the minimal degree of atrophy (i.e., 2/15 (~13%) animals responding with a severity scoring of minimal at the low dose of 150 ppm) observed at this response level. This response level is also within the range of the experimental data, minimizing extrapolation uncertainty. The critical effect, olfactory atrophy, is compound related, biologically significant, consistent with lesion progression at higher exposure concentrations, and not noted in control groups.

Overall, the data were best fit by the Weibull model, which calculated a BMC_{10} of 149.8 ppm or 366 mg/m^3 and a $BMCL_{10}$ of 53.7 ppm or 128 mg/m^3 (for details of this BMD calculation see Appendix B). A BMR of 5% extra risk was also considered for comparison purposes, and resulted in a $BMCL_{05}$ of 26.1 ppm, about twofold lower than the $BMCL_{10}$ (see Appendix B). The $BMCL_{10}$ was adjusted for duration from the experimental exposure regimen of 6 hours/day, 7 days/week for 7 weeks (52 total exposures) to a continuous exposure as follows:

$$BMCL_{10\,ADJ} = 128\ mg/m^3 \times 6/24 \times 7/7$$
$$= 32\ mg/m^3$$

In accordance with the guidance for deriving inhalation RfCs (EPA, 1994), a regional gas dose ratio (RGDR) for a gas with extrathoracic (i.e., nasal region to larynx) respiratory effects was then derived by using a calculated ventilation rate (V_E) of 0.264 L/minute (based on the average body weight of the male CD rats reported in the principal study) and a default value of 13.8 L/minute for humans, along with default extrathoracic region surface area (SA) values of 15.0 cm^2 for the rat and 200 cm^2 for humans. The resulting equation is as follows:

$$RGDR = \frac{V_E\ (rat) / SA\ (rat)}{V_E\ (human) / SA\ (human)}$$
$$= \frac{0.264 / 15}{13.8 / 200}$$
$$= 0.26$$

Applying the RGDR of 0.26 to the $BMCL_{10/ADJ}$ of 32 mg/m^3 yields a $BMCL_{10/ADJ}$ dosimetrically adjusted to a human equivalent concentration (HEC) ($BMCL_{10\ HEC}$) of 3.4 ppm or 8 mg/m^3.

The $BMCL_{10/HEC}$ of 3.4 ppm (8 mg/m^3) was used as the POD for calculating the RfC, and to this a total UF of 1,000 was applied: 3 ($10^{1/2}$) for extrapolation from animals to humans (UF_A), 10 for intrahuman variability (UF_H), 10 for subchronic to chronic duration (UF_S), and 3 for database deficiency (UF_D).

A default UF_A of 3 ($10^{1/2}$) was applied to account for interspecies (animal-to-human extrapolation). This factor incorporates two areas of uncertainty given equal weight: pharmacokinetics and pharmacodynamics. Because the pharmacokinetic component was addressed in this assessment by the calculation of the HEC by applying the RGDR in extrapolating from animals to humans according to the procedures in the RfC methodology (EPA, 1994), only the pharmacodynamic component of this factor of uncertainty remains.

A default UF_H of 10 was applied for intraspecies uncertainty to account for human variability and sensitive subpopulations as there was very limited information available to definitively address the variability in the severity or range of response from propionaldehyde exposure among individuals, and available data suggest there are differences among humans in metabolism of propionaldehyde. Recent PBPK modeling investigating the impact of ALDH2 polymorphisms on rat and human nasal tissue dosimetry demonstrated a negligible impact on olfactory tissue dose (Teeguarden et al., 2008). Additionally, application of this UF considers the potential sensitivity of children and individuals with conditions such as asthma.

A default UF_S of 10 was applied to account for adjustment from subchronic to chronic duration. A subchronic study was used to derive the RfC, as no other supportive studies of similar or longer durations were available for propionaldehyde.

A UF_D of 3 ($10^{1/2}$) was applied to account for database deficiencies. The database for propionaldehyde consists of several short-term inhalation animal studies, ranging from 6 days to 7 weeks in duration, and two reproductive/developmental toxicity studies. The database is lacking a multigeneration reproductive toxicity study. Although the principal study used for the RfC derivation was a reproductive/developmental study (Teeguarden et al., 2008), this study provided limited reproductive and developmental information, since the pups were sacrificed on PND 4 and pathology in the pups was not evaluated; only an external examination for the presence of malformations was performed. Although limited nasal sectioning (i.e. 2–3 sections compared to typical 4–6) was performed at necropsy, the critical effect identified was atrophy of the olfactory epithelium in adult male rats (also observed in females), which is concordant with the portal-of-entry effects attributable to the aldehydes acrolein, formaldehyde, acetaldehyde, and isobutyraldehyde as well as other irritant gases. In addition, none of these aldehydes appear to induce direct systemic effects, as measured by clinical chemistry and pathology, at exposure concentrations that produce initial portal-of-entry effects. Similarly, propionaldehyde would not be anticipated to have significant systemic distribution based on its deposition, solubility, and reactivity in the respiratory tract. The uptake of propionaldehyde in the upper respiratory tract measured in dogs is approximately 70–80% (Egle, 1972a). In the same study, moderate to high respiratory tract uptake was observed for both acrolein (~80%) and formaldehyde (near 100%). In the rat, acetaldehyde uptake in the upper respiratory tract averaged from 76 to 26% over a concentration range of 1–1,000 ppm (Stanek and Morris, 1999; Morris and Blanchard, 1992). In general, the toxicological information and limited kinetic information available for propionaldehyde is consistent with other structurally related aldehydes and provides support for

the critical effect chosen. However, the lack of a multigeneration reproductive toxicity study warrants the application of a UF_D of 3.

No LOAEL to NOAEL UF was applied since BMC analysis was used to determine the POD, and this factor was addressed as one of the considerations in selecting the BMR. Based on the data, a BMR of 10% change in the incidence of minimal olfactory atrophy was selected under an assumption that it represents a minimal biologically significant change.

Application of a total UF of 1,000 ($10^{1/2} \times 10 \times 10 \times 10^{1/2}$) to the $BMCL_{10\ HEC}$ of 8 mg/m^3 yields an RfC of 8×10^{-3} mg/m^3.

5.3. CANCER ASSESSMENT

No studies are available on the carcinogenic effects of propionaldehyde on which to base a cancer assessment.

5.4. GENERAL UNCERTAINTY IN THE PROPIONALDEHYDE NONCANCER AND CANCER ASSESSMENT

The paucity of data for this compound, especially for those effects that could serve as alternate sources for quantitative evaluation, prevent a further meaningful in-depth quantitative analysis of uncertainty. It is anticipated, however, that the potential uncertainty of this assessment could be informed both in qualitative and quantitative terms from the more robust databases of the structurally related aldehydes, formaldehyde, acetaldehyde and isobutyraldehyde. The areas of uncertainty for consideration in the assessment for propionaldehyde are outlined in Table 5-2.

Table 5-2. Summary of general uncertainty in the propionaldehyde noncancer and cancer risk assessments

Area of consideration	Potential impact[a]	Decision	Justification
Choice of study	No RfC.	Union Carbide (1993) study chosen.	No alternative choices are available.
Choice of noncancer endpoint	Use of cardiac responses vs. olfactory epithelium atrophy could ↑ RfC several-fold.	RfC is based on the most biologically relevant endpoint, atrophy of olfactory epithelium.	Chosen endpoint is consistent with expected chemical irritation properties of agent and is reasonably anticipated to be relevant for humans for the same reasons. Cardiac responses observed in acute studies conducted at exposure concentrations at least eightfold higher than those showing nasal effects.

Area of consideration	Potential impact[a]	Decision	Justification
Human relevance of data (portal-of-entry vs. site-specific respiratory tract effect)	Assuming no relevance of results would indicate that RfC may be unnecessarily low or not applicable.	Assume human relevancy.	Due to the irritation-type mode of action involving the general reactivity of the functional group (i.e., aldehyde) with tissue constituents regardless of source or site within the respiratory tract, there is comparatively little uncertainty concerning applicability of relevance to humans. This same reasoning may be used to assume site concordance (i.e., portal-of-entry) although the relative effects at different sites in the respiratory tract may differ between species due to differences in airflow patterns and regional uptake within the respiratory tract.
Potential deficiency in necropsy of target tissue	Limited sectioning per animal may have resulted in missed lesions that could underestimate actual incidence per exposure group, assuming such lesions would be observed in all sections and underestimate risk such that the RfC could possibly be ↓.	Use Union Carbide (1993) study (only available repeated-concentration study).	Although sectioning in target tissues (nasal tract) was limited (two sections vs. typical three to six per animal), effects, including atrophy, were found at all concentrations. The pathology findings are consistent with nasal lesions observed after exposure to other aldehydes and irritants.
Choice of gender	RfC could be ↑ or ↓ if based on another gender.	RfC is based on olfactory atrophy in males. Males are observed to be more sensitive possibly as a result of study design.	Although progression of nasal effects is seen in both males and females, there was a clear decrease in incidence and decreased severity in females (likely to be attributable to the differences in exposure duration approximate 6-day period between cessation of exposures after GD 20 and sacrifice on PND 4 versus continued exposure in males during this period). Comparable incidence data from females not available based on this study design.
Choice of species	RfC could be ↑ or ↓ if based on another species.	RfC is based on the most clearly relevant endpoint in the only species tested, rat.	Only species tested in the available study. Comparable effects for propionaldehyde in other strains or species not known.
POD derivation method for noncancer RfC	Little difference as LOAEL is at 13% response and thus is near the $BMCL_{10}$.	BMD method used.	Advantages include capacity to account for sample size that is quantitatively reflected in providing confidence bounds on dose.
Choice of model for BMCL derivation	Other models ↑ (approx. 1.5-fold) or ↓ (approx. 1.3-fold) RfC.	Weibull model chosen.	U.S. EPA (2000c) BMD technical guidance used to choose best fitting model.
Statistical uncertainty at POD	POD would be ~40% higher if BMC (vs. BMCL) were used.	BMCL used per U.S. EPA BMD guidance (EPA, 2000c).	Limited size of bioassay results in sampling variability; lower bound is 95% confidence interval on administered exposure.
Use of dosimetry in calculation of HEC	Use of dosimetry increases scientific robustness of assessment.	Apply dosimetry.	Dosimetry methodology accommodates estimation of dose at the site of toxicity (nasal tract), thus providing target-tissue dosimetry.

Area of consideration	Potential impact[a]	Decision	Justification
Human population variability	Risk unknown.	Default 10-fold uncertainty factor applied to derive the RfC value.	10-fold UF is applied principally because of lack of definitive and quantifiable information on the variability of response with this mode of action. Specific subgroups (e.g. asthmatics and children) may be more sensitive to inhaled irritants and aldehydes, but definitive information for propionaldehyde is lacking. The default factor for intrahuman variability is used to ensure that the risk to chemicals and stressor are not underestimated.
Potential for cancer	Risk unknown.	Note concern for carcinogenic potential.	The presence of the more resilient squamous metaplasia (without atypia) is an anticipated response of airway portal-of-entry tissues being exposed to irritants such as aldehydes. However, the presence of nasal tumors in conjunction with squamous metaplasia in lifetime studies of related aldehydes (formaldehyde and acetaldehyde) raises a concern that cannot be addressed with the propionaldehyde since the Union Carbide (1993) study was only 7 weeks in duration.

[a]↑ = increase; ↓ = decrease.

6. MAJOR CONCLUSIONS IN THE CHARACTERIZATION OF HAZARD AND DOSE RESPONSE

6.1. HUMAN HAZARD POTENTIAL

Propionaldehyde is an aldehyde used primarily to manufacture polyvinyl, other plastics, and propionic acid. It is released to the environment mainly through wood and gasoline combustion and from municipal waste incinerators. Propionaldehyde has been detected in ambient air, indoor air, and drinking water (NLM, 2004). Propionaldehyde is also a component of both mainstream and sidestream cigarette smoke (Counts et al., 2005). The primary route of exposure to propionaldehyde is expected to be via inhalation. No studies on the effects of propionaldehyde administered by the oral route have been performed. Propionaldehyde has also been approved by both U.S. FDA and WHO/JECFA as a synthetic flavoring ingredient for direct addition to food; the alcohol (propanol) and acid (propionic acid) are similarly approved (FDA, 2003; WHO, 1999; IPCS, 1998).

Limited data are available on the pharmacokinetics of propionaldehyde. In an inhalation study conducted in dogs, Egle (1972a) determined that the animals retained approximately 70–80% of the inspired concentration of propionaldehyde. An in vitro study in a rat hepatoma cell line showed propionaldehyde to be efficiently metabolized via aldehyde dehydrogenase (Bassi et al., 1997). Wang et al. (2002) performed a genotype analysis of the ALDH2 gene in human volunteers and found polymorphisms in the ALDH gene that appeared to alter propionaldehyde metabolism. It is not clear, however, if this alteration would lead to a significant increase in parent aldehyde exposure in those individuals with specific polymorphisms of this gene. A rat study demonstrated increased urinary excretion of propionaldehyde, formed via lipid peroxidation, with age and for animals on a restricted diet (De Tata et al., 2001).

No studies in humans are available for propionaldehyde. No subchronic or chronic oral animal studies are available for the chemical. However, three short-term inhalation animal studies, ranging from 6 days to 7 weeks in duration, are available. Gage (1970) exposed male and female rats to 90 ppm propionaldehyde 6 hours/day for 20 exposures or to 1,300 ppm propionaldehyde 6 hours/day for 6 days. No changes in body weight or clinical signs were noted. Microscopic examination revealed liver cell vacuolation in animals exposed to 1,300 ppm propionaldehyde. Two short-term rat developmental inhalation studies conducted by Union Carbide (1993, 1991) are also available. In a range-finding study (Union Carbide, 1991), maternal toxicity was noted as exposure-related decreases in body weight gain were observed at exposure concentrations of 1,000 ppm and above. However, these decreases in body weight gain were accompanied by decreases in food consumption throughout the gestation period. In the high concentration group, there was a significant reduction in fetal body weights, but no other evidence of any treatment-related external malformations or variations was observed. In the second study, young adult male and female rats were exposed to propionaldehyde during a

2-week premating period and a 14-day mating phase (Union Carbide, 1993). The mated females were exposed daily through GD 20 for a minimum of 35 days and a maximum of 48 days. The males continued to be exposed until sacrifice in week 7, for a total of 52 exposures. No significant effects of exposure on any of the reproductive parameters assessed were found. Litter size and viability were similar among the groups. Absolute pup body weights on PND 0 and 4 were not affected by exposure, although, at the high concentration, body weight gain for that period was significantly depressed. The biological significance of this finding is difficult to assess, since changes in absolute body weight were not demonstrated and the period of observation was relatively short. The most significant exposure-related effects were found in the nasal cavity. In the adult females, microscopic examination revealed propionaldehyde-induced vacuolization in the low and intermediate exposure groups and atrophy of the olfactory epithelium in the low, intermediate, and high exposure groups. The incidence of atrophy increased with exposure concentration. No evidence of squamous metaplasia was found in olfactory or respiratory epithelium. In the adult males, as in the females, microscopic examination revealed exposure-related effects in the olfactory epithelium, consisting of vacuolization and atrophy in the low, intermediate, and high exposure groups. The incidence of atrophy increased with exposure concentration and was greater than observed in the females. In both males and females, the severity of this nasal lesion increased with exposure concentration. In males only, a low incidence of squamous metaplasia in the respiratory epithelium was reported in both the intermediate and high exposure groups. A decrease in incidence and decrease in severity of the nasal lesions in females relative to males was observed and could be attributable to the differences in exposure duration and approximate 6-day period between cessation of exposures after GD 20 and sacrifice on PND 4. This observation may also indicate that these effects are reversible and that repair and regeneration of the olfactory epithelium has been initiated. However, pathological indications (e.g., cell proliferation, hyperplasia) that these processes have started in the female rats were not noted.

Squamous metaplasia was noted as a compound-related lesion in the upper airways of rats exposed to propionaldehyde. Although the occurrence of this lesion, especially in the upper airways, may occur as a response to repeated irritation whereby a resistant type of epithelium replaces a more susceptible one, it has also been noted along with nasal tumors in lifetime studies of related aldehydes, including formaldehyde and acetaldehyde. Thus, this pattern of nasal tissue effects in this relatively short-term study and nasal carcinogenicity of related aldehydes raises some concern for the carcinogenic potential of this compound.

The genotoxicity of propionaldehyde has been studied in bacteria and a number of mammalian cells in vitro. Propionaldehyde was found to be mutagenic in *S. typhimurium* strain TA1534 (Sampson and Bobik, 2008) and nonmutagenic in all other strains tested (Dillon et al., 1998; Aeschbacher et al., 1989; Mortelmans et al., 1986), but produced concentration-related increases in HGPRT (with notable decreases in cell viability) and ouabain mutants in V79

hamster cells (Brambilla et al., 1989). Propionaldehyde produced a concentration-related increase in chromosome aberrations in Chinese hamster embryonic cells (Furnus et al., 1990) and chromosome breaks in CHO cells (Seoane and Dulout, 1994). In addition, propionaldehyde induced a concentration-related increase in unscheduled DNA synthesis in rat, but not human, hepatocytes (Martelli, 1997; Martelli et al., 1994) and a weak, concentration-related increase in DPXs in cultured human lymphoma cells (Costa et al., 1997). Propionaldehyde also formed protein adducts with hemoglobin in vitro (Hoberman and San George, 1988).

Two studies have shown that propionaldehyde produces concentration/dose-related changes in blood pressure and heart rate after inhalation or i.v. administration in rats (Egle et al., 1973; Egle, 1972b). A study on mouse lymphocytes demonstrated significant inhibition of T-lymphocyte and B-lymphocyte proliferation, with no effects on cell viability (Poirier et al., 2002). Studies on the toxicity relationships (in terms of cytotoxicity) among propionaldehyde and other aldehydes showed that acrolein was the most toxic compound, formaldehyde next, followed by acetaldehyde, and finally propionaldehyde, with the conclusion that cytotoxicity generally decreased with increasing (saturated) aldehyde chain length (Bombick and Doolittle, 1995; Koerker et al., 1976). Similar relationships among various aldehydes were noted when comparing RD_{50} values in mice (Steinhagen and Barrow, 1984). The α,β-unsaturated aliphatic aldehydes (acrolein and crotonaldehyde) and formaldehyde were approximately two orders of magnitude more potent than the saturated aliphatic aldehydes (e.g., propionaldehyde, acetaldehyde butyraldehyde, and isobutyraldehyde) in producing a 50% decrease in respiration rate. In a review by Guth (1996), it was concluded from a comparison of the effects of propionaldehyde and acetaldehyde for a variety of endpoints that there should not be major differences in toxicity between acetaldehyde and propionaldehyde. Similarly, analysis and comparison of the nasal lesion data between acetaldehyde and propionaldehyde supports this conclusion.

Based on the information provided from animal studies, the most likely adverse human health effects that would be anticipated from exposure to propionaldehyde would be primarily respiratory tract irritation and secondarily cardiovascular perturbations. No human health effects data or chronic animal bioassay studies are available that assess the carcinogenic effects of propionaldehyde. Therefore, in accordance with the *Guidelines for Carcinogen Risk Assessment* (EPA, 2005a), there is “inadequate information to assess the carcinogenic potential” for propionaldehyde.

6.2. DOSE RESPONSE

Quantitative estimates of cancer risk for propionaldehyde were not developed due to the lack of data on the potential carcinogenicity of the compound.

Quantitative estimates of noncancer risk from the oral route of exposure were not developed for propionaldehyde because of the lack of human or animal data.

A quantitative estimate of the noncancer risk for the inhalation route of exposure was developed from animal data, since no human data are available. An RfC of 8×10^{-3} mg/m^3 was derived from the incidence data of olfactory atrophy in adult male rats reported in a 7-week (52 total exposures) reproductive and developmental study conducted by Union Carbide (1993). BMC analysis of this data was best fit by the Weibull model, which calculated a $BMCL_{10}$ of 53.7 ppm or 128 mg/m^3.

The RfC was derived by duration adjusting the $BMCL_{10}$ of 128 mg/m^3 from the experimental exposure regimen of 6 hours/day, 7 days/week for 7 weeks (52 total exposures) to a continuous exposure yielding a $BMCL_{10/ADJ}$ of 32 mg/m^3. Applying the RGDR calculated for a gas with extrathoracic respiratory effects of 0.26 (EPA, 1994) resulted in an HEC ($BMCL_{10/HEC}$) of 8 mg/m^3. The $BMCL_{10/HEC}$ was used as the POD for calculating the RfC. A total UF of 1000 was applied: 3 ($10^{1/2}$) for extrapolation from animals to humans (UF_A), 10 for intrahuman variability (UF_H), 10 for subchronic to chronic duration (UF_S), and 3 for database deficiency (UF_D). Application of a total UF of 1000 ($10^{½} \times 10 \times 10 \times 10^{½}$) to the $BMCL_{10/HEC}$ of 8 mg/m^3 yielded an RfC of 8×10^{-3} mg/m^3.

Confidence in the principal study (Union Carbide, 1993) is judged to be low to medium because few details were provided specific to the study results. In addition, the key study provided limited developmental information as the pups were sacrificed on PND 4 and pathology was not evaluated; only an external examination for the presence of malformations was performed. However, the critical effect identified was atrophy of the olfactory epithelium in adult male rats (also observed in females), which is concordant with the portal-of-entry effects attributable to irritant gases and other aldehydes. Thus, this endpoint is supported by the aldehyde inhalation exposure-effects database as a whole. Confidence in the critical effect identified in the principal study is medium. Confidence in the overall database specific to propionaldehyde is low because there are no additional and/or supporting subchronic or chronic animal studies available to evaluate and support the concentration-response effect of propionaldehyde on multiple endpoints. Therefore, confidence in the RfC is judged to be low to medium.

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APPENDIX A. SUMMARY OF EXTERNAL PEER REVIEW AND PUBLIC COMMENTS AND DISPOSITION

The "Toxicological Review of Propionaldehyde" has undergone a formal external peer review performed by scientists in accordance with EPA guidance on peer review (EPA, 2006b). For the external peer review, the reviewers were tasked with providing written answers to general questions on the overall assessment and on chemical-specific charge questions, addressing key scientific issues of the assessment. A summary of significant comments made by the external reviewers and EPA's responses to these comments arranged by charge question follow. Editorial comments were considered and incorporated into the document as appropriate and are not discussed further. EPA also received comments from the public. A summary of public comments and EPA's responses are also included.

EXTERNAL PEER REVIEWER COMMENTS

General Charge Questions:

Charge Question 1: Is the Toxicological Review logical, clear and concise? Has EPA accurately, clearly and objectively represented and synthesized the scientific evidence for noncancer and cancer hazard?

Comment:

All four reviewers commented that the Toxicological Review was written in a logical and generally clear and concise manner, although there is some repetition in various sections. The document provides a strong review of the available data relative to derivation of an RfC value for propionaldehyde. It does fall short of the ideal in some key respects resulting from the lack of a dedicated long-term inhalation toxicity study which would address the question of possible carcinogenicity. Two of the reviewers agreed that a strength of the document is that it evaluates the toxicity information on propionaldehyde in the context of the complete database on structurally similar aldehydes such as formaldehyde and acetaldehyde while recognizing that a full structure activity relationship analysis is not possible. The use of this comparative structure-activity approach to address uncertainties and data gaps in regard to propionaldehyde is particularly useful in presenting a coherent overall picture. In this regard inclusion of information on isobutyraldehyde toxicity would be highly valuable. Weaknesses in the database are clearly delineated; the document appropriately identifies the principal study while clearly indicating its deficiencies. Two of the reviewers also commented that the document correctly identifies the critical effect and does so in a logical, clearly expressed and transparent fashion. The overall conclusion that olfactory atrophy represents the critical effect is sound and demonstrates a strong knowledge of the nasal toxicological issues that represent important considerations in a risk evaluation. Since the structurally related compound acetaldehyde also produces this lesion the

text correctly highlights the current information available on this compound. One reviewer commented that the derivations are consistent with EPA policy but that the scientific basis for the default nasal dosimetric assumptions is questionable. Overall, the four reviewers agreed that the review accurately and succinctly synthesizes the available scientific evidence for noncancer effects in a clear manner. The available studies are accurately represented and the selection of the principal study is presented in an objective manner.

Response:

For the sake of completeness and clarity, information on the structurally-related aldehydes (i.e. butyraldehyde and isobutyraldehyde) was added to the genotoxicity section where available. The results and a discussion of the chronic NTP study (1999) conducted for isobutyraldehyde was also added to complete the comparison discussion of related aldehyde-induced portal-of-entry effects. For this assessment, an attempt was made to include and compare only the genotoxicity and portal-of-entry results from the other aldehydes (formaldehyde, acetaldehyde, butyraldehyde and isobutyraldehyde) that are relevant to those observed for propionaldehyde. Therefore, the review is not meant to reflect information from the aldehyde database as a whole. However, a few genotoxicity results for longer-chain aldehydes are included for comparison although in vivo toxicity studies are lacking. Comments regarding EPA policy on nasal dosimetry assumptions will be considered whenever EPA revisits this guidance issue.

Charge Question 2: Please identify any additional studies that should be considered in the assessment of the noncancer and cancer health effects of propionaldehyde.

Comment:

Two of the four reviewers were unaware of any additional studies that should be considered in the assessment of propionaldehyde. Two of the four reviewers suggested the additional studies by Dorman et al. (2008), Teeguarden et al. (2008), Sampson and Bobik (2008), Oyama et al. (2007), and the NTP (1999) study conducted for isobutyraldehyde should be considered in the draft assessment. Additional studies for possible inclusion were noted similarly in response to other charge questions.

Response:

These references, as well as others cited specifically in response to other charge questions, were reviewed and incorporated into the assessment as appropriate.

Charge Question 3: Please discuss research that you think would be likely to increase the confidence in the database for propionaldehyde in future assessments.

In response to this question, the reviewers offered the following points:

- The identified areas of uncertainly provide sound direction for future research. For

example, a well designed and performed chronic inhalation study for propionaldehyde which includes complete nasal sectioning would enhance the database, as would a multigenerational study. In addition, since there are no carcinogenicity data, a two year bioassay would provide useful information. The priority for such a study depends on the degree of importance one places on the carcinogenic response to acetaldehyde vs. isobutylaldehyde relative to the potential response to propionaldehyde. Finally, since the current dosimetric extrapolation procedures of the US EPA are so controversial, precise information on the inhalation dosimetry of propionaldehyde would strongly aid in the formation of a scientifically based quantitative inhalation risk assessment of this compound.

- A major deficiency of the existing database is the lack of a long-term inhalation carcinogenicity study. Supporting studies of deposition in the respiratory tract, cell proliferation and formation of DNA-protein crosslinks have provided extensive additional understanding of the effects of formaldehyde and, to a lesser extent, acetaldehyde. It would be helpful if at least some of these studies were extended to include propionaldehyde.

- It was stated that the literature search was conducted before July, 2007. We found no other studies with propionaldehyde that are relevant to health effects. However, a main argument in the RfC derivation is that propionaldehyde is toxicologically similar in many aspects to acetaldehyde. There were recently two publications on acetaldehyde inhalation: Teeguarden et al., 2008. A PBPK Model for Evaluating the Impact of Aldehyde Dehydrogenase Polymorphisms on Comparative Rat and Human Nasal Tissue Acetaldehyde Dosimetry. Inhalation Toxicology 20:375-390, 2008, and Dorman et al., 2008. Derivation of an Inhalation Reference Concentration Based Upon Olfactory Neuronal Loss in Male Rats Following Subchronic Acetaldehyde Inhalation. Inhalation Toxicology 20:245-256, 2008. These publications should be considered in future risk assessments of propionaldehyde. As far as the current review is concerned, these publications only strengthen the argument for using olfactory atrophy as the critical effect, since this was also the endpoint selected for acetaldehyde.

Response:

The assessment has been updated to incorporate the newer information available from the studies on acetaldehyde published since July 2007 as well as the results from the new study on propionaldehyde mutagenicity in salmonella.

Charge Question 4: Please comment on the identification and characterization of sources of uncertainty in sections 5 and 6 of the assessment document. Please comment on whether the key sources of uncertainty have been adequately discussed. Have the choices and assumptions made in the discussion of uncertainty been transparently and objectively described? Has the impact of the uncertainty on the assessment been transparently and objectively described?

Comment:

All four reviewers commented that the majority of uncertainties were appropriately identified and characterized, and that Table 5-1 is quite useful in this regard. The impact of the uncertainties on the assessment has been transparently and objectively described.

One of the four reviewers noted that the potential for reactive irritants to exacerbate conditions such as asthma should be addressed in the document.

Two of the four reviewers commented that the human relevance of data in the uncertainty discussion could be enhanced by adding points that the relative effects at different sites in the respiratory tract may differ between species due to differences in airflow patterns and regional uptake within the respiratory tract. The major consideration being that animals with more extensive nasal passages than found in humans may have greater effect in the upper respiratory tract, while there may be greater penetration into the lower respiratory tract in humans.

Response:

A discussion of the effect irritants may have on sensitive subpopulations such as asthmatics was added to the document (Section 4.7.4).

Additional discussion points concerning the human relevancy of the animal data in consideration of potential differences of specific site of effect in the respiratory tract was added to the document.

Chemical-Specific Charge Questions:

(A) Oral reference dose (RfD) for propionaldehyde

Charge Question 1: No oral RfD has been derived in the current draft assessment based on the lack of studies available that examine the effects of propionaldehyde administered via the oral route. Are there available studies missing from the draft document that might be useful for deriving an oral RfD or that should be considered in this decision?

Comment:

None of the four reviewers were aware of any studies that would inform development of an RfD. One of the four reviewers suggested that a reference could be made that formaldehyde and acetaldehyde appear to be less hazardous by the oral route compared to the inhalation route

(Morris et al., 1996). One of the four reviewers suggested that some insight into tolerable levels of propionaldehyde taken in orally would be useful.

Response:

The write up in section 2 of the assessment does provide information on the intake levels of propionaldehyde considered to be tolerable as a food additive (WHO, 1999). The Morris et al. 1996 citation was added to the text.

(B) Inhalation reference concentration (RfC) for propionaldehyde

Charge Question 1: The current draft IRIS assessment for propionaldehyde uses a combined reproductive/developmental exposure study by Union Carbide (1993) as the principal study for the derivation of the RfC. Please comment on whether the selection of this study as the principal study has been scientifically justified. Has this study been transparently and objectively described in the document? Please identify and provide the rationale for any other studies that should be selected as the principal study. Is this study appropriate for use in this assessment?

Comment:

Two of four reviewers commented that the selection of this study of the principal study was scientifically justified. One of four reviewers commented that the selection of this study was transparently and objectively described. Two of the four reviewers also commented that the description of the principal study was appropriately or clearly described in the document. Two of four reviewers also commented that as appropriately noted, this study is far from ideal for the purpose, is the only study available, but nevertheless is sufficient to provide a basis for the RfC. One reviewer also commented that the concerns in using this study have been adequately addressed in this document.

One of the four reviewers also commented that the section on the comparative toxicity of aldehydes represents a strong component of the overall risk assessment. In addition, given the structural similarity between acetaldehyde and propionaldehyde and the similarity of nasal lesions induced by both compounds, the recent study of Dorman et al., (2008) on subchronic acetaldehyde inhalation toxicity should appropriately be included. Similarly information on inhalation toxicity of butyraldehyde and isobutyraldehyde including the NTP studies should be included as well.

Response:

Discussions of the data relevant to propionaldehyde from studies on acetaldehyde, butyraldehyde, and isobutyraldehyde have been added to the appropriate sections of the document.

Charge Question 2: Has the most appropriate critical effect (increase incidence of olfactory

atrophy in male rats,) presented in Sections 4.3 and 4.5.2 of the Toxicological Review been selected? Is the rationale for this selection transparently and objectively described in the document? Please comment on whether the selection of this critical effect has been scientifically justified. Please comment on the choice of olfactory atrophy as the critical effect as opposed to other endpoints (e.g., vacuolization) and the rationale that this endpoint was chosen because it is on the continuum leading to overtly adverse effects such as cell death. Has the qualitative pathological relationship between effects observed been adequately and appropriately characterized? Please provide a detailed discussion. Please identify and provide the rationale for any other endpoints that should be used instead of increased incidence of olfactory atrophy in male rats to develop the RfC.

Comment:

Based on the propionaldehyde database, three of the four reviewers were in general agreement that the choice of the critical endpoint lesion is scientifically justified, reasonable, appropriate, and represents the critical response. One reviewer noted, however, due to the paucity of the database this was the only effect that could be selected for derivation of the RfC. Had other studies been available, perhaps this effect would not have been the one of greatest biological significance. One reviewer further commented that the rationale for the selection of the critical response is scientifically sound, transparently and objectively described, and is consistent with the critical effects for other reactive aldehydes such as formaldehyde, acetaldehyde and acrolein. One reviewer also noted that the description of the lesions is adequate to relate propionaldehyde-induced lesions to the lesions induced by these other nasal toxicants and that olfactory atrophy represents a toxic lesion. Two of the four reviewers commented that the data clearly indicate a concentration response continuum for these lesions and use of 150 ppm as the LOAEL, based on olfactory atrophy and vacuolization is appropriate. The incidence of olfactory atrophy has a well-defined dose response curve for establishing a POD and extrapolating to human health effects.

Three of the four reviewers commented and were in general agreement on the characterization of the continuum of the qualitative pathological lesions and their concentration-response relationships - with vacuolization at the lower end and more severe effects, including various degrees of metaplasia and even carcinogenesis, at the upper end. However, one reviewer commented that the justification for placing a specific cut-off level for these effects at the level of atrophy as opposed to vacuolization is questionable and the discussion could be improved in that it is inappropriate to argue that the vacuolization is for some reason an “adaptive” or “compensatory” response which is not relevant, as opposed to the slightly more severe atrophy.

Response:

The choice of atrophy as the critical endpoint instead of vacuolization was not meant to imply that a level of vacuolization as a response is not relevant. The choice was made for atrophy as the

critical endpoint because it is the endpoint most closely associated with adversity (a decrease in cell function). Nothing in the literature could be cited indicating vacuolization is a precursor effect to atrophy (or any other lesion) in nasal tissue – only that the two effects often are observed together and are part of a continuum possibly leading to more severe effects with increasing exposure concentration and duration. Similar to propionaldehyde, the presence of vacuolization was noted along with olfactory degeneration in rats exposed to acetaldehyde (Dorman et al., 2008). In this study, the incidence of vacuolization decreased as atrophy increased with exposure concentration. The severity of vacuolization was not noted in this study and olfactory degeneration was considered to be the most sensitive endpoint. In addition, degenerative olfactory lesions were observed prior to the detection of vacuolization upon interim sacrifice at all exposure concentrations tested. Vacuolization was not detected at exposure concentrations that did not induce degeneration.

As noted elsewhere, discussion of the Dorman et al. (2008) study was added to the appropriate sections of the document.

Charge Question 3: BMD methods were applied to incidence data on olfactory atrophy in male rats to derive the POD for the RfC. Please provide comments with regard to whether BMD modeling is the best approach for determining the POD. Has the BMD modeling been appropriately conducted and objectively and transparently described? Has the BMR selected for use in deriving the POD (i.e., 10% extra risk of olfactory atrophy) been scientifically justified? Please comment on EPA's decision to treat all cases of olfactory atrophy similarly, without consideration of the severity of the atrophy seen at different dose levels. Please provide a detailed discussion and any suggestions for consideration of severity in determining the POD including identifying and provide rationales for any alternative approaches for the determination of the POD and discussion of whether such approaches are preferred to EPA's approach considering the available data.

Comment:

All four reviewers commented that the BMD approach is the preferred method and suitable for determining the POD for this data.

Two of the four reviewers commented that the choice of a 10% response rate was justifiable and consistent with the animal data and represents a biologically minimal significant response level. One of these two reviewers also commented that the value in the severity scores (increasing with exposure concentration) serves as justification for the use of olfactory atrophy as the critical effect.

Two reviewers commented that in consideration of severity and incidence, there may be some justification for reduction to the 5% level from the proposed 10% because the data appear more like a LOAEL than a NOAEL for straightforward quantal responses in animal toxicity studies. Therefore, it might be more appropriate to choose a BMR of 5%, and the 95% lower confidence limit on the dose producing this response rate, as the POD for this type of data.

Response:

All endpoints observed were considered for BMC modeling, however, only the atrophy data were amenable to this approach. Other modeling approaches (e.g. Categorical Regression) were considered for the data as a means to incorporate severity. However, it was determined that based on the nature of the responses observed – vacuolization and atrophy – that a degree of subjectivity in grading the severity among responses would be introduced. For example, would marked vacuolization be considered more severe than mild atrophy? A logical pathological progression model would be needed to definitively address such issues. In addition, evaluation of the individual animal data did not result in any definitive correlation between severity of vacuolization and atrophy. Therefore, the spectrum and severity of incidence effect data was used qualitatively to support our choice of endpoint to be modeled using BMD - atrophy.

As noted in response to the comments for Question 4, justification for using a BMR of 10% in determining the POD is provided in the text and consistent with EPA guidance and the power of the study (i.e. n = 15).

Charge Question 4: Please comment on the selection of the uncertainty factors applied to the POD for the derivation of the RfC. For instance, are they scientifically justified and transparently and objectively described in the document?

Comment:

Two of the four reviewers commented that the selection of uncertainty factors is clearly and transparently described, appear to follow EPA policy, and are consistent with precedent. One reviewer further commented that the factor of 10 for inter-individual differences is appropriate because of the known human polymorphisms in aldehyde dehydrogenase and the likely role of this enzyme in detoxifying propionaldehyde. Presumably this factor of 10 is sufficient to account for the potential sensitivity of persons with chronic lung disease such as asthma or COPD. This reviewer commented that these points might be explicitly stated in the text.

One reviewer commented that the basis for the default value of 3 for interspecies extrapolation was not clear.

One reviewer commented that if the proper POD (i.e. the lower 95% confidence limit on the dose producing a 5% rather than 10% response) for a quantal analysis had been selected the UF estimates selected and their justification would be acceptable. This reviewer discussed the use an alternative pseudo-continuous score-based variable assuming that any statistically distinguishable deviation constitutes an unacceptable impact (especially if the continuous change constitutes a demonstrably adverse and undesirable change at higher levels of response, as here).

Response:

Text describing the presumptions and intent of the application of the UF for inter-individual differences was added to the document.

Other approaches (e.g., Categorical Regression) and PODs for the data were considered in accordance with EPA guidance. However, each approach was considered to add subjectivity into analyzing the data specifically in regards to grading severity among the responses. Converting the incidence data to continuous data as suggested would also increase this subjectivity. Therefore, the spectrum and severity of incidence effect data was used qualitatively to support our choice of endpoint to be modeled using BMD - atrophy. The choice of a 10% BMR is consistent for the type of incidence data, effect level, and number of animals in accordance with the BMD Technical Guidance. The POD calculated (53 ppm) is also consistent with the observation of a NOAEL for acetaldehyde-induced nasal effects (vacuolization and degeneration) of 50 ppm (Dorman et al., 2008). Justification for this approach is provided in the document.

The use of a factor of 3 (to account for dynamics) for interspecies extrapolation is used when the RGDR approach (accounting for kinetics) is used to calculate an HEC from animal data.

Charge Question 5: Please comment specifically on the database uncertainty factor of 3 applied in the RfC derivation. Please comment on the body of information regarding reproductive and developmental toxicity on propionaldehyde, the relevance of toxicity data on other aldehydes, and the relevance of toxicokinetic data regarding the likelihood of portal-of-entry effects as the critical effects in the determination of the database uncertainty factor. Please comment on whether the selection of the database uncertainty factor for the RfC has been scientifically justified. Has this selection been transparently and objectively described in the document?

Comment:

Three of the four reviewers agreed that a database UF of 3 is appropriate for the data cited, which is restricted to consideration of possible deficiencies in the animal study database due to the lack of a multi-generational study. One of these three reviewers noted a limitation of the database is the absence of chronic toxicity data, however a UF = 10 was included for subchronic to chronic extrapolation. This reviewer also noted that a UF = 3 for this deficiency is consistent with other EPA documents previously reviewed. One of these three reviewers was concerned that the UF database does not take into account possible post-natal effects such as asthma. In addition, one reviewer commented on highlighting the modeling results for acetaldehyde (Dorman et al., 2008; Teeguarden et al., 2008) to provide insight into the interspecies extrapolation for propionaldehyde. One of these three reviewers also commented that the lack of nasal sectioning performed for propionaldehyde compared to typical practices warrants mention here as well as in Table 5-2.

One of the four reviewers commented that the justification provided in the document does not support the value of 3 but would support a value of 10 since the database is clearly lacking a long term study.

Response:

The justification of the application of a UF of 3 for database deficiencies in deriving the RfC was clarified in the document. The aldehyde database – which includes longer-term studies showing lack of systemic effects at concentrations producing similar portal-of-entry effects and information on respiratory tract dosimetry for three structurally-related aldehydes – was used to support the choice of endpoint as well as the limited propionaldehyde database. Information specific to propionaldehyde (and definitive studies for other aldehydes) on the exacerbation of asthma is scant. A database UF of 3 was applied primarily due to the lack of a multigenerational study and is consistent with EPA practices.

Lack of a chronic study is addressed under a separate UF.

A discussion of the acetaldehyde modeling results in the context of interspecies extrapolation was added to the uncertainty factor discussion.

Consideration of limited nasal sectioning was also added to the text. Although limited sectioning was performed, had nasal pathology not been evaluated – especially in light of the known nasal effects induced by other aldehydes – consideration for a database UF of 10 would have been warranted.

(C) Carcinogenicity of propionaldehyde

Charge Question 1: Under the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* (www.epa.gov/iris/backgr-d.htm), the Agency concluded that *data are inadequate for an assessment of the human carcinogenic potential* of propionaldehyde Please comment on the scientific justification for the cancer weight of evidence characterization. In addition, has the Agency properly characterized the potential for concern for carcinogenicity of propionaldehyde based on the available data on propionaldehyde and other aldehydes?

Comment:

All four reviewers commented that the document properly concludes that there are insufficient data to characterize the carcinogenic potential of propionaldehyde. In addition, the reviewers agreed with the effort to use structure/activity comparisons with other aldehydes for both carcinogenicity and mutagenicity in order to place the potential concern for carcinogenicity in context. However, one reviewer commented that the database for comparison should also include isobutyraldehyde for the sake of completeness and transparency. The most compelling aspect of the comparison between upper respiratory tract lesions in these three compounds is that all three show progression with exposure concentration and duration on a similar continuum of lesion severity. Three of the four reviewers noted that the finding of increased DPX in vitro for propionaldehyde (and acetaldehyde) compared to formaldehyde should be placed into context as one reviewer commented that formaldehyde may represent a special case because its deposition is so focal and because it's ability to form DPX is so much greater (orders of magnitude?) than the other aldehydes. One reviewer also noted that the recent positive finding of mutagenicity in Salmonella (Sampson and Bobik, 2008) be put into context as well considering that the majority of other mutagenicity tests were negative.

Response:

The results for isobutyraldehyde in comparison with the other aldehydes discussed were added where appropriate. In addition, the DPX results for formaldehyde, acetaldehyde and propionaldehyde have been added and put into context. The study results on mutagenicity have also been added to the genotoxicity section as well as the genotoxicity summary.

Other comments from the External Peer Reviewers:

All reviewers provided editorial comments on the document as well as additional text and studies that could be added to further improve the clarity of the assessment.

Response:

These comments were all addressed and incorporated as appropriate within the scope of the assessment and in accordance with EPA policy and procedures.

Comments from the Public

Comment:

One reviewer commented on the analysis of the genotoxicity and carcinogenicity in the draft assessment concerning what they viewed as inappropriate degree of weight given to comparisons with formaldehyde and acetaldehyde, but not with other structurally-related aldehydes (e.g. isobutyraldehyde), thus suggesting an incomplete analysis of the data available on other aldehydes.

Response:

This comment was given serious consideration and aspects of it were incorporated into the assessment to provide a more complete analysis. It should be noted that this assessment was not meant to be a complete analysis of the available data on all aldehydes, only those structurally-related aldehydes for which data were available on similar genotoxic, nonneoplastic, and carcinogenic endpoints in order to provide a degree of potency and effect comparisons with propionaldehyde. That being stated, more complete information, where available, is provided in the text for all of these endpoints, including the addition of comparative information for isobutyraldehyde for which a 2-year bioassay is available from NTP (1999). Therefore, EPA believes a more complete and robust analysis is provided.

Comment:

One reviewer provided the link to the Material Safety and Data Sheet (MSDS) for propionaldehyde: http://www.sciencelab.com/xMSDS-Propionaldehyde-9924730. And provided the following comment: “Since there is no information available on safety of this product on humans it should never be used on this earth. It is clear that not enough testing has been done.”

Response:

MSDS sheets are readily available for public reading from a variety of sources and thus, are not part of the assessment document.

APPENDIX B. BENCHMARK CONCENTRATION MODELING RESULTS

Benchmark concentration modeling was performed to identify potential critical effect levels for derivation of the RfC for propionaldehyde. The modeling was conducted according to draft EPA guidelines (EPA, 2000c) by using benchmark dose software (BMDS) Version 1.4.1, available online from EPA (http://www.epa.gov/ncea/bmds.htm). A brief discussion of the modeling results is presented below.

The incidence data for atrophy of the olfactory epithelium in male rats from the Union Carbide (1993) study were chosen as the critical endpoint for benchmark analysis. The incidence data are depicted in Table B-1, and the various modeling output results at the designated BMR of 10% (BMC_{10}) are summarized in Table B-2. A BMR of 10% change in the incidence of minimal olfactory atrophy was selected under an assumption that it represents a minimal biologically significant change (see Section 5.2.3). Graphical representation of the model of choice is shown in Figure B-1. As shown in Table B-2, several of the models had similar Akaike Information Criteria (AICs) and overall chi-square values (scaled residuals) and fit for the data at the lowest exposure concentration, 150 ppm. In accordance with benchmark dose technical guidance (U.S. EPA, 2000c), the Weibull model was chosen as the model for use in derivation of the RfC because it was the model with the lowest AIC and it had a lower-scaled residual at the exposure concentration closest to the BMC_{10} compared to the model with the next lowest AIC (i.e., the multistage 1). The corresponding $BMCL_{10}$ of 53.7 ppm was used in further derivation of the RfC. For comparison purposes, the modeling results depicting a BMR of 5% change in the incidence of minimal olfactory atrophy are shown in Figure B-2. The BMC_{05} was calculated to be 94.6 ppm, and the corresponding $BMCL_{05}$ to be 26.1 ppm.

Table B-1. Olfactory atrophy incidence data in male rats exposed to various concentrations of propionaldehyde

Exposure concentration	Incidence of olfactory atrophy
0 ppm	0/15
150 ppm	2/15
750 ppm	10/15
1,500 ppm	15/15

Source: Union Carbide (1993).

Table B-2. BMC model outputs for olfactory atrophy

Model	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)	AIC	χ^2	*p* Value	χ^2 residual, 150 ppm
Weibull[a]	149.8	**53.7**[b]	35.97	0.81	0.6659	0.4275
Multistage1	61.2	42.6	36.33	2.24	0.5238	–0.871
Gamma	142.6	50.2	36.42	1.07	0.5852	0.3104
Probit	145.7	79.5	37.52	1.87	0.3912	0.3387
Logistic	146.9	62.9	37.86	2.04	0.3612	0.3737

[a]Model of choice (see text for details).
[b]53.7 ppm = 128 mg/m^3.

Source: Union Carbide (1993).

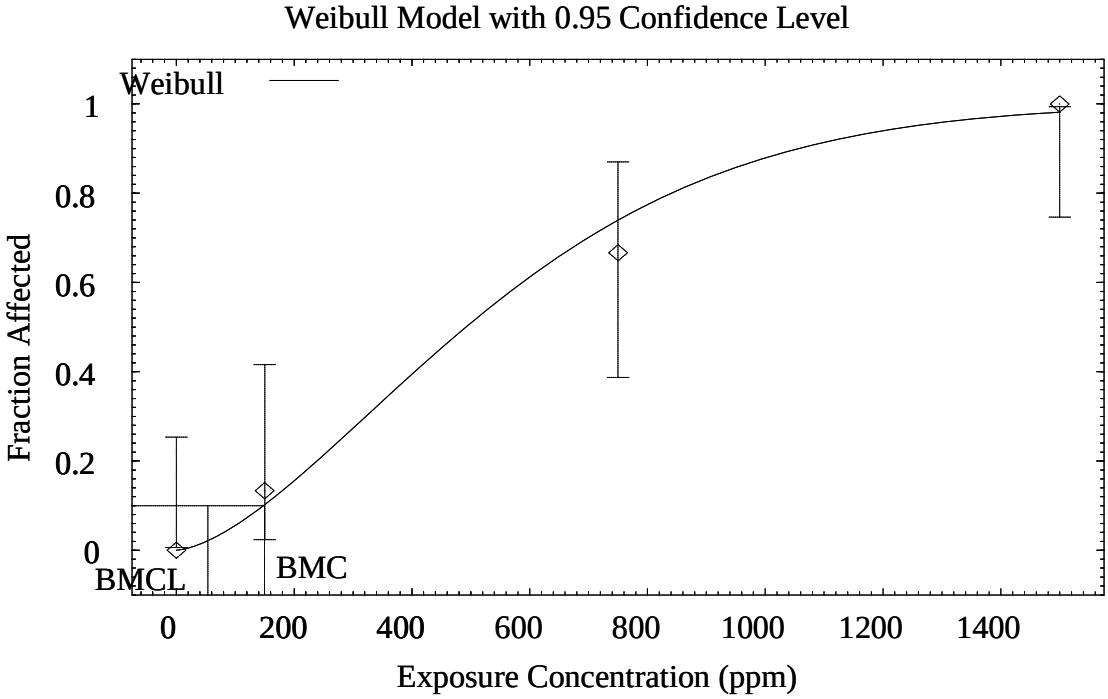

Figure B-1. BMC_{10} Weibull model for olfactory atrophy (Union Carbide, 1993).

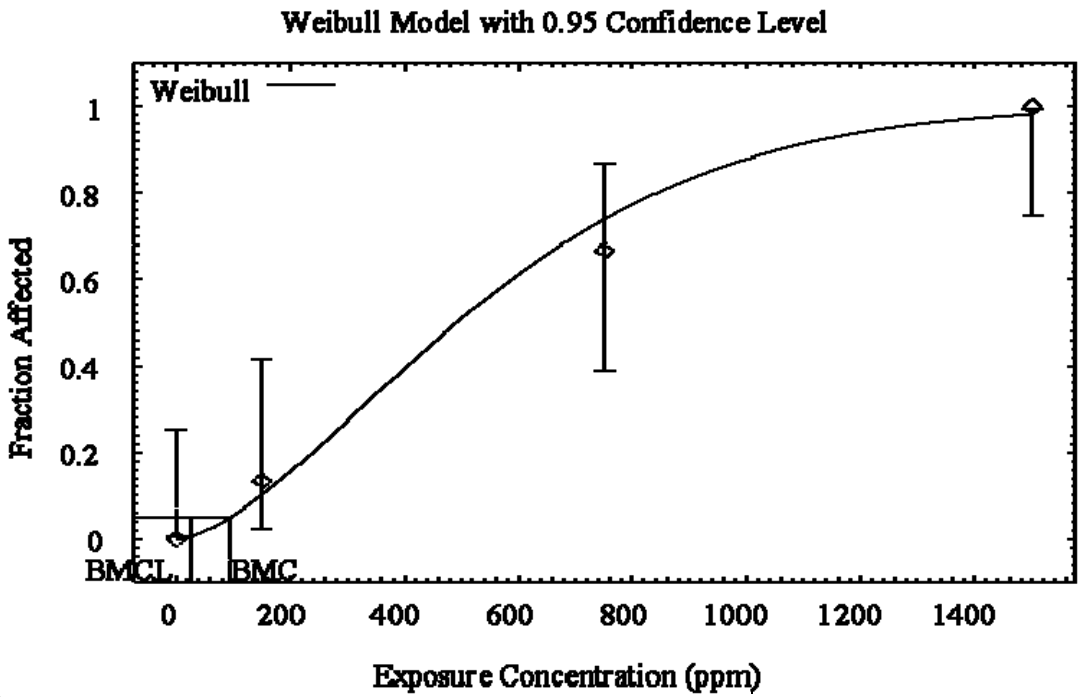

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Figure B-2. BMC_{05} Weibull model for olfactory atrophy (Union Carbide, 1993).