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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)

February 2008

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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
CHO	Chinese hamster ovary
DPX	DNA protein cross-link
EC50	median effective concentration
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
GD	gestation day
HEC	human equivalent concentration
IC_{50}	median inhibitory concentration
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
i.v.	intravenous
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MR	molecular reactivity
NLM	National Library of Medicine, Hazardous Substances Database
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
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
SA	surface area
UDS	unscheduled DNA synthesis
UF	uncertainty factor
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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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 an upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, an inhalation unit risk is an 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 (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* (U.S. EPA, 1986), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1987), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry*

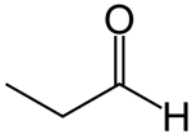
(U.S. EPA, 1994), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998), *Science Policy Council Handbook*: *Risk Characterization* (U.S. EPA, 2000a), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000b), *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002), *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 2006a), and *A Framework for Assessing Health Risks of Environmental Exposures to Children* (U.S. EPA, 2006b).

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 July 2007.

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	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 (National Library of Medicine [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 ppb (0.014 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 (U.S. 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 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. Ventilation rates were varied, ranging from 6 to 20 L/minute. The time period of exposure was not 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.

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 (Bogdanffy et al., 1998, 1986; Zhang et al., 2005). In the rat, the distribution and localization of ALDH in the respiratory tract has been examined (Bogdanffy et al., 1986). ALDH activity 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. 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.

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.

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 1,300 ppm (3,094 mg/m^3) propionaldehyde for 6 hours/day for 6 days via whole-body inhalation. 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 in 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, 1000, 1500, or 2500 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 1500 ppm. Indications of maternal effects related to propionaldehyde exposure were most notable at 2500 ppm.

In the second study, young adult male and female CD rats (15/sex/group) were exposed to 0, 150, 750, or 1500 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 males continued to be exposed for a total of 52 exposures until sacrifice in week 7. The mated females were exposed daily through GD 20

[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.

only. The females were then allowed to deliver their litters naturally and raise their offspring until postnatal day (PND) 4 both free of exposure to propionaldehyde. 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 the first two sections of the nasal cavity, 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. 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. Low incidences of minimal to mild rhinitis 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. 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	Olfactory lesion	Exposure concentration (ppm)			
		0	150	750	1500
Females[a]	Vacuolization	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	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	0/15	0/15	0/15	1/15
	moderate	0	0	0	1
	Rhinitis	0/15	1/15	6/15[c]	1/15
	minimal	0	1	0	0
	mild	0	0	6	1
Males[a]	Vacuolization	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	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	0/15	0/15	1/15	2/15
	mild	0	0	1	0
	moderate	0	0	0	2
	Rhinitis	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 (primarily localized to the olfactory 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 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 aliphatic, saturated aldehydes, including acetaldehyde, formaldehyde, butyraldehyde (butanal), pentanal, hexanal, and nonanal, were evaluated concurrently for their genotoxic potential by the same laboratories using the same protocols as were used for propionaldehyde. The results of these other aldehydes tested concurrently are included in the evaluation of propionaldehyde for comparative purposes where available. 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 nonmutagenic in *Salmonella typhimurium* 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 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	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
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	–	1,000 µg/plate	Dillon et al., 1998
Butyraldehyde	TA1535	Plate test	None, rat	–	2.5 µmol/plate (180 µg/plate)	Pool and Wiessler, 1981

[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 ≤1000 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).

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 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).

In concordance with the results with propionaldehyde, additional aldehydes tested, including butanal, 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 butanal and 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 butanal and 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. The results for 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
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
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 cells treated with concentrations of 5×10^{-4}, 1×10^{-3}, and 2×10^{-3}% (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.

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

Aldehyde	Cells	Endpoint	Results[a]	LED (HTD)[b]	Reference
Propionaldehyde	CHO	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	CHO	Aneuploidy	+	5×10^{-4}% (4.3 µg/mL)	Furnus et al., 1990

[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.

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

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

Aldehyde	Species	Cells	Endpoint	Results[a]	LED (HTD)[b]	Reference
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)	Marinari et al., 1984
Hexanal	Hamster	CHO-K1	Cross-links	–	4.5 mM (0.45 mg/mL)	Marinari et al., 1984
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 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 nonmutagenic in salmonella (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 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. In general, this information indicates that the rank order of potency of aldehydes across similar endpoints appears to be as follows: acrolein > formaldehyde >> acetaldehyde ≈ propionaldehyde.

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 1,260–84,000 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 (3,000)	↑ 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 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.

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 stimulation of higher centers 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 over the concentration range of 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 indirect 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 in the range of 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. Compounds that specifically inhibit lymphocyte proliferation without affecting lymphocyte cell viability may create favorable conditions for tumor cell growth (Poirier et al., 2002).

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 concentrations producing a 50% change from control in each cytotoxic endpoint after 24 hours of exposure ranged from 1×10^{-2} to 2×10^{-4}.

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, 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, acetaldehyde and propionaldehyde exhibit similar median lethal doses (LD_{50}s) after oral exposure (1,930 and 1,410 mg/kg, respectively) and subcutaneous dosing (640 and 820 mg/kg). In comparing the RD_{50}s 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 (Appelman et al., 1986, 1982). Appelman et al. (1982) exposed male and female Wistar rats to 400, 1,000, 2,200, or 5,000 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. Although studies of comparable design examining the effects of propionaldehyde on the nasal epithelium are unavailable, increases in olfactory epithelium atrophy 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). This effect in the nasal epithelium was observed at 150, 750, and 1,500 ppm propionaldehyde. In toto, these comparisons suggest that acetaldehyde and propionaldehyde produce similar respiratory and cardiac effects.

Steinhagen and Barrow (1984) compared the RD_{50}s 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 in expiration. The RD_{50}s 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}s 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)
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}s) were determined. The EC_{50}s 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, formaldehyde, acetaldehyde, and acrolein 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.

Benigni et al. (2003) generated a quantitative structure-activity relationship model for the mutagenicity and carcinogenicity of eight simple aldehydes, including propionaldehyde. The negative mutagenicity result from Aeschbacher et al. (1989) in *S. typhimurium* strain TA100 was used as input to the model. The model used the properties of electrophilicity, bulkiness (molecular reactivity or MR), and hydrophobicity (log partition coefficient) to inform on the genetic activity of the aldehydes. By using the information available (hydrophobicity and MR), propionaldehyde was classified by the model as inactive. Formaldehyde, acetaldehyde, and chloroacetaldehyde were classified as active. Based on this model, the authors concluded that the differences in the biological activity of the simple aldehydes are modulated by hydrophobicity and bulkiness. These results are based on selected published literature and a limited number of structural analogues.

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

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

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 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 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 males continued to be exposed until sacrifice in week 7, for a total of 52 exposures. The mated females were exposed daily through GD 20. The females were then allowed to deliver their litters naturally and raise their offspring until day 4 of lactation, when they were sacrificed.

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. 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. Small incidences of minimal to mild rhinitis 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. 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). 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 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 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 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 4.3).

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. Egle (1972a) demonstrated in dogs that approximately 70–80% of inspired 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 but slightly more potent than acetaldehyde (Steinhagen and Barrow, 1984). This reflex decrease in respiratory rate is mediated via stimulation of nasal trigeminal nerves and is characterized as a pause in 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 stimulation of higher centers 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 indirect sympathomimetic activities.

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* (U.S. 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 nonmutagenic in *S. typhimurium* (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). Although the information provided in these 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 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., 1986, 1984; Appelman et al., 1982). 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, 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 susceptibility to propionaldehyde.

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.

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).

The Union Carbide (1993) study was selected as the principal study for derivation of the RfC. The critical endpoint chosen for analysis from this study was the incidence of atrophy of the olfactory epithelium in male rats. Furthermore, the critical effect in male rats was chosen as it was the most biologically relevant concentration-response effect observed 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. Similarly, the atrophy observed at the middle exposure concentration (750 ppm) was characterized as being of minimal to moderate severity. 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 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 and formaldehyde).

Both vacuolization and atrophy of the olfactory epithelium were also considered for the critical effect. Vacuolization (i.e., intracellular autophagy) is a normal cellular functional, homeostatic, and adaptive response. It is a characteristic of and often observed in cells/tissues undergoing atrophy (Renne et al., 2007; Kumar et al., 2004). 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 progression to atrophy (diminished cell size and function) is unclear and unknown. In

general, atrophied cells/tissue may have diminished function, but they are not dead. However, atrophy may progress to more severe cell injury and eventually cell death with continued exposure (Kumar et al., 2004). For propionaldehyde exposure at 1,500 ppm, it appears that olfactory epithelium atrophy has progressed to the point where cellular function is sufficiently diminished so that vacuolization is not observed in this exposure group. Therefore, atrophy 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 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 have started in the female rats were not noted.

Taken together, the nasal lesion data for propionaldehyde over the range of exposure concentrations tested suggest a progression in both severity and incidence from no effects in controls to normal cellular adaptive and functional-type responses to insult and effects (i.e., vacuolization) and, finally, to the hallmarks and manifestations of more definitive cellular injury, diminished cellular function, and nasal tissue toxicity (i.e., atrophy, necrosis, and squamous metaplasia). This progression was observed in whole or in part in both males and females. In addition, this pattern of nasal lesion progression is very similar to that observed with exposure to acetaldehyde (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. Exposure to formaldehyde for 13 weeks also produces 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 benchmark concentration (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 was considered appropriate for derivation of the RfC as this response level is within the range of the experimental data (2/15 animals responding at 150 ppm, ~13%) and under the assumption that it represents a minimally biologically significant response level. 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). 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:

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

In accordance with the guidance for deriving inhalation RfCs (U.S. 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:

$$\text{RGDR} = \frac{V_E \text{ (rat)} / \text{SA (rat)}}{V_E \text{ (human)} / \text{SA (human)}}$$

$$= \frac{0.264 / 15}{13.8 / 200}$$

$$= 0.26$$

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, according to the procedures in the RfC methodology (U.S. 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.

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. The principal study used for the RfC derivation was a reproductive/developmental study (Union Carbide, 1993). 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. 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, and acetaldehyde, as well as other irritant gases. 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 and acetaldehyde. The areas of uncertainty for consideration in the assessment for propionaldehyde are outlined in Table 5-1.

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Table 5-1. 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 could ↑ RfC several-fold.	RfC is based on the most biologically relevant endpoint, atrophy of olfactory epithelium.	Chosen endpoint is consistent with expected chemical irritative 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.
Human relevance of data	Assuming no relevance of results would indicate that RfC may be unnecessarily low or not applicable.	Assume human relevancy.	Due to the irritative-type mode of action involving the general reactivity of the functional group (i.e., aldehyde) with tissue constituents regardless of Source, 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).
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 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 (2000) 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 (U.S. EPA, 2000).	Limited size of bioassay results in sampling variability; lower bound is 95% confidence interval on administered exposure.

Table 5-1. Summary of general uncertainty in the propionaldehyde noncancer and cancer risk assessments

Area of consideration	Potential impact[a]	Decision	Justification
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.
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 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 raises a concern that cannot be addressed with the propionaldehyde since the Union Carbide (1993) study is 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 (U.S. 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 males continued to be exposed until sacrifice in week 7, for a total of 52 exposures. The mated females were exposed daily through GD 20. 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 PNDs 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 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 was reported in both the intermediate and high exposure groups.

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 nonmutagenic in salmonella (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, butyraldehyde, and acetaldehyde) 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.

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* (U.S. 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 (U.S. 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 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). Application of a total UF of 1,000 ($10^{½} \times 10 \times 10 \times 10^{½}$) 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 the 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

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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 (U.S. 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.

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, 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).

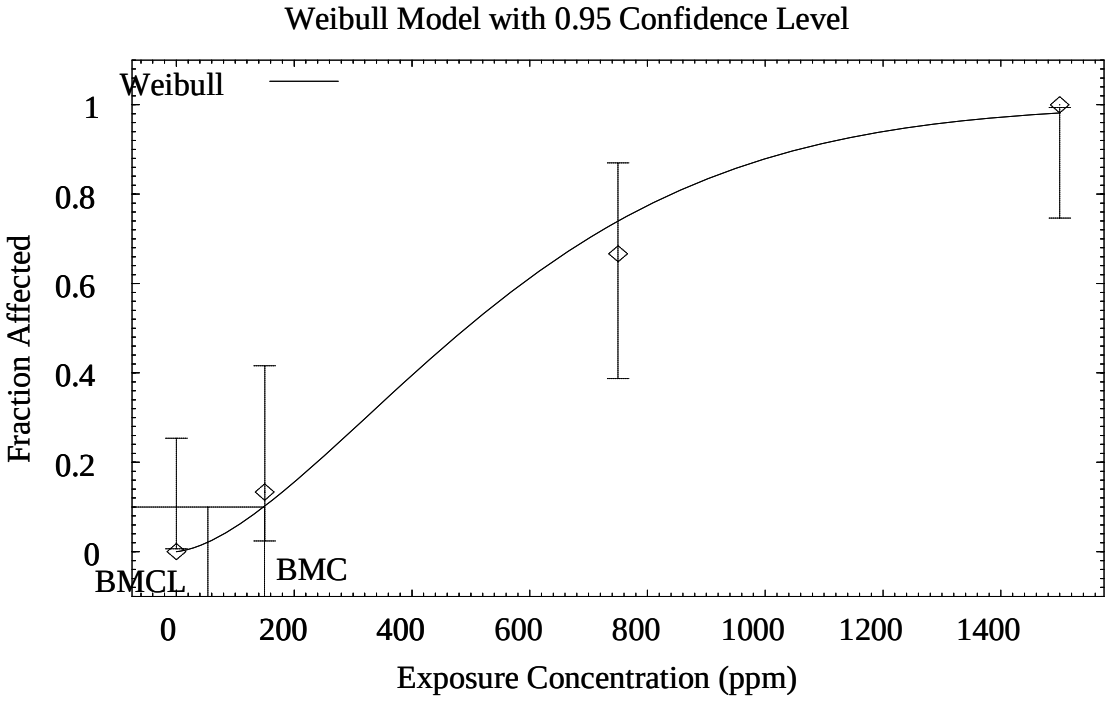

Figure B-1. BMC Weibull model for olfactory atrophy (Union Carbide, 1993).