

**FOREWORD**

**INTRODUCTION**

**N-VALERALDEHYDE**

**CAS N°: 110-62-3**

**SIDS Initial Assessment Report**  
**for**  
**21<sup>st</sup> SIAM**

Washington, D.C., 18-22 October 2005

- 1. Chemical Name:** n-Valeraldehyde
- 2. CAS Number:** 110-62-3
- 3. Sponsor Country:** United States of America  
National SIDS Contact Point in Sponsor Country:  
Mr. Oscar Hernandez, Director  
U.S. Environmental Protection Agency  
Risk Assessment Division (7403 M)  
1200 Pennsylvania Avenue, NW  
Washington DC 20460  
Phone: (202) 564-7461
- 4. Shared Partnership with:** American Chemistry Council, Oxo Process Panel
- 5. Roles/Responsibilities of the Partners:**
  - Name of industry sponsor /consortium: American Chemistry Council  
Barbara Francis, Oxo Process Panel  
1300 Wilson Blvd  
Arlington, VA 22209  
Phone: (703) 741-5609
  - Process used: Robust Summaries/dossiers, the SIAR, and the SIAP were drafted by the Oxo Process Panel's toxicologists. Documents were reviewed by the Oxo Process Panel and the United States Environmental Protection Agency.
- 6. Sponsorship History**
  - How was the chemical or category brought into the OECD HPV Chemicals Programme? The American Chemistry Council's Oxo Process Panel submitted a test plan and robust summaries for this chemical to the U.S. Environmental Protection Agency in December 2001, under the International Council of Chemical Associations (ICCA) Global Initiative on High Production Volume (HPV) Chemicals Program.
- 7. Review Process Prior to the SIAM:** Members of the Oxo Process Panel conducted a comprehensive literature search. Documents were prepared by the Panel and reviewed by industry toxicologists prior to submission to the United States Environmental Protection Agency (U.S. EPA).

8. **Quality check process:** The quality of existing data was determined using guidance provided in the Manual for Investigation of HPV Chemicals, Chapter 3: Data Evaluation (OECD, 2002).
9. **Date of Submission:** July 26, 2005
10. **Date of last Update:** October 5, 2005
11. **Comments:**

**SIDS INITIAL ASSESSMENT PROFILE**

<b>CAS No.</b>	110-62-3
<b>Chemical Name</b>	n-valeraldehyde
<b>Structural Formula</b>	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH=O

**SUMMARY CONCLUSIONS OF THE SIAR****Analog Justification**

As a group, aliphatic aldehydes have similar structures, reactivities, and effects (e.g., respiratory irritation). As a result, their data can be used to assess the potential toxicity of valeraldehyde. *In vitro* and *in vivo* studies have demonstrated that aliphatic aldehydes are oxidized to their respective acids. Valeraldehyde is metabolized to valeric acid. Following the metabolic series approach, studies investigating the toxicity of valeric acid are considered useful in evaluating the potential systemic toxicity of valeraldehyde. Data from the supporting chemicals propionaldehyde (CAS# 123-38-6), butyraldehyde (CAS# 123-72-8), isobutyraldehyde (CAS# 78-84-2) and isovaleraldehyde (CAS# 590-86-3) are used to support and address the data gaps for the mammalian endpoints.

**Human Health**

Data for valeraldehyde are available for acute toxicity, skin and eye irritation, as well as skin sensitization. The acute oral LD<sub>50</sub> value for male rats was 4590 mg/kg. The dermal LD<sub>50</sub> in male rabbits was 4865 mg/kg; necrosis was observed at the application site. There was 50 percent mortality among rats exposed to 4000 ppm (11600 mg/m<sup>3</sup>) valeraldehyde vapor for 4 hours. Valeraldehyde is a corrosive liquid. Valeraldehyde causes severe skin and eye irritation and necrosis. Animal studies show it to be an upper respiratory tract irritant but not a skin sensitizer.

There are no repeated-dose toxicity studies for n-valeraldehyde. Repeated-dose toxicity studies with other aldehydes (n-butyraldehyde, isobutyraldehyde and propionaldehyde) have demonstrated mortality and localized lesions in response to irritation as well as some effects on hematology and clinical chemistry; however, systemic effects have not been observed. A similar toxicity profile is expected for n-valeraldehyde. Thirteen-week rat and 14-week dog inhalation studies at **n-butyraldehyde** concentrations of 125, 500, and 2000 ppm (363, 1450, and 5800 mg/m<sup>3</sup>) resulted in nasal lesions at all doses with LOAECs of 125 ppm for both species. A subsequent 12-week rat study determined a NOAEC for **n-butyraldehyde** vapor in rats of 50 ppm (145 mg/m<sup>3</sup>, the highest dose tested). A 13-week gavage study with **n-butyraldehyde** in rats and mice at doses of 75, 150, 300, 600, and 1200 mg/kg bw/day resulted in nasal lesions at all doses and lesions of the stomach at 600 and 1200 mg/kg bw/day in rats. A dose-related increase in mortality was also observed in rats. In mice, treatment-related nasal lesions were noted at 300 mg/kg and above and mortality, stomach lesions, and decreased body weight gain were observed at 1200 mg/kg bw/day, resulting in a NOAEL of 150 mg/kg bw/day.

In a 103-week inhalation study with **isobutyraldehyde** vapor, rats and mice were exposed to 0, 500, 1000, or 2000 ppm (0, 1450, 2900, 5800 mg/m<sup>3</sup>). There was no treatment-related dose-dependent increase in the incidence of tumors in rats or mice. Non-neoplastic nasal lesions were significantly increased at all doses (females only at 500 ppm), resulting in a LOAEC of 500 ppm for rats. Survival of mice was reduced at 2000 ppm and mean body weights of females were reduced at 1000 and 2000 ppm. Degeneration of the olfactory epithelium was observed at the two highest doses in mice, for a NOAEC of 500 ppm in mice. A shorter (13-week) inhalation study in rats and mice using **isobutyraldehyde** vapor concentrations of 0, 500, 1000, 2000, 4000, and 8000 ppm (0, 1450, 2900, 5800, 11600, and 23200 mg/m<sup>3</sup>) resulted in mortality at 4000 and 8000 ppm in both species. Non-neoplastic lesions of the nasal cavity occurred at concentrations of 2000 ppm and greater in rats and 1000 ppm and greater in mice resulting in NOAECs of 1000 ppm and 500 ppm, respectively. Nasal lesions observed included necrosis, hyperplasia, squamous metaplasia, and olfactory epithelial degeneration.

In a combined repeated-dose toxicity study with reproduction and developmental toxicity screening test, rats were exposed to **propionaldehyde** vapor concentrations of 150, 750, and 1500 ppm (345, 1725, and 3450 mg/m<sup>3</sup>) via inhalation. Effects on the nasal epithelium were seen at all doses, including vacuolization in the low and intermediate

dose groups and squamous metaplasia (in a few animals) and atrophy in the intermediate and high dose groups. Some effects on hematology (increased erythrocytes, hemoglobin and hematocrit values) and increased monocytes were observed at 1500 ppm. Increased kidney weights were also observed at the highest dose. The LOAEC is 150 ppm.

*In vitro* data on genetic toxicity are available for valeraldehyde and *in vivo* data are available for valeric acid. Valeraldehyde tested negative both in the presence and absence of a metabolic activation systems in several bacterial reverse mutation assays with several strains of *Salmonella typhimurium*. When tested in assays conducted in the absence of metabolic activation, valeraldehyde was positive in a mouse lymphoma assay and gene mutation assays in Chinese hamster V79 cells; it was negative in sister chromatid exchange assay in human lymphocytes. When tested in the presence of inherent or added metabolic activation, valeraldehyde was negative in a UDS (DNA repair) assay in human and rat hepatocytes and a mouse lymphoma gene mutation assay. Valeric acid, the “downstream” metabolite of valeraldehyde, did not result in increased micronuclei in an *in vivo* mouse micronucleus assay. These results show that valeraldehyde is genotoxic in some *in vitro* test systems in the absence of metabolic activation. However, negative results were obtained in those assays with inherent or added metabolic activation systems. Similar genotoxicity results were obtained for the structural analog, isobutyraldehyde. Isobutyraldehyde was negative in a two-year chronic inhalation bioassay in mice and rats; the only effects related to treatment were non-neoplastic degenerative lesions of the nasal olfactory epithelium. There is insufficient evidence to suggest that the chemical is mutagenic in humans.

Several studies with structurally similar aldehydes evaluated reproductive organs and one evaluated fertility. In a combined repeated-dose study with a reproduction/developmental toxicity screening test, no reproductive effects were observed in male and female rats exposed to 150, 750, or 1500 ppm (345, 1725, or 3450 mg/m<sup>3</sup>) **propionaldehyde** vapor resulting in a reproductive NOAEC of 1500 ppm. Male and female rats exposed to **isobutyraldehyde** concentrations up to 2000 ppm (5800 mg/m<sup>3</sup>) for 103 weeks had normal reproductive organs and tissues. Male and female rats exposed 0, 500, 1000, 2000, or 4000 ppm (1450, 2900, 5800, or 11600 mg/m<sup>3</sup>) **isobutyraldehyde** for 13 weeks had normal reproductive organs and tissues; no effect on sperm motility, density or morphology was observed in male rats exposed to 4000 and 2000 ppm, however motility was decreased at 500 and 1000 ppm. Significant mortality was observed in female rats at 4000 ppm, at which some differences in the relative time in different stages of estrous were observed in the surviving females. No effects were observed on vaginal cytology or average estrous cycle length. In the same study, male and female mice showed no reproductive effects.

Developmental toxicity data are available for propionaldehyde, isobutyraldehyde, and valeric acid. No external physical abnormalities were observed in neonates in the combined repeated-dose toxicity study with reproduction/developmental toxicity screening test using **propionaldehyde** vapor described above. However, pup body weight gain between lactation day 0 and 4 in the high dose group was slightly decreased resulting in a NOAEC of 750 ppm. The parental LOAEC was 150 ppm. Groups of pregnant female rats were exposed by inhalation to 0, 1000, 2500, or 4000 ppm (2900, 7250, or 11600 mg/m<sup>3</sup>) **isobutyraldehyde** vapor for 6 hr/day for ten consecutive days during gestational days (GD) 6 through 15. Maternal toxicity, as evidenced by a significant decrease in body weight gain, was observed in dams exposed to 2500 and 4000 ppm resulting in a maternal NOAEC of 1000 ppm. There was no effect on gestational or litter parameters; no embryofetal toxicity or fetal malformations were observed at any exposure level, resulting in a developmental NOAEC of 4000 ppm. A developmental toxicity study using **valeric acid** on groups of timed pregnant female rats by oral gavage during GD 6 through GD 15 at doses of 0, 50, 100, and 200 mg/kg bw/day resulted in severe maternal toxicity. Vocalization, rales, and dyspnea were noted in dams immediately after dosing of the material, and mortality occurred in all treatment groups (4% at 50 mg/kg, 13% at 100 mg/kg, and 42% at 200 mg/kg). Fetal body weights were reduced at all dose levels. Although maternal toxicity makes it difficult to interpret the significance of the results, the percent incidence of fetuses with small sternebrae or reduced ossification was statistically increased at all dose levels. No fetal malformations or other variations were observed. Due to severe maternal toxicity a NOAEL couldn't be established for developmental toxicity.

The odor threshold for valeraldehyde (0.028 to 0.060 ppm) is well below the 8-hour TWA occupational exposure limit of 50 ppm established by ACGIH to prevent irritation. There are no human studies that evaluated the relationship between odor threshold and irritation.

### Environment

The melting point of n-valeraldehyde is -91.5°C, the boiling point is 103°C, and the vapor pressure is 35 hPa at 20°C. The water solubility is 11,700 mg/L at 25°C. The photochemical removal of valeraldehyde, as mediated by hydroxyl radicals, occurs with a calculated half-life of 9.0 hours. Valeraldehyde is not anticipated to hydrolyze in water. Based on Level III fugacity modelling, and assuming all releases are to air and none to water or soil, it is estimated that the majority of valeraldehyde released into the environment will partition into air (93.4%), with a

smaller amount into water (5.65%), soil (0.961%) and sediment (<0.1%). Valeraldehyde will volatilise readily from moving rivers, but only moderately from quiescent lakes and other surface water bodies (calculated volatilisation half-lives of 8.3 hours from a river and 5.4 days from a lake). Valeraldehyde is readily biodegradable under aerobic conditions. The octanol:water partitioning coefficient (log  $K_{ow}$ ) for valeraldehyde ranges from 1.31 to 1.39 at 25°C (preferred value 1.38), and the estimated bioconcentration factors (BCF) range from 2.3 to 5.8 (preferred value 2.3). These data indicate that valeraldehyde has a low potential to bioaccumulate.

Data are available from valeraldehyde to address the acute aquatic toxicity endpoints. A GLP analytical study conducted according to OECD Guideline 203 with rainbow trout (*Oncorhynchus mykiss*) in a flow-through system demonstrated a 96-hr LC50 of 27.9 mg/L. Two additional flow-through studies with fathead minnows (*Pimephales promelas*) resulted in 96-hr LC50s of 12.4 mg/L and 13.4 mg/L. Two static studies that examined the toxicity of valeraldehyde to *Daphnia magna* resulted in 48-hr EC50s of 70.7 and > 100 mg/L for immobilization. A single 96-hr GLP study in algae conducted according to OECD Guideline 201 with *Pseudokirchnerilla subcapitata* (formerly known as *Selenastrum capricornutum*) resulted in 72-hr and 96-hr EC50 values for growth inhibition of 32.4 mg/L and 42.2 mg/L, respectively; the 72- and 96-hr EC50 values for biomass (area under the curve) were 31.4 mg/L and 37.1 mg/L, respectively.

### Exposure

Valeraldehyde is used primarily as an industrial intermediate in the production of valeric acid and amyl alcohol. Reported minor uses include use in resin chemistry and to make rubber accelerators. Manufactured valeraldehyde does not appear intentionally in commercial or consumer products, although naturally-occurring valeraldehyde may be used as a flavoring agent in foods. Valeraldehyde has been identified as a naturally-occurring plant volatile and it has been detected in foods and beverages at low ppm concentrations. Consumption in 2006 is projected at 38,000 tonnes in the US, 32,000 tonnes in Western Europe, and approximately 100 tonnes in Japan in 2006. Valeraldehyde is a flammable liquid with a flammable range of 2.1 – 7.8 volume % in air (21,000 – 78,000 ppm) and a flash point of 5°C (41°F). In the US, due to its physical/chemical properties, valeraldehyde is manufactured in an enclosed, continuous process and stored in vapor-tight equipment under an atmosphere of oxygen-free nitrogen. Engineering controls and vapor collection systems are utilized during production, transfer, and loading operations to minimize flammability hazards as well as worker exposure. Workplace exposure during manufacture and use as industrial intermediate is also limited in the US by an occupational exposure limit of 50 ppm; the odor threshold for n-valeraldehyde (28-60 ppb) is well below the exposure limit and is expected to decrease the potential for significant worker exposure. Valeraldehyde may be released to the environment as a fugitive emission during production and use, or as naturally occurring emissions from vegetation, food products, and wood fires.

## RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

**Human Health:** The chemical is currently a low priority for further work. The chemical possesses properties indicating a hazard for human health (skin, eye, respiratory irritation and potential reproductive/developmental effects based on data for analogous compounds). Based on data presented by the Sponsor country (relating to production in one country which accounts for 50-60% of the consumption in OECD countries and relating to the use pattern in several OECD countries), adequate risk management measures are being applied (engineering controls, occupational standards, Material Safety Data Sheets (MSDSs), and regulation as a food additive). Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

**Environment:** The chemical has properties indicating a hazard for the environment (acute aquatic EC/LC50 values between 1 and 100 mg/l). However, the chemical is currently of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.

## SIDS Initial Assessment Report

### 1.0 IDENTITY

#### 1.1 Identification of the Substance

CAS Number:	110-62-3
IUPAC Name:	n-Valeraldehyde
Molecular Formula:	C <sub>5</sub> H <sub>10</sub> O
Structural Formula:	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH=O
Molecular Weight:	86.13 g/mol
Synonyms:	1-valeraldehyde valeraldehyde valeric aldehyde valerianic aldehyde valeric acid aldehyde n-valeric acid aldehyde valerylaldehyde 1-pentanal n-pentanal pentanal n-amyl aldehyde butyl formal

#### 1.2 Purity/Impurities/Additives

Purity:	>99% weight/weight
Impurities:	2-ethyl propanal, CAS 96-17-3: < 1%
Additives:	None

#### 1.3 Physico-Chemical Properties

**Table 1: Summary of Physicochemical Properties**

Property	Value	Reference
Physical state	liquid	
Melting point	-91.5 °C	Lide (ed), 1996
Boiling point	103 °C	Lide (ed), 1996
Relative density	0.8095 g/cm <sup>3</sup>	Lide (ed), 1996
Vapor pressure	35 hPa at 20°C	Flick, 1991; USEPA, 2003
Water solubility	11,700 mg/l at 25°C	Yalkowsky and Dannenfelser, 1992; USEPA, 2003
Partition coefficient n-octanol/water (log value)	1.38 at 25°C	KOWWIN, v. 1.66;
Henry's law constant	1.47 x 10 <sup>-4</sup> atm-m <sup>3</sup> / mole at 25°C 2.62 x 10 <sup>-4</sup> atm-m <sup>3</sup> / mole at 25°C	Buttery et al., 1969 HENRYWIN, v. 3.10
Flashpoint (ASTM D56)	12 °C (41°F)	The Dow Chemical Company, 2002; NFPA, 2002

Flammable range	2.1 – 7.8 vol %	NFPA, 2002
Odor Threshold	0.028 ppm 0.060 ppm	ACGIH, 1992 Amoore et al., 1976
Vapor density	3.0 (air = 1)	NFPA, 2002
Conversion factors	1 ppm = 3.5 mg/m <sup>3</sup> 1 mg/m <sup>3</sup> = 0.28 ppm	Verschuren, 2001

Valeraldehyde is a liquid at standard temperature and pressure, with a boiling point of approximately 103°C and a melting point of approximately -91.5°C. It is less dense than water with a specific gravity of 0.8095 g/cm<sup>3</sup> at 20° C. The solubility limit in water is approximately 11.7 g/L at 25 °C. This value indicates that valeraldehyde is very soluble in water. Valeraldehyde is a flammable liquid with a flash point of 5 °C and a flammable range of 2.1 to 7.8% by volume. The vapor density of valeraldehyde is 3.0 times greater than air; it has a vapor pressure of 35 hPa at 20 °C; by this measure, valeraldehyde is considered a volatile chemical. Given its solubility limits of 11.7 g/L at 25 °C and its molecular weight of 86.13 g/mole, a range of Henry's law constants at 25 °C has been calculated to be 1.47 to 2.62 x 10<sup>-4</sup> atm·m<sup>3</sup>/mole. In general, for chemicals with a Henry's law constant less than 1.0 x 10<sup>-3</sup> atm·m<sup>3</sup>/mole, volatilization from water is expected to be moderate (Lyman et al., 1982).

#### 1.4 Analog Justification

As a group, aliphatic aldehydes have similar structures, reactivities, and effects (e.g., respiratory irritation) as a result their data can be used to assess the potential toxicity of valeraldehyde. Valeraldehyde is metabolized rapidly to valeric acid, and therefore exists only transiently systemically; therefore, toxicity studies with valeric acid can be useful in determining the potential systemic toxicity of valeraldehyde. Data from the structural analogs propionaldehyde (CAS# 123-38-6), butyraldehyde (CAS# 123-72-8), isobutyraldehyde (CAS# 78-84-2), and isovaleraldehyde (CAS# 590-86-3) are used to support and address the data gaps for the mammalian endpoints.

#### Use of Structurally Similar Aldehydes

The structural formulas and molecular weights for these chemicals are listed in Table 2. This table shows the similarity in structures.

**Table 2: Identity of Structurally Similar Aldehydes**

Compound	CAS Number	Structural Formula	Molecular Weight
Propionaldehyde	123-38-6	CH <sub>3</sub> -CH <sub>2</sub> -CH=O	58.08
n-Butyraldehyde	123-72-8	CH <sub>3</sub> -CH <sub>2</sub> -CH <sub>2</sub> -CH=O	72.11
Isobutyraldehyde	78-84-2	CH <sub>3</sub> -CH(CH <sub>3</sub> )-CH=O	72.11
Isovaleraldehyde	590-86-3	CH <sub>3</sub> -CH(CH <sub>3</sub> )-CH <sub>2</sub> -CH=O	86.13

The major route of aldehyde oxidation is via aldehyde dehydrogenase (ALDH), which is a soluble enzyme found in liver and many other tissues. Studies using human liver indicate that valeraldehyde, butyraldehyde, and propionaldehyde are readily oxidized and that their relative rates of oxidation are similar when tested *in vitro* at substrate concentrations between 0.5 and 3.0 mM using partially purified human liver aldehyde dehydrogenase (ALDH). Under these conditions, the rate of oxidation for C3 to C5 aldehydes was comparable to acetaldehyde (Blair and Bodley, 1969). Similar studies using human liver also demonstrated formation of isobutyraldehyde and isobutyric acid during *in vitro* metabolism of isobutyl alcohol (Ehrig et al., 1988). Rat liver mitochondrial



studies have also indicated that short- and long-chain aldehydes are oxidized by a mitochondrial enzyme, which acts directly on the aldehyde, and that the oxidation product is the corresponding acid (Walkenstein and Weinhouse, 1953).

Further, *in vivo* studies with aliphatic alcohols have demonstrated the metabolism of the alcohol to its corresponding aldehyde which is in turn rapidly metabolized to the aliphatic acid. This pathway has been demonstrated for isobutyl alcohol in humans (Rudell, et al., 1983) and for propyl alcohol, isopropyl alcohol, isobutyl alcohol, butyl alcohol, and pentyl alcohol in rats (Poet, 2003a,b,c; Deisinger and English, 2001; Poet, 2004). In a pharmacokinetic study with rats, butyric acid was the major blood metabolite following administration of butyl alcohol; demonstration of the transient nature of the butyraldehyde intermediate was possible only by direct intravenous injection (Deisinger and English, 2001). In respiratory bioavailability studies, valeric (pentanoic) acid was the major metabolite following exposure to n-pentyl alcohol (Poet, 2004b). In these studies, based on previous experience with n-butyl alcohol, no attempt was made to demonstrate the transient nature of valeraldehyde formed during alcohol metabolism.

Finally, data presented in Section 4 below show that aldehydes result in similar toxicities, which include primarily respiratory effects (e.g., nasal lesions).

#### Use of the Metabolic Product Valeric Acid

The results of selected studies with valeric acid (CAS No. 109-52-4) can be used to identify the hazards associated with exposure to valeraldehyde for certain health effects endpoints. The use of valeric acid for valeraldehyde is known as the “metabolic series approach.”

As noted above in both *in vitro* and *in vivo* studies, the use of valeric acid is possible because metabolism of alcohols to their corresponding aldehydes and further, to their corresponding acids is well studied. As indicated above, experiments with inhalation exposure n-pentyl alcohol have demonstrated the metabolism of the alcohol to valeric acid (Poet, 2004a,b). Similarly, oxidation of valeraldehyde to valeric acid has been suggested based on evidence obtained *in vivo* (Haggard, Miller, and Greenberg, 1945; Poet, 2004a,b) and *in vitro* (Blair and Bodley, 1969). In this way, information from toxicity studies for valeric acid inherently provides information on the toxicity of valeraldehyde. These data are supplemented by the data on other aldehydes described above.

The use of valeric acid results to supplement valeraldehyde data does have some limitations, however. It should be noted that the metabolic series approach is only appropriate for endpoints directly related to the systemic blood levels of the series members (i.e. the parent compound and its metabolites). It is not relevant for all routes of exposure, for site-of-contact effects, or for any endpoints dependent upon the physical-chemical properties of the material. Thus, it would be inappropriate to use surrogate data for skin irritation, eye irritation, skin sensitization, certain *in vitro* mutagenicity studies, dermal studies of any type, aquatic studies, or any other environmental studies. These types of data extrapolations are inappropriate because studies have not yet been conducted to confirm metabolism under specialized exposure conditions such as skin contact, eye contact, *in vitro*, dermally, in fish, or in other non-mammalian species. The endpoints addressed with the use of surrogate valeric acid data is *in vivo* genetic toxicity and developmental toxicity.

## 2.0 GENERAL INFORMATION ON EXPOSURE

### 2.1 Production Volumes and Use Patterns

#### 2.1.1 Manufacture and Consumption

Valeraldehyde is manufactured in an enclosed, continuous process by the hydroformylation of butene-1 or Raffinate 2. Consumption of valeraldehyde in the United States (US) in 2001 was approximately 34 thousand metric tons and is projected to be 38 thousand metric tons in 2006 (Bizzari et al., 2002). Total consumption in Western Europe was approximately 32 thousand metric tons in 2001 and is projected to be the same in 2006 (Bizzari et al., 2002). Current production in Japan is negligible, with a demand of less than 100 metric tons being met by imports. World consumption in 2001 was approximately 65 thousand metric tons, and is projected to increase to 69 thousand metric tons in 2006 (Bizzari et al., 2002).

#### 2.1.2 Uses and Functions

In the United States and Western Europe the consumption of valeraldehyde can be summarized as follows (Bizzari et al., 2002):

**Table 3: Uses of Valeraldehyde (Thousands of Metric Tonnes)**

	Production of Amyl Alcohol	Production of Valeric Acid	Other uses	Total Consumption
United States	20	14	0	34
Western Europe	26	5	1	32

Thus, slightly over 70% of valeraldehyde produced is used to manufacture amyl alcohol, and slightly less than 30% is converted to valeric acid. There are no other uses in the United States, but there are some additional uses in Western Europe (Bizzari et al., 1999, 2002).

Reported minor uses of valeraldehyde include use in resin chemistry and to make rubber accelerators (Budavari, 1996, Lewis, 1993, HSDB, 2002, Bizzari et al., 1999). Valeraldehyde has been identified among the naturally-occurring constituents of several essential oils, and in distillates from leaves of various eucalyptus species (Furia and Bellance, 1975). As a constituent of essential oils and plant distillates, naturally-occurring valeraldehyde may be used to produce some flavor compounds.

Nearly 100% of use of valeraldehyde in the United States is as an industrial intermediate for the manufacture of valeric acid and amyl alcohol. Therefore, valeraldehyde does not appear intentionally in commercial/consumer products in the U.S.. Valeraldehyde has, however, been identified as a naturally-occurring plant volatile. The concentration of valeraldehyde is relatively high in unripe apples, but decreases to undetectable levels as the fruit ripens (Graedel et al., 1986). Valeraldehyde has also been detected in baked potatoes, cassava, French mountain cheese, raw beef, roasted filberts, clams, scrambled eggs, apples and fried chicken (HSDB, 2002).

Valeraldehyde has a warm slightly fruity taste that has also been described as nut-like at low concentrations (Furia and Bellance, 1975). Its flavor has also been described as pleasant with a chocolate aroma and taste (Furia, 1980). Valeraldehyde is approved for direct use by the U.S. Food and Drug Administration (USFDA) for use as a flavoring agent (21 CFR Title 21, Part 172.515).

Valeraldehyde is also available as a flavor/aroma material which meets Food Chemical Codex (FCC) specifications. It has been assigned a Flavor and Extract Manufacturing Association (FEMA) number of 3098 (Aldrich, 1996). Burdock, 2002 notes that valeraldehyde has been found in the following foods:

Food Category	Usual level (ppm)	Maximum level (ppm)
Alcoholic beverages	1.0	2.53
Baked goods	4.53	5.87
Fats, oils	0.10	0.20
Frozen dairy	4.91	6.15
Gelatin, pudding	0.82	1.94
Gravies	1.23	2.47
Hard candy	54.52	64.03
Imitation dairy	0.50	2.00
Meat products	0.01	0.03
Non-alcoholic beverages	1.70	2.88
Soft candy	4.32	6.15

**Source:** FEMA, 1994 as cited in Burdock, 2002

[The above info was shared by the UK delegation and updates the information previously in the SIAR.]

## 2.1 Environmental Exposure and Fate

### 2.2.1 Sources of Environment Exposure

Valeraldehyde is a volatile, flammable liquid that must be stored in vapor-tight equipment under an atmosphere of oxygen-free nitrogen (The Dow Chemical Company, 2001). Valeraldehyde is manufactured and utilized as a chemical intermediate in the United States within enclosed equipment, which minimizes release to the environment. Process wastes are collected for recycling, treatment in biodegradation facilities, or incineration on site. Valeraldehyde is shipped in bulk in tank railcars or trucks. Smaller quantities are transported in drums. Valeraldehyde may be released to the environment during transfer, transportation, storage and disposal activities. Any spillage during loading or handling would be recovered according to facility regulations, and prevented from entering sewers or waterways. Emissions of valeraldehyde during manufacture and use are not anticipated to be large, since manufacturing and process equipment is enclosed.

Minor reported uses of valeraldehyde include the manufacture of flavor compounds, use in resin chemistry and to make rubber accelerators (Budavari, 1996; Lewis, 1993; HSDB, 2002; Bizzari *et al.*, 1999). Releases into the environment may occur during these uses, especially when engineering controls are not utilized. Valeraldehyde is a naturally-occurring plant volatile and is emitted from many foods. It is also an emission product of microorganisms and animal waste. It may be emitted from burning logs and forest fires (Lipari *et al.*, 1984). Through its manufacture and intended uses, valeraldehyde releases into the environment are mainly into the atmosphere.

### 2.1.2 Photodegradation

Valeraldehyde is readily removed from the atmosphere by photooxidative processes. In the atmosphere, valeraldehyde will react with photochemically-produced hydroxyl (OH) radicals and undergo direct photolysis (Lloyd, 1978). This reaction is the rate-limiting step governing the overall residence time of valeraldehyde in the air. Other processes, such as wet deposition (rain-out) and dry deposition (aerosol formation) are not expected to play an important role in the atmospheric removal of valeraldehyde. Using a global average tropospheric hydroxyl radical

concentration of  $1.5 \times 10^6$  OH molecules/cm<sup>3</sup>, a second-order photo-oxidation rate constant of  $2.85 \times 10^{-11}$  cm<sup>3</sup>/molecule-sec at 25°C, and a 12-hour daylight period, the tropospheric half-life of valeraldehyde is 9.0 hours (EPIWIN, v. 3.10, Atkinson, 1989).

### 2.1.3 Water Stability

Valeraldehyde does not possess a functional hydrolysable group and cannot form a stable bond with water. Therefore, valeraldehyde is not anticipated to hydrolyze in water.

### 2.1.4 Transport Between Environmental Compartments

According to a model of gas/particle partitioning of semi-volatile organic materials in the atmosphere, valeraldehyde is expected to exist solely as a vapor under ambient conditions (Daubert and Danner, 1989). Upon release in ambient atmosphere, valeraldehyde is expected to volatilize from dry soil surfaces, based on a vapor pressure of 35 hPa at 20°C (Flick, 1991). In water, volatilization half-lives for a model river and lake have been estimated at 8.3 hours and 5.4 days, respectively (Lyman et al, 1982).

Fugacity modeling (Level III) was conducted for valeraldehyde using EPIWIN (v.3.12). Input parameters included a molecular weight of 86.13 g/mol, melting point of -91.5°C, boiling point of 103°C, water solubility of 11,700 mg/L, log Kow of 1.38, and a Henry's law constant of  $1.47 \times 10^{-4}$  atm-m<sup>3</sup>/mol. Releases were assumed to be 100% to air and none to water or soil. Media-specific half-lives were selected or calculated by the model. The model selected  $28.5 \times 10^{-12}$  cm<sup>3</sup>/molecule-sec as the second order rate constant for atmospheric photo-oxidation (Atkinson, 1989). The half-life in air was calculated to be 9.0 hours. Biodegradation half-lives in water, soil and sediment (208 h, 416 h, and 1870 h, respectively) were selected by the model based on the biodegradation submodels within EPIWIN (v.3.12). All other parameters used were the model default values. The results support the above conclusions regarding the movement of valeraldehyde in the environment with 93.4% distributing to air, 5.65% to water, 0.961% to soil, and < 0.1% to sediment.

### 2.2.5 Biodegradation

Several studies have been conducted to assess the biodegradation of valeraldehyde (Appendix A). A 28-day OECD guideline study was conducted using secondary effluent from domestic wastewater; degradation measured after 28 days was 64.1% (Davis and Marty, 2004). A 20-day test was also conducted (Union Carbide, 1993) using non-acclimated domestic wastewater; degradation measured after 5, 10, 15 and 20 days was 48, 67, 73, and 76% of the ThOD. A short term (24 hour) biological oxygen demand (BOD) test estimated the BOD/chemical oxygen demand (ThOD) ratio at 17.8% using activated sludge (Gerhold and Malaney, 1966). These studies demonstrate that valeraldehyde should be considered "readily biodegradable."

### 2.2.6 Bioaccumulation

The bioaccumulation potential of valeraldehyde is low to moderate. Log K<sub>ow</sub> values have been reported for valeraldehyde in the range of 1.31 to 1.39 (Merck Chemical Database, 2000; Verschuren, 2001; Meylan, and Howard, 1995; KOWWIN, Version 1.66); these values suggest that valeraldehyde would only accumulate in biological tissue to a moderate degree, but would not biomagnify in food chains (Meylan and Howard, 1992). An estimated bioconcentration factor of 2.3 L/kg was calculated using the preferred log Kow value of 1.38, which further suggests a low to moderate bioaccumulation potential (EPIWIN v.3.12).

## 2.3 Human Exposure

The majority of valeraldehyde is used as a chemical intermediate in the production of valeric acid and amyl alcohol. However, in Europe, about 1,000 metric tonnes are used for other purposes. Valeraldehyde is a naturally-occurring plant volatile, and is found in a variety of food products (Furia, 1980). It is also an emission product of microorganisms and animal waste, and has been detected as an emission product of gasoline, diesel, and turbine engines (Graedel et al., 1986). Valeraldehyde may also be emitted from burning logs and forest fires (Lipari et al., 1984). The potential exposures from these sources are relatively small due to the degradation of valeraldehyde in the environment (HSDB, 2002).

### 2.3.1 Occupational Exposure

Valeraldehyde is primarily an industrial intermediate, manufactured in continuous process in enclosed equipment. It is stored in tanks and typically chemically converted on-site to valeric acid and amyl alcohol. There is one manufacturer of valeraldehyde in the United States and two manufacturers in Western Europe (CEH, 1999). In the United States, worker exposure is expected to be minimal, since manufacture and use activities are typically conducted in closed systems, using engineering controls. Engineering controls and vapor collection systems are also utilized during production and loading operations to minimize flammability hazards as well as worker exposure. The flash point of valeraldehyde is 5 °C (41 °F), the lower flammable limit of is 2.1% or 21,000 ppm; the flammable range is 21,000 – 78,000 ppm (The Dow Chemical Company, 2002).

In comprehensive guidance to workers who use or make flavoring agents, both the Flavor and Extract Manufacturers Association of the United States and NIOSH have issued information to workers about methods to limit inhalation exposure to flavoring agents (FEMA, 2004; NIOSH, 2003). Although valeraldehyde is listed as a flavoring agent in both documents, occupational exposures to valeraldehyde will be minimized in the United States and other countries that have established occupational exposure limits for this material. Occupational exposure limits for valeraldehyde are presented below (ACGIH, 2005, 1991; James, 2000):

**Table 4: Exposure Limits for n-Valeraldehyde**

Exposure Limit	Value (mg/m <sup>3</sup> )	Value (ppm)
ACGIH TLV (USA)	176	50
OSHA PEL (USA)	None	
NIOSH REL (USA)	176	50
SMAC* (USA)	176	50
Australia	176	50

\*Spacecraft Maximum Allowable Concentration (24 hr value).

### 2.3.2 Consumer Exposure

Valeraldehyde is a naturally occurring volatile in food products and is used in the manufacture of flavoring agents. The general population may be exposed to valeraldehyde through consumption of food products or by inhalation of plant volatiles from food products. With the exception of its occurrence in food products, valeraldehyde does not intentionally appear in consumer products. There are no consumer products containing n-valeraldehyde registered in Scandinavian countries (SPIN database).

### 2.3.3 Indirect Exposure via the Environment

Human exposure to valeraldehyde may occur by indirect exposure to air and water with low concentrations of valeraldehyde from both natural and man-made sources. Valeraldehyde may be released as a fugitive emission during production and use, or in the emissions from vegetation, food products, wood fires, and combustion engines. Valeraldehyde was found in an EPA survey of drinking water in 10 cities to be present at approximately 0.5 ug/l in the drinking water of Ottumwa, IA, but was not detected in the drinking water of Miami FL, Seattle WA, Philadelphia PA, Cincinnati OH, Grand Forks MI, Lawrence MA, New York NY, Terrebonne Parrish LA, and Tucson AZ (Keith et al., 1976).

Valeraldehyde has been detected in the air around waste disposal sites, in urban/suburban air, and in indoor air. In eight tests, valeraldehyde emissions from a fireplace with different types of logs ranged from non-detectable to 0.010 g/kg wood (Lipari et al., 1984). Valeraldehyde emissions from particle board with glued-on carpet, and plywood coated with polyurethane occurred at rates of 0.031 and 0.014 mg/m<sup>2</sup>/hr, respectively (Colombo et al., 1990). Concentrations of valeraldehyde ranging from non-detectable to 38 ug/m<sup>3</sup> were found in ambient air surrounding the Kin-Buc Waste Disposal Site in New Jersey (Pellizzari, 1982). Valeraldehyde levels in air were determined at three sites in the Netherlands; the mean and maximum concentrations of valeraldehyde at these sites were 0.05 ppb and 0.40 ppb, respectively (Guicherit and Schulting, 1985). Air concentrations of valeraldehyde were determined at four urban sites in Stockholm, Sweden. Mean 1-hr concentrations ranged from 0.15 to 1.07 ppb; the mean concentration at a recreation site outside the central city was 0.49 ppb (Jonsson et al., 1985). Ambient levels of valeraldehyde measured on the Pomona College campus in Claremont, CA ranged from < 0.1 to 0.6 ppb, with a median of 0.1 ppb (Grosjean, 1988). Valeraldehyde was detected in one of ten samples in the Kanawha Valley, WV and in four of nine air samples in the Shenandoah Valley VA in 1977 (Erickson and Pellizzari, 1978). Valeraldehyde has also been detected in indoor air in EPA headquarters' building above the 0.06 ug/ m<sup>3</sup> quantitation limit (USEPA, 1990).

## 3.0 HUMAN HEALTH HAZARDS

For some human health endpoints, data from valeraldehyde are available. In addition, structurally similar aldehydes and valeric acid (the metabolic product of valeraldehyde) have been used to augment available data for valeraldehyde. Based on structural similarities and short carbon chain length, data for propionaldehyde, butyraldehyde, isobutyraldehyde, and isovaleraldehyde are considered suitable as supporting chemicals for valeraldehyde. Also, data showing the metabolism of pentyl alcohol to the valeraldehyde and subsequently to valeric acid (as well as data on the metabolism of similar aldehydes) support the use of valeric acid for certain endpoints.

The toxicology of n-valeraldehyde has been thoroughly reviewed in the n-valeraldehyde SIDS dossier. Only those data that are considered most relevant to the assessment of potential human health hazards are summarized here.

### 3.1 Effects on Human Health

#### 3.1.1 Toxicokinetics, Metabolism and Distribution

##### In Vitro Study

Studies using human liver indicate that valeraldehyde, butyraldehyde, and propionaldehyde are readily oxidized and that their relative rates of oxidation are similar when tested *in vitro* at substrate concentrations between 0.5 and 3.0 mM using partially purified human liver aldehyde dehydrogenase (ALDH). Under these conditions, the rate of oxidation for C3 to C5 aldehydes was comparable to acetaldehyde (Blair and Bodley, 1969).

##### Studies in Animals

Low (1.9 mg per 100 ml) blood levels of valeraldehyde were detected 15 minutes after 1 g/kg n-pentyl alcohol was administered intraperitoneally to rats; negligible amounts of valeraldehyde were detected in expired air. When 1 g/kg valeraldehyde was administered by intraperitoneal injection, measured blood levels 15 minutes after administration were 1.4 mg/100 ml (Haggard, Miller, and Greenberg, 1945). The detection of minimal amounts of valeraldehyde after injection with n-pentyl alcohol and the detection of comparably small amounts after injection of valeraldehyde itself, indicates both the formation and the extremely transient nature of valeraldehyde *in vivo*.

In another study, valeric acid was also produced from metabolism of n-pentyl acetate and n-pentyl alcohol (Poet, 2004a,b). Because of its transient nature, no attempt to measure valeraldehyde, which is rapidly oxidized to valeric acid. Production of valeric acid from inhaled primary amyl acetate (mixture of 65% n-pentyl acetate, 35% 2-methylbutyl acetate) demonstrated the rapid hydrolysis of these acetate esters to their corresponding alcohols and metabolism of the alcohols to the corresponding acids (Poet, 2004a). Blood levels of the corresponding acids (valeric acid and 2-methylbutyric acid) reached peak levels of 3  $\mu\text{M}$  n-valeric acid and 17  $\mu\text{M}$  2-methylbutyric acid. The rapid formation of the alcohol isomers following inhalation exposures to the primary amyl acetate mixture demonstrates that *in vivo* exposures to amyl acetate isomers will lead to blood levels of the acid metabolites via the amyl alcohol and aldehyde intermediates.

Similar experiments with primary amyl alcohol (mixture of 62-68% n-pentyl alcohol, 32-38% 2-methylbutyl alcohol) provided additional evidence for the metabolism of amyl alcohols by alcohol and aldehyde dehydrogenases (Poet, 2004b). Exposure of rats to 2000 ppm primary amyl alcohol resulted in peak blood levels of 7  $\mu\text{M}$  valeric acid and 25  $\mu\text{M}$  2-methylbutyric acid at 20 minutes after start of exposure.

The formation of the acid isomers following the amyl acetate and amyl alcohol inhalation exposures demonstrates that *in vivo* exposures will lead to blood levels of the acid metabolites upon rapid oxidation of the aldehyde intermediates.

#### 3.1.2 Acute Toxicity

##### Studies in Animals

##### *Inhalation*

Smyth *et al.* (1969) exposed groups of male rats to n-valeraldehyde vapors (purity not specified) for 4 hours. Fifty percent of the rats exposed to 4000 ppm (14000  $\text{mg}/\text{m}^3$ ) died, but there was no

mortality among rats exposed to 2000 ppm (7000 mg/m<sup>3</sup>). Rats appeared anesthetized during exposure.

In a single-exposure inhalation toxicity study of aliphatic aldehydes (C3 through C7), several species of laboratory animals (rabbits, guinea pigs, mice) were exposed to 2359 mg/m<sup>3</sup> n-valeraldehyde aerosol (purity not specified) for up to 10 hours. Exposure to valeraldehyde aerosol produced an initial increase in activity, followed by signs of eye and respiratory irritation. No rabbits died during exposure or during or after exposure. Necropsy of animals dying on study (4/50 mice, 5/20 guinea pigs) revealed expanded, edematous, and hemorrhagic lungs, indicating the likely cause of death was severe pulmonary irritation. The authors concluded that toxicity decreased with chain length; valeraldehyde was considered less toxic than the shorter-chained saturated aldehydes (Salem and Cullumbine, 1960).

#### *Dermal*

The dermal LD<sub>50</sub> value for valeraldehyde (purity not specified) from the most robust study (Smyth et al., 1969) was 4865 mg/kg in male rabbits. Necrosis was noted at the application site.

#### *Oral*

The LD<sub>50</sub> value for n-valeraldehyde (purity not specified) from the most robust study (Smyth et al., 1969) was 4590 mg/kg for male rats. Animals exhibited narcosis and had discoloured, mottled lungs, liver, and gastrointestinal tract.

#### Conclusion

Available information suggests that valeraldehyde is slightly toxic to animals via inhalation, ingestion and dermal contact. Signs of decreased central nervous system function were observed following high acute exposures to valeraldehyde. This effect is commonly observed following exposure to short chain alcohols and esters of these alcohols and aldehydes.

### **3.1.3 Irritation**

#### Skin Irritation

##### *Studies in Animals*

When allowed to remain on the skin for 4 hours, covered application of 0.5 ml of undiluted valeraldehyde to the skin of rabbits produced necrosis (Union Carbide Corporation, 1974). Smaller volumes (0.01 ml) of n-valeraldehyde (purity not specified) applied to the skin and left uncovered for 24 hours produced slight irritation (Smyth et al., 1962; Union Carbide Corporation, 1957).

#### Eye Irritation

##### *Studies in Animals*

Instillation of 0.02 ml of undiluted valeraldehyde resulted in severe corneal necrosis; 0.005 ml of n-valeraldehyde (purity not specified) produced moderate corneal necrosis (Union Carbide Corporation, 1957). In rabbits, mice, and guinea pigs, a single exposure to 2359 mg/m<sup>3</sup> n-valeraldehyde aerosol (purity not specified) for up to 10 hours produced signs of eye irritation.



Respiratory Tract Irritation*Studies in Animals*

n-Valeraldehyde (> 97% pure) produced a dose-related decrease in respiratory rate, a measure of sensory irritation, in two strains of male mice during head-only exposure; the concentration that reduced respiratory frequency by 50 percent (RD<sub>50</sub>) was determined to be 3923 mg/m<sup>3</sup> in Swiss-Webster mice, and 4165 mg/m<sup>3</sup> in B6C3F1 mice (Steinhagen and Barrow, 1984). Structurally similar aldehydes (propionaldehyde, butyraldehyde, isobutyraldehyde, and isovaleraldehyde) tested using the same protocol and test conditions also produced sensory irritation; however, there was no clear relationship between chain length and irritancy.

**Table 5: Sensory Irritancy Produced by Valderaldehyde and Supporting Aliphatic Aldehydes Measured by RD<sub>50</sub> in Two Strains of Mice**

Substrate (C#)*	RD <sub>50</sub> (ppm) B6C3F1	RD <sub>50</sub> (ppm) Swiss
Propionaldehyde (C3)	2078	2052
Butyraldehyde (C4)	1532	1015
Isobutyraldehyde (C4)	3016	4167
Valeraldehyde (C5)	1190	1121
Isovaleraldehyde (C5)	757	1008

\* Number of carbons present in each substrate

In rabbits, mice, and guinea pigs, a single exposure to 2359 mg/m<sup>3</sup> n-valeraldehyde (purity not specified) aerosol for up to 10 hours produced signs of respiratory irritation. Necropsy of animals dying on study (4/50 mice, 5/20 guinea pigs) revealed evidence of severe pulmonary irritation (Salem and Cullumbine, 1960).

Conclusion

Valeraldehyde is a corrosive material. Undiluted valeraldehyde can produce severe skin and eye irritation and necrosis. It is an upper respiratory tract irritant.

**3.1.4 Sensitization**Studies in Animals*Skin*

Although few details were available on original studies, valeraldehyde did not sensitize any test animal in a standardized skin sensitization test in guinea pigs (Eastman Kodak Company, 1991).

Studies in Humans

There are no human studies available for n-valeraldehyde. Human patch testing of C-6, C-8, and C-9 aldehydes failed to produce sensitization (Opkyke, 1973).

Conclusion

Data from animal studies for valeraldehyde and an analogous aldehyde suggest that valeraldehyde is not a sensitizer.

### 3.1.5 Repeated Dose Toxicity

There are no repeated-dose toxicity studies available for valeraldehyde. Data from the supporting aldehydes propionaldehyde, isobutyraldehyde and butyraldehyde are used to address this endpoint.

#### Studies in Animals

##### *Inhalation*

Repeated dose inhalation studies from propionaldehyde, butyraldehyde and isobutyraldehyde, have produced rhinitis, and atrophy and vacuolization of the olfactory epithelium in laboratory animals. Similar effects are anticipated with valeraldehyde.

Groups of male and female CD rats were exposed by inhalation to propionaldehyde vapor at concentrations of 0, 150, 750, or 1500 ppm (0, 345, 1725, or 3450 mg/m<sup>3</sup>) for 6 hr/day, 7 days a week, for 7 weeks in a combined repeated-dose toxicity study and reproduction/developmental screening study. Treatment-related effects on the nasal epithelium were observed in both sexes in all propionaldehyde-exposed groups. The incidence and severity of nasal lesions were dose-related and included vacuolization and atrophy of the epithelium in the anterior portion of the nasal cavity (Driscoll, 1993). The mean total erythrocyte count in males exposed to 1500 ppm was 104.3% of controls; this increase, although slight, was significant ( $p < 0.05$ ). A slight increase in mean hemoglobin (104.2% of controls) and hematocrit (103.2% of controls) values were also noted in 1500 ppm males, but these values were not significant. A significant increase ( $p < 0.05$ ) in the mean monocyte count was observed in males exposed to 1500 ppm (165% of controls); this increase was considered the result of severe nasal irritation. Increased relative kidney weights were also observed in males at the highest dose ( $p < 0.01$ ). There were no other significant changes in organ weights, or blood or clinical chemistry parameters. The LOAEC for parental toxicity based on the presence of nasal lesions is 150 ppm.

Male and female F344 rats were exposed by inhalation to n-butyraldehyde vapor at concentrations of 0, 125, 500, or 2000 ppm (0, 363, 1450, or 5800 mg/m<sup>3</sup>) for 6 hr/day, 5 days per week, for 13 weeks (Union Carbide Corporation, 1979). Animals in all treatment groups displayed a significant increase in the incidence of squamous metaplasia of the nasal cavity. No other treatment-related lesions were noted. This study resulted in a LOAEC of 125 ppm. A subsequent 12-week inhalation study in male and female rats employing lower doses of 0, 1, 10, and 50 ppm (145 mg/m<sup>3</sup>) n-butyraldehyde did not result in any adverse effects on the nasal, olfactory, or respiratory epithelial tissues resulting in a NOAEC of 50 ppm (Union Carbide Corporation, 1980). In another study, beagle dogs were exposed by inhalation to n-butyraldehyde vapor at concentrations of 0, 125, 500, and 2000 ppm for 6 hr/day, five days a week, for 14 weeks. Dogs exposed to 125 and 500 ppm displayed goblet cell hyperplasia within the nasal mucosa; dogs in the 2000 ppm treatment group displayed hyperplasia, inflammation, and squamous metaplasia of the nasal tissues (Union Carbide Corporation, 1979). Therefore, the LOAEC is 125 ppm.

The National Toxicology Program (NTP) conducted two-year bioassays for a structurally similar aldehyde, isobutyraldehyde, in mice and rats. Male and female F344 rats and B6C3F1 mice were exposed to isobutyraldehyde vapor at concentrations of 0, 500, 1000, and 2000 ppm (0, 1450, 2900, 5800 mg/m<sup>3</sup>) for 103 weeks. Survival in male mice exposed to 2000 ppm was significantly reduced; body weights of female mice exposed to 1000 and 2000 ppm were reduced. Among rats, there was no significant difference in survival between exposed and control groups. The only exposure-related effects observed were non-neoplastic nasal lesions which included degeneration of the olfactory epithelium in mice and rats; rats also displayed suppurative inflammation and squamous metaplasia

of the epithelium. Incidences of minimal to mild squamous metaplasia was significantly increased in male and female rats exposed to 1000 and 2000 ppm, and in females exposed to 500 ppm isobutyraldehyde. The nasal lesions were determined to be a direct contact effect associated with the irritation properties of aldehydes (Abdo et al., 1998). The results indicate a LOAEC of 500 ppm for rats and a NOAEC of 500 ppm for mice.

Thirteen week range-finding studies were also conducted with isobutyraldehyde as part of the testing program sponsored by the NTP. Groups of male and female F344 rats and B6C3F1 mice were exposed by inhalation to isobutyraldehyde vapor at concentrations of 0, 500, 1000, 2000, 4000, and 8000 ppm (0, 1450, 2900, 5800, 11,600, and 23,200 mg/m<sup>3</sup>) for 6 hr/day, five days per week for 13 weeks (Abdo, Haseman, and Nyska, 1998). All animals in the 8000 ppm group died before the end of the study, and there was significant mortality among mice exposed to 4000 ppm. Significant increases in the incidence of non-neoplastic lesions of the nasal cavity were observed in rats at concentrations of 2000 ppm or greater, and in mice at concentrations of 1000 ppm or greater. Nasal lesions included necrosis, suppurative inflammation, hyperplasia, and squamous metaplasia of the epithelium, olfactory epithelial degeneration, and osteodystrophy of the nasal turbinate bone. These results indicate NOAECs of 1000 and 500 ppm for rats and mice, respectively.

### *Oral*

There are no repeated-dose ingestion studies for valeraldehyde. Repeated-dose oral gavage studies in rats and mice with the supporting chemical, butyraldehyde, have demonstrated a dose-related increase in mortality and lesions in the nasal cavity and stomach. Similar effects are anticipated with valeraldehyde.

Groups of male and female F344 rats and B6C3F1 received butyraldehyde in corn oil by gavage at dose levels of 75, 150, 300, 600, or 1200 mg/kg bw/day. Animals were dosed 5 days per week for 13 weeks. All animals in the 1200 mg/kg bw/day groups displayed decrease body weight gain. Among rats, a dose-related increase in mortality was observed. Nasal cavity lesions were noted in all dose groups in rats; stomach lesions were observed in the 1200 and 600 mg/kg bw/day groups. Among mice, nasal lesions were noted in animals that received 300 mg/kg bw/day and greater; stomach lesions were observed in the high dose group (Wolfe et al., 1987). The LOAEL for rats 75 mg/kg bw/day and the NOAEL for mice is 150 mg/kg bw/day.

### Conclusion

Repeated-dose data are not available for valeraldehyde. Instead, data from the supporting chemicals propionaldehyde (Driscoll, 1993), isobutyraldehyde (Abdo et al., 1998), and butyraldehyde (Union Carbide Corporation, 1979, 1980; Wolfe et al., 1987) have been used to address this endpoint. In chronic and subchronic inhalation studies, lesions were limited to the nasal cavity and included vacuolization and atrophy, hyperplasia, inflammation, and squamous metaplasia of the nasal and olfactory epithelium. Repeated oral administration of butyraldehyde in corn oil to mice and rats resulted in nasal and stomach lesions. However, these lesions are considered to be due to the localized effects produced in response to irritation.

**Table 6: Repeated-Dose Toxicity Studies**

Test substance (C#) <sup>1</sup>	Species	Dose Levels	Route/ Duration	Lesions Observed	Other Effects Observed	Reference
<b>Inhalation Studies</b>						
Propionaldehyde (C3)	Rat (M/F)	0, 150 <sup>2</sup> , 750, 1500 ppm [0, 345, 1725, 3450 mg/m <sup>3</sup> ]	Inhalation/ 7 weeks	Degeneration of nasal epithelium	increased erythrocyte, hemoglobin, hematocrit, and monocyte values; increased kidney weights	Driscoll, 1993
n-Butyraldehyde (C4)	Rat (M/F)	0, 125 <sup>2</sup> , 500, 2000 ppm [0, 363, 1450, 5800 mg/m <sup>3</sup> ]	Inhalation/ 13 weeks	Hyperplasia, metaplasia, and inflammation of nasal epithelium		Union Carbide Corp., 1979
n-Butyraldehyde (C4)	Beagle Dog	0, 125 <sup>2</sup> , 500, 2000 ppm [0, 1450, 2900, 5800 mg/m <sup>3</sup> ]	Inhalation/ 13 weeks	Hyperplasia, metaplasia, and inflammation of nasal epithelium		Union Carbide Corp., 1979
Isobutyraldehyde (C4)	Rat (M/F) Mouse (M/F)	0, 500 <sup>3-m</sup> , 1000 <sup>3-r</sup> , 2000, 4000, 8000 ppm [0, 1450, 2900, 5800, 11600, 23200 mg/m <sup>3</sup> ]	Inhalation/ 13 weeks	Hyperplasia, metaplasia, and inflammation of nasal epithelium; osteodystrophy of turbinate bone	Mortality, decreased body weights	Abdo et al., 1998
Isobutyraldehyde (C4)	Rat (M/F) Mouse (M/F)	0, 500 <sup>2-r, 3-m</sup> , 1000, 2000 ppm [0, 1450, 2900, 5800 mg/m <sup>3</sup> ]	Inhalation/ 103 weeks	degeneration of the olfactory epithelium; suppurative inflammation; squamous metaplasia of the epithelium.	Mortality	Abdo et al., 1998
<b>Oral Study</b>						
n-Butyraldehyde (C4)	Rat (M/F) Mouse (M/F)	0, 75 <sup>2-r</sup> , 150 <sup>3-m</sup> , 300, 600, 1200 mg/kg bw/day	Oral gavage/ 13 weeks	Stomach lesions	Mortality, decreased body weight gain	Wolfe et al., 1987

1: Number of carbons present in each substrate

2: LOAEC or LOAEL; r = rat., m = mouse

3: NOAEC or NOAEL; r = rat., m = mouse

### 3.1.6 Genetic Toxicity

There are several *in vitro* genetic toxicity studies for valeraldehyde and an *in vivo* micronucleus assay using valeric acid.

In Vitro Studies

Valeraldehyde was tested in *S. typhimurium* strains TA 100, TA 102, and TA104 in the presence and absence of Arochlor-induced liver S-9 mix from F344 rats and B6C3F1 mice, at doses of 50, 100, 333, 500, 1000, 3333, 5000, and 10,000 ug/plate (Dillon, Combes, and Zeiger, 1998). A pre-incubation protocol was used (Maron and Ames, 1983). The highest dose tested was limited by toxicity which was determined by a thinning of the background lawn, and/or a reduction in the number of colonies per plate. Valeraldehyde was toxic at the highest doses and scoring was performed within the dose range of 333 to 3333 ug/plate. Valeraldehyde did not induce a mutagenic response in any strain, at any dose, both in the presence and absence of rat and mouse metabolic activation systems.

Valeraldehyde was also tested in the standard plate incorporation assay at doses of 10 to 10,000 ug/plate as part of a testing program sponsored by the NTP. Valeraldehyde was negative under all test conditions, both in the presence and absence of metabolic activation using liver S-9 from Arochlor 1254-induced Sprague Dawley rats and Syrian hamsters (NTP, 1996).

In another study, Florin and coworkers (1980) tested a series of compounds (including many aldehydes) found in tobacco smoke in *Salmonella typhimurium* tester strains TA 98, 100, 1535, and 1537 using the spot test protocol (Ames et al., 1975). Valeraldehyde as well as structurally similar chemicals were tested qualitatively at a dose of 3 umoles per plate (approximately 258 ug per plate) both in the presence and absences of an S-9 metabolic activation system derived from Sprague-Dawley rats induced by Arochlor 1254 or 3-methylcholanthrene. Valeraldehyde (and other aldehydes) did not produce a mutagenic response.

When tested *in vitro* in Chinese hamster V79 cell cultures without a metabolic activation system, valeraldehyde induced an increase in mutant frequency (MF) in two mutation assays (Table 10). Mutagenicity was expressed at the hypoxanthine-guanine phosphoribosyltransferase (HGPRT) locus as resistance to 6-thioguanine (TG), or at the Na/K ATPase locus as resistance to ouabain (OUA). V79 cells were incubated with test aldehydes in serum-free medium for 60 minutes and then re-plated in fresh medium for a six-day (HGPRT) or 8-day (OUA) mutant expression interval. There was a dose-dependent decrease in cell survival that was accompanied by an increase in mutant frequency at the HGPRT locus with thioguanine (TG) as the selective agent. A similar response was noted NA/K ATPase locus, with ouabain (OUA) as the selective agent (Brambilla et al., 1989).

**Table 7: Mutagenicity Testing in Chinese Hamster V79 Lung Cells<sup>1</sup>**

Substrate	Dose (ug/ml) <sup>2</sup>	TG MF <sup>3</sup>	OUA MF <sup>4</sup>
Negative control	0	15.1 +/- 0.3	1.4 +/- 0.8
Valeraldehyde	2580	66.6 +/- 18.5*	6.5 +/- 2.3*

1: data from Brambilla, G., Cajelli, E., Canonero, R. et al. 1989

2: dose per ml for 30 mM test concentration

3: represents number of TG-resistant colonies per 10E6 viable cells at HGPRT locus

4: represents number of OUA-resistant colonies per 10E6 viable cells at Na/K ATPase locus

\*: statistically significant (p<0.01) compared to negative control

In a L5178Y TK+/- mouse lymphoma mutagenesis assay, valeraldehyde was tested first in a range-finding test (at concentrations up to 5000 ug/ml). In the definitive test, non-activated culture concentrations from 60 to 150 ug/ml and activated cultures of 150 to 500 ug/ml were evaluated for

toxicity and mutations. In the absence of metabolic activation, there was a dose-dependent increase in mutant frequency and toxicity. Increases in small, medium, and large colonies compared with solvent controls indicated n-valeraldehyde was positive for both gene mutations and chromosomal mutations. In the presence of metabolic activation, n-valeraldehyde was negative for both chromosomal and gene mutations (NCI, 2000).

Valeraldehyde was tested *in vitro* in human lymphocytes at concentrations of 0.002 and 0.003 volume percent (equivalent to approximately 16 and 24 ug/ml, respectively) in a sister chromatid exchange (SCE) assay (Obe and Beek, 1979). Human lymphocytes were incubated with aldehyde test solutions for 24 or 48 hours in synthetic medium supplemented with 10% calf serum. Valeraldehyde did not produce evidence of sister chromatid exchange.

Valeraldehyde did not induce unscheduled DNA synthesis (UDS) when tested *in vitro* in primary human hepatocytes at doses of 0, 3, 10, and 30 mM (equivalent to 258, 861, and 2580 ug/ml, respectively). There was, however, a slight increase in primary rat hepatocytes, which did not demonstrate a dose response (Martelli et al., 1994). The increase observed did not meet the minimum criteria for a positive response (Butterworth et al., 1987).

**Table 8: UDS in Primary Hepatocytes from Rats and Humans**

Doses tested (mg/ml) <sup>1</sup>	NNGC <sup>2</sup> in Rat Hepatocytes	NNGC in Human Hepatocytes
0	0.63 +/- 4.76	0.55 +/- 1.69
258	2.35 +/- 4.24*	0.85 +/- 2.07
861	2.30 +/- 3.78*	0.86 +/- 2.63
2580	2.65 +/- 3.88*	1.09 +/- 3.02

1: dose per ml, based on reported test concentrations of 0, 3, 10, 30 mM.

2: mean net nuclear grain count +/- SD

\*: statistically significant (p<0.001) compared to untreated controls

**Table 9: Summary of Genotoxicity Studies**

Assay	Dose Levels	Metabolic Activation	Results	Reference
<i>In vitro</i> Studies				
Ames Assay/ preincubation protocol with <i>S. typhimurium</i> tester strains TA 100, 102, 104	0, 33 to 3333 ug/plate	Rat and mouse liver S-9	Negative with and without metabolic activation	Dillon et al., 1998
Ames Assay/ standard plate protocol with tester strains TA98, 100, 1535, 1537	0, 10 to 10,000 ug/plate	Rat and hamster liver S-9	Negative with and without metabolic activation	NTP, 1996
Ames Assay/ Test with TA98, 100, 1535, 1537	0, 216 ug/plate	Rat liver S-9	Negative with and without metabolic activation	Florin et al., 1980
HGPRT Forward Mutation Assay	0, 2580 ug/ml	None	Positive	Brambilla et al.,

Chinese hamster V79 cells					1989
Ouabain (OUA) Mutation Assay Chinese hamster V79 cells	0, 2580 ug/ml	None		Positive	Brambilla et al., 1989
L5178Y TK+/- Mouse Lymphoma Assay	60 to 150 ug/ml	Rat liver S-9		Negative for chromosomal mutations and gene mutations with activation; Positive without activation	NCI, 1999
SCE Cytogenetics Assay in human lymphocytes	0, 80, 120 ug/culture	None		Negative	Obe and Beck, 1979
UDS/DNA Repair Assay in primary human hepatocytes	0, 258, 861, 2580 mg/ml	None		Negative	Martelli et al., 1994
UDS/DNA Repair Assay in primary rat hepatocytes	0, 258, 861, 2580 mg/ml	None		Negative	Martelli et al., 1994
<i>In Vivo Study</i>					
Micronucleus Assay in Swiss Webster mice	0, 83, 166, 266 mg/kg IP injection	None		Negative at all doses and sampling times (30, 48, 72 hr after dosing)	Slesinski, R.S., 1985.

### *In Vivo Study*

There is a mouse micronucleus assay for valeric acid, a metabolite of valeraldehyde. Valeric acid was tested at concentrations up to 80% of the LD50, in male and female mice. Groups of male and female Swiss Webster mice (5 per sex) received valeric acid, administered in corn oil by intraperitoneal injection, at doses of 83, 166, or 266 mg/kg. Control animals received corn oil only. Blood samples were collected at approximately 30, 48, and 72 hours after dosing and examined for the presence of micronuclei. Valeric acid did not produce an increase in the incidence of micronuclei in test animals at any time interval after dosing as compared to corn oil controls (Slesinski, 1985).

### Conclusion

*In vitro* genotoxicity studies on valeraldehyde have been conducted in bacteria as well as animal and human cell cultures. Valeraldehyde was not mutagenic in the bacteria, *Salmonella typhimurium*, even when tested at concentrations up to 10 mg/plate. When tested in the absence of metabolic activation, valeraldehyde induced cytotoxicity and a mutagenic response in Chinese hamster V79 cells. Valeraldehyde produced both chromosomal mutations and gene mutations in the absence of activation in the L5178Y TK +/- mouse lymphoma assay, but was negative in the presence of activation. The chemical was negative in a sister chromatid exchange assay in freshly isolated human lymphocytes and did not induce DNA repair when tested in primary human hepatocytes. Although no dose response was observed, valeraldehyde did produce a small increase in DNA repair in primary rat hepatocytes; the increase observed did not meet the minimum criteria for a positive response.

An *in vivo* micronucleus assay using valeric acid did not produce an increased incidence in micronuclei.

These results show that valeraldehyde is genotoxic in some *in vitro* test systems in the absence of metabolic activation. However, negative results were obtained in those assays with inherent or added metabolic activation systems. There is insufficient evidence to suggest that the chemical is mutagenic to humans *in vivo*.

Similar genotoxicity results were obtained for the structural analog, isobutyraldehyde. In addition, isobutyraldehyde was negative in a two-year chronic inhalation bioassay in mice and rats; the only effects related to treatment were non-neoplastic degenerative lesions of the nasal epithelium.

### 3.1.7 Carcinogenicity

No carcinogenicity study for valeraldehyde is available. Data for a structurally similar chemical, isobutyraldehyde, are available.

The National Toxicology Program (NTP) conducted two-year bioassays on isobutyraldehyde in mice and rats. Male and female F344 rats and B6C3F1 mice were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, and 2000 ppm (0, 1450, 2900, and 5800 mg/m<sup>3</sup>) for 103 weeks. Survival in male mice exposed to 2000 ppm was significantly reduced; body weights of female mice exposed to 1000 and 2000 ppm were reduced. Among rats, there was no significant difference in survival between exposed and control groups. There was no treatment-related dose-dependent increase in the incidence of tumors in rats or mice. The only definite exposure-related effects observed were non-neoplastic nasal lesions which included degeneration of the olfactory epithelium in mice and rats; rats also displayed suppurative inflammation and squamous metaplasia of the epithelium. The nasal lesions were determined to be a direct contact effect with the irritating aldehyde (Abdo, Haseman, and Nyska, 1998).

### 3.1.8 Reproductive/Developmental Toxicity

#### Effects on Fertility and Reproductive Organs

There are no reproductive toxicity studies available for valeraldehyde. Data are available from the structurally similar chemicals (propionaldehyde, butyraldehyde, and isobutyraldehyde) to address this endpoint.

Propionaldehyde was tested by inhalation in a combined repeated-dose toxicity study with a reproduction/developmental toxicity screening test at vapor concentration of 0, 150, 750, or 1500 ppm (0, 345, 1725, and 3450 mg/m<sup>3</sup>) (Driscoll, 1993). Male and female rats were exposed for 6 hr/day, 7 days a week. The pre-mating exposure interval was 14 days and the mating interval was up to 14 days. Males continued exposure after mating for a total exposure of up to 52 days. Females were exposed through day 20 of gestation, and then allowed to litter and raise pups until day 4 of lactation. Maternal toxicity, as evidenced by decreased food consumption and body weight gain, was observed in females in the 750 and 1500 ppm groups. There were no significant effects on any of the reproductive parameters assessed; litter size and variability were similar among groups. Pup body weights were not affected. However, pup body weight gains between lactation day 0 and 4 were slightly depressed in the high dose group. The NOAEC for reproductive toxicity was 1500 ppm; the NOAEC for pup toxicity, based upon a slight reduction in body weight gain on day 4, was 750 ppm.



Groups of male and female F344 rats were exposed by inhalation to isobutyraldehyde vapor at concentrations of 0, 500, 1000, 2000, or 4000 ppm (0, 1450, 2900, 5800, or 11600 mg/m<sup>3</sup>) for 6 hr/day, five days per week for 13 weeks; groups of male and female B6C3F1 mice were similarly exposed to 0, 500, 1000, or 2000 ppm (Morrissey, et al., 1988; NTP, 1999). At the end of the study, animals were screened for potential reproductive effects as part of the National Toxicology Program (NTP) Sperm Motility and Vaginal Cytology Examinations (SMVCE) program.

There was 30% mortality among male rats exposed to 4000 ppm. Decreased body weights and decreased absolute weights of the cauda epididymis and epididymis were noted in the 4000 ppm group; there was no effect on the absolute weight of the testes, or the relative weights of the epididymis, cauda epididymis, and testes. No effects on body weights or reproductive organ weights were noted in male rats or male mice at dose levels of 2000 ppm or less. Isobutyraldehyde had no effect on sperm motility, density, or morphology at any dose level in mice. In rats, there was a decrease in sperm motility at the 500 and 1000 ppm, but not at 2000 and 4000 ppm. Because of the variability between groups and the lack of a dose response, the overall effect on sperm motility in rats was difficult to interpret. The study authors concluded that the effect was negative and provided a NOAEC of 2000 ppm for male reproductive effects examined in this study for rats and mice. Among female rats, there was significant mortality (60% in females, 30% in males) in rats exposed to isobutyraldehyde at concentrations of 4000 ppm. There were no significant effects on vaginal cytology and average estrous cycle length. However, the relative frequency of estrous stages differed from controls in the few remaining females exposed to 4000 ppm. Due to the significant mortality, a NOAEC for study-specific reproductive effects cannot be presented for female rats. However, the significant mortality would suggest a NOAEC of 2000 ppm in female rats (Morrissey et al., 1988).

Groups of F344 rats and B6C3F1 mice of both sexes were exposed to isobutyraldehyde for 6 hr/day, five days per week, for 103 weeks as part of a testing program sponsored by the NTP (Abdo, Haseman, and Nyska, 1998). Exposure concentrations for both species were 0, 500, 1000, and 2000 ppm (0, 1450, 2900, and 5800 mg/m<sup>3</sup>). The survival rate of male mice exposed to 2000 ppm was significantly reduced; there was no effect on survival among female mice or among male and female rats. At the end of the 2-year study, the only exposure-related effects observed were non-neoplastic nasal lesions. Reproductive organs were normal upon gross and histopathological examination.

**Table 10: Summary of Reproductive Toxicity Studies**

Test substance	Species	Dose Levels	Route/ Duration	Results	Reference
Propionaldehyde (C3)	Rat (M/F)	0, 150, 750, 1500 <sup>1</sup> ppm [0, 345, 1725, 3450 mg/m <sup>3</sup> ]	Inhalation 14 days prior to mating, 48-52 days total exposure	Maternal toxicity at 750, 1500 ppm; no effect on fertility, litter size/viability, pup weight. No abnormalities in male/female gonads. Slight decrease in pup weight gain in 1500 ppm group	Driscoll, 1993
Isobutyraldehyde (C4)	Rat (M/F)	0, 500, 1000, 2000, 4000, ppm [0, 1450, 2900, 5800, 11600 mg/m <sup>3</sup> ]	Inhalation 13 weeks	4000 ppm: decreased male body weight gain, decreased absolute weight of epididymis.  No effect on sperm density/morphology/ motility at two highest exposure levels, decrease in sperm motility was seen at the lower doses but due to no dose-response, the overall	Morrissey et al., 1988

				effects was considered negative; no effect on absolute weight of testes and relative weights of male reproductive organs; 4000 ppm: increased female mortality; one test of significance showed that the time spent in estrous cycle stages differed in surviving females but two other tests did not show significant differences from controls.	
Isobutyraldehyde (C4)	Mouse (M/F)	0, 500, 1000, 2000 <sup>1</sup> ppm [0, 1450, 2900, 5800 mg/m <sup>3</sup> ]	Inhalation 13 weeks	2000 ppm: no effect on sperm density/morphology/motility; no effect on male reproductive organ weights or female parameters	Morrissey et al., 1988
Isobutyraldehyde (C4)	Rat and Mouse (M/F)	0, 500, 1000, 2000 ppm [0, 1450, 2900, 5800 mg/m <sup>3</sup> ]	Inhalation 103 weeks	2000 ppm: decreased survival in male mice; no effect on reproductive organ weights, reproductive organs and tissues normal upon gross and microscopic examination	Abdo et al., 1998
Butyraldehyde (C4)	Rat (M/F)	0, 125, 500, 2000 ppm [363, 1450, 5800 mg/m <sup>3</sup> ]	Inhalation 13 weeks	2000 ppm: reproductive organs and tissues normal upon gross and microscopic examination	Union Carbide Corp., 1979

1: NOAEC for reproductive toxicity

Male and female F344 rats were exposed by inhalation to n-butyraldehyde at vapor concentrations of 0, 125, 500, or 2000 ppm (363, 1450, or 5800 mg/m<sup>3</sup>) for 6 hr/day, 5 days per week, for 13 weeks (Union Carbide Corporation, 1979). Animals in all treatment groups displayed a significant increase in the incidence of squamous metaplasia of the nasal cavity. Reproductive organs and tissues examined at the end of the study were normal upon gross and microscopic examination.

#### Developmental Toxicity

There are no developmental toxicity studies available for n-valeraldehyde. However, data from isobutyraldehyde and propionaldehyde and the metabolite valeric acid are available to address the endpoint.

Groups of pregnant female Wistar rats were exposed by inhalation to 0, 1000, 2500, or 4000 ppm (0, 2900, 7250, or 11600 mg/m<sup>3</sup>) isobutyraldehyde for 6 hr/day for ten consecutive days during gestational days (GD) 6 through 15 (Garmer, Hellwig, and Hildebrand, 1996). Maternal toxicity, as evidenced by a significant decrease in body weight gain, was observed in dams exposed to 4000 and 2500 ppm. There was no effect on gestational or litter parameters; no developmental toxicity or fetal malformations were observed at any exposure level. The NOAEC for maternal toxicity was 1000 ppm; the NOAEC for developmental toxicity was 4000 ppm.

As noted under *Effects on Fertility and Reproduction*, propionaldehyde was tested by inhalation in a combined repeated-dose toxicity study with a reproduction/developmental toxicity screening test at vapor concentration of 0, 150, 750, or 1500 ppm (0, 345, 1725, or 3450 mg/m<sup>3</sup>) (Driscoll, 1993). Maternal toxicity, as evidenced by decreased food consumption and body weight gain was observed in females in the 750 and 1500 ppm groups. Pup body weight gains between lactation day 0 and 4 were slightly depressed in the high dose group (although statistically significant at  $p < 0.01$ ). Therefore, the NOAEC for developmental toxicity was 750 ppm; the parental LOAEC was 150 ppm.

A developmental toxicity study is also available for valeric acid, the “downstream” metabolite of valeraldehyde. The study was conducted on groups of timed pregnant female Sprague-Dawley rats. Valeric acid in corn oil was administered once per day by oral gavage on 10 consecutive days during GD 6 through GD 15 at doses of 0, 50, 100, and 200 mg/kg bw/day. This study demonstrates the difficulties encountered when testing materials that are severe irritants. Vocalization, rales, and dyspnea were noted in animals immediately after oral gavage of the test material, and mortality occurred in all treatment groups (1/24 at 50 mg/kg, 3/24 at 100 mg/kg, and 10/24 at 200 mg/kg). The authors state that the corn oil/valeric acid dosing solution produced respiratory effects upon gastroesophageal reflux into the lungs. There was evidence of respiratory irritation and distress. Gastric irritation was observed at necropsy in 6 of 10 rats in the 200 mg/kg bw/day group that died on study. No data are available for maternal food or water consumption. However, maternal body weight gains were lower in all valeric acid groups, and the decrease in body weight gain was significant in the 100 and 200 mg/kg bw/day groups (Narotsky, Francis, and Kavlock, 1994; Narotsky, and Kavlock, 1989).

There were no differences in gestational or litter parameters with the exception of fetal body weights that were reduced at all dose levels. The decrease in fetal body weights was significant in the 100 and 200 mg/kg groups; at these doses, significant maternal toxicity and mortality were also observed. Despite evidence of maternal toxicity, there was no evidence of fetal malformations. When assessed on a % litter affected basis, there was a non-dose related decrease in sternbrae ossification (defined as small sternbrae and sternbrae with reduced or no ossification); these percentages were 8.7 (control), 62.7 (50 mg/kg), 71.3 (100 mg/kg), and 62.5 (200 mg/kg). However, there were no sternbrae effects when the data were evaluated on the standard basis of mean number of pups affected per litter. No other significant skeletal or visceral effects were observed (Narotsky, Francis, and Kavlock, 1994; Narotsky, and Kavlock, 1989). No NOAELs or LOAELs could be determined from this study due to the severe irritation and mortality in dams from all treatment groups.

**Table 11: Summary of Developmental Toxicity Studies**

Test substance	Species	Dose Levels	Route/ Duration	Results	Reference
Isobutylaldehyde	Rat (F)	0, 1000, 2500, 4000 <sup>1</sup> ppm [0, 2900, 7250, or 11600 mg/m <sup>3</sup> ]	Inhalation 10 consecutive days, GD6 - 15	Maternal toxicity at 2500 and 4000 ppm  4000 ppm: no effect on gestational or litter parameters; no embryofetal toxicity or fetal malformations	Garmer et al., 1996
Propionaldehyde	Rat (M/F)	0, 150, 750 <sup>1</sup> , 1500 ppm [0, 345, 1725, or 3450 mg/m <sup>3</sup> ]	Inhalation M/F 14 days pre-mating; mated females GD1- 20, then allowed to litter; pups examined LD0 through LD4	Maternal toxicity at 750, 1500 ppm; no effect on fertility, litter size/viability, pup weight. No gross malformations observed; slight decrease in pup weight gain in 1500 ppm group	Driscoll, 1993

Valeric Acid	Rat (F)	0, 50, 100, 200 mg/kg bw/day	Oral gavage 10 consecutive days, GD6 - 15	Maternal toxicity and mortality at all doses, mortality associated with respiratory congestion caused by reflux of dosing solution into lungs; fetal body weight decreased at 100 and 200 mg/kg; .no fetal malformations, statistically significant increase in percent incidence of sternebrae that are small, unossified or have reduced ossification.	Narotsky et al., 1994; Narotsky and Kavlock, 1989
--------------	---------	------------------------------	---	--	---

1: Developmental NOAEC

### Conclusion

An inhalation combined repeated-dose toxicity study with a reproduction/developmental toxicity screening test in rats has been conducted on propionaldehyde; the NOAEC for reproductive toxicity was 1500 ppm. Repeated-dose inhalation toxicity studies, which examined the effect of exposure on reproductive organ weights and histology, have also been conducted for isobutyraldehyde and butyraldehyde. Testing of these materials resulted in minimal effects, which were observed at concentrations accompanied by mortality or clinical signs of toxicity; dose responses were not observed or were difficult to determine due to high mortality. No lesions were observed upon microscopic examination of male and female reproductive organs in any study cited above. It is anticipated that exposure to valeraldehyde would produce a similar response.

Developmental toxicity studies have been conducted via inhalation with propionaldehyde and isobutyraldehyde. In the inhalation study using propionaldehyde, decreased pup body weight gain was observed at the highest dose (1500 ppm); the NOAEC for developmental toxicity was 750 ppm. In the inhalation developmental study using isobutyraldehyde, there was no effect on gestational or litter parameters; also no developmental toxicity or fetal malformations were observed at any exposure level. An oral gavage study with valeric acid, a metabolite of valeraldehyde, cannot be used to make definitive conclusions because the study resulted in severe irritation and maternal mortality in all treatment groups (with mortality exceeding 10 percent in the two highest dose groups). However, at all three dose levels in the valeric acid study, there was a decrease in fetal body weights and the percent incidence of fetuses per litter with sternebrae that had reduced or no ossification or were small was significantly increased. None of the studies resulted in malformations even at maternally toxic doses. It is anticipated that exposure to valeraldehyde will produce a similar response.

#### **3.1.9 Human Cases**

The odor threshold for valeraldehyde in an aqueous solution in normal human subjects was reported as 60.6 ppb (Amoore *et al.*, 1976). No reports of human exposure were located. However, several chemists reportedly exposed to high concentrations of isovaleraldehyde developed signs of chest discomfort, nausea, headache, and vomiting; all recovered without residual effects (Wilkinson, J.F., 1940). Also, a monograph on aliphatic aldehydes reported that patch testing did not result in sensitization in human subjects (Okdyke, 1973).

### 3.2 Initial Assessment for Human Health

Data for valeraldehyde are available for acute toxicity, skin and eye irritation, as well as skin sensitization. The acute oral LD<sub>50</sub> value for male rats was 4590 mg/kg. The dermal LD<sub>50</sub> in male rabbits was 4865 mg/kg; necrosis was observed at the application site. There was 50 percent mortality among rats exposed to 4000 ppm (11600 mg/m<sup>3</sup>) valeraldehyde vapor for 4 hours, but no mortality among rats exposed to 2000 ppm (5800 mg/m<sup>3</sup>). Valeraldehyde is a corrosive liquid and produces necrosis after occluded skin exposure (4 or 24 hr). When undiluted, valeraldehyde can produce severe skin and eye irritation and necrosis. Animal studies show it to be an upper respiratory tract irritant, but not a skin sensitizer.

Repeated-dose toxicity studies with other aldehydes (n-butyraldehyde, isobutyraldehyde and propionaldehyde) have demonstrated mortality and localized lesions in response to irritation as well as some effects on hematology and clinical chemistry; however, systemic effects have not been observed. A similar toxicity profile is expected for n-valeraldehyde. Thirteen-week rat and 14-week dog inhalation studies at n-butyraldehyde concentrations of 125, 500, and 2000 ppm (363, 1450, and 5800 mg/m<sup>3</sup>) resulted in nasal lesions at all doses with LOAECs of 125 ppm for both species. A subsequent 12-week rat study determined a NOAEC for n-butyraldehyde vapor in rats of 50 ppm (145 mg/m<sup>3</sup>, the highest dose tested). A 13-week gavage study with n-butyraldehyde in rats and mice at doses of 75, 150, 300, 600, and 1200 mg/kg bw/day resulted in nasal lesions at all doses and lesions of the stomach at 600 and 1200 mg/kg bw/day in rats. A dose-related increase in mortality was also observed in rats. In mice, treatment-related nasal lesions were noted at 300 mg/kg and above and mortality, stomach lesions, and decreased body weight gain were observed at 1200 mg/kg bw/day, resulting in a NOAEL of 150 mg/kg bw/day.

In a 103-week inhalation study with isobutyraldehyde vapor, rats and mice were exposed to 0, 500, 1000, or 2000 ppm (0, 1450, 2900, 5800 mg/m<sup>3</sup>). Non-neoplastic nasal lesions were significantly increased at all doses (females only at 500 ppm), resulting in a LOAEC of 500 ppm for rats. Survival of mice was reduced at 2000 ppm and mean body weights of females were reduced at 1000 and 2000 ppm. Degeneration of the olfactory epithelium was observed at the two highest doses in mice, for a NOAEC of 500 ppm in mice. A shorter (13-week) inhalation study in rats and mice using isobutyraldehyde vapor concentrations of 0, 500, 1000, 2000, 4000, and 8000 ppm (0, 1450, 2900, 5800, 11600, and 23200 mg/m<sup>3</sup>) resulted in mortality at 4000 and 8000 ppm in both species. Non-neoplastic lesions of the nasal cavity occurred at concentrations of 2000 ppm and greater in rats and 1000 ppm and greater in mice resulting in NOAECs of 1000 ppm and 500 ppm, respectively. Nasal lesions observed included necrosis, hyperplasia, squamous metaplasia, and olfactory epithelial degeneration.

In a combined repeated-dose toxicity study with reproduction and developmental toxicity screening test, rats were exposed to propionaldehyde vapor concentrations of 150, 750, and 1500 ppm (345, 1725, and 3450 mg/m<sup>3</sup>) via inhalation. Effects on the nasal epithelium were seen at all doses, including vacuolization in the low and intermediate dose groups and squamous metaplasia (in a few animals) and atrophy in the intermediate and high dose groups. Some effects on hematology (increased erythrocytes, hemoglobin and hematocrit values) and increased monocytes were observed at 1500 ppm. Increased kidney weights were also observed at the highest dose. The LOAEC is 150 ppm.

*In vitro* data on genetic toxicity are available for valeraldehyde and *in vivo* data are available for valeric acid. Valeraldehyde tested negative both in the presence and absence of a metabolic activation systems in several bacterial reverse mutation assays with several strains of *Salmonella typhimurium*. When tested in assays conducted in the absence of metabolic activation,

valeraldehyde was positive in a mouse lymphoma assay and gene mutation assays in Chinese hamster V79 cells; it was negative in a sister chromatid exchange assay in human lymphocytes. When tested in the presence of inherent or added metabolic activation, valeraldehyde was negative in a UDS (DNA repair) assay in human and rat hepatocytes and a mouse lymphoma gene mutation assay. Valeric acid, the “downstream” metabolite of valeraldehyde, did not result in increased micronuclei in an *in vivo* mouse micronucleus assay.

Several studies with structurally similar aldehydes evaluated reproductive organs and one evaluated fertility. In a combined repeated-dose study with a reproduction/developmental toxicity screening test, no reproductive effects were observed in male and female rats exposed to 150, 750, or 1500 ppm (345, 1725, or 3450 mg/m<sup>3</sup>) propionaldehyde vapor resulting in a reproductive NOAEC of 1500 ppm. Male and female rats exposed to isobutyraldehyde concentrations up to 2000 ppm (5800 mg/m<sup>3</sup>) for 103 weeks had normal reproductive organs and tissues. Male and female rats exposed 0, 500, 1000, 2000, or 4000 ppm (1450, 2900, 5800, or 11600 mg/m<sup>3</sup>) isobutyraldehyde for 13 weeks had normal reproductive organs and tissues; no effect on sperm motility, density or morphology was observed in male rats exposed to 4000 and 2000 ppm, however motility was decreased at 500 and 1000 ppm. Significant mortality was observed in female rats at 4000 ppm, at which some differences in the relative time in different stages of estrous were observed in the surviving females. No effects were observed on vaginal cytology or average estrous cycle length. In the same study, male and female mice showed no reproductive effects.

Developmental toxicity data are available for propionaldehyde, isobutyraldehyde, and valeric acid. No external physical abnormalities were observed in neonates in the combined repeated-dose toxicity study with reproduction/developmental toxicity screening test using propionaldehyde vapor described above. However, pup body weight gain between lactation day 0 and 4 in the high dose group was slightly decreased resulting in a NOAEC of 750 ppm. The parental LOAEC was 150 ppm. Groups of pregnant female rats were exposed by inhalation to 0, 1000, 2500, or 4000 ppm (2900, 7250, or 11600 mg/m<sup>3</sup>) isobutyraldehyde vapor for 6 hr/day for ten consecutive days during gestational days (GD) 6 through 15. Maternal toxicity, as evidenced by a significant decrease in body weight gain, was observed in dams exposed to 2500 and 4000 ppm resulting in a maternal NOAEC of 1000 ppm. There was no effect on gestational or litter parameters; no developmental toxicity or fetal malformations were observed at any exposure level, resulting in a developmental NOAEC of 4000 ppm. A developmental toxicity study using valeric acid on groups of timed pregnant female rats by oral gavage during GD 6 through GD 15 at doses of 0, 50, 100, and 200 mg/kg bw/day, resulted in severe maternal toxicity. Vocalization, rales, and dyspnea were noted in dams immediately after dosing of the material, and mortality occurred in all treatment groups (4% at 50 mg/kg, 13% at 100 mg/kg, and 42% at 200 mg/kg). Fetal body weights were reduced at all dose levels. Although maternal toxicity makes it difficult to interpret the significance of the results, the percent incidence of fetuses with small sternebrae or reduced ossification was statistically increased at all dose levels. No fetal malformations or other variations were observed. Due to severe maternal toxicity a NOAEL couldn't be established for developmental toxicity.

The odor threshold for valeraldehyde (0.028 to 0.060 ppm) is well below the 8-hour TWA occupational exposure limit of 50 ppm established by ACGIH to prevent irritation. There are no human studies that evaluated the relationship between odor threshold and irritation.

## 4.0 HAZARDS TO THE ENVIRONMENT

### 4.1 Aquatic Effects

In general, information on the aquatic toxicity of valeraldehyde is limited to acute studies. Several different species were tested with valeraldehyde for the assessment of aquatic toxicity (Table 15). Fish appear to be the more sensitive to valeraldehyde than aquatic invertebrates such as *Daphnia*.

#### Acute Toxicity Test Results

Several studies examining the toxicity of valeraldehyde in fish are available. A GLP analytical study conducted according to OECD guideline 203 in rainbow trout (*Oncorhynchus mykiss*) in a flow-through test system demonstrated a 96-hr LC<sub>50</sub> of 27.9 mg/L and a NOEC of 7.78 mg/L (Marino et al., 2003a). Two acute studies (valid without restrictions) were conducted using fathead minnows (*Pimephales promelas*) using a flow-through test system (Geiger et al., 1985; 1986). In both studies, the concentration of valeraldehyde in test solutions was determined daily. In the first study, there was no mortality among fish exposed to 5.6 and 9.3 mg/kg; however mortality was significant at higher dose levels. A 96-hr LC<sub>50</sub> of 12.4 (95% CI 11.3-13.6) mg/L was calculated (Geiger et al., 1985). Similar results were obtained in the second study, which determined a 96-hr LC<sub>50</sub> of 13.4 (95% CI 12.8-14.0) mg/L (Geiger et al., 1986). A 96-hour static test was also conducted with fathead minnows. The 96-hr LC<sub>50</sub> was reported as 42 mg/L, the NOEC was reported as 21.6 mg/L (Union Carbide, 1993).

Two studies are available which examine the toxicity of valeraldehyde to invertebrates. A GLP guideline study evaluated the toxicity of valeraldehyde to the aquatic invertebrate, *Daphnia magna* Straus. The static 48-hr EC<sub>50</sub> for immobilization was determined to be 70.7 mg/L, the NOEC was 25.0 mg/L (Marino et al., 2003). An additional *Daphnia magna* study, conducted under static conditions, determined a 48-hr EC<sub>50</sub> for immobilization greater than 100 mg/L, and the EC<sub>100</sub> was 500 mg/L (Union Carbide, 1993).

There is one acute toxicity study in algae available for valeraldehyde. A 96-hr guideline study was conducted with *Pseudokirchneriella subcapitata* (formerly known as *Selenastrum capricornutum*). The 72-hr and 96-hr EC<sub>50</sub> values for growth inhibition were 32.4 mg/L and 42.2 mg/L. The 72- and 96-hr EC<sub>50</sub> values for biomass (area under the curve) were 31.4 mg/L and 37.1mg/L, respectively. The NOEC for both intervals was 18.8 mg/L (Hancock et al., 2003).

**Table 12: Environmental Toxicity Data for Valeraldehyde**

Test Organism	LC <sub>50</sub> or EC <sub>50</sub> (mg/L)	Fresh / Marine	Duration/ Endpoint	Reference
Rainbow trout <i>Oncorhynchus mykiss</i>	LC <sub>50</sub> = 27.9 NOEC = 7.78	F	96 hr flow-through; mortality	Marino et al., 2003a
Fathead minnow <i>Pimephales promelas</i>	LC <sub>0</sub> = 9.33 LC <sub>50</sub> = 12.4 LC <sub>100</sub> = 22.1	F	96 hr flow- through; mortality	Geiger et al., 1985
Fathead minnow <i>Pimephales promelas</i>	LC <sub>50</sub> = 13.4	F	96 hr flow- through; mortality	Geiger et al., 1986
Fathead minnow <i>Pimephales promelas</i>	LC <sub>0</sub> = 21.6 LC <sub>50</sub> = 42.0	F	96 hr static; mortality	Union Carbide, 1993
Water flea <i>Daphnia magna</i> .	EC <sub>50</sub> = 70.7 NOEC = 25.0	F	48 hr static; immobilization	Marino et al., 2003b

Water flea <i>Daphnia magna</i> .	EC <sub>50</sub> =>100 EC <sub>100</sub> =>500	F	48 hr static; immobilization	Union Carbide, 1993
<i>Pseudokirchneriella subcapitata</i> (formerly known as <i>Selenastrum capricornutum</i> )	72 hr EC <sub>50</sub> = 32.4 96 hr EC <sub>50</sub> = 42.2  72 hr EC <sub>50</sub> = 31.4 96 hr EC <sub>50</sub> = 37.1  NOEC = 18.8	F	96 hr static growth inhibition  biomass (area under curve)	Hancock et al., 2003

Toxicity data for valeraldehyde are available from one 14-day toxicity test conducted using the freshwater guppy, *Poecilia reticulata* (Deener *et al.*, 1988). The assay was performed in a semi-static testing system with test solutions renewed daily. The concentration of valeraldehyde was determined before and after each renewal. The 14-day LC<sub>50</sub> for valeraldehyde was 13.0 mg/L.

#### Toxicity to Microorganisms

One toxicity test which measured growth inhibition relative to controls was conducted with non-acclimated sewage microorganisms (Union Carbide, 1993). The EC<sub>50</sub> was determined to be 140 mg/L after 16-hours of exposure.

#### **4.2 Terrestrial Effects**

No ecotoxicological data for valeraldehyde were identified for terrestrial wildlife (*i.e.*, birds and mammals) or other terrestrial organisms (*e.g.*, plants, invertebrates, and bacteria).

#### **4.3 Other Environmental Effects**

No other data were found.

#### **4.4 Initial Assessment for the Environment**

The available physicochemical data are adequate to describe the properties of valeraldehyde. Valeraldehyde has a vapor pressure of 35 hPa at 20 °C, a water solubility of 11,700 mg/l at 25°C and a log K<sub>ow</sub> of 1.38. The photochemical removal of valeraldehyde in air as mediated by hydroxyl radicals occurs with a calculated half-life of 9.00 hours. Valeraldehyde is readily biodegradable under aerobic conditions, based on a 28-day ready biodegradation test. Valeraldehyde volatilises easily from moving rivers, but only moderately from quiescent lakes and other surface water bodies (calculated volatilisation half-lives of 8.3 hours from a river and 5.4 days from a lake). Valeraldehyde is not persistent in the environment and is not likely to bioaccumulate in food webs. Based on Level III Fugacity distribution modelling, it is estimated that the majority of valeraldehyde released to the environment will remain in air (93.4%), with small amounts partitioning into water (5.65%), soil (0.96%), and sediment (<0.1%). Aquatic toxicity data are available for valeraldehyde.

For fish, a GLP OECD guideline 203 study in the rainbow trout *Oncorhynchus mykiss* in a flow-through test system demonstrated a 96-hr LC<sub>50</sub> of 27.9 mg/L and a NOEC of 7.78 mg/L. Two other flow-through studies with fathead minnow reported acute 96-hr LC<sub>50</sub>s of 12.4 and 13.4 mg/L. A static fish study determined a 96-hr LC<sub>50</sub> of 42 mg/L. A 48-hr EC<sub>50</sub> value of 70.7 mg/L and a NOEC of 25.0 mg/L was reported for the invertebrate *Daphnia magna* in a GLP guideline study. A 96-hr EC<sub>50</sub> value of 42.2 mg/L was reported for the green alga *Pseudokirchneriella subcapitata* (formerly known as *Selenastrum capricornutum*), in a GLP guideline study; the 96-hr NOEC was 18.8 mg/L. Calculated ECOSAR (EPISuite, 2000) acute toxicity values for valeraldehyde are



11.302 mg/L for fish, 10.927 mg/L for daphnids, and 151.314 mg/L for green algae. These data provide an adequate assessment of the acute toxicity of this chemical.

Terrestrial data are not available.

## 5.0 RECOMMENDATIONS

**Human Health:** The chemical is currently a low priority for further work. The chemical possesses properties indicating a hazard for human health (skin, eye, respiratory irritation and potential reproductive/developmental effects based on data for analogous compounds). Based on data presented by the Sponsor country (relating to production in one country which accounts for 50-60% of the consumption in OECD countries and relating to the use pattern in several OECD countries), adequate risk management measures are being applied (engineering controls, occupational standards, Material Safety Data Sheets, and regulation as a food additive). Countries may desire to check their own risk management measures to determine whether there is a need for additional measures.

**Environment:** This chemical has properties indicating a hazard for the environment (EC/LC50 values between 1 and 100 mg/l). However, the chemical is currently of low priority for further work for the environment because of its rapid biodegradation and its limited potential for bioaccumulation.

## 6.0 REFERENCES

- Abdo, K.M., Haseman, J.K. and Nyska, A. 1998. Isobutyraldehyde administered by inhalation (whole body exposure) for up to 13 weeks or two years was a respiratory toxicant but was not carcinogenic in F344 rats and B6C3F1 mice. *Toxicol. Sci.* 42: 136-151.
- AIHA (American Industrial Hygiene Association). 2001a. Workplace Environmental Exposure Level – Isobutyraldehyde.
- AIHA (American Industrial Hygiene Association). 2001b. Workplace Environmental Exposure Level – Propionaldehyde.
- Alarie, Y., Schaper, M., Nielsen, G.D. and Abraham, M.H. 1998. Structure-activity relationships of volatile organic chemicals as sensory irritants. *Arch. Toxicol.* 72: 125-140.
- Aldrich Chemical Company. 1996. Aldrich Flavors and Fragrances. Milwaukee, WI.
- American Conference Governmental Industrial Hygienists (ACGIH). 2005. 2005 Guide to Occupational Exposure Values. ACGIH, Inc.: Cincinnati, OH.
- Ames, B.N., McCann, J. and Yamasaki, E. 1975. Methods for detecting carcinogens and mutagens with the Salmonella /mammalian microsome mutagenicity test. *Mutat. Res.* 31: 347-364.
- Amoore, J.E., Forrester, L.J. and Pelosi, P. 1976. Specific anosmia to isobutyraldehyde: the malty primary odor. *Chem. Senses Flavor* 2: 17-25.
- AOPWIN. Version 1.91. Atmospheric Oxidation. EPIWIN (Estimation Program for Windows) Version 3.12. U.S. Environmental Protection Agency, 2005.
- Atkinson, R. 1989. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. *J. Phys. Chem. Ref. Data. Monograph No 1.*
- Barton, H.A., Deisinger, P.J., English, J.C., Gearhart, J.M., Faber, W.D., Tyler, T.R., Banton, M.I., et al. 2000. Family approach for estimating reference concentrations/doses for series of related organic chemicals. *Toxicol. Sci.* 54: 251-261.
- BASF Aktiengesellschaft Ludwigshafen. 1997. Safety Data Sheet. CAS No. 110-62-3. Version 5.00. Revised, 10/09/97.
- BCFWIN. Version 2.15. BCF Estimate from Log Kow. EPIWIN (Estimation Program Interface for Windows). Version 3.10. U.S. Environmental Protection Agency, 2000.
- Bizzari, S.N., Fenelon, S. and Ishikawa-Yamaki, M. 1999. CEH Marketing Research Report, dated May 1999.
- Bizzari, S.N., Gubler, R., and Kishi, A. 2002. CEH Marketing Research Report: Oxo Chemicals.
- Blair, A.H. and Bodley, F.H. 1969. Human liver aldehyde dehydrogenase. Partial purification and properties. *Can. J. Biochem.* 47: 265-272.

- Brabec, M.J. 1993. Aldehydes and Acetals. *in*: Clayton, G.D., Clayton, F.E. (Eds.). *Patty's Industrial Hygiene and Toxicology*, New York, NY: John Wiley & Sons.
- Brambilla, G., Cajelli, E., Canonero, R., Martelli, A., and Marinari, U.M. 1989. Mutagenicity in V79 Chinese hamster cells of n-alkanals produced by lipid peroxidation. *Mutagenesis* 4: 277-279.
- Budavari, S.B. (ed.). 1996. *The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals*, 12<sup>th</sup> Edition. Whitehouse Station, NJ: Merck & Co., Inc.
- Burdock, G.A. 2002. *Handbook of Flavor Ingredients. Fourth Edition.* CRC Press, USA. pp. 1767-1768.
- Butterworth, B.E., Ashby, J., Bermudex, E. Casciano, D., Mirsalis, J., Probst, G. and Williams, G. 1987. A protocol for the *in vitro* rat hepatocyte DNA-repair assay. *Mutat Res.* 189: 113-21.
- Buttery, R.G. et al. 1969. *J. Agric. Food Chem.* 17: 385-389.
- Carlson, G.P. and Olson, R.M. 1995. Comparison of the metabolism of alcohols by rat hepatic and pulmonary dehydrogenase. *Biochem. Mol. Biol. Int.* 37: 65-71.
- Chou, C-C. and Que-Hee, S.S. 1994. Saliva-available carbonyl compounds in some chewing tobaccos. *J. Agric. Food Chem.* 42: 2225-2230.
- Chun, H.N. and Kim, Z.U. 1992. Evaluation of vegetable oil rancidity by headspace gas chromatographic analysis. *Han'guk Nonghwa Hakhoechi* 35: 36-41.
- Collins, D.W. and Richey, F.A., Jr. 1992. Synthetic organic chemicals. In: Kent, J.A. (Ed). *Riegel's Handbook of Industrial Chemistry*, 9<sup>th</sup> Edition. New York: Van Nostrand Reinhold.
- Colombo, A. et al. 1990. *Sci. Total Environ.* 91: 237-249.
- CPI Consulting Associates, Inc 1995.
- Dahl, A.R., Miller, S.C. and Petridou-Fischer, J. 1987. Carboxylesterases in the respiratory tracts of rabbits, rats and Syrian hamsters. *Toxicology Letters* 36: 129-136.
- Daubert, T.E. and Danner, R.P. 1989. *Physical and Thermodynamic Properties of Pure Chemicals: Data Compilation.* New York, NY: Hemisphere Publishing Corp.
- Davis,, J.W. and Marty, G.T. 2004. Valeraldehyde: Evaluation of ready biodegradability according to OECD Guideline 301D: Closed Bottle Test (unpublished study). *Toxicology & Environmental Research and Consulting.* Study ID 031115. The Dow Chemical Company, Midland, MI.
- DeBortoli, M. et al. 1986. *Environ. Internat.* 12: 343-350.
- Deener, J.W., Seinen, W. and Hermens, J.L.M. 1988. The acute toxicity of aldehydes to the guppy. *Aquatic Toxicol.* 12: 185-192.
- Deisinger, P.J. and English, J.C. Pharmacokinetics of n-Butyl Acetate and Its Metabolites in Rats After Intravenous Administration. *Toxicological Health Sciences Laboratory, Health and*

Environment Laboratory, Eastman Kodak Company, Rochester, NY. Report TX2000-277, prepared for the OxoProcess Panel, Chemstar, American Chemistry Council, Arlington, VA.

Dillon, D., Combes, R. and Zeiger, E. 1998. Effectiveness of Salmonella strains TA 100, TA102 and TA104 for detecting mutagenicity of some aldehydes and peroxides. *Mutagenesis* 134: 19-26.

The Dow Chemical Company. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 01/14/2002. The Dow Chemical Company, Midland, MI.

Driscoll, J.C. 1993. Propionaldehyde: Combined repeated-exposure reproductive/developmental toxicity study in CD Rats. Bushy Run Research Center Report 91U0086, dated April 6, 1993. Union Carbide Corporation, Danbury, CT.

Eastman Kodak Company. 1991. Toxicity and health hazard summary, material data sheet, and toxicity report on pentanal. Eastman Kodak Health and Safety Laboratory. (EPA/OATS Doc # 86-920000053). *Cited in*: National Toxicology Program (NTP). 1996. Chemical Selection Working Group (SCWG). Summary of Data for Chemical Selection. n-Valeraldehyde.

Ehrig, T., Bohren, K.M., Wermuth, B., and von Wartburg, J-P. 1988. Degradation of aliphatic ethanol and pharmacokinetic implications. *Alcoholism: Clinical and Experimental Research* 26: 789-794.

Erickson M.D. and Pellizzari, E.D. 1978. Analysis of organic Air Pollutants in the Kanawha Valley, WV and the Shenandoah Valley VA USEPA-903/9-78-007.

Falbe, J. Lappe, P. and Weber, J. 1985. Aldehydes, aliphatic and araliphatic. *Cited in*: Ullmann's Encyclopaedia of Industrial Chemicals, 5<sup>th</sup> Edition. Volume A-1.

FEMA (The Flavor and Extract Manufacturers Association of the United States). 2004. Respiratory Health and Safety in the Flavor Manufacture Workplace. Available at <http://www.femaflavor.org/html/public/RespiratoryRpt.pdf>.

Flick, E.W. 1991. Industrial Solvents Handbook, 4<sup>th</sup> Edition. Park Ridge, NJ: Noyes Data Corp.

Florin, I., Ruthberg, L., Curvall, M. and Enzell, C.R. . 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' Test. *Toxicology* 15: 219-232.

Frankel, E.N., Selke, E., Neff, W.E., and Miyashita, K. 1992. Autoxidation of polyunsaturated triacylglycerols. IV. Volatile decomposition products from triacylglycerols containing linoleate and linolenate. *Lipids* 27: 442-446.

Fugacity Model Level III. EPISuite Version 3.12. U.S. Environmental Protection Agency, 2004.

Furia, T.E. (Ed). 1972. CRC Handbook of Food Additives. Cleveland, OH: CRC Press.

Furia, T.E. (Ed.). 1980. CRC Handbook of Food Additives. 2<sup>nd</sup> Edition, Volume 2. Boca Raton, FL: CRC Press, Inc

Furia, T.E. and Bellance, N. (Eds). 1975. Fenaroli's Handbook of Flavor Ingredients. Volume 2. Cleveland: The Chemical Rubber Co.

Garmer, A.O., Hellwig, J. and Hildebrand, B. 1996. Isobutyraldehyde - Prenatal vapor inhalation toxicity study in Wistar rats. Unpublished report. Laboratory Project Identification 31R0140/93049. BASF Aktiengesellschaft D-67056 Ludwigshafen/Rhein, FRG.

Geiger, D.L., Northcott, C.E., Call, D.J., and Brooke, L.T. (Eds). 1985. Acute Toxicities of Organic Chemicals to Fathead Minnows (*Pimephales promelas*). Volume II. Center for Lake Superior Environmental Studies. University of Wisconsin-Superior.

Geiger, D.L., Poirier, S.H., Brooke, L.T., Call, D.J. (Eds.). 1986. Acute Toxicities of Organic Chemicals to Fathead Minnows (*Pimephales promelas*). Vol. III. Center for Lake Superior Environmental Studies, University of Wisconsin-Superior

Gerhold, R.M. and Malaney, G.W. 1966. Structural determinants in the oxidation of aliphatic compounds by activated sludge. *J. Water Pollut. Control Fed.* 38: 562-579.

Graedel, T.E. et al. 1986. Atmospheric Chemical Compounds. NY: Academic Press

Grosjean, D. 1988. *Atmos. Environ.* 22: 1637-1648.

Guicherit, K. and Schulting, F.L. 1985. *Sci. Total Environ.* 43: 193-219.

Guth, D.J. 1996. Dose-response assessment of non-cancer effects of propionaldehyde based on comparative toxicity with other short-chained aldehydes. *Human Ecol. Risk Assess.* 2: 580-590.

Haggard, H.W., Miller, D.P., and Greenberg, L.A. 1945. The amyl alcohols and their ketones: their metabolic fates and comparative toxicities. *J. Hyg. Toxicol.* 27: 1-14.

Hancock, G.A., McClymont, E.L., and Staley, J.L. 2003. n-Valeraldehyde: Growth Inhibition Test with the Freshwater Green Alga *Pseudokirchneriella subcapitata*. (unpublished study). Toxicology & Environmental Research and Consulting. Study ID 031086. The Dow Chemical Company, Midland, MI.

HENRYWIN. Version 3.10. Henry's Law Constant. EPIWIN (Estimation Program Interface for Windows). Version 3.05. Syracuse Research Corporation, Syracuse, NY.

Howard, P.H. (ed.). 1990. Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Volume II Solvents. Lewis Publishers. Chelsea, Michigan.

HSDB (Hazardous Substance Database), 2002. Valeraldehyde (Pentanal), CASRN 110-62-3. HSDB No. 815. Complete update on 11/08/02.

James, J.T.J. 2000. C3 to C8 Aliphatic Saturated Aldehydes. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants. Washington, DC: National Academy of Science.

Jonsson, A., Persson, E.A., and Grigoriadis, V. 1985. Measurements of some low-molecular-weight oxygenated, aromatic, and chlorinated hydrocarbons in ambient air and in vehicle emissions. *Environ. Intl.* 11: 383-392.

Keith, L.H. et al. 1976. Identification Analysis of Organic Pollutants in Water. Ann Arbor, MI: Ann Arbor Press.

KOWWIN, Version 1.67. Log Octanol-Water Partition Coefficient. EPIWIN (Estimation Program for Windows) Version 3.12. U.S. Environmental Protection Agency, 2005.

Lewis, R.L., Sr. 1993. Hawley's Condensed Chemical Dictionary, 12<sup>th</sup> ed. New York: Van Nostrand Reinhold.

Lide, D.R. (ed) CRC Handbook of Chemistry and Physics, 76<sup>th</sup> ed. Boca Raton, FL: CRC Press Inc., 1995-1996.

Lipari, F. et al. 1984. Environ. Sci. Technol. 18: 326-330.

Lloyd, A.C. 1978. Tropospheric Chemistry of Aldehydes. National Bureau of Standards. Washington, DC.

Luo, J.E. et al. 1993. Study of sensory irritancy of series of aldehydes and the prediction of safe levels of exposure (TLV). The Toxicologist 13: 263.

Lyman, W.J. et al. 1982. Handbook of Chemical Property Estimation Methods. NY: McGraw Hill Book Company.

Marino, T.A, McClymont, E.L., and Yaroch, A.M. 2003a. n-Valeraldehyde: An Acute Toxicity Study with the Rainbow Trout, *Oncorhynchus mykiss* Walbaum (unpublished study). Toxicology & Environmental Research and Consulting, Study ID 031104. The Dow Chemical Company, Midland, MI.

Marino, T.A, McClymont, E.L., and Yaroch, A.M.. 2003b. n-Valeraldehyde: An Acute Toxicity Study with the Daphnid, *Daphnia magna* Straus (unpublished study). Toxicology & Environmental Research and Consulting, Study ID 031103. The Dow Chemical Company, Midland, MI.

Maron, D.M. and Ames, B.N. 1983. Revised methods for the Salmonella mutagenicity test. Mutat. Res. 113:173-215.

Martelli, A., Canonero, R., Cavanna, M., Ceradelli, M., and Marinari, U.M. 1994. Cytotoxic and genotoxic effects of five n-alkanals in primary cultures of rat and human hepatocytes. Mutat. Res. 323: 121-126.

Mattheis, J.P. et al. 1991. J. Agric. Food. Chem. 39: 1902-1906.

Merck-Schuchardt. Safety Data Sheet. Pentanal for synthesis. 04.2000. The Merck Chemical Database-online: <http://www.merck.de> (accessed October 16, 2000).

Meylan, W.M. and Howard, P.H. 1992. Group contribution method for estimating octanol-water partition coefficients. SETAC Meeting, Cincinnati, OH, p. 8-12.

Meylan, W.M. and Howard, P.H. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84: 83-92.

Meylan, W.M. and Howard, P.H. 1997. Handbook of Physical Properties of Organic Chemicals. Boca Raton, FL: Lewis Publishers.

- Meylan, W.M. and Howard, P.H. 1993. Computer estimation of the atmospheric gas-phase reaction rate of organic compounds with hydroxy radicals and ozone. *Chemosphere* 26: 2293-2299.
- Miglietta, A., Gabriel, L., and Gadoni, E. 1987. *Cell Biochem. Function* 5: 189-194.
- Morris, E.M. 1993. Union Carbide Corporation (unpublished report). Primary Amyl Acetate. Study of *In vitro* Hydrolysis of n-Pentyl and 2-Methylbutyl Isomers. Bushy Run Research Center, Project Report 91U0142 dated March 14, 1993.
- Morris, J.B., Hassett, D.N. and Blanchard, K.T. 1993. A physiologically based pharmacokinetic model for nasal uptake and metabolism of nonreactive vapors. *Toxicol. Appl. Pharmacol.* 123: 120-129.
- Morrissey, R.E., Schwetz, B.A., Lamb, J.C., IV, Ross, M.D., Teague, J.L., and Morris, R.W. 1988. Evaluation of rodent sperm, vaginal cytology, and reproductive organ weight data from National Toxicology Program 13-week studies. *Fundam. Appl. Toxicol.* 11: 343-358.
- Mukerjee, N. and Pietruszko, R. 1992. Human mitochondrial aldehyde dehydrogenase substrate specificity: comparison of esterase with dehydrogenase reaction. *Arch. Biochem. Biophys.* 299: 23-29.
- Muller, W.J. and Black, M.S. 1995. Sensory irritation in mice exposed to emissions from indoor products. *Am. Ind. Hyg. Assoc. J.* 56: 794-803.
- Narotsky, M.G. and Kavlock, R.J. 1989. Pentanoic Acid Developmental Toxicity Testing. ManTech Environmental Technology Inc. Contract No. 68-02-4450. Report dated October 10, 1989.
- Narotsky, M.G., Francis, E.Z., and Kavlock, R.J. 1994. Developmental toxicity and structure-activity relationships of aliphatic acids, including dose-response assessment of valproic acid in mice and rats. *Fundam. Appl. Toxicol.* 22: 251-265.
- National Cancer Institute. Short-term Test Program Sponsored by the Division of Cancer Etiology, Dr. David Longfellow, Project Officer. *cited in* Valeraldehyde (Pentanal), CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, Complete update on 11/08/02.
- National Cancer Institute, 1999. L5178Y TK+/- Mouse Lymphoma Mutagenesis Assay. Contract No: N01-CB-87016, Task 1. BiorReliance Study No. G96CC31.703. February 8.
- NFPA. 2002. National Fire Protection Association. Fire Protection Guide to Hazardous Materials. 13th edition. NFPA. Quincy, MA.
- NIOSH (National Institute for Occupational Safety and Health). 2003. Preventing Lung Disease in Workers Who Use or Make Flavorings. DHHS (NIOSH) Publication Number 2004-110. Available at <http://www.cdc.gov/niosh/docs/2004-110/>
- NIOSH. 1997. NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) Publication 97-140.
- NIOSH. 1989. NIOSH Occupational Exposure Survey (NOES) for 1981-1983.

- Noma, E. et al. 1988. *Atmos. Environ.* 22: 451-460.
- Obe, G. and Beek, B. 1979. Mutagenic activity of aldehydes. *Drug Alcohol Depend.* 4: 91-94.
- Onstot, J.D. et al. 1987. Characterization of HRGC/MS Unidentified Peaks from the Broad Scan Analysis of the FY82 NHATS Composites. Volume 1. USEPA 68-02-4252.
- Opdyke, D.L.J. 1973. Monographs on Fragrance Raw Materials. *Food Cosmet. Toxicol.* 11: 95-115.
- Opdyke, D.L. 1979. Monographs on fragrance raw materials. n-Valeraldehyde. *Food Cosmet. Toxicol.* 17 (Suppl.): 919-921.
- Oswald, A.A., Jermasen, T.G., Westner, A.A., and Huang, I.D., 1987. Selective hydroforylation process using alkyl diaryl phosphine rhodium carbonyl hydride catalysts. Exxon Research and Engineering Co. (Patent No. US4687874 A). *Cited in:* National Toxicology Program (NTP). 1996. Chemical Selection Working Group (SCWG). Summary of Data for Chemical Selection. n-Valeraldehyde.
- PCKOCWIN. Version 1.66. Soil Adsorption Coefficient. EPIWIN (Estimation Program Interface for Windows). Version 3.05. Syracuse Research Corporation, Syracuse, NY.
- Pellizzari, E.D. 1982. Analysis for organic vapor emissions near industrial and chemical waste disposal sites. *Sci. Total Environ.* 16: 781-785.
- Pellizzari, E.D, Hartwell, T.D., Harris, B.S., Waddell, R.D., Whitaker, D.A., and Erickson, M.D. 1982. Purgeable organic compounds in mother's milk. *Bull. Environ. Contam. Toxicol.* 28: 322-328.
- Poet, T. 2003a. Unpublished data on Propyl Acetate. Battelle, Pacific Northwest National Laboratory, U.S. Dept. of Energy. Sponsored by the Oxo-Process Panel, Chemstar, American Chemistry Council, Arlington, VA, 22209.
- Poet, T. 2003b. Unpublished data on Isopropyl Acetate. Battelle, Pacific Northwest National Laboratory, U.S. Dept. of Energy. Sponsored by the Oxo-Process Panel, Chemstar, American Chemistry Council, Arlington, VA, 22209.
- Poet, T. 2003c. Unpublished data on Isobutyl Acetate. Battelle, Pacific Northwest National Laboratory, U.S. Dept. of Energy. Sponsored by the Oxo-Process Panel, Chemstar, American Chemistry Council, Arlington, VA, 22209.
- Poet, T. 2004a. Unpublished data on the components of Primary Amyl Acetate: n-Pentyl Acetate and 2-Methyl Butyl Acetate. Battelle, Pacific Northwest National Laboratory, U.S. Dept. of Energy. Sponsored by the Oxo-Process Panel, Chemstar, American Chemistry Council, Arlington, VA, 22209.
- Poet, T. 2004b. Unpublished data on the components of Primary Amyl Alcohol: n-Pentyl Alcohol and 2-Methyl Butyl Alcohol. Battelle, Pacific Northwest National Laboratory, U.S. Dept. of Energy. Sponsored by the Oxo-Process Panel, Chemstar, American Chemistry Council, Arlington, VA, 22209.
- Rekker, R.F. 1977. *The Hydrophobic Fragment Constant.* Amsterdam: Elsevier.



Rogers, J.A. 1981. Oils, Essential. *In*: Grayson, M. and Eckroth, D. eds., Kirk-Othmer Encyclopaedia of Chemical Technology, 3<sup>rd</sup> Edition. Volume 16. John Wiley & Sons.

Rudell, E., Bonte, W., Sprung, R., and Kulnholz, B. 1983. Zur Pharmakokinetik der Hoheren Aliphatischen Alkohole (On the Pharmacokinetics of Higher Aliphatic Alcohols). *Beitr. Gerichtl. Med.* 41: 211-218.

Salem, H. and Cullumbine, H. 1960. Inhalation toxicities of some aldehydes. *Toxicol. App. Pharmacol.* 2: 183-187.

Savolainen, H., Pfaffli, P., and Elovaara, E. 1985. Blood and brain n-pentanol in inhalation exposure. *Acta Pharmacol. Toxicol.* 56: 206-264.

Sax, I.N. and Lewis, R.J., Sr. (eds). 1987. *Hawley's Condensed Chemical Dictionary*, 11<sup>th</sup> Edition. New York, NY: Van Nostrand Reinhold Company.

Shibamoto, T. 1990. A new analytical method for low-molecular weight aldehydes. *In*: Charalamboris, G. (Ed.). *Developments in Food Science, Flavors and Off-Flavors*. Amsterdam: Elsevier Science Publishers.

Slesinski, R.S. 1985. Union Carbide Corporation (unpublished report). n-Valeric Acid. *In Vivo* Mouse Micronucleus Study. Bushy Run Research Center Project Report 48-106, dated September 9, 1985.

Smyth, H.F. Jr., Carpenter, C.P., West, C.S., Pozzani, U.C., and Striegel, J.A. 1962. Range-finding toxicity data: List VI. *Industrial Hygiene Journal* 23: 95-107.

Smyth, H.F. Jr., Carpenter, C.P. and Weil, C.S. et al. 1969. Range-finding toxicity data: List VII. *Am. Ind. Hyg. Assoc. J.* 30: 470-476.

Snyder, J.M. 1995. Volatile analysis of oxidized oils by direct supercritical fluid extraction method. *J. Food Lipids* 2: 25-33.

SPIN database available at <http://www.spin2000.net/spin.html>.

Steinhagen, W.H. and Barrow, C.S. 1984. Sensory irritation structure-activity study of inhaled aldehydes in B6C3F1 and Swiss-Webster mice. *Toxicol. Appl. Pharmacol.* 75: 495-503.

Swann, R.L. et al. 1983. *Res.Rev.* 85: 17-28. *Cited in* : Pentanal. CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, revised 02/09/2000.

Union Carbide Chemicals and Plastics Company Inc. 1993. *Ecological Fate and Effects Testing of UCC&P Products and Wastewaters During 1992*. File Report No. 39860, dated February 12, 1993.

Urbach, G. 1987. Dynamic headspace gas chromatography of volatile compounds in milk. *J. Chromatography* 404: 163-174.

U.S. Department of Transportation (U.S.DOT). 1996. *North American Emergency Response Guidebook. A Guidebook for First Responders During the Initial Phase of a Hazardous Material/Dangerous Goods Incident*. U.S.DOT Research and Special Programs Administration, Washington, DC.

U.S.EPA (U.S. Environmental Protection Agency). 1990. Indoor Air Quality and Work Environment Study. EPA Headquarters' Buildings. Volume 2. Results of Indoor Air Environmental Monitoring Study. Atmos. Res. and Exposure Assess. Lab, RTC, NC.

U.S.EPA (U.S. Environmental Protection Agency). 2003. Experimental water solubility and vapor pressure values reported by EPI Suite software, version 3.11. United States Environmental Protection Agency, Office of Pollution Prevention and Toxics, Washington, DC. Available at <http://www.epa.gov/oppt/exposure/docs/episuitedi.htm>

U.S. National Toxicology Program (NTP). 1999. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Isobutyraldehyde (CAS NO. 78-84-2) in F344/N Rats and B6C3F1 Mice. NTP TR-472, Research Triangle Park, NC.

Van Netten, C. et al. Bull. Environ. Contam. Toxicol. 40: 672-677.

Verschueren, K. 2001. Handbook of Environmental Data on Organic Chemicals, 4<sup>th</sup> Edition. New York, NY: John Wiley & Sons, Inc.

Walkenstein, S.S. and Weinhouse, S. 1953. Oxidation of aldehydes by mitochondria of rat tissues. J. Biol. Chem. 200: 515-523.

Walker, J. 1995. Communication transmitted from Executive Director, TSCA Interagency Testing Committee, U.S. Environmental Protection Agency. *Cited in:* National Toxicology Program (NTP). 1996. Chemical Selection Working Group (SCWG). Summary of Data for Chemical Selection. n-Valeraldehyde.

Wilkinson, J.F. 1940. J. Hyg. 40: 555. *cited in:* Brabec, M.J. 1993. Aldehydes and Acetals. *in:* Clayton, G.D., Clayton, F.E. (Eds.). Patty's Industrial Hygiene and Toxicology, New York, NY: John Wiley & Sons.

Wolfe, C.W. et al. 1987. Thirteen week subchronic toxicity study of butyraldehyde in F344 rats and B6C3F1 mice. The Toxicologist, Volume 7.

WSKOW. Version 1.37. Water Solubility Estimate from Log Kow. EPIWIN (Estimation Program for Windows) Version 3.05. Syracuse Research Corporation, Syracuse, NY.

Yalkowsky, S.H. and Dannenfelser, R.M. 1992. The Aquasol Database of Aqueous Solubility, 5<sup>th</sup> Edition. University of Arizona, College of Pharmacy, Tucson, AZ.

**SIDS DOSSIER**

**And**

**ROBUST STUDY SUMMARIES**

**for: VALERALDEHYDE**

**CAS No. 110-62-3**

**1.1 GENERAL SUBSTANCE INFORMATION**

- A. Type of Substance** element [ ]; inorganic [ ]; natural substance [ ]; organic [ X ]; organometallic [ ]; petroleum product [ ]
- B. Physical State** (at 20°C and 1.013 hPa) gaseous [ ]; liquid [ X ]; solid [ ]
- C. Purity** (indicate the percentage by weight/weight) >99% weight/weight

**1.2 SYNONYMS**

valeraldehyde  
 valeric aldehyde  
 valerianic aldehyde  
 valeric acid aldehyde  
 n-valeric acid aldehyde  
 valerylaldehyde  
 pentanal  
 valeral  
 n-pentanal  
 amyl aldehyde  
 butyl formal

**1.3 IMPURITIES**

CAS No: 96-17-3  
 EINECS No:  
 Name: 2-ethyl propanal  
 Value: < 1%  
 Remarks:  
 Reference: The Dow Chemical Company. Material Safety Data Sheet for Valeraldehyde (CAS 110-62-3). MSDS# 5422, effective date 01/14/2002. The Dow Chemical Company, Midland, MI.

**1.4 ADDITIVES**

CAS No: None  
 EINECS No:  
 Name:  
 Value:  
 Remarks: Inhibitors and stabilizers are not applicable. Store in vapor-tight equipment under an atmosphere of oxygen-free nitrogen.  
 Reference: The Dow Chemical Company. Material Safety Data Sheet for Valeraldehyde (CAS 110-62-3). MSDS# 5422, effective date 01/14/2002. The Dow Chemical Company, Midland, MI.

**1.5 QUANTITY**

70,000 metric tons  
 Remarks: production in 1997  
 Reference: Bizzari, S.N., Fenelon, S. and Ishikawa-Yamaki, M. 1999. CEH Marketing Research Report dated May 1999.

**1.6 LABELLING AND CLASSIFICATION**Labelling

Type:

Specific limits:

Symbols:

Note:

R-phrases: R-10 flammable

S-phrases: S-2, S-23

Text of S-phrases: S-2: Keep out of reach of children

S-23: Do not breathe gas, fumes, vapour or spray

Remarks:

Classification

Type:

None

Category of danger:

R-phrases:

Remarks:

**1.7 USE PATTERN****A. General****Type of Use:****Category: Non dispersive**

Use resulting in inclusion into or onto matrix

**Type of Use:****Category: Wide dispersive**

industrial

Basic industry: basic chemicals

industrial

Chemical industry: synthesis of valeric acid

industrial

Chemical industry: synthesis of amyl alcohol

Chemical industry: synthesis of rubber accelerators

use

Manufacture of acetal resins

use

Manufacture of flavoring agents

use

Manufacture of fragrances

References:

Budavari, S.B. (ed.). 1996. The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals, 12<sup>th</sup> Edition. Whitehouse Station, NJ: Merck & Co., Inc.

Bizzari, S.N., Fenelon, S. and Ishikawa-Yamaki, M. 1999. CEH Marketing Research Report, dated May 1999.

Falbe, J. Lappe, P. and Weber, J. 1985. Aldehydes, aliphatic and araliphatic. *Cited in:* Ullmann's Encyclopedia of Industrial Chemicals, 5<sup>th</sup> Edition. Volume A-1.Lewis, R.L., Sr. 1993. Hawley's Condensed Chemical Dictionary, 12<sup>th</sup> Ed. New York: Van Nostrand Reinhold.

Pentanal (Valeraldehyde). CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.

**B. Uses in Consumer Products**

Natural and synthetic flavoring agent; a component of rose oil used to flavor foods, beverages, and chewing tobacco. Plant volatile, occurs naturally in foods, released as a combustion emission from burning wood, gasoline and diesel engines.

**1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE**

- (a) Type of Limit: ACGIH TWA (US)  
 Value: 50 ppm  
 Short Term Exposure  
 Limit Value:  
 Time Schedule: 8-hour time weighted average (TWA)  
 Remark: 176 mg/m<sup>3</sup>  
 Reference: American Conference Governmental Industrial Hygienists (ACGIH). 2005. 2005 TLVs® and BEIs®. ACGIH, Inc.: Cincinnati, OH.
- (b) Type of Limit other: SMAC (US)  
 Value: 1-24 hr: 50 ppm  
 1 to 7 days: 6 ppm  
 8 to 30 days: 1.5 ppm  
 up to 180 days: 1.5 ppm  
 Short Term Exposure  
 Limit Value: None  
 Remark: Spacecraft Maximum Allowable Concentration (SMAC)  
 Reference: James, J.T.J. 2000. C3 to C8 Aliphatic Saturated Aldehydes. *in*: Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants. Washington, DC: National Academy of Science. p42-59.
- (c) Type of Limit: NIOSH REL (US)  
 Value: 50 ppm  
 Short Term Exposure  
 Limit Value: None  
 Time Schedule: 10-hour TWA  
 Remark: 175 mg/m<sup>3</sup>  
 References: NIOSH. 1997. NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) Publication 97-140.  
  
 American Conference Governmental Industrial Hygienists (ACGIH). 2005. 2005 Guide to Occupational Exposure Values. ACGIH, Inc.: Cincinnati, OH.

**1.9 SOURCES OF EXPOSURE**

Remark Valeraldehyde may be released to the environment through industrial wastes, resulting in general population exposures to low concentrations via inhalation of ambient air and indoor air. Exposures may also occur through ingestion of fruits, vegetables, and other foods that contain the substance naturally. Nearly 100% of all valeraldehyde produced is as an industrial intermediate for conversion to amyl alcohol and valeric acid. Workplace exposures are generally limited by the closed, continuous nature of the manufacturing process and the small number of manufacturers (one

- in the U.S. and two in Europe). These factors also limit emissions and any potential general population exposure from industrial sources.
- Reference: Bizzari, S.N., Fenelon, S. and Ishikawa-Yamaki, M. 1999. CEH Marketing Research Report, dated May 1999.
- Remark: NIOSH has statistically estimated that 1557 workers, of which 276 are females, are exposed to valeraldehyde in the U.S.A.
- Reference: NIOSH. 1990. NIOSH Occupational Exposure Survey (NOES) as of 12/06/90. National Institute for Occupational Safety and Health (NIOSH), Cincinnati, OH.
- Remark: There is potential for consumer exposures to low levels of valeraldehyde as a component (0.05-0.07%) of rose oil. Rose oil is used a fragrance ingredient in cosmetics, toilet waters and perfumes and as a flavoring agent for food and tobacco products, particularly chewing tobaccos.
- Reference: Rogers, J.A. 1981. Oils, Essential. *In*: Grayson, M. and Eckroth, D. eds., Kirk-Othmer Encyclopedia of Chemical Technology, 3<sup>rd</sup> Edition. Volume 16. New York: John Wiley & Sons.
- Remark: Valeraldehyde has been identified as a volatile component in the following foods: baked potatoes, cassava, Korean chamchwi, French mountain cheese, raw beef, roasted filberts, boiled short-necked clams, clams, scrambled eggs, Delicious apples, and fried chicken.
- Reference: *multiple references cited in*: HSDB. Valeraldehyde (Pentanal). CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.
- Remark: Valeraldehyde is a plant volatile. The concentration of valeraldehyde is relatively high in undeveloped (unripe) apples, but decreases to undetectable levels as harvest approaches.
- References: Graedel, T.E. et al. 1986. Atmospheric Chemical Compounds. NY: Academic Press.
- Mattheis, J.P. et al. 1991. J. Agric. Food. Chem. 39: 1902-1906. *references cited in*: HSDB. Valeraldehyde (Pentanal). CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.
- Remark: There is potential for low level oral exposures to valeraldehyde through its presence in many foods and beverages, as well as its use as a meat flavoring agent. Valeraldehyde has been detected in oxidized heated or stored fats and oils, including meat fats, fish and vegetable oils, in some fruits, and in milk and cheese products, coffee beans, and cocoa beans.
- References: Chun, H.N. and Kim, Z.U. 1992. Evaluation of vegetable oil rancidity by headspace gas chromatographic analysis. Han'guk Nonghwa Hakhoechi 35: 36-41.
- Frankel, E.N., Selke, E., Neff, W.E., and Miyashita, K. 1992. Autoxidation of polyunsaturated triacylglycerols. IV. Volatile decomposition products from triacylglycerols containing linoleate and linolenate. Lipids 27: 442-446.

Opdyke, D.L. 1979. Monographs on fragrance raw materials. n-Valeraldehyde. Cosmeti. Toxicol. 17 (Suppl.): 919-921.

Shibamoto, T. 1990. A new analytical method for low-molecular weight aldehydes. In: Charalamboris, G., Ed. Developments in Food Science, Flavors and Off-Flavors. Amsterdam: Elsevier Science Publishers.

Snyder, J.M. 1995. Volatile analysis of oxidized oils by direct supercritical fluid extraction method. J. Food Lipids 2: 25-33.

Urbach, G. 1987. Dynamic headspace gas chromatography of volatile compounds in milk. J. Chromatography 404: 163-174.

Remark: Valeraldehyde is a product of micro organisms and animal waste. It may be emitted from burning logs.

References: Graedel, T.E. et al. 1986. Atmospheric Chemical Compounds. NY: Academic Press.

Lipari, F. et al. 1984. Environ. Sci. Technol. 18: 326-330. *cited in:* HSDB. Valeraldehyde (Pentanal).. CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.

Remark: Valeraldehyde may be emitted as a combustion by-product of gasoline, diesel and turbine engines.

Reference: Graedel, T.E. et al. 1986. Atmospheric Chemical Compounds. NY: Academic Press. *cited in:* HSDB. Valeraldehyde (Pentanal). CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.

### 1.10 ADDITIONAL REMARKS

Remark: The odor characteristics of valeraldehyde have been described as woody, vanilla, fruity, nutty upon dilution.

Reference: Aldrich Chemical Company. 1996. Aldrich Flavors and Fragrances. Milwaukee, WI.

Remark: Valeraldehyde is available as a flavor/aroma material which meets Food Chemical Codex (FCC) specifications. It has been assigned a Flavor and Extract Manufacturing Association (FEMA) number of 3098.

Reference: Aldrich Chemical Company. 1996. Aldrich Flavors and Fragrances. Milwaukee, WI.

Remark: Valeraldehyde is a generally recognized as safe (GRAS) substance by the Flavor and Extract Manufacturing Association and approved for direct use by the U.S. Food and Drug Administration (USFDA).

References: Furia, T.E. (Ed). 1972. CRC Handbook of Food Additives. Cleveland, OH: CRC Press.

Code of Federal Regulations (CFR) Title 21, Part 172.515.

Remark: Valeraldehyde can be prepared by the oxidation of its corresponding alcohol, n-pentanol. Valeraldehyde is industrially prepared by the



- oxo process, which involves the reaction of the alcohol with carbon monoxide and hydrogen in the presence of a catalyst. Use of a cobalt carbonyl complex as a catalyst in an older process required high pressures. A low-pressure process based on rhodium carbonyl catalysts is now used.
- References: Falbe, J. Lappe, P. and Weber, J. 1985. Aldehydes, aliphatic and araliphatic. *Cited in:* Ullmann's Encyclopedia of Industrial Chemicals, 5<sup>th</sup> Edition. Volume A-1.
- Oswald, A.A., Jermasen, T.G., Westner, A.A., and Huang, I.D., 1987. Selective hydroforylation process using alkyl diaryl phosphine rhodium carbonyl hydride catalysts. Exxon Research and Engineering Co. (Patent No. US4687874 A). *Cited in:* National Toxicology Program (NTP). 1996. Chemical Selection Working Group (SCWG). Summary of Data for Chemical Selection. n-Valeraldehyde.
- Collins, D.W. and Richey, F.A., Jr. 1992. Synthetic organic chemicals. In: Kent, J.A. (Ed). Riegel's Handbook of Industrial Chemistry, 9<sup>th</sup> Edition. New York: Van Nostrand Reinhold.
- Remark: Valeraldehyde is prepared by oxidation of the corresponding alcohol, n-pentanol or by reduction of n-valeric acid. Valeraldehyde can be produced for marketing as a natural flavoring agent in an enzymatic bioindustrial process from pentanol using the methylotrophic yeast, *Pichia pastoris*.
- Reference: Williams, R.E., Armstrong, D.W., Murray, W.D., and Welsh, F.W. 1988. Enzyme and who cell production of flavor and fragrance compounds. Ann. N.Y. Acad. Sci. 542: 406-412.
- Remark: Valeraldehyde is listed in the USEPA TSCA Inventory. United States production of valeraldehyde in 1989 was reported to be in the range of 25 to 100 million pounds, based on non-confidential data received by the USEPA.
- Reference: Walker, J. 1995. Communication transmitted from Executive Director, TSCA Interagency Testing Committee, U.S. Environmental Protection Agency. *Cited in:* National Toxicology Program (NTP). 1996. Chemical Selection Working Group (SCWG). Summary of Data for Chemical Selection. n-Valeraldehyde.
- Remark: NFPA Hazard Classifications:  
Flammability: 3 (easily ignited under almost all normal conditions)  
Reactivity: 1 (may become unstable at elevated temperatures and pressures or may react with water with some release of energy)  
Health: 3 (material extremely hazardous to health but area may be entered with extreme care. Full protective clothing required. No skin surface should be exposed.)
- Reference: NPFA. 2002. National Fire Protection Association. Fire Protection Guide to Hazardous Materials, 13<sup>th</sup> Edition. NFPA, Quincy, MA..
- Remark: HMIS Hazard Ratings:  
Flammability: 3 (liquids and solids that can be ignited under all ambient temperature conditions.

---

	Reactivity: 1 (material can become unstable at elevated temperatures and pressures or may react with water and release energy non-violently).
	Health: 3 (major injury likely unless prompt action is taken and medical treatment given)
Reference:	Union Carbide Corporation. Material Safety Data Sheet# 5422: Valeraldehyde. Effective date 06/26/2000. Union Carbide Chemicals and Plastics Technology Corporation, The Dow Chemical Company, Danbury, CT.
Remark:	Disposal: dissolve liquid in combustible solvent and incinerate in furnace with afterburner.
Reference:	International Technical Information Institute (ITII). 1988. Toxic and Hazardous Industrial Chemicals Safety Manual. ITT, Tokyo, Japan.
Remark:	Disposal: incinerate in a furnace where permitted under Federal, State and local regulations.
Reference:	Union Carbide Corporation. Material Safety Data Sheet# 5422: Valeraldehyde. Effective date 06/26/2000. Union Carbide Chemicals and Plastics Technology Corporation, The Dow Chemical Company, Danbury, CT.
Remark:	USDOT/UN/NA/IMO number: 2058 IMO Standard transportation number: class: 3,8 label: 3,8 pack. gr.: PGII Marine pollutant: yes Label: Flammable liquid Proper shipping name: Valeraldehyde
Reference:	Union Carbide Corporation. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 06/26/2000. Union Carbide Chemicals and Plastics Technology Corporation, The Dow Chemical Company, Danbury, CT.

### 2.1 MELTING POINT

- (a) Preferred result reliability score = 2, valid with restriction; data from handbook or collection of data  
Value: -91.5 degree C  
Remark: freezing point, -132.7 degree F  
Reference: Lide, D.R. (ed). 1996. CRC Handbook of Chemistry and Physics, 76<sup>th</sup> Edition. Boca Raton, FL: CRC Press Inc.
- (b) Value: -91 degree C  
Remark : -131.8 degree F  
Reliability: score = 2, valid with restriction; data from handbook or collection of data  
References: Sax, I.N. and Lewis, R.J., Sr. (eds). Hawley's Condensed Chemical Dictionary, 11<sup>th</sup> Edition. New York, NY: Van Nostrand Reinhold Company, 1987. 74.  
  
Verschueren, K. 2001. Handbook of Environmental Data on Organic Chemicals, 4<sup>th</sup> Edition. New York, NY: John Wiley & Sons, Inc. 2171.
- (c) Value: -92 degree C  
Remark: -133.6 degree F  
Reliability: score = 4, not assignable  
Reference: Merck-Schuchardt. Safety Data Sheet. Pentanal for synthesis. 04.2000. The Merck Chemical Database-online. <http://www.merck.de> (accessed October 16, 2000).

### 2.2 BOILING POINT

- (a) Preferred result reliability score = 2, valid with restriction; data from handbooks or collections of data  
Value: 103 degree C  
Remark: 217.4 degree F (reported as 217 degree F by NFPA)  
References: NFPA. 2002. National Fire Protection Association. Fire Protection Guide to Hazardous Materials. 13<sup>th</sup> edition. NFPA. Quincy, MA.  
  
Lide, D.R. (Ed). 1996. CRC Handbook of Chemistry and Physics, 76<sup>th</sup> ed. Boca Raton, FL: CRC Press Inc.  
  
Verschueren, K. 2001. Handbook of Environmental Data on Organic Chemicals, 4<sup>th</sup> Edition. New York, NY: John Wiley & Sons, Inc. 2171
- (b) Value: 102-103 degree C  
Remark: 215-217 degree F  
Reliability: score = 2, valid with restriction; data from handbook or collection of data  
References: Budavari, S.B. (ed.). 1996. The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals, 12<sup>th</sup> Edition. Whitehouse Station, NJ: Merck & Co., Inc.

Sax, I.N. and Lewis, R.J., Sr. (eds). Hawley's Condensed Chemical Dictionary, 11<sup>th</sup> Edition. New York, NY: Van Nostrand Reinhold Company, 1987.

(c) Value: 102 degree C  
 Remark: 215.6 degree F  
 Reliability: score = 4, not assignable  
 Reference: Merck-Schuchardt. Safety Data Sheet. Pentanal for synthesis. 04.2000. The Merck Chemical Database-online. <http://www.merck.de> (accessed October 16, 2000).

(d) Value: 99 to 104 degree C  
 Remark: median value, 101.5 degree C or 214.7 degree F  
 Reliability: score = 4, not assignable  
 Reference: BASF Aktiengesellschaft Ludwigshafen. Safety Data Sheet. CAS No. 110-62-3. Version 5.00. Revised 10.09.1997.

### 2.3 DENSITY

(a) Preferred result reliability score = 2, valid with restriction; data from handbooks or collections of data  
 Value: 0.8095 g/cm<sup>3</sup>  
 Temperature: 20 degree C  
 Method: no data  
 Year:  
 GLP: no data  
 References: Budavari, S.B. (ed.). 1996. The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals, 12<sup>th</sup> Edition. Whitehouse Station, NJ: Merck & Co., Inc.

Sax, I.N. and Lewis, R.J., Sr. (eds). Hawley's Condensed Chemical Dictionary, 11<sup>th</sup> Edition. New York, NY: Van Nostrand Reinhold Company, 1987. 74.

Lide, D.R. (ed) CRC Handbook of Chemistry and Physics, 76<sup>th</sup> ed. Boca Raton, FL: CRC Press Inc., 1995-1996.

(b) Value: 0.82 g/cm<sup>3</sup>  
 Temperature: 11 degree C  
 Method other:  
 Year:  
 GLP: no data  
 Reliability: score = 2, valid with restriction; data from handbook or collection of data  
 Reference: Verschueren, K. 2001. Handbook of Environmental Data on Organic Chemicals, 4<sup>th</sup> Edition. New York, NY: John Wiley & Sons, Inc. 2171

(c) Value: 0.811 – 0.814 g/cm<sup>3</sup>  
 Temperature: 20 degree F  
 Reliability: score = 4, not assignable  
 Reference: Merck-Schuchardt. Safety Data Sheet. Pentanal for synthesis. 04.2000. The Merck Chemical Database-online. <http://www.merck.de> (accessed October 16, 2000).

**2.4 VAPOUR PRESSURE**

- (a) Preferred result reliability score = 2, valid with restriction; data from handbook or collection of data  
 Value: 35 hPa  
 Temperature: 20 degree C  
 Remark: Reported as 3.5 kPa, 26 mm Hg  
 Reference: Flick, E.W. 1991. Industrial Solvents Handbook, 4<sup>th</sup> Edition. Park Ridge, NJ: Noyes Data Corp.
- (b) Value: 35 hPa  
 Temperature: 20 degree C  
 Remark: Reported as 26 mm Hg  
 Reliability: score = 2, valid with restriction; accepted calculation method  
 Reference: U.S. Environmental Protection Agency (USEPA). 2005. Experimental water solubility and vapor pressure values reported by EPI Suite software, Version 3.12. USEPA, Office of Pollution Prevention and Toxics, Washington, DC. Available at: <http://www.epa.gov/oppt/exposure/docs/episuitedi.htm>
- (c) Value: 66 hPa  
 Temperature: 25 degree C  
 Remark: Reported as 50 mm Hg at 25 degree C  
 Reliability: score = 2, valid with restriction; data from handbook or collection of data  
 Reference: Verschueren, K. 2001. Handbook of Environmental Data on Organic Chemicals, 4<sup>th</sup> Edition. New York, NY: John Wiley & Sons, Inc. 2171

**2.5 PARTITION COEFFICIENT  $\log_{10}P_{ow}$** 

- (a) Preferred result reliability score = 2, valid with restriction; data from handbook or collection of data  
 $\log P_{oct}$ : 1.38  
 Method: calculated  
 Year: 1995  
 Remark: atom/fragment contribution method  
 Reliability: score = 2, valid with restriction; accepted calculation method  
 References: Meylan, W.M. and Howard, P.H. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84: 83-92.  
  
 KOWWIN, Version 1.67. Log Octanol-Water Partition Coefficient. EPIWIN (Estimation Program for Windows) Version 3.12. U.S. Environmental Protection Agency, 2000.
- (b)  $\log P_{oct}$ : 1.39  
 Method: calculated  
 Year: 2001  
 Remark:  $\log P_{oct}$  calculated using the regression equation  
 $\log P_{oct} = 4.5 - 0.75 \log S$ ,  
 where S is the solubility of valeraldehyde (14,000 mg/l)  
 Reliability: score = 2, valid with restriction; accepted calculation method

Reference:	Verschueren, K. 2001. Handbook of Environmental Data on Organic Chemicals, 4 <sup>th</sup> Edition. New York, NY: John Wiley & Sons, Inc.
(c) log P <sub>oct</sub> :	1.31
Method:	calculated
GLP:	no data
Year:	
Test substance:	valeraldehyde, >98% purity
Remark:	
References:	Merck-Schuchardt. Safety Data Sheet. Pentanal for synthesis. 04.2000. The Merck Chemical Database-online. <a href="http://www.merck.de">http://www.merck.de</a> (accessed October 16, 2000).  BASF Aktiengesellschaft Ludwigshafen. Safety Data Sheet. CAS No. 110-62-3. Version 5.00. Revised 10.09.97.

## 2.6 WATER SOLUBILITY

(a) Preferred result	reliability score = 2, accepted calculation method
Value:	11,700 mg/l at 25 degree C
Description:	very soluble (>10,000 mg/l)
Remark:	
Reference:	U.S. Environmental Protection Agency (USEPA). 2003. Experimental water solubility and vapor pressure values reported by EPI Suite software, Version 3.11. USEPA, Office of Pollution Prevention and Toxics, Washington, DC. Available at: <a href="http://www.epa.gov/oppt/exposure/docs/episuitedl.htm">http://www.epa.gov/oppt/exposure/docs/episuitedl.htm</a>
(b) Value:	11,700 mg/l at 25 degree C
Description:	very soluble (>10,000 mg/l)
Remark:	
Reliability:	score = 2, valid with restriction; data from handbook or collection of data
Reference:	Yalkowsky, S.H. and Dannenfelser, R.M. 1992. The Aquasol Database of Aqueous Solubility, 5 <sup>th</sup> Edition. University of Arizona, College of Pharmacy, Tucson, AZ.
(c) Value:	9718 mg/l at 25 degree C
Description:	soluble (1,000 to 10,000 mg/l)
Remark:	calculated using Log Kow of 1.31 (estimated); no melting point was used in this calculation
Reliability:	score = 2, valid with restriction; accepted calculation method
Reference:	WSKOW. Version 1.37. Water Solubility Estimate from Log Kow. EPIWIN (Estimation Program for Windows) Version 3.10. U.S. Environmental Protection Agency, 2000.
(d) Value:	13,500 mg/l at 20 degree C
Description:	very soluble (>10,000 mg/l)
Remark:	reported as 13.5 g/l at 20 degree C
Reliability:	score = 4, not assignable
Reference:	BASF AG. Safety Data Sheet CAS No. 110-62-3. Version 5.00. Revised 10.09.1997.

**2.7 FLASH POINT (*liquids*)**

- (a) Preferred result reliability score = 2; data from handbook or collection of data  
 Value: 12 degrees C  
 Type: Tag Open Cup  
 Method:  
 Test substance: valeraldehyde, 100%  
 Remark: equivalent to 54 degree F  
 References: NFPA. 2002. National Fire Protection Association. Fire Protection Guide to Hazardous Materials. 13<sup>th</sup> Edition. NFPA. Quincy, MA.  
 Sax, I.N. and Lewis, R.J., Sr. (eds). Hawley's Condensed Chemical Dictionary, 11<sup>th</sup> Edition. New York, NY: Van Nostrand Reinhold Company, 1987.
- (b) Value: 5 degree C  
 Type: Tag closed cup  
 Method: ASTM D56  
 Test substance: valeraldehyde, 100%  
 Remark: 41 degree F  
 Reliability: score = 2, national standard method (ASTM)  
 Reference: The Dow Chemical Company. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 01/14/2002. The Dow Chemical Company, Midland, MI.
- (c) Value: 12 degree C  
 Type: Tag Open Cup  
 Method: ASTM D1310  
 Test substance: valeraldehyde, 100%  
 Remark: 54 degree F  
 Reliability: score = 2, national standard method  
 Reference: The Dow Chemical Company. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 01/14/2002. The Dow Chemical Company, Midland, MI.
- (d) Value: 7 degree C  
 Type:  
 Method: other: DIN 51755  
 Remark: 44.6 degree F  
 Reliability: score = 2, valid with restriction; national standard method  
 Reference: BASF AG. Safety Data Sheet CAS No. 110-62-3. Version 5.00. Revised 10.09.1997.

**2.8 AUTO FLAMMABILITY (*solid/gases*)**

- (a) Preferred result reliability score = 2, valid with restriction; data from handbook or collection of data  
 Value: 222 degree C  
 Remark: autoignition temperature; reported as 432 degree F  
 Reference: NFPA. 2002. National Fire Protection Association. Fire Protection Guide to Hazardous Materials. 13<sup>th</sup> edition. NFPA. Quincy, MA.

**2.9 FLAMMABILITY**

Preferred result reliability score = 2, valid with restriction; data from handbook or collection of data

Value: Flammable range 2.1 – 7.8 vol %

Remark: 21,000 ppm – 78,000 ppm

Test substance: valeraldehyde, 100%

Reference: NFPA. 2002. National Fire Protection Association. Fire Protection Guide to Hazardous Materials. 13<sup>th</sup> edition. NFPA. Quincy, MA.

**2.10 EXPLOSIVE PROPERTIES**

Remark: Vapors may form explosive mixtures with air. Vapors may travel back to source of ignition and flash back. Vapor explosion hazard indoors, outdoors, or in sewers. Runoff to sewer may create fire or explosion hazard. Containers may explode when heated.

Reference: U.S. Department of Transportation (U.S.DOT). 1996. North American Emergency Response Guidebook. A Guidebook for First Responders During the Initial Phase of a Hazardous Material/Dangerous Goods Incident. U.S.DOT Research and Special Programs Administration, Washington, DC.

**2.11 OXIDIZING PROPERTIES**

Remark: Not an oxidizer. Avoid contact with oxygen and oxidizers. Avoid air (oxygen). Contact with air results in carboxylic acid formation. Oxidation can also cause formation of hazardous peroxides or peracids. Avoid contamination with iron oxides (rust) as this can result in rapid exothermic reaction.

Reference: The Dow Chemical Company. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 01/14/2002. The Dow Chemical Company, Midland, MI.

**2.12 ADDITIONAL REMARKS**

Remark: Very soluble in ethanol and ether.

References: Lide, D.R. (ed). 1995. CRC Handbook of Chemistry and Physics, 76<sup>th</sup> ed. Boca Raton, FL: CRC Press Inc.

Sax, I.N. and Lewis, R.J., Sr. (eds). Hawley's Condensed Chemical Dictionary, 11<sup>th</sup> Edition. New York, NY: Van Nostrand Reinhold Company, 1987.

Remark: Avoid contamination with basic materials (examples: sodium hydroxide, caustic soda, amines [especially monoethanolamine and diethanolamine], ammonia). Contamination with basic materials can result in rapid exothermic reaction. Avoid contamination with strong mineral acids. Contamination with strong mineral acids can result in a rapid exothermic reaction.

Reference: The Dow Chemical Company. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 01/14/2002. The Dow Chemical Company, Midland, MI.



- Remark: Incompatible materials: avoid contact with air (oxygen), amines, alcohols, alkalis, ammonia, strong mineral acids, caustics, halogen compounds.
- Reference: The Dow Chemical Company. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 01/14/2002. The Dow Chemical Company, Midland, MI.
- Remark: Hazardous polymerization may occur. May condense with evolution of heat in presence of alkalis, amines, and mineral acids.
- Reference: The Dow Chemical Company. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 01/14/2002. The Dow Chemical Company, Midland, MI.
- Remark: Avoid air (oxygen). Contact with air results in carboxylic acid formation. Oxidation can also cause formation of hazardous peroxides or peracids. Avoid contamination with iron oxides (rust) as this can result in rapid exothermic reaction.
- Reference: The Dow Chemical Company. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 01/14/2002. The Dow Chemical Company, Midland, MI.
- Remark: This product should be stored and handled in vapor-tight equipment under an atmosphere of oxygen-free nitrogen.
- Reference: The Dow Chemical Company. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 01/14/2002. The Dow Chemical Company, Midland, MI.

### 2.13 ADDITIONAL DATA

- Remark: An odor threshold concentration of 0.028 ppm has been reported for valeraldehyde.
- Reference: ACGIH. 1992. Documentation of Threshold Limit Values and Biological Exposure Indices, 6<sup>th</sup> Edition. Cincinnati, OH: American Conference of Governmental Industrial Hygienists (ACGIH).
- Remark: An odor threshold concentration of 0.060 ppm has been reported for valeraldehyde in normal human subjects.
- Reference: Amoore, J.E., Forrester, L.J. and Pelosi, P. 1976. Specific anosmia to isobutyraldehyde: the malty primary odor. Chem. Senses Flavor 2: 17-25.
- Remark: Vapor density: 2.97 (air = 1.0)  
Evaporation rate: 2.62 (butyl acetate = 1.0)
- Reference: The Dow Chemical Company. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 01/14/2002. The Dow Chemical Company, Midland, MI.
- Remark: Vapour density: 3.0 (air = 1.0)
- Reference: NFPA. 2002. National Fire Protection Association. Fire Protection Guide to Hazardous Materials. 13<sup>th</sup> edition. NFPA. Quincy, MA.
- Remark: Lower explosion limit (LEL): 2.1 vol % (21,000 ppm)  
Upper explosion limit (UEL): 7.8 vol % (78,000 ppm)

## 2. PHYSICAL CHEMICAL DATA

ID: 110-62-3

DATE: 09.01.2005

- 
- Reference: The Dow Chemical Company. Material Safety Data Sheet 5422: Valeraldehyde. Effective date 01/14/2002. The Dow Chemical Company, Midland, MI.
- Remark: 1 mg/m<sup>3</sup> = 0.28 ppm  
1 ppm = 3.5 mg/m<sup>3</sup>
- Reference: Verschueren, K. 2001. Handbook of Environmental Data on Organic Chemicals, 4<sup>th</sup> Edition. New York, NY: John Wiley & Sons, Inc
- .

**3.1 STABILITY****3.1.1 PHOTODEGRADATION**

- (a) Preferred result reliability score = 2, valid with restriction; accepted calculation method
- Atmospheric photooxidation  
 Type: other  
 Light source:  
 Relative intensity: based on intensity of sunlight  
 Sensitizer:  
 Conc. of Sensitizer:  
 Rate Constant:  
 Degradation: 9.00 hours  
 Method: calculated, see remarks  
 GLP:  
 Test substance: n-valeraldehyde  
 Remark: Atmospheric photo-oxidation potential was estimated using the submodel AOPWIN (Meylan and Howard, 1993). The estimation methods employed by AOPWIN were developed by Dr. Roger Atkinson and co-workers that rely on structural features of the test substance. The model calculates a second order half-life with units of cm<sup>3</sup>/molecules-cm. In the atmosphere, valeraldehyde will react with photochemically produced hydroxyl (OH) radicals and undergo direct photolysis (Lloyd, A.C., 1978. Tropospheric Chemistry of Aldehydes. National Bureau of Standards. Washington, DC. NTIS PB-299-439. p. 27-48). The calculated 2<sup>nd</sup> order rate constant for valeraldehyde is 2.85 x 10E-11 cm<sup>3</sup>/molecule-sec at 25 degree C. Based on 1.5 x10E6 OH molecules/cm<sup>3</sup>, and assuming 12 hours of sunlight per day (per AOPWIN v. 1.91), the estimated half-life of valeraldehyde in the atmosphere is 9.00 hours.
- References: Atkinson, R. 1989. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. J. Phys. Chem. Ref. Data. Monograph No 1.
- AOPWIN. Version 1.91. Atmospheric Oxidation. EPIWIN (Estimation Program for Windows) Version 3.12. U.S. Environmental Protection Agency, 2005.
- (b) Atmospheric photooxidation  
 Type: other  
 Light source:  
 Relative intensity: based on intensity of sunlight  
 Sensitizer:  
 Conc. of Sensitizer:  
 Rate Constant:  
 Degradation: 9.36 hours  
 Method: calculated, see remarks  
 GLP:  
 Test substance: n-valeraldehyde  
 Remark: The calculated 2<sup>nd</sup> order rate constant for valeraldehyde is 2.742 x 10E-11 cm<sup>3</sup>/molecule-sec at 25 degree C. Based on 1.5 x10E6 OH molecules/cm<sup>3</sup>, and assuming 12 hours of sunlight per day (per

- Reliability: AOPWIN v. 1.91), the estimated half-life of valeraldehyde in the atmosphere is 9.36 hours.
- Reference: score = 2, valid with restriction; accepted calculation method AOPWIN. Version 1.91. Atmospheric Oxidation. EPIWIN (Estimation Program for Windows) Version 3.12. U.S. Environmental Protection Agency, 2005.
- (c) Remark: In the atmosphere, pentanal (valeraldehyde) will react with photochemically-produced OH radicals. Its half-life resulting from interaction with hydroxyl radicals is 13.5 hours. Direct photolysis is also expected to be an important degradative process in the atmosphere.
- Reference: Pentanal (Valeraldehyde). CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.

### 3.1.2 STABILITY IN WATER

- Remark: With the exception of formaldehyde, saturated alkyl aldehydes do not have a hydrolysable functional group and cannot form a stable bond with water. Valeraldehyde is not anticipated to hydrolyze in water.
- Reference: Morrison, R.T. and Boyd, R.N. 1966. Organic Chemistry, 2<sup>nd</sup> Edition. Boston: Allyn and Bacton, Inc.

### 3.1.3 STABILITY IN SOIL

No data available

## 3.2 MONITORING DATA (ENVIRONMENT)

- (a) Type of Measurement  
Media: human tissue  
Remark: Results from EPA National Human Adipose Tissue Survey (NHATS) for 1982. All 46 composite samples analyzed contained valeraldehyde.  
Reference: Onstot, J.D. et al. 1987. Characterization of HRGC/MS Unidentified Peaks from the Broad Scan Analysis of the FY82 NHATS Composites. Volume 1. USEPA 68-02-4252.
- (b) Type of Measurement  
Media: human milk  
Remark: Valeraldehyde was detected but not quantified in 7 of 8 samples of mother's milk analyzed from 4 U.S. urban communities.  
Reference: Pellizzari, E.D, Hartwell, T.D., Harris, B.S., Waddell, R.D., Whitaker, D.A., and Erickson, M.D. 1982. Purgeable organic compounds in mother's milk. Bull. Environ. Contam. Toxicol. 28: 322-328.
- (c) Type of Measurement  
Media: air (volatile emissions from burning wood logs)  
Remark: In eight tests, the valeraldehyde emission rate from a fireplace with different types of logs ranged from non-detectable to 0.010 g/kg wood.  
Reference: Lipari, F. et al. 1984. Environ. Sci. Technol. 18: 326-330. Cited in: Valeraldehyde. CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.

- (d) Type of Measurement  
 Media: drinking water  
 Remark: In an EPA survey of drinking water in 10 cities, valeraldehyde was found in the drinking water of Ottumwa, IA at approximately 0.5 ug/l, but not detected in the drinking water of Miami, FL, Seattle, WA, Philadelphia, PA, Cincinnati, OH, Grand Forks, MI, Lawrence, MA, New York, NY, Terrebonne Parrish, LA, and Tucson, AZ.  
 Reference: Keith, L.H. et al. 1976. Identification Analysis of Organic Pollutants in Water. Ann Arbor, MI: Ann Arbor Press. *Cited in:* Valeraldehyde. CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.
- (e) Type of Measurement  
 Media: air  
 Remark: Valeraldehyde was emitted from samples of particle board with glued-on carpet, and plywood coated with polyurethane at rates of 0.031 and 0.014 mg/m<sup>2</sup>/hr.  
 Reference: Colombo, A. et al. 1990. Sci. Total Environ. 91: 237-249. *Cited in:* Valeraldehyde. CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.
- (f) Type of Measurement  
 Media: air  
 Remark: Valeraldehyde was detected in ambient air surrounding the Kin-Buc Waste Disposal site in New Jersey at levels ranging from non-detectable to 38 ug/m<sup>3</sup>  
 Reference: Pellizzari, E.D. 1982. Analysis for organic vapor emissions near industrial and chemical waste disposal sites. Sci. Total Environ. 16: 781-785.
- (g) Type of Measurement  
 Media: air  
 Remark: Air concentrations of valeraldehyde were determined between 1979 and 1981 at three sites in The Netherlands: an unpolluted island, a small city, and a heavily industrialized area. The mean and maximum concentrations of valeraldehyde in the air at these sites were 0.05 and 0.40 ppb, respectively.  
 Reference: Guicherit, K. and Schulting, F.L. 1985. Sci. Total Environ. 43: 193-219. *Cited in :* Valeraldehyde. CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.
- (h) Type of Measurement  
 Media: air  
 Remark: Air concentrations of valeraldehyde were determined at four urban sites in Stockholm, Sweden. Mean 1 hr valeraldehyde concentrations ranged from 0.15 to 1.07 ppb. The mean concentration at a recreation site 12 km outside the central city was 0.49 ppb.  
 Reference: Jonsson, A., Persson, E.A., and Grigoriadis, V. 1985. Measurements of some low-molecular-weight oxygenated, aromatic, and chlorinated hydrocarbons in ambient air and in vehicle emissions. Environ. Intl. 11: 383-392.
- (i) Type of Measurement  
 Media: air

- Remark: Ambient levels of valeraldehyde measured on Sept 11-19, 1985 on the campus of Pomona College, Claremont, CA ranged from <0.1 to 0.6 ppb, with a median of 0.1 ppb. These levels were much lower than those measured previously during a photochemical smog episode.
- Reference: Grosjean, D. 1988. *Atmos. Environ.* 22: 1637-1648. *Cited in* : HSDB. Valeraldehyde. CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.
- (j) Type of Measurement  
Media: air  
Remark: Valeraldehyde was found in two of six samples of indoor air analyzed in Italy at concentrations of 8 and 15 ug/m<sup>3</sup>. Valeraldehyde was present in two pre-schools in Stockholm, Sweden and one of four Swedish dwellings that were part of a study on emissions from floor finishes.  
References: DeBortoli, M. et al. 1986. *Environ. Internat.* 12: 343-350.  
Noma, E. et al. 1988. *Atmos. Environ.* 22: 451-460.  
Van Netten, C. et al. *Bull. Environ. Contam. Toxicol.* 40: 672-7. *All refs cited in* : HSDB. Valeraldehyde. CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.
- (k) Type of Measurement  
Media: air  
Remark: Valeraldehyde was one of the top five volatile organic chemicals (VOCs) recovered at a concentration of 342 ug/m<sup>3</sup> during the initial one hour exposure interval from oak veneer heated to 70 degree C. Formaldehyde was recovered at a concentration of 6076 ug/m<sup>3</sup>.  
Reference: Muller, W.J. and Black, M.S. 1995. Sensory irritation in mice exposed to emissions from indoor products. *Am. Ind. Hyg. Assoc. J.* 56: 794-803.
- (l) Type of Measurement  
Media: air  
Remark: Valeraldehyde was a major carbonyl compound present at 13 to 36% in the headspace of five Burley chewing tobacco samples, and at 31-67% in the headspace of 13 flue-cured tobacco samples.  
Reference: Chou, C-C. and Que-Hee, S.S. 1994. Saliva-available carbonyl compounds in some chewing tobaccos. *J. Agric. Food Chem.* 42: 2225-2230.
- (m) Media: air  
Remark: Valeraldehyde was detected in one of ten samples in the Kanawha Valley, WV and in four of nine air samples in the Shenandoah Valley VA in 1977.  
Reference: Erickson M.D. and Pellizzari, E.D. 1978. Analysis of organic Air Pollutants in the Kanawha Valley, WV and the Shenandoah Valley VA USEPA-903/9-78-007.
- (n) Media: air  
Remark: Valeraldehyde been detected in indoor air in EPA headquarters' building above the 0.06 ug/ m<sup>3</sup> quantitation limit.

- Reference: U.S.EPA (U.S. Environmental Protection Agency). 1990. Indoor Air Quality and Work Environment Study. EPA Headquarters' Buildings. Volume 2. Results of Indoor Air Environmental Monitoring Study. Atmos. Res. and Exposure Assess. Lab, RTC, NC.
- 3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAY**
- 3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS**
- (a) Type: volatility  
 Media: soil – air  
 Method other: estimate  
 Year:  
 Remark: Valeraldehyde has a Henry's Law constant of  $1.47 \times 10^{-4}$  atm-m<sup>3</sup>/mole. The high Henry's law constant and low adsorptivity to soil indicates that it should readily volatilize from moist soil. With a vapor pressure of 26 mm Hg, valeraldehyde should readily volatilize from dry soil surfaces.  
 Reliability: score = 2, valid with restriction; accepted calculation method  
 Reference: Lyman, W.J. 1982. Handbook of Chemical Estimation Methods. NY: McGraw Hill.
- (b) Remark: Based on a Henry's Law constant of  $1.47 \times 10^{-4}$  atm-m<sup>3</sup>/mole, the volatilization half-life of valeraldehyde from a model river, 1 m deep flowing at 1 m/sec with a 3 m/sec wind, is 8.3 hours. The volatilization half-life of valeraldehyde from a model lake, 1 m deep, with a 0.05 m/sec current and a 0.5 m/sec wind, is estimated at 5.4 days.  
 Reliability: score = 2, valid with restriction; accepted calculation method  
 References: Lyman, W.J. et al. 1982. Handbook of Chemical Property Estimation Methods. New York, NY: McGraw Hill.  
 Flick, E.W. 1991. Industrial Solvents Handbook, 4<sup>th</sup> Edition. Park Ridge, NJ: Noyes Data Corp.  
 Buttery, R.G. et al. 1969. J. Agric. Food Chem. 17: 385-389. *cited in*: Valeraldehyde. CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.
- (c) Remark: Using a water solubility value of 13,500 mg/l for valeraldehyde, a Koc of 1040 can be estimated. According to Swann's classification scheme, a material with a Koc of 1040 would have a low mobility in soil.  
 Reliability: score = 2, valid with restriction; accepted calculation method  
 Reference: Swann, R.L. et al. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. Res.Rev. 85: 17-28.
- (d) Media other: water-air  
 Method other: estimate  
 Year:

Remark:	Estimated half-life = 8.3 hr (model river, 1 m deep, 1 m/sec current, 3 m/sec wind); Estimated half-life = 5.4 days (model lake, 1 m deep, 0.5 m/sec current, 0.5 m/sec wind). Half-lives in environmental water estimated using the (experimental) Henry's Law constant of 1.47 E-4 atm-m <sup>3</sup> /mol at 25 degree C.
Reliability:	score = 2, valid with restriction; accepted calculation method
Reference:	Lyman, W.J. et al. 1982. Handbook of Chemical Property Estimation Methods. McGraw Hill, NY. Chapters 15 and 16.
(e) Media other:	air - suspended atmospheric particles
Method other:	estimate
Year:	
Remark:	According to a model of gas/particle partitioning of semi-volatile organic materials in the atmosphere, valeraldehyde is expected to exist solely as a vapour in the ambient atmosphere, based on a vapour pressure of 26 mm Hg at 20 degree C.
Reliability:	score = 2, valid with restriction; accepted calculation method
Reference:	Daubert, T.E. and Danner, R.P. 1989. Physical and Thermodynamic Properties of Pure Chemicals: Data Compilation. New York, NY: Hemisphere Publishing Corp.

### 3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Preferred value	reliability score = 2, valid with restriction; accepted calculation method
Media:	other: air, water, soil, and sediment
Method Calculation:	fugacity model level III, part of EPIWIN v. 312
Year:	2004
Remark:	Air: half-life = 9.01 hr, emissions = 1000 kg/hr Water: half-life = 208 hr, emissions = 0 kg/hr Soil: half-life = 416 hr, emissions = 0 kg/hr Sediment: half-life = 1870 hr, emissions = 0 kg/hr Persistence Time: 12.3 hr Physical properties used for the distribution modeling at 25° C were water solubility 11,700 mg/l, vapor pressure of 26 mm Hg, log Kow 1.38, melting point -91.5 deg. C; boiling point 103 degree C. Air (Level III): 93.4% Water (Level III): 5.65% Soil (Level III): 0.961% Sediment: < 0.1%
Remark:	Reliability score of 2 assigned as a result of using an accepted method of estimation. No measured data available to confirm the calculated values.
Reliability:	score = 2, valid with restriction; accepted calculation method.
Reference:	Fugacity Model Level III. EPISuite Version 3.12. U.S. Environmental Protection Agency, 2004.

### 3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE



**3.5 BIODEGRADATION**

(a)	Preferred value	reliability score = 1; OECD guideline study
	Type:	aerobic
	Inoculum:	domestic wastewater, secondary effluent
	Concentration:	2.64 mg/l
	Contact time:	28 days
	Degradation:	64.1% after 28 days
	Results:	readily biodegradable
	Kinetic:	3 day = $41.0 \pm 0.5\%$ 5 day = $52.6 \pm 2.1\%$ 10 day = $61.4 \pm 0.9\%$ 21 day = $65.0 \pm 1.1\%$ 28 day = $64.1 \pm 0.1\%$
	Control:	sodium benzoate, 4.02 mg/l
	Method:	OECD Guidelines for Testing of Chemicals. 1992. Guideline No. 301D: Ready Biodegradability, Closed Bottle Test.
	GLP:	yes
	Test substance:	n-valeraldehyde, CAS 110-62-3, purity 99.6%
	Method:	The microbial inoculum consisted of secondary effluent, collected from City of Midland municipal domestic wastewater treatment plant. Effluent was collected one day prior to test initiation, and filtered through Whatman 114V filter paper prior to use. Mineral medium specified by OECD Guideline 301D was prepared in Milli-Q® water (ingredients and preparation methods described in detail in report). Mineral medium was inoculated with the filtered effluent at a concentration of 4 ml/L; a total of 16 liters of inoculated mineral medium was prepared. The inoculated mineral medium was aerated for a minimum of 30 minutes, and allowed to stand at test temperature for at least 20 hours prior test initiation. The pH of the inoculated mineral medium was 7.4 and did not require adjustment. Dissolved oxygen concentration in the equilibrated, inoculated mineral medium was 8.7 mg O <sub>2</sub> /L prior to test initiation.

Inoculum blanks were prepared by volumetrically removing 6 liters of inoculated mineral medium and dispensing into 300 ml glass BOD bottles. A procedure control suspension containing 4.02 mg sodium benzoate per liter of inoculated mineral medium was prepared and dispensed into 300 ml glass BOD bottles. Test suspensions were prepared by adding 18 ml of a 1174 mg/L stock solution of n-valeraldehyde in Milli-Q® water to 8 liters of inoculated mineral medium for a final concentration of 2.64 mg/L. Test suspensions were dispensed into 300 ml glass BOD bottles. Toxicity controls containing 4.02 mg/L sodium benzoate and 2.64 mg/L n-valeraldehyde were also prepared and dispensed into 300 ml glass BOD bottles (see table below for experimental matrix). BOD bottles were filled to capacity, and sealed with ground glass stoppers and plastic covers to prevent entrapment of air bubbles and evaporation of the aqueous media.

**Matrix for Evaluation of Biodegradability of n-Valeraldehyde**

Description of Mixture	Contents	Sampling Interval (days)*	Number of Replicates
------------------------	----------	---------------------------	----------------------

Inoculum blanks	Inoculated mineral medium	0,3,5,7,10,14,17,21,28	18
Test suspensions	Inoculated mineral medium + 2.64 mg/L valeraldehyde	0,3,5,7,10,14,17,21,28	18
Procedure controls	Inoculated mineral medium + 4 mg/L sodium benzoate	0, 7, 14	6
Toxicity controls	Inoculated mineral medium + 4 mg/L sodium benzoate + 2.64 mg/L valeraldehyde	0, 7, 14	6

\* two 300-ml BOD bottles from each group were sampled at each interval

Inoculum blanks were used for duplicate measurements for each sampling interval (day 0, 3, 5, 7, 10, 14, 17, 21, 28). Blanks were used to determine mean values for oxygen consumption due to endogenous respiration of the inoculum. A total of 18 test suspensions were prepared containing 2.64 mg/L of the test material to allow duplicate measurements at each sampling interval. The concentration of test material at test initiation was not verified by chemical analysis, and the concentration remaining at the end of each sampling interval was not determined.

Procedure control mixtures which contained 4.02 mg/L sodium benzoate were sampled in duplicate on days 0, 7, and 14. Similarly, six replicate toxicity control bottles containing the test material and sodium benzoate were prepared and sampled on days 0, 7, and 14.

Reaction mixtures were statically incubated in a walk-in incubator which was maintained in complete darkness except when dissolved oxygen measurements were taken. Air temperature was automatically recorded at 3-hour intervals during the test; the average air temperature was  $19.2 \pm 0.3$  °C. Dissolved oxygen measurements were performed using an Orion model 97-08 dissolved oxygen electrode connected to an Orion model 920A+ pH meter. The meter and electrode were calibrated prior to performing oxygen measurements at each sampling interval. Dissolved oxygen measurements were performed in duplicate for inoculum blanks and test suspensions on days 0, 3, 5, 7, 10, 14, 17, 21, and 28. Dissolved oxygen measurements were performed in duplicate for procedure and toxicity controls on days 0, 7, and 14.

Calculations: The biological oxygen demand (BOD) was determined for each reaction mixture at each sampling interval using the following formula:

$$\text{BOD} = \frac{\text{mg O}_2 \text{ uptake by test substance} - \text{mean mg O}_2 \text{ uptake by blanks}}{\text{mg test substance in vessel}}$$

The percent degradation (%DO<sub>2</sub>) at each sample interval was determined by dividing the BOD by the theoretical oxygen demand (ThOD) for each reaction mixture:

$$\%DO_2 = \frac{BOD}{ThOD} \times 100$$

Where ThOD is the theoretical oxygen demand required for complete mineralization of the test material to carbon dioxide and water.

Statistical methods: descriptive statistics (mean, standard deviation) were used where applicable.

Results: Complete dissolution of the test material was confirmed by dissolved organic carbon analysis of the test stock suspension. Of the calculated 818 mg carbon/L available, 103% was recovered. Incubation temperatures ranged from 18.6 to 19.7 °C, and averaged  $19.2 \pm 0.3$  °C. Onset of n-valeraldehyde biodegradation was rapid and over 60% biodegradation was achieved by day 10. The maximum difference among replicates was 2.3% occurring on day 17. Percent biodegradation in the procedure controls was  $80.6 \pm 0.1$  on day 14. Biodegradation in toxicity controls was 61.4% on day 14, indicating that the test material was not inhibitory on the inoculum.

Biodegradation Selected Sampling Intervals

Sampling Interval (days)	Biodegradation (mean $\pm$ SD, n=2) %		
	Test Material	Procedure Control	Toxicity Control
	$1.0 \pm 0.5$		
	$2.5 \pm 2.1$		
	$8.2 \pm 1.5$	$8.5 \pm 0.6$	$2.7 \pm 0.1$
0	$1.4 \pm 0.9$		
4	$1.7 \pm 0.4$	$0.6 \pm 0.1$	$1.4 \pm 0.1$
7	$1.3 \pm 2.3$		
11	$5.0 \pm 1.1$		
14	$4.1 \pm 0$		

Remark: OECD 301D criterion for “readily biodegradable” classification requires reaching 60% biodegradation within a 10-day window, following onset of biodegradation, within a test interval not to exceed 28 days. Based on results described above, valeraldehyde can be considered readily biodegradable according to OECD criteria.

OECD 301D guidelines specify that maximum oxygen consumption in inoculum blanks must not exceed 1.5 mg/L over 28 days, and dissolved oxygen levels in test suspensions must not fall below 0.5 mg/L. In this test, maximum oxygen consumption in inoculum blanks after 28 days was only 0.95 mg/L, while the minimum dissolved oxygen concentration observed in the test suspensions was 3.38 mg/L (see table below). These results demonstrate that current OECD criteria for a valid test have been satisfied.

#### Dissolved Oxygen (DO<sub>2</sub>) Measurements at Selected Time Intervals

Test Suspension Valeraldehyde 2.64 mg/L		Inoculum Blank Mineral Media + Inoculum Only		Procedure Control Sodium Benzoate mg/L		Toxicity Control Valeraldehyde + Sodium Benzoate	
Sampling Interval (days)	O <sub>2</sub> in mg/L	Sampling Interval (days)	O <sub>2</sub> in mg/L	Sampling Interval (days)	O <sub>2</sub> in mg/L	Sampling Interval (days)	O <sub>2</sub> in mg/L
	.74		.74		.69		.70
	.75		.72		.70		.64
	.93		.72				
	.88		.72				
	.12		.63				
	.92		.64				
	.77		.68		.46		.20
	.62		.71		.40		.17
0	.32	0	.59				
0	.41	0	.58				
4	.25	4	.44	4	.10	4	.18
4	.29	4	.58	4	.11	4	.16
7	.34	7	.38				
7	.12	7	.50				
1	.97	1	.41				

1	.86	1	.35				
8	.38	8	.78				
8	.38	8	.78				

Reliability: score = 1, OECD GLP guideline study  
 Reference: Davis, J.W. and Marty, G.T. 2004. Valeraldehyde: Evaluation of ready biodegradability according to OECD Guideline 301D: Closed Bottle Test (unpublished study). Toxicology & Environmental Research and Consulting, Study ID 031115. The Dow Chemical Company, Midland, MI.

- (b) Type: aerobic  
 Inoculum: activated sludge  
 Concentration: 500 mg/l related to test substance  
 Degradation: 17.8% after 24 hours  
 Kinetics: 12.7% after 6 hours  
 16.5% after 12 hours  
 17.8% after 24 hours  
 Method: other: BOD-Test (Warburg respirometer, BOD of THOD)  
 The test material was added to obtain a concentration of 500 mg/l, based on a total volume of 20 ml. Flask temperature was 20 degree C. A control flask for measurement of endogenous respiration was included with each run. Pressure changes resulting from auto-oxidation and from volatility of the substrate were also determined. Readings were made for 24 hr at 0.5 to 5 hour intervals, depending on the rate of oxygen uptake.  
 Year: 1966  
 GLP: no  
 Test substance: n-valeraldehyde (CAS No. 110-62-3), analytical grade  
 Test condition: 20 deg C  
 Remark: Pressure changes produced by auto-oxidation or volatility were negligible. Propionaldehyde, butyraldehyde, isobutyraldehyde, isovaleraldehyde, and heptaldehyde were also tested using the same protocol and test conditions. Aldehydes were oxidized much more readily and completely than their parent alkanes.

Percent Biodegradation of Aldehydes by Activated Sludge

Aldehyde	6hr	12 hr	24hr
Propionaldehyde	14.4	24.9	28.8
Butyraldehyde	14.2	21.7	22.8
Isobutyraldehyde	8.7	15.4	24.3
Valeraldehyde	12.7	16.5	17.8
Isovaleraldehyde	9.2	14.2	16.1
Heptaldehyde	5.0	7.0	14.7

Reliability: score = 2, reliable with restrictions  
 Reference: Gerhold, R.M. and Malaney, G.W. 1966. Structural determinants in the oxidation of aliphatic compounds by activated sludge. J. Water Pollut. Control Fed. 38: 562-579.

- (c) Type: aerobic

Inoculum:	domestic sewage, non-acclimated
Contact time:	20 days
Results:	readily biodegradable
Degradation:	76% after 20 days
Kinetic:	48% at 5 days 67% at 10 days 73% at 15 days 76% at 20 days
Method other:	Dilution bottle BOD test following procedures published in Standard Methods for the Examination of Water and Wastewater, 17 <sup>th</sup> Edition, American Public Health Association, 1989.

Settled domestic wastewater was filtered through glasswool and then added (3 ml/bottle) as seed material to clean BOD bottles. Bottles were half-filled with aerated dilution water containing minerals specific to the method were added to the bottles as well buffer. The test material was then added to each test bottle. Dissolved oxygen (DO) was monitored with a commercial DO meter fitted with an agitated probe. Bottles were opened for sampling and DO measurements were made on Day 0, 5, 15, and 20. Samples were routinely tested for nitrites and nitrates during the test. Biooxidation was calculated as the percentage ratio of BOD to ThOD (BOD/ThOD x 100).

Year:	1989
GLP:	no data
Test substance:	n-valeraldehyde (CAS No. 110-62-3), purity not specified
Test condition:	20 degree C
Remark:	Biodegradation of valeraldehyde demonstrated steadily increasing oxidation from test initiation to Day 10, followed by a less rapid increase through Day 20. Valeraldehyde is readily biodegradable.
Reliability:	score = 2, valid with restrictions
Reference:	Union Carbide Chemicals and Plastics Company Inc. 1993. Ecological Fate and Effects Testing of UCC&P Products and Wastewaters During 1992. File Report No. 39860, dated February 12, 1993.

### 3.6 BOD<sub>5</sub>, COD OR RATIO BOD<sub>5</sub>/COD

#### BOD<sub>5</sub>

(a) preferred value	reliability score = 2, valid with restrictions
Method other:	Dilution bottle BOD test following procedures published in Standard Methods for the Examination of Water and Wastewater, 17 <sup>th</sup> Edition, American Public Health Association, 1989.

Biooxidation calculated as percentage ratio of BOD to ThOD (BOD/ThOD x 100). Settled domestic wastewater was filtered through glasswool and then added (3 ml/bottle) as seed material to clean BOD bottles. Bottles were half-filled with aerated dilution water; minerals and buffer were added to each bottle.

Aliquots of the test material was then added. Dissolved oxygen (DO) was monitored with a commercial DO meter fitted with an agitated probe. Bottles were opened for sampling and DO

measurements were made on Day 0, 5, 15, and 20. Samples were routinely tested for nitrites and nitrates during the test.

BOD<sub>5</sub>: 48%

GLP: no data

Remark: BOD<sub>10</sub> = 67%  
BOD<sub>15</sub> = 73%  
BOD<sub>20</sub> = 76%

Reference: Union Carbide Chemicals and Plastics Company Inc. 1993. Ecological Fate and Effects Testing of UCC&P Products and Wastewaters During 1992. File Report No. 39860, dated February 12, 1993.

**COD**

Preferred value: reliability score = 2, valid with restrictions

Method other: Method based on procedures published in Standard Methods for the Examination of Water and Wastewater, 17<sup>th</sup> Edition, American Public Health Association, Washington, DC, 1989.

COD: 2.70 mg/mg

Reference: Union Carbide Chemicals and Plastics Company Inc. 1993. Ecological Fate and Effects Testing of UCC&P Products and Wastewaters During 1992. File Report No. 39860, dated February 12, 1993.

**Ratio BOD<sub>5</sub>/COD:**

BOD<sub>5</sub>/COD: BOD<sub>5</sub>/ThBOD x 100 =

Remark: 48% at 5 days  
67% at 10 days  
76% at 20 days

Reference: Union Carbide Chemicals and Plastics Company Inc. 1993. Ecological Fate and Effects Testing of UCC&P Products and Wastewaters During 1992. File Report No. 39860, dated February 12, 1993.

**3.7 BIOACCUMULATION**

- (a) BCF: 5.8
- Method other: calculated using Kow of 1.31 (Meylan and Howard, 1992)
- Year:
- Remark: Valeraldehyde is not expected to bioaccumulate in fish or other aquatic organisms.
- Reliability: score = 2, accepted calculation method
- References: Lyman, W.J. et al. 1982. Handbook of Chemical Property Estimation Methods. NY: McGraw Hill Book Company.
- Meylan, W.M. and Howard, P.H. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. J. Pharm. Sci. 84: 83-92.
- (b) BCF: 2.3
- Method other: calculated BCFWIN
- Year:
- Remark: Log Kow used for calculation = 1.38 (Merck-Schuchardt, 2000)

Reliability: score = 2, accepted calculation method  
Reference: BCFWIN. Version 2.14. BCF Estimate from Log Kow. EPIWIN (Estimation Program Interface for Windows). Version 3.10. U.S. Environmental Protection Agency, 2000. .

### 3.8 ADDITIONAL REMARKS

Remark: Henry's Law Constant =  $1.47 \times 10^{-4}$  atm-m<sup>3</sup>/mol at 25 degree C (measured). Valeraldehyde is expected to readily volatilize from moist soil.

Reference: Buttery, R.G. et al. 1969. J. Agric. Food Chem. 17: 385-389. *Cited in : Valeraldehyde*. CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.

Remark: Henry's Law Constant =  $2.62 \times 10^{-4}$  atm-m<sup>3</sup>/mol at 25 degree C. Calculated from water solubility (11,700 mg/L), vapor pressure (27.07 mm Hg), and molecular weight (86.14 at 25 degree C).

Reference: HENRYWIN. Version 3.10. Henry's Law Constant. EPIWIN (Estimation Program Interface for Windows). Version 3.10. U.S. Environmental Protection Agency, 2000.

Remark: Koc = 9.4 (calculated)

Reference: PCKOCWIN. Version 1.66. Soil Adsorption Coefficient. EPIWIN (Estimation Program Interface for Windows). Version 3.10. U.S. Environmental Protection Agency, 2000.



**4.1 ACUTE/PROLONGED TOXICITY TO FISH**

- (a) Preferred result reliability = 1, valid without restrictions. GLP guideline study  
 Type: flow-through  
 Test: LC50  
 Species: *Oncorhynchus mykiss* Walbaum, freshwater rainbow trout  
 Unit: mg/L  
 Exposure Period: 96 hours  
 LC50: 27.9  
 NOEC: 7.78  
 Test substance: n-valeraldehyde, purity 99.6%  
 Analyt Monitoring.: yes  
 Year: 1992  
 GLP: yes  
 Methods: OECD Guideline 203, Fish Acute Toxicity Test, 7/17/92  
 Directive 92/69/EEC, C.1 Acute Toxicity for Fish, Vol. 35, 12/29/92  
 USEPA Fish Acute Toxicity Test 40 CFR 797.1400, 1992  
 Rainbow trout *Oncorhynchus mykiss* Waldbaum were obtained as juveniles from Thomas Fish Company, Anderson, CA. Juvenile fish were visually inspected on arrival and placed in a holding tank. All fish were maintained on a 16-hour light/8-hour dark transitional photoperiod and observed for at least 14 days prior to testing. During the observational interval, fish were fed a standard aquatic diet (Harlan-Teklad, Madison, WI) at least once daily. Fish were acclimated to 13.0 ± 1 °C for at least 7 days prior to testing.
- Laboratory water is obtained from the upper Saginaw Bay of Lake Huron; before use, water is sand-filtered, pH-adjusted with carbon dioxide, carbon-filtered, and UV-irradiated. Water quality criteria in control/dilution water used during the test were as follows:
- |                                       |           |
|---------------------------------------|-----------|
| Hardness (mg CaCO <sub>3</sub> /L):   | 68 - 76   |
| Alkalinity (mg CaCO <sub>3</sub> /L): | 28 - 40   |
| Conductivity (umhos/cm):              | 155 - 162 |
| Residual chlorine:                    | <10 ppb   |
- Fish averaging 4.2 ± 0.3 cm and weighing 0.623 ± 0.125 gm were used as test organisms. Fish were held without food at least 48 hr prior to testing. Definitive testing was conducted in test aquaria constructed of double-strength glass with an approximate volume of 3.7 L.
- An intermittent-flow proportional diluter system (Microlab<sup>®</sup> 500 Precision Dosing System, Hamilton Company, Reno, NV) was used to maintain constant exposure concentrations during the 4-day study interval. The system was designed to deliver up to six test concentrations, vehicle control, and a water control. The diluter was calibrated so that the concentration of the test substance in each treatment below the high concentration was approximately 60% of that in the next higher treatment level. When the diluter cycled, the test substance was blended and flowed into mixing/splitting chambers. During each cycle of the diluter, a volume of 0.444 ml n-valeraldehyde was injected into 6.0 L of laboratory water which resulted in a nominal target concentration of 60 mg/L; subsequent lower nominal test concentrations were 36.0, 21.6, 13.0, 7.78, 4.67,

and 0 (water control) mg/L. Silicone delivery tubes provided approximately 1L test solution to each of two replicate test aquaria for each test dose. The diluter was calibrated prior to test initiation and delivered an average of 7.1 volume turnovers in test aquaria for concentration for each 24-hour interval during the study.

Test aquaria and diluter were positioned in a temperature-controlled water trough and provided a 16-hr light/8-hr dark transitional photoperiod during testing. Temperature, pH, and dissolved oxygen were monitored throughout the 96-hour exposure interval and recorded for each vessel at 0, 24, 48, 72, and 96 hours. Ten fish 60, (two replicates of 5 fish each) were exposed to each nominal concentration. The loading rate of the test vessels did not exceed 1.0 gm fish per liter of test solution. This loading rate resulted in dissolved oxygen levels that were equal to or greater than 60% of saturation throughout the exposure interval; aeration was not required. Fish were not fed during the test. Fish were observed for mortality, and physical and behavioral effects throughout the exposure interval. Dead fish were removed when observed. Terminal body weights and total length measurements were recorded; surviving fish were euthanized with tricaine methanesulfonate prior to taking measurements.

Valeraldehyde test concentrations were selected based on range-finding tests using one replicate of 5 fish per dose level. Fish were exposed to nominal test concentrations of 100, 36.0, 21.6, 13.0, and 7.78 mg/L, and a water control. The estimated 96-hr LC<sub>50</sub> was estimated to be between 36.0 and 21.6 mg/L. Since all dose levels tested exhibited sublethal effects at termination, a 96-hr NOEC for the range-finding test could not be estimated.

For the definitive study, ten fish (5 fish per replicate; two replicates per dose level) were exposed to nominal test concentrations of n-valeraldehyde at nominal target concentrations of 4.67, 7.78, 13.0, 21.6, 36.0, 60.0, and 100 mg/L plus a water control. Fish were added to each test vessel within 30 minutes of solution preparation and initial test solution sampling. The concentration of valeraldehyde was confirmed by collecting test solution samples on days 0 and 4 from each test vessel. Study average percent of nominal values ranged from 103 to 143%. The overall average percent of nominal for the entire study was  $128 \pm 17.3\%$ . The resulting mean measured n-valeraldehyde concentrations were 4.82, 8.73, 18.5, 27.5, 51.2, and 85.6 mg/L.

Samples of the initial test solutions were analyzed by HPLC/UV analysis using an Agilent HP1100 Gradient HPLC System YMC ODS-AQ analytical column (standard preparation, detector calibration, instrument conditions for HPLC/UV analysis described in detail in report). Replicates were analyzed at 96 hours at test termination.

Statistical analysis: The USEPA Trimmed Spearman-Kärber Program, Version 1.5 was used to calculate the LC<sub>50</sub> values, confidence limits, and corresponding trim values. Values were determined using nominal target n-valeraldehyde concentrations.

The NOEC was determined based on biological interpretation of the data and the highest exposure level exhibiting no fish mortality or sub lethal effects.

Results:

Day 0 analysis of test solutions for n-valeraldehyde demonstrated that dose solutions ranged from 112% to 149% of target nominal values; Day 4 (96 hr) analysis of replicate test solutions yielded percent of nominal values ranging from 94 to 145%. The overall average percent of nominal and standard deviation values for the entire study was  $128 \pm 17.3\%$ . Mean measured concentrations were calculated for all dose levels by averaging the day 0 concentrations and day 4 exposure solution concentrations (see table below).

Results of Analysis of Test Solutions for n-Valeraldehyde

Target Concentration (mg/L)	Day 0 Solution Concentrations* (mg/L)	Day 4 Solution Concentrations (mg/L)	Mean Measured Concentrations <sup>1</sup> (mg/L)
Control	<LLQ <sup>2</sup>	<LLQ	NA <sup>3</sup>
4.67	5.24	4.39	4.82
7.78	9.50	7.95	8.73
13.0	19.4	17.5	18.5
21.6	29.6	25.4	27.5
36.0	52.1	50.3	51.2
60.0	84.3	86.8	85.6

\*Average % of target dose on Day 0:  $134 \pm 14.4$ ; on Day 4:  $122 \pm 21.1$

1: Mean measured concentration = mean of day 0 and day 4 concentration values

2: less than Lowest Level Quantified: 0.404 mg/L

3: Not Applicable

Observations were made for mortality (no response to contact with the caudal peduncle and no opercula movement), behavioral effects (lethargy, hyperactivity, swimming at surface, complete or partial loss of body equilibrium, erratic movement) and gross pathological effects (exophthalmia, ascites, hemorrhage, excess mucus, sloughing of epidermis, melanosis) in response to exposure to n-valeraldehyde. Fish mortality was 100% at the highest concentration at all time intervals. There was a dose-response effect observed in fish at lower concentrations (see table below)

Biological Response to n-Valeraldehyde Exposure

MMC (mg/L) <sup>1</sup>	Target (mg/L)	Biological Response Observed			
		24 hours	48 hours	72 hours	96 hours
LLQ <sup>2</sup>	Control	10N	10N	10N	10N
4.82	4.67	10N	10N	10N	10N
8.73	7.78	10N	10N	10N	9N, 1L
18.5	13.0	10N	10N	10N	10N
27.5	21.6	10N	7N, 2PE, 1CE	4N, 1L, 4PE, 1CE	4N, 1L, 4PE, 1CE
51.2	36.0	3PE,	9D, 1CE+I	10D	10D

		7CE+I			
85.6	60.0	10D	10D	10D	10D

N = normal; L = lethargic; D = dead; PE = partial loss of equilibrium; CE = complete loss of equilibrium; I = immobility

1: Mean measured concentration

2: Less than Lowest Level Quantified: 0.80 mg/L

Because chemical analysis of test solutions resulted in high average percent recovery of target values, the biological data were statistically evaluated using nominal concentrations to provide a more conservative LC<sub>50</sub> and NOEC values. The resulting values are listed below:

The 24-hour LC<sub>50</sub> value was 46.5 mg/L, with a Spearman-Kärber trim of 0.0%; no reliable 95% confidence interval could be determined.

The 48-hour LC<sub>50</sub> value was each 29.4 mg/L, with a 95% confidence interval of 26.6-32.3 mg/L; the Spearman-Kärber trim was 0.0%.

The 72- and 96-hour LC<sub>50</sub> value was 27.9 mg/L, with a Spearman-Kärber trim of 0.0%; no reliable 95% confidence interval could be determined.

The 96-hour NOEC was 7.78 mg/L and was determined based on biological interpretation of the data and the highest exposure level exhibiting no mortality or sub lethal effects.

Reliability:  
Reference:

score = 1; valid without restriction. GLP guideline study Marino, T.A, McClymont, E.L., and Yaroch, A.M. 2003a. n-Valeraldehyde: An Acute Toxicity Study with the Rainbow Trout, *Oncorhynchus mykiss* Walbaum (unpublished study). Toxicology & Environmental Research and Consulting, Study ID 031104. The Dow Chemical Company, Midland, MI.

- (b) Type: flow through  
 Species: *Pimephales promelas* (fathead minnow)  
 Unit: mg/l  
 Exposure Period: 96 hour  
 EC50: 12.4  
 LC50: 12.4  
 Analyt. Monitoring: yes  
 Method other: USEPA  
 GLP: no data  
 Test substance: n-valeraldehyde (CAS No. 110-62-3), purity 99%  
 Remark: Fathead minnows used in the tests were cultured from brood stock provided by the USEPA Environmental Research Laboratory-Duluth. Adults were maintained in a flow-through system at 25 deg. C with a 16-h light/dark photoperiod. Organisms were fed frozen adult brine shrimp (*Artemia* sp.). Fry were fed freshly hatched brine shrimp nauplii three times daily until 24-h before test initiation.

The test was initiated using 20 organisms (31-days old, randomly distributed in each of five test concentrations and an untreated

control. The test fish had a mean length of 19.8 +/- 1.7 mm and a mean weight of 0.119 +/- 0.030 g. Dechlorinated tap water or Lake Superior water was used as control and dilution water. The water had a hardness of 37.5 +/- 0.71 mg/l as CaCO<sub>3</sub> and alkalinity of 44.1 +/- 1.93 mg/l as CaCO<sub>3</sub>. The test temperature ranged from 24.2 to 24.8 deg. C. The dissolved oxygen concentration was 5.4-6.8 mg/L; pH was 7.47-7.57. The tank volume was 1.0 l and the loading rate was 2.38 g/l.

The purity of the test material was verified daily by gas-liquid chromatography. Nominal (average measured) concentrations were 0 (<0) mg/l, 10.0 (5.64) mg/l, 15.4 (9.33) mg/l, 23.7 (11.7) mg/l, 36.4 (22.1) mg/l, and 56.0 (34.8) mg/l.

The 96-h EC/LC50 and 95 % confidence limits were calculated based on measured data using the Trimmed Spearman-Kärber method (Hamilton et al. 1977).

Result: There was no mortality in the control group or the 10.0 and 15.4 mg/l test concentrations. 13 of 20 fish in the 23.7 mg/l concentration died within 72 hours. All fish in the 36.4 and 56.0 mg/l test concentrations died within 48 hours. Flocculent material in the tanks may have contributed to the decrease in dissolved oxygen. Authors note that affected fish lost schooling behavior, were under-reactive to external stimuli, and lost equilibrium prior to death. 96 hr LC50 (95% confidence limits) = 12.4 (11.3-13.6) mg/l.

Reliability: score = 1, valid without restriction; comparable to guideline study

Reference: Geiger, D.L., Northcott, C.E., Call, D.J., and Brooke, L.T. (Eds). 1985. Acute Toxicities of Organic Chemicals to Fathead Minnows (*Pimephales promelas*). Volume II. Center for Lake Superior Environmental Studies. University of Wisconsin-Superior. ISBN 0-964968-1-9.

(c) Type: flow through  
 Species: *Pimephales promelas* (fathead minnow)  
 Unit: mg/l  
 Exposure Period: 96 hour  
 EC50: 13.4  
 LC50: 13.4  
 Analyt. Monitoring: yes  
 Method other: USEPA  
 GLP: no data  
 Test substance: n-valeraldehyde (CAS No. 110-62-3), purity 99% (Aldrich)  
 Remark: Fathead minnows used in the tests were cultured from brood stock provided by the USEPA Environmental Research Laboratory-Duluth. Adults were maintained in a flow-through system at 25 deg. C with a 16-h light/dark photoperiod. Organisms were fed frozen adult brine shrimp (*Artemia* sp.) Fry were fed freshly hatched brine shrimp nauplii three times daily until 24-h before test initiation.

The test was initiated using 20 organisms (28-d old; 18.8 mm in length) randomly distributed in each of five test concentrations and an untreated control. Dechlorinated tap water or Lake Superior water was used as control and dilution water. The purity of the test

	<p>material was verified by gas-liquid chromatography. Nominal (average corrected measured) concentrations were 0 (0) mg/l, 12.0 (7.30) mg/l, 18.4 (10.9) mg/l, 28.3 (17.2) mg/l, 43.6 (27.2) mg/l, and 67.1 (43.8) mg/l.</p> <p>Test concentrations were measured daily. The test temperature averaged 24.1±0.31 deg. C. The dissolved oxygen concentration averaged 6.9±0.29 mg/L; pH averaged 7.48 ± 0.07 SU. Hardness and alkalinity averaged 45.3±0.50 and 49.6 ± 0.48 mg/L as CaCO<sub>3</sub>, respectively.</p>
Remark:	<p>The 96-h EC/LC50 and 95 % confidence limits were calculated based on measured data using the Trimmed Spearman-Kärber method (Hamilton et al. 1977).</p> <p>There was no control mortality, except at 48 hours in one tank. Mortalities were attributed to residual soap left in the cleaned tank. Authors note that affected fish lost schooling behavior, swam near the tank bottom and had increased respiration.</p>
Reliability:	96-h EC50/LC50 and 95 % CL = 13.4 (12.8 - 14.0) mg/L
Reference:	<p>score = 1, valid without restriction; comparable to guideline study Geiger, D.L., Poirier, S.H., Brooke, L.T., Call, D.J. (Eds.). 1986. Acute Toxicities of Organic Chemicals to Fathead Minnows (<i>Pimephales promelas</i>). Vol. III. Center for Lake Superior Environmental Studies, University of Wisconsin-Superior.</p>
(d) Type:	static
Species:	<i>Pimephales promelas</i> (fathead minnow)
Unit:	mg/l
Exposure Period:	96 hour
NOEC:	21.6
LC50:	42
Analyt. Monitoring:	no data
Method other:	<p>Test conducted according to U.S. EPA Methods or Measuring the Acute Toxicity of Effluents to Freshwater and Marine Organisms, EPA/600/4-85/013, dated March 1985. and Annual Book of ASTM Standards, Water and Environmental Technology, Volume 111.04, 1990.</p> <p>The test was initiated using 20 fathead minnows (1.5 to 3.0 cm) per test concentration in a total volume of 0.75 liters. Fish were randomly distributed in each of the test concentrations and an untreated control. Dechlorinated municipal tap water was used as control and dilution water. The water had a hardness of 40 to 60 mg/l as CaCO<sub>3</sub> and a pH very close to 7.0. Temperature, fish survival, pH and dissolved oxygen levels were monitored during the 96-hr test interval. Minimal aeration was supplied when dissolved oxygen levels approached 4 mg/l.</p>
Year:	1992
GLP:	no data
Test substance:	n-valeraldehyde (CAS No. 110-62-3), purity not specified
Reliability:	score = 2, valid with restriction
Reference:	<p>Union Carbide Chemicals and Plastics Company, Inc. 1993. Ecological Fate and Effects Testing of UCC&amp;P Products and Wastewaters During 1992. File Report No. 39860, dated February 12, 1992.</p>

- (e) Type: semi-static  
 Species: *Poecilia reticulata* (guppy, fresh water fish)  
 Exposure period: 14 day  
 Unit: mg/l  
 Anal monitoring: yes  
 LC50: 13.04  
 Method: Semi-static (daily renewal) test. Tests were conducted in 1.5 liter glass vessels which contained 1.4 liters of solution. Containers were covered with glass lids. At least five concentrations, geometrically increasing by a factor of 1.8 were tested. Test solutions were renewed daily. Ten fish (2-3 months old) were laboratory-reared and acclimated to control test water for at least 12 days prior to testing. Control fish were exposed to the carrier solvent, acetone at a concentration of 72 ul/L. Temperature was maintained at 21-23 degree C, with a photoperiod of 12 hours light/12 hours dark. Oxygen content, pH, and test compound concentrations were determined four times immediately before, and four times immediately after renewal of the test solutions. Test material concentrations in water were determined by a gas chromatograph equipped with a flame ionization detector. Recovery factors were calculated as the geometric mean of concentrations found immediately before and after renewal of solutions. The LC50 was calculated by logit transformation, based on the nominal concentration of test material. The resulting LC50 was then corrected for loss of compound through evaporation, by multiplication with its recovery factor determined by gas chromatography.
- Year: 1988  
 GLP: no data  
 Test substance: valeraldehyde, purity not specified  
 Result: Toxicity results were reported as log LC50 in umoles/L. The 14-day LC50 = 13.04 mg/l (Log LC50 = 2.18 umol/l)  
 Remark: Propionaldehyde, butyraldehyde, isobutyraldehyde, isovaleraldehyde, hexaldehyde and heptaldehyde were also tested using the same protocol and test conditions. LC50 values for these materials are presented in the table below. These data indicate that the alkyl aldehydes exhibit similar toxicity in this assay, with a slight decrease in toxicity as chain length increases.

14-day toxicity in guppies

Aldehyde	Log LC50*	LC 50**
Propionaldehyde	2.41	14.9
Butyraldehyde	2.28	13.7
Valeraldehyde	2.18	13.0
Hexaldehyde	1.99	9.79
Heptaldehyde	1.89	8.85
Isobutyraldehyde	2.57	26.75
Isovaleraldehyde	2.19	13.3

\*14-day LC50 in umoles/l

\*\*14-day LC50 in mg/l

- Reliability: Score = 2; valid with restriction, test material purity not specified  
 Reference: Deener, J.W., Seinen, W. and Hermens, J.L.M. 1988. The acute toxicity of aldehydes to the guppy. *Aquatic Toxicol.* 12: 185-192.

(f)	Type:	semi-static (test solution changed every 24 hours)
	Test:	LC50
	Species:	<i>Oryzias latipes</i> , Japanese Medaka
	Unit:	mg/L
	Exposure Period:	96 hours
	LC50:	13.2
	NOEC:	2.8
	Test substance:	n-valeraldehyde, purity $\geq 97.0\%$
	Analyt Monitoring.:	yes
	Year:	1992
	GLP:	yes
	Methods:	OECD Guideline for Testing of Chemicals No.203, Fish Acute Toxicity Test, adopted 7/17/92

Japanese Medaka, *Oryzias latipe*, were obtained from the Rokuotsu Fishery. All fish were reared and acclimated for 12 or more days under a 16-hour light/8-hour dark transitional photoperiod. Fish were fed a commercial food (TetraMin). Fish were acclimated to  $24 \pm 1$  °C and held without food for at least 24 hours prior to testing.

Nagoya municipal tap water was used as dilution water after it was dechlorinated by passage through activated carbon. The dilution water had a hardness of 30.0 mg/L (converted to CaCO<sub>3</sub>), and a pH of 6.9. Electrical conductivity was 0.97 mS/m.

Fish averaging 2.02 (1.77-2.47) cm, and weighing 0.1282 (0.0818-0.2361) g, were used as test organisms. Definitive testing was conducted in glass beakers with a volume of 3.0 L which were positioned in an isothermal water tank and provided a 16-hr light/8-hr dark transitional photoperiod during testing. Temperature, pH, and dissolved oxygen were monitored once each day during the 96-hour exposure interval and recorded for each vessel. Ten fish (one replicates of 10 fish) were exposed to each nominal concentration of valeraldehyde. Fish were not fed during the test. Fish were observed for mortality, and physical and behavioral effects throughout the exposure interval. Dead fish were removed when observed.

Because valeraldehyde does not dissolve readily in waer, hardened castor oil (HCO-50) was used as a dispersion adjuvant. The test substance was dissolved in HCO-50 which was then filtered-sterilized to make the original test solution. Each test solution was prepared by adding the original test solution to dilution water. Valeraldehyde test concentrations were selected based on a preliminary range-finding test which determined, at 96-hr that 50% mortality occurred at a nominal concentration of 55 mg/L and 0% mortality occurred at 25 mg/L. Based on results, the target or nominal concentrations selected for the definitive test were 9.5, 17.1, 30.9, 55.6, and 100 mg valeraldehyde/L. One control vessel contained dilution water with no other additions. An dispersant adjuvant control contained dilution water plus 100 mg/L HCO-50. Ten fish were exposed to each test concentration plus water controls. Test and control solutions were replenished every 24 hours. Test solutions were sampled when freshly prepared (0 hr), and again at the end of the 24-hr exposure interval at the beginning of the test (day 0), and at 24, 48, and 96 hours. Analysis of the test solutions demonstrated that the nominal test concentrations of 9.5, 17.1, 30.9, 55.6, and 100 mg/L were significantly decreased, even in the freshly prepared solutions. The test



substance concentrations of in freshly prepared solutions ranged between 3.8 to 68.8 mg/L, while the test substance concentration in 24-hr old solutions ranged between 2.0 and 57.8 mg/L.

Test solutions from each vessel were sampled for analytical confirmation using an a gas chromatograph equipped with a flame ionization detector (FID). The original standard solution was diluted and the standard solution was measured at 5 points, beginning at the limit of detection and including predicted measurement concentrations. Linearity was confirmed. One point on the standard curve was analyzed every measurement day. The GC/FID instrumentation exhibited a linear response over the calibration range of 2.0 to 100 mg valeraldehyde/L.

Statistical analysis: Death rates (%) were calculated from the number of deaths and the number of fish (10) used in each concentration group. The LC50 and 95% confidence limits were calculated by the binomial method, using the ToxDat Multi-Method Program developed by the U.S.EPA.

Results:

Analysis of test solutions for valeraldehyde demonstrated that concentrations in freshly prepared solutions ranged from 40 to 68.8% of target nominal values; analysis of test solutions after 24 hours yielded percent of nominal values ranging from 17 to 57.8%. The geometric mean measured concentrations for each test concentration were calculated by averaging the measured concentrations in freshly prepared and 24-hour old solutions (see table below).

**Results of Analysis of Test Solutions for Valeraldehyde**

Target Concentration (mg/L)	0-Hour Solution Concentration* (mg/L)	24-Hour Solution Concentration* (mg/L)	Mean Measured Concentration <sup>1</sup> (mg/L)
Control	<2.0 <sup>2</sup>	<2.0	-
Adjuvant Control	<2.0	<2.0	-
9.5	3.8	2.0	2.8
17.1	8.3	2.9	4.9
30.9	16.6	10.5	13.2
56.6	36.2	26.9	30.8
100.0	68.8	57.8	63.1

\*Average of 4 replicate test solutions

1: Mean measured concentration = mean of 0-hour and 24-hour concentration values

2: analytical detection limit for valeraldehyde

pH values in test solutions during the test interval ranged between 6.5 and 6.9. The dissolved oxygen concentrations during the test interval were in the range of 5.1 to 11.2 mg/L; dissolved oxygen levels were 60% or greater in all test vessels during the study (saturated dissolved oxygen concentration at 24°C = 8.25 mg/L). The water temperatures in test vessels ranged between 23.4 and 23.9 °C.

There was 100% and 90% mortality observed at 24 hours at the two highest valderaldehyde concentrations, 63.1 and 30.8 mg/L, respectively. Mortality at 13.2 mg/L was observed at 72 and 96 hours. Signs of toxicity, including abnormal respiration, abnormal swimming behavior, and inability to swim were observed at 13.2 and 30.8 mg/L. No signs of toxicity or abnormal

behavior were observed at other test concentrations (2.8 and 4.9 mg/L) or in the control groups (see table below).

Biological Response to n-Valeraldehyde Exposure in Fish

Mean Measured Concentration (mg/L)	Biological Resonse Observed			
	24 hours	48 hours	72 hours	96 hours
-	10N	10N	10N	10N
-	10N	10N	10N	10N
2.8	10N	10N	10N	10N
4.9	10N	10N	10N	10N
13.2	6R, 4N	6R, 2S, 2N	2R, 2S, 2E, 3D	2R, 2S, 1E, 5D
30.8	1R, 9D	1E, 9D	10D	10D
63.1	10D	10D	10D	10D

( ) = number of fish; N = normal; R = abnormal respiration; S = abnormal swimming behavior; D = dead; E = loss of equilibrium or swimming ability

Based on these results, the NOEC for this study was empirically determined as the concentration immediately below the region of uncertainty (4.9 mg/L), which results in a conservative (lowest value) estimation of the NOEC at 2.8 mg/L.

The 24-hour LC<sub>50</sub> value for valeraldehyde was calculated using the binomial method, and was determined to be 22.0 mg/L with a 95% confidence interval of 13.2 to 30.8 mg/L.

The 48-hour LC<sub>50</sub> value, calculated using the binomial method, was 22.0 mg/L with a 95% confidence interval of 13.2 to 30.8 mg/L.

The 72-hour LC<sub>50</sub> value, calculated using the binomial method, was 16.0 mg/L with a 95% confidence interval of 4.9 to 30.8 mg/L.

The 96-hour LC<sub>50</sub> value, calculated using the binomial method, was 13.2 mg/L with a 95% confidence interval of 4.9 to 30.8 mg/L.

Reliability: score = 2, valid with restrictions. GLP guideline study which lacks detailed documentation

Reference: Ministry of the Environment (MOE). 1999c. Study of the acute toxicity of valeric aldehyde to Japanese Madaka (*Oryzias latipes*). Study number NMMP/E98/4050. Toray Research Center, Nagoya Laboratory, Japan

- (g) Type: Model calculation  
 Value: 11.302 mg/L  
 Test substance: n-valeraldehyde  
 Method: ECOSAR v. 0.99g  
 Remark: An acute fish 96-hr LC<sub>50</sub> was calculated using the USEPA ECOSAR. The SAR for neutral organics was used. The structure was determined from the CAS RN as stored in the accompanying database of SMILES notations within ECOSAR.  
 Reliability: score = 2, valid with restriction; accepted calculation method.

Reference: ECOSAR Model Version 0.99g. EPIWIN (Estimation Program Interface for Windows), Version 3.10. U.S. Environmental Protection Agency, 2000.

## 4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

### A. *Daphnia*

(a) Preferred result reliability score = 1, valid without restriction; GLP guideline study  
 Type: static  
 Test: EC50 (immobilization)  
 Species: *Daphnia magna* Straus, freshwater invertebrate  
 Unit: mg/L  
 Exposure Period: 48 hours  
 EC50: 70.7  
 NOEC: 25.0  
 Test substance: Valeraldehyde, purity 99.6%  
 Analyt Monitoring.: yes  
 Year: 1992  
 GLP: yes  
 Methods: OECD Guideline 202, *Daphnia sp.*, Acute Immobilization Test, Part 1. 4 April 1984.  
 Annex to Commission Directive 92/69/EEC. C.2 Acute Toxicity Test for *Daphnia* Vol. 35. 29 December 1992.  
 EC Directive 91/414 Annex I 8.2.5  
 USEPA TSCA Test Guidelines 40CFR797.1300 *Daphnid* Acute Toxicity Test. 07/01/92 Edition.

The test organism, *Daphnia magna* Straus, was originally obtained from New England Bioassay, Inc. Of Manchester, CT. *Daphnid* instars less than 24 hours old from laboratory-reared cultures were used as the test organism. *Daphnid* cultures were maintained under illumination (cool-white fluorescent, 2050 ± 350 lux) on a 16-hour light/8-hour dark photoperiod at a temperature of 20 ± 2 °C. *Daphnia* were fed a mixed diet of algae (*Selenastrum capricornutum*) and YCT (yeast-ceraphyll trout) trout chow five times per week. First instar *daphnids* (< 24-hr old) were separated from adults and older instars on the day of testing by gentle screening through a nylon mesh and metal sieve.

Laboratory water was obtained from the upper Saginaw Bay of Lake Huron; before use, water was sand-filtered, pH-adjusted with carbon dioxide, carbon-filtered, and UV-irradiated. *Daphnid* dilution water (referred to as ALDW or adjusted laboratory dilution water) was prepared by adjusting laboratory water to a hardness of about 170 mg/L (as CaCO<sub>3</sub>) before autoclaving at 250 °F (121 °C) and 18 psi for 30 minutes. DDW was cooled, then aerated for approximately 24 hours before use. Water quality parameters of ALDW were as follows:

Hardness (mg CaCO <sub>3</sub> /L):	166
Alkalinity (mg CaCO <sub>3</sub> /L):	36
Conductivity (umhos/cm):	418
Residual chlorine:	<10 ppb

Definitive testing was conducted in 250 ml covered glass beakers with a test solution volume of 200 ml. Test vessels were placed in an incubator thermostated at  $20 \pm 1$  °C. Temperature, pH, and dissolved oxygen were monitored and recorded for each bulk solution on Day 0 and for all spent test solutions on Day 2 (48 hours). Daphnids were not fed during the test. Daphnids were observed for immobility (inability to swim within 15 seconds after gentle agitation of the test container) after 24 and 48 hours of exposure.

n-Valeraldehyde nominal test concentrations were selected based on a 48-hour static probe study; the test material was considered to be unstable in aqueous solutions, therefore the range-finding test was conducted under static-renewal conditions (renewal of test solutions after 24 hours). Replicates of 10 *Daphnia* per dose level were exposed to nominal n-valeraldehyde concentrations of 0 (water control), 10, 50, 100, 250, 500, and 1000 mg/L. There was 100% daphnid immobility at 250 through 1000 mg/L after 48 hours exposure. Immobility was 80% and 50% at dose levels of 100 and 50 mg/L, respectively. No immobility was observed in the water control or at 10 mg/L valeraldehyde. The definitive test was also performed under static-renewal conditions; test solutions were replaced after 24 hours.

In the definitive study, twenty *Daphnia* (10 per replicate; two replicates per dose level) were exposed to nominal test concentrations of n-valeraldehyde at 6.25, 12.5, 25.0, 50.0, 100, and 200 mg/L plus a water control. These nominal target concentrations were equivalent to mean measured concentrations of 6.39, 13.7, 27.3, 49.0, 113, and 211 mg n-valeraldehyde/L, respectively. Bulk test solutions were prepared at test initiation and renewed approximately 24 hours. Initial bulk solutions were prepared by direct addition of the test substance to daphnid dilution water without pH adjustment and then apportioned between two replicate test vessels per dose. At test initiation (Day 0), daphnids were added to each test vessel within 30 minutes of solution preparation and initial test solution sampling. After 24 hours (Day 1), fresh solutions were prepared and daphnids were transferred, via pipette, to freshly prepared solutions of the same test concentration.

Test solutions were sampled for analytical confirmation of n-valeraldehyde concentrations on Day 0 (bulk dose solutions), Day 1 (bulk dose solutions and replicate spent solutions), and Day 2 (replicate spent solutions) of the study. Samples were analyzed by HPLC/UV analysis using an Agilent HP1100 Gradient HPLC System YMC ODS-AQ analytical column (standard preparation, detector calibration, instrument conditions for HPLC/UV analysis described in detail in report).

Statistical analysis: Based on the biological response observed in the study, the USEPA Trimmed Spearman-Kärber Program, Version 1.5 was used to calculate the 24-hour EC50 values and corresponding 95% confidence intervals. The USEPA Probit Program Version 1.5 was used to calculate the 48-hour EC50 values

and corresponding confidence intervals. The 48-hour NOEC was determined based on biological interpretation of the data and the highest exposure level exhibiting no *Daphnia* immobility.

Results: Day 0 analysis of bulk test solutions for n-valeraldehyde demonstrated that dose solutions ranged from 143% to 152% of target nominal values; the average % of target for day 0 solutions was  $148 \pm 3.14\%$ . Similarly, measured concentrations from Day 1 renewal solutions ranged from 147 to 166%, with an average % of target of  $158 \pm 6.83\%$ . Analysis of spent test solutions yielded percent of nominal values ranging from 49 to 78% for Day 1 solutions, and 45-73% for Day 2 solutions.

Results of Analysis of Test Solutions for n-Valeraldehyde

Target Concentration (mg/L)	Valeraldehyde Measured Concentration (mg/L) in Fresh and Spent Solutions				Mean Measured Concentration (mg/L) <sup>1</sup>
	Day 0 Fresh	Day 1 Renewal	Day 1 Spent	Day 2 Spent	
Control	<LLQ <sup>2</sup>	<LLQ	<LLQ	<LLQ	<LLQ
6.25	9.14	9.16	3.57	3.70	6.39
12.5	18.5	19.3	7.96	9.17	13.7
25.0	37.9	40.4	14.5	16.3	11.97
50.0	71.7	77.4	24.7	22.3	49.0
100	147	161	78.0	66.4	113
200	299	332	123	NT	211

1: Mean measured concentration = mean of day 0, day 1 spent, day 1 renewal,

and day 2 spent concentration values for all dose levels except 200 mg/L

2: less than Lowest Level Quantified: 0.505 mg n-valeraldehyde/L ALDW

3: Not Tested; no Day 2 test solution due to complete mortality by Day 1.

Mean measured concentrations were calculated for all dose levels by averaging the Day 0, Day 1 spent, Day 1 renewal, and Day 2 spent concentrations (see table above).

Based on the mean measured concentrations, the average percent of target values ranged from 98 to 113%; the overall average percent of target and standard deviation values calculated across all dose levels for the entire study was  $106 \pm 5.54\%$ . pH values measured during the test ranged from 7.3 to 7.7 ( $7.5 \pm 0.1$ ). Temperature during the test was between 20.0 and 21.0 ( $20.6 \pm 0.3$ ) °C; light intensity 1729-2550 ( $2098 \pm 321$ ) lux. Dissolved oxygen was between 7.1-9.2 ( $8.5 \pm 0.8$ ) mg/L. Percent oxygen saturation averaged 96% and remained greater than 80% throughout the exposure interval, based on a theoretical oxygen saturation value of 8.9 mg/L.

Observations were made for immobility in response to exposure to n-valeraldehyde. At 24 hours, 100% immobility (20/20) was observed in *Daphnia* exposed to the highest nominal dose of 200 mg/L; 60% (12/20) of *Daphnia* exposed to 100 mg/L were immobilized. At 48 hours, immobility was observed in 75% (15/20),

and 25% (5/20) of exposed daphnids at the nominal test concentration of 100 and 50 mg/L, respectively (see table below).

Biological Response to n-Valeraldehyde Exposure

Target Concentration (mg/L)	Valeraldehyde Concentration (mg/L) <sup>1</sup>	Biological Response Observed	
		24 hours	48 hours
Control	<LLQ	20N	19N <sup>4</sup>
6.25	6.39	20N	19N <sup>4</sup>
12.5	13.7	20N	20N
25.0	11.97	20N	20N
50.0	49.0	20N	15N, 5I
100	113	8N, 12I	5N, 15I
200	211	20I <sup>3</sup>	20I <sup>3</sup>

N = normal; I = immobile.

1: Mean measured concentration

2: Less than Lowest Level Quantified: 0.505 mg/L

3: 100% immobilization/mortality observed on Day 1

4: One daphnid accidentally killed in control and 6.25 mg/L dose levels during transfer of daphnids during test solution renewal. These daphnids not used in statistical evaluation of 48-hour data.

Chemical analysis of bulk test solutions exhibited high average percent recovery of target values and resulted in study average percent of target values ranging from 98.0 to 113% (overall average percent recovery for the entire study (n=6) was 106 ± 5.54%). Therefore, to provide lower, more conservative LC50 and NOEC values for this study, the biological data were statistically evaluated using nominal concentrations instead of mean measured concentrations.

The 24-hour EC50 value was 93.3 mg/L, with a 95% confidence interval of 80.2-93.3 mg/L; the Spearman Karber trim was 0.0%.

The 48-hour EC50 was 70.7 mg/L, with a 95% confidence interval of 58.3-85.7 mg/L; the Probit slope was 5.3 with a 95% confidence interval of 3.3-7.3.

The 48-hour NOEC was 25.0 mg/L and was determined based on biological interpretation of the data and the highest exposure level exhibiting no *Daphnia* immobility.

Reference:

Marino, T.A, McClymont, E.L, and Yaroeh, A.M.. 2003b. n-Valeraldehyde: An Acute Toxicity Study with the Daphnid, *Daphnia magna* Straus (unpublished study). Toxicology & Environmental Research and Consulting, Study ID 031103. The Dow Chemical Company, Midland, MI.

(b) Test substance: valeraldehyde  
Type: Static  
Species: *Daphnia magna* Straus  
Unit: mg/l

<p>Exposure Period: NOEC: EC0: EC50: EC100: Analyt. Monitoring: Method other:</p>	<p>48 hours  100 – 500 &gt;500 none Test conducted according to U.S. EPA Methods for Measuring the Acute Toxicity of Effluents to Freshwater and Marine Organisms, EPA/600/4-85/013, dated March 1985. and Annual Book of ASTM Standards, Water and Environmental Technology, Volume 111.04, 1990.</p>
	<p>First-instar <i>Daphnia</i> neonates (less than 24 hr old) were obtained from a laboratory-culture initially derived from the USEPA laboratory in Duluty, MN. The culture is maintained at 19-23 degree C. Groups of five daphnids were exposed in 125 ml containers, each containing 100 ml of the test solution. Aged dechlorinated tap water, aerated to saturation before use, was used to prepare all test and control solutions.</p>
	<p>The following analyses were obtained: total hardness: 40-60 mg/l as CaCO<sub>3</sub> total alkalinity: 20-38 mg/l as CaCO<sub>3</sub> pH: 7.0 –7.2 conductivity: 100-200 umhos/cm Dissolved oxygen and pH were determined initially and at 48 hours for all test concentrations and controls. Mortality or immobilization data were recorded at 24 and 48 hr.</p>
<p>GLP: Remark:</p>	<p>no Test was conducted at 19-23 degrees C, daphnids were fed daily with a 50:50 mixture of 1) concentrated suspensions of green algae from a laboratory culture and 2) pulverized Purina trout chow, baker's yeast, and alfalfa flour suspended in aged tap water.</p>
<p>Test Substance: Reliability: Reference:</p>	<p>n-valeraldehyde (CAS No. 110-62-3), purity not specified. score = 2, valid with restrictions Union Carbide Chemicals and Plastics Company Inc. 1993. Ecological Fate and Effects Testing of UCC&amp;P Products and Wastewaters During 1992. File Report No. 39860, dated February 12, 1993.</p>
<p>(c) Type: Test: Species: Unit: Exposure Period: EC50: NOEC: Test substance: Analyt Monitoring.: Year: GLP: Methods:</p>	<p>semi-static (test solution changed every 24 hours) EC50 (immobilization) <i>Daphnia magna</i> Straus, freshwater invertebrate mg/L 48 hours 31.5 20.6 n-valeraldehyde, purity ≥ 97.0% yes 1984 yes OECD Guideline for Testing of Chemicals No. 202, <i>Daphnia sp.</i>, Acute Swimming Inhibition and Propagation Tests on Water Fleas, 1984.</p>

The test organism, *Daphnia magna* Straus, was originally obtained from National Institute for Environmental Studies and subsequent generations were raised at the test facility. Daphnid instars less than 24 hours old from laboratory-reared cultures were used as the test organism. Daphnid cultures were maintained under room on a 16-hour light/8-hour dark photoperiod at a temperature of  $20 \pm 1$  °C. Daphnids were fed a diet of freshwater green algae (*Chorella regularis*). First instar daphnids (< 24-hr old) were separated from adults and older instars on the day of testing. Dilution water was Elendt M4 as described in Annex 2 of the OECD Revised Guidelines No. 211. The hardness of the dilution water was 224 (converted to mg CaCO<sub>3</sub>/L), and the pH was 7.3.

Definitive testing was conducted in glass beakers with a test solution volume of 100 ml. An additional vessels with no test material added were used as water control as was an adjuvant control with 100 mg/L HCO-50. Test vessels were placed in a isothermal tank maintained at water temperature of  $20 \pm 1$  °C. Daphnids were not fed during the test. Daphnids were observed for immobility (inability to swim within 15 seconds after gentle agitation of the test container) after 24 and 48 hours of exposure. Daphnids that crawled the bottom of the test vessel were included in the inhibited category.

Because valeraldehyde does not dissolve readily in water, hardened castor oil (HCO-50) was used as a dispersion adjuvant. The test substance was dissolved in HCO-50 which was then filtered-sterilized to make the original test solution. Each test solution was prepared by adding the original test solution to dilution water.

Valeraldehyde nominal test concentrations for the definitive test were selected based on a 48-hour static probe study. In the definitive test, twenty *Daphnia* (5 per replicate; four replicates per dose level) were exposed to nominal test concentrations of valeraldehyde of 15.9, 28.6, 51.4, 92.6, 166.7, and 300.0 mg/L plus controls. Test solutions were freshly prepared at 0 hr, and then replenished after 24 hours. Test solution concentrations were measured for freshly prepared solutions and after the 24 hr exposure interval. Analysis of the test solutions demonstrated that the nominal test concentrations of 15.9, 28.6, 51.4, 92.6, 166.7, and 300.0 mg/L were significantly decreased, even in the freshly prepared solutions. The mean measured concentrations of freshly prepared solutions were 2.1, 10.1, 25.2, 54.4, 79.3, and 195.6 mg valeraldehyde/L; the mean measured concentrations of the test solutions after the 24 hour exposure interval were <2.0, 2.2, 16.9, 42.6, 81.9, and 160.3 mg/L. The geometric mean measured concentrations of the test solutions were <2.0, 4.7, 20.6, 48.2, 80.6, and 177.1 mg/L. Test solutions from each vessel were sampled for analytical confirmation using an a gas chromatograph equipped with a flame ionization detector (FID). The original standard solution was diluted and the standard solution was measured at 5 points, beginning at the limit of detection and including predicted measurement concentrations. Linearity was confirmed. One point on the standard curve was analyzed every measurement day. The GC/FID instrumentation exhibited a linear response over the calibration range of 2.0 to 100 mg valeraldehyde/L.

Statistical analysis: The 24- and 48-hr 50% inhibition concentrations (EC50) were calculated by the Toxdat Multi-Method Program Binomial methodology developed by the U.S.EPA. The 95% confidence limits were



also calculated. The NOEC was determined based on biological interpretation of the data and the highest exposure level exhibiting no *Daphnia* immobility.

Results: pH values ranged from 7.0 to 7.6. Temperature during the test ranged between 19.6 and 19.9 °C; light intensity 739-950 lux. Dissolved oxygen was between 7.9-8.9 mg/L (89-100% oxygen saturation).

Analysis of freshly prepared test solutions (0-hour) for valeraldehyde demonstrated that mean measured dose solutions ranged from 13.2% to 65.2% of target nominal values. Analysis of test solutions after 24 hours yielded percent of nominal values ranging from 7.7 to 53.4%. Geometric mean measured concentrations were calculated for all dose levels by averaging the all 0-hour concentrations and all 24-hour solution concentrations (see table below).

#### Results of Analysis of Test Solutions for Valeraldehyde

Target Concentration (mg/L)	0-Hour Solution Concentrations* (mg/L)	24-Hour Solution Concentrations* (mg/L)	Mean Measured Concentrations <sup>1</sup> (mg/L)
Control	<2.0 <sup>2</sup>	<2.0	-
15.9	2.1	<2.0	<2.0
28.6	10.1	2.2	4.7
51.4	25.2	16.9	20.6
92.6	54.5	42.6	48.2
166.7	79.3	81.9	80.6
300.0	195.6	160.3	177.1

\*Average of eight replicate test solutions

1: Mean measured concentration = mean of 0-hour and 24-hour concentration values

2: analytical detection limit for valeraldehyde

Observations were made for immobility in response to exposure to n-valeraldehyde. At 24 and 48 hours, no immobility was observed at the three lowest test concentrations or in the water control. There was an increase in immobility at higher concentrations (see table below); at 48 hours, there was 100% immobility at the three highest test concentrations.

#### Biological Response to n-Valeraldehyde Exposure

Target Concentration (mg/L)	Mean Measured Concentration <sup>1</sup> (mg/L)	Biological Response Number Immobilized (Percent of total exposed)	
		24 hours	48 hours
Control	<2.0	0	0
15.9	<2.0	0	0
28.6	4.7	0	0
51.4	20.6	0	0
92.6	48.2	16 (80)	20 (100)
166.7	80.6	20 (100)	20 (100)
300.0	177.1	20 (100)	20 (100)

1: Mean measured concentration = mean of 0-hour and 24-hour concentration values

2: analytical detection limit for valeraldehyde

Based mean measured n-valeraldehyde concentrations:

		The 24-hour EC50 value, calculated by the Binomial method, was 37.0 mg/L, with a 95% confidence interval of 20.6 to 48.2 mg/L. The 48-hour EC50 value, calculated by the Binomial method, was 31.5 mg/L, with a 95% confidence interval of 20.6 to 48.2 mg/L. The 24- and 48-hour NOEC value was 20.6 mg/L and was determined based on the highest exposure level exhibiting no daphnid immobility or change in behavior or appearance.
Reliability:		score = 2, valid with restrictions. GLP guideline study which lacks detailed documentation
Reference:		Ministry of the Environment (MOE). 1999a. Study of the acute swimming inhibition of water fleas ( <i>Daphnia magna</i> ) by valeric aldehyde. Study number NMMP/E98/2050. Toray Research Center, Nagoya Laboratory, Japan
(d)	Type:	Model calculation
	Value:	10.927 mg/L
	Test substance:	n-valeraldehyde
	Method:	ECOSAR v. 0.99g
	Remark:	An acute fish 96-hr LC50 was calculated using the USEPA ECOSAR. The SAR for neutral organics was used. The structure was determined from the CAS RN as stored in the accompanying database of SMILES notations within ECOSAR.
	Reliability:	score = 2, valid with restriction; accepted calculation method.
	Reference:	ECOSAR Model Version 0.99g. EPIWIN (Estimation Program Interface for Windows), Version 3.10. U.S. Environmental Protection Agency, 2000.

**B. Other**

No data available.

**4.3 TOXICITY TO AQUATIC PLANTS e.g. Algae**

(a)	Preferred result	reliability = 1, valid without restrictions
	Type:	static
	Test:	EC50, growth inhibition
	Species:	<i>Pseudokirchneriella subcapitata</i> (formerly known as <i>Selenastrum capricornutum</i> ), freshwater green algae
	Unit:	mg/L
	Exposure Period:	96 hours
	EC0:	
	EC50:	37.1
	NOEC:	18.8
	Test substance:	n-valeraldehyde (CAS No. 110-62-3), purity 99.6%
	Analyt Monitoring.:	yes
	Year:	1992
	GLP:	yes
	Method:	OECD Guideline 201, Algal Growth Inhibition Test EEC Directive 92/69/EEC, C.3 Algal Inhibition Test USEPA Algal Acute Toxicity Test 40CFR797.150/revision of TSCA guidelines Federal Register Vol 50 No.188.

The green alga *Pseudokirchneriella subcapitata* (formerly known as *Selenastrum capricornutum*) was maintained in the laboratory and originated from the University of Toronto Algal Collection, Toronto,

Ontario, Canada. Cultures were maintained in algal assay medium (AAM) designed by Miller et al. for the EPA Algal Assay Bottle Test (EPA-600/9-78-018.5) in flasks under continuous cool-white fluorescent illumination of  $7509 \pm 435$  lux at  $24.8 \pm 0.1^\circ\text{C}$  and continuously shaken at 100 oscillations per minute.

Algal assay medium (AAM) was prepared by adding requisite amounts of each of the macro- and micro-nutrients into de-ionized water. Test media was pH adjusted to  $7.5 \pm 0.1$  and stored in the dark at approximately  $4^\circ\text{C}$  prior to use. AAM was used for toxicity tests and maintenance of algal stock cultures.

Test solutions were prepared by direct addition of the test substance to the test medium without pH adjustment. Nominal concentrations of 0, 7.81, 15.6, 31.3, 62.5, 125, 250, and 500 mg/L were selected based on a range-finding test. In the range-finding assay, the percent decrease in cell density across test concentrations (0.10 to 1000 mg/L) was -8 to 98% (negative percent indicates stimulation of growth).

Test vessels were sterilized 250-mL Erlenmeyer flasks fitted with Shimadzu closures, each containing 100 ml assay medium. Three replicate flasks were prepared for each concentration; an additional flask was not inoculated with algae and served as a control blank. At test initiation and termination, the pH was measured for each test concentration and control blank replicates. Each flask (except the fourth control blank flask) was inoculated with 0.71 mL of the algae containing approximately  $1.0 \text{ E}+6$  cells/mL, resulting in an initial cell density of approximately  $1.0 \text{ E}+4$  cells/mL. Flasks were placed in an environmental chamber and maintained at  $24 \pm 2^\circ\text{C}$  under continuous illumination at  $8000 \pm 1600$  lux and continuously shaken at 100 oscillations/minute. Light intensity was measured daily; temperature was monitored continuously during the test interval.

Algal cell counts were determined by electron particle counting using a Coulter Multisizer 3. Total cell counts were determined at approximately 24, 48, 72, and 96 hours. Three separate cell count reading were made per replicate. At test termination, algal cell morphology was microscopically evaluated at 20x or 40x magnification in a hemacytometer counter chamber.

Samples of the initial test solutions were analyzed for valeraldehyde concentration using Agrilent HP1100 Gradient HPLC equipped with a YMC ODS-AQ 2.0 x 50 mm analytical column. Replicates were analyzed at 96 hours at test termination.

Statistical analysis: study endpoints were evaluated based on the mean measured n-valeraldehyde concentrations and are expressed in terms of algal growth (cells per ml). Endpoints analyzed were cell density, growth rate per day, and biomass (area under the growth curve). EC<sub>50</sub> values for cell density were determined by a least squares linear regression of cell density against the log of the concentration at 72 and 96 hours. The EC<sub>gr</sub>50 value for growth inhibition was calculated by regressing the percent reduction in mean specific growth rate for each dose group compared to the control group against the natural logarithm of the concentrations for the 0-72 hr and 0-96 hr exposure intervals. The EC<sub>bm</sub>50 value for biomass inhibition was calculated by regression of the differences in area under the

growth curves for each dose compared to the control against the log of the concentrations for 72 and 96 hours. Prior to evaluation of NOEC concentrations, data were tested for normality using the Shapiro-Wilk's Test and for homogeneity of variance using the Bartlett's Test. To meet assumptions of normality and/or homogeneity, the 96-hr cell density data, and 72- and 96-hr biomass data were log transformed and the 72-hr cell density data were square root transformed. The raw data for growth rate met the assumptions of normality and homogeneity of variance.

Results: Day 0 analysis of test solutions for n-valeraldehyde demonstrated mean measured test concentrations of 0, 4.26, 8.72, 18.8, 36.3, 75.2, 150, and 234 mg/l n-valeraldehyde. Day 4 (96 hr) test solutions yielded no quantifiable concentrations of valeraldehyde. Mean measured concentrations were calculated for all dose levels by averaging the day 0 concentrations and day 4 exposure solution concentrations. Since day 4 measured concentrations were all less than the lowest level quantified (LLQ = 0.673 mg/L), a value of 0.3365 mg/L (one-half the LLQ) was used in calculations as a conservative estimate of day 4 concentrations (see table below).

Results of Analysis of Test Solutions for n-Valeraldehyde

Target Concentration (mg/L)	Day 0 Solution Concentrations* (mg/L)	Day 4 Solution Concentrations (mg/L)	Mean Measured Concentrations <sup>1</sup> (mg/L)
Control	<LLQ <sup>2</sup>	<LLQ	NA <sup>3</sup>
7.81	8.19	<LLQ	4.26
15.6	17.1	<LLQ	8.72
31.3	37.3	<LLQ	18.8
62.5	72.2	<LLQ	36.3
125	150	<LLQ	75.2
250	300	<LLQ	150
500	467	<LLQ	234

\*Average % of target dose on Day 0: 112 ± 9.93

1: Mean measured concentration = mean of day 0 and day 4 concentration values

2: less than Lowest Level Quantified: 0.656 mg/L

3: Not Applicable

Test solution pH values ranged from 6.0 to 6.7 at test initiation, from 6.5 to 9.5 in replicates with algae at test termination, and from 6.7) to 7.1 in blank control replicates without algae at test termination (see below).

Valeraldehyde (mg/L) <sup>1</sup>	pH values		
	Day 0	Day 4	
		with algae	no algae
<LLQ <sup>2</sup>	6.7	9.5	7.1
4.26	6.7	9.4	7.1
8.72	6.7	9.4	7.1
18.8	6.7	9.4	7.1
36.3	6.7	8.9	7.0
75.2	6.6	7.4	6.9
150	6.4	6.7	6.9
234	6.0	6.5	6.7

1: Mean measured concentration = mean of day 0 and day 4 concentration values

Despite the increase pH, the integrity of the test was deemed unaffected, since the control performance was unaffected.

At 72 and 96 hours, the control had 151.7 E+4 and 359.9 E+4 cells/mL, respectively, indicating an acceptable test. The mean number of cells at 72 and 96 hours ranged from 149 E+4 and 400 E+4 cells/mL, respectively in the measured 4.26 mg/L treatment. At the highest concentration, the mean number of cells at 72 and 96 hours was to 3.01 E+4 and 1.96 E+4 cells/mL, respectively.

Mean Cell Density after 72 and 96 Hours

Valeraldehyde (mg/L) <sup>1</sup>	Mean Cell Density (x104 cells/ml)			
	72 hr	% Inhibit <sup>3</sup>	96 hr	% Inhibit
<LLQ <sup>2</sup>	151.7	NA <sup>4</sup>	395.9	NA
4.26	148.8	2	400.7	-1 <sup>5</sup>
8.72	133.4	12	375.3	5
18.8	133.7	12	369.5	7
36.3	44.01 <sup>^</sup>	71	188.3 <sup>^</sup>	52
75.2	8.376 <sup>^</sup>	94	49.02 <sup>^</sup>	88
150	2.006 <sup>^</sup>	99	4.099 <sup>^</sup>	99
234	3.009 <sup>^</sup>	98	1.955 <sup>^</sup>	100

1: Mean measured concentration = mean of day 0 and day 4 concentration values

2: less than Lowest Level Quantified: 0.673 mg valeraldehyde/L

3: % inhibition relative to control value at 72 or 96 hours

4: Not Applicable

5: negative value indicates growth stimulation

<sup>^</sup>: indicates significant difference from controls;  $p \leq 0.05$  using Dunnett's t-test

The mean biomass (area under the growth curve) values at 72 and 96 hours displayed a similar response as that observed for cell density. For all parameters evaluated, statistical significance ( $p < 0.05$ ) was not observed in the three lowest test concentrations.

Based mean measured n-valeraldehyde concentrations, the 72 hour results were as follows:

72-hr EC<sub>25</sub> = 14.7 mg/L based on cell density

72-hr EC<sub>50</sub> = 32.4 mg/L based on cell density

72-hr EC<sub>b50</sub> = 31.4 mg/L based on biomass (area under the growth curve)

72-hr EC<sub>g50</sub> = 68.7 mg/L based on growth rate per day

72-hr NOEC = 18.8 mg/L for all three criteria

Based mean measured n-valeraldehyde concentrations, the 96 hour results were as follows:

96-hr EC<sub>25</sub> = 21.3 mg/L based on cell density

96-hr EC<sub>50</sub> = 42.2 mg/L based on cell density

96-hr EC<sub>b50</sub> = 37.1 mg/L based on biomass (area under the growth curve)

96-hr EC<sub>g50</sub> = 85.5 mg/L based on growth rate per day

96-hr NOEC = 18.8 mg/L for all three criteria

Reference:

Hancock, G.A., McClymont, E.L., and Staley, J.L. 2003. n-Valeraldehyde: Growth Inhibition Test with the Freshwater Green Algae, *Pseudokirchneriella subcapitata* (unpublished study). Toxicology &

Environmental Research and Consulting, Study ID 031086. The Dow Chemical Company, Midland, MI.

(b)	Type:	semi-static (test solution changed every 24 hours)
	Test:	LC50 (mortality) EC50 (inhibition of propagation)
	Species:	<i>Daphnia magna</i> Straus, freshwater invertebrate
	Unit:	mg/L
	Exposure Period:	21 days
	LC50:	4.8 (1.8-8.2)
	EC50:	3.0 (2.9-3.2)
	NOEC:	2.5
	Test substance:	n-valeraldehyde, purity $\geq 97.0\%$
	Analyt Monitoring.:	yes
	Year:	1984
	GLP:	yes
	Methods:	OECD Guideline for Testing of Chemicals No. 202, <i>Daphnia sp.</i> , Acute Swimming Inhibition and Propagation Tests on Water Fleas, 1984.

The test organism, *Daphnia magna* Straus, was originally obtained from National Institute for Environmental Studies and subsequent generations were raised at the test facility. Daphnid instars less than 24 hours old from laboratory-reared cultures were used as the test organism. Daphnid cultures were maintained under room on a 16-hour light/8-hour dark photoperiod at a temperature of  $20 \pm 1$  °C. Daphnids were fed a diet of freshwater green algae (*Chorella regularis*, 0.1-2 µg/day/daphnid). Female adults (raising density no more than 20/L) with larvae in their brood chambers were selected and the larvae which were produced the next day (within 24 hours) were used for the test. Rearing density for immature daphnids was 20-40/L. Dilution water was Elendt M4 as described in Annex 2 of the OECD Revised Guidelines No. 211. The hardness of the dilution water was 226(converted to mg CaCO<sub>3</sub>/L), and the pH was 7.7.

Definitive testing was conducted in glass beakers with a test solution volume of 80 ml. Additional vessels with no test material added were used as water control. Test vessels were placed in a isothermal tank maintained at water temperature of  $20 \pm 1$  °C. Daphnids were fed a diet of freshwater green algae (*Chorella regularis*, 0.1-2 µg/day/daphnid). Daphnids were observed daily for abnormalities and for births, deaths, and swimming behavior. Dead daphnids were removed. The number of larvae born from the initial daphnids was counted daily and the larvae removed. The incidence of dead larvae, miscarried eggs, and dormant eggs was observed and removed daily.

Because valeraldehyde does not dissolve readily in water, hardened castor oil (HCO-50) was used as a dispersion adjuvant. The test substance was dissolved in HCO-50 which was then filtered-sterilized to make the original test solution. Each test solution was prepared by adding the original test solution to dilution water.

Valeraldehyde nominal test concentrations for the definitive test were selected based on a 48-hour semi-static test which determined an EC50 for immobility of 31.5 mg/L. Based on this result, the concentrations of the test material selected for the definitive 21-day test the nominal concentrations selected were 0, 5.7, 10.3, 18.5, 33.3, and 60.0 mg valeraldehyde/L. One

control vessel contained dilution water with no other additions. An adjuvant control contained dilution water plus 100 mg/L HCO-50. Test solutions were replenished after 24 hours. Test solutions were sampled during preparation, at 0 hr prior to water change, and again at the end of the 24-hr exposure interval at the beginning of the test (day 0), and on day 7 and 15. Analysis of the test solutions demonstrated that nominal test concentrations of 5.7, 10.3, 18.5, 33.3, and 60.0 mg/L were significantly decreased, even in the freshly prepared solutions. The test substance concentrations of in freshly prepared solutions ranged between 48.8 to 79.9% of nominal concentrations, while the test substance concentration in 24-hr old solutions were <1.9 to 55.8% of the nominal target concentrations. The time-weighted mean measured concentrations for each test solution was determined based on the concentration of the test substance at 0-hour and 24-hours (see table below). The time-weighted mean measured concentrations for the 21-day test were 2.5, 3.5, 9.1, 18.9, and 34.1 mg valeraldehyde/L.

Test samples were submitted for analytical confirmation using a gas chromatograph equipped with a flame ionization detector (FID). The original standard solution was diluted and the standard solution was measured at 5 points, beginning at the limit of detection and including predicted measurement concentrations. Linearity was confirmed. One point on the standard curve was analyzed every measurement day. The GC/FID instrumentation exhibited a linear response over the calibration range of 2.0 to 100 mg valeraldehyde/L.

Statistical analysis: The LC50 for the 21-day exposure and its 95% confidence limits were calculated by the Probit method from the number of deaths of parent fleas and the number of fleas tested (10) for each concentration. Using the mean cumulative number of births (surviving larvae), the 50% inhibition concentration for propagation and its 95% confidence limits were calculated for the 21-day exposure. To calculate the mean number of daphnids used in the test, the mean number of daphnid births of the controls was determined. To calculate the number of live offspring, the mean cumulative number of births at each concentration was determined. The cumulative number of births (surviving larvae) per surviving parent in 21 days was calculated for each test concentration. Bartlett's equal variance test, the Kruskal-Wallis ranking order test, and Dunnett's multi-comparison test were performed for the control group and each test concentration group. The highest concentration which showed no significant difference from the control group was determined to be the 21-day NOEC. For statistical analysis, the EcoTox-Statics (version 1.1), developed by Yashimasa Hoshioka was utilized to calculate the EC50, LC50, and NOEC.

Results: The water temperatures during the 21-day exposure interval ranged between 19.4 and 21 °C; the dissolved oxygen concentrations were between 7.1 and 9.0 mg/L; dissolved oxygen concentrations were maintained at 60% or more in all test and control solutions (at 20°C, 100% saturation occurs at 8.84 mg/L). pH values ranged from 7.4 to 7.4. Total hardness values were in the range of 225 to 234 mg/L (converted to CaCO<sub>3</sub>).

Analysis of freshly prepared test solutions for valeraldehyde and at days 0, 7 and 15 demonstrated mean measured concentrations that ranged from 48.8% to 79.9% of target nominal values. Analysis of test solutions after 24 hours yielded percent of nominal values ranging from <1.9 to 55.8%. Time-

weighted means of measured concentrations of valeraldehyde were calculated for all dose levels by averaging the all 0-hour concentrations and all 24-hour solution concentrations for days 0, 7, and 15 (see table and calculations below).

$$\text{Time-weighted mean} = \frac{\text{Total area}}{\text{Total}}$$

$$\text{Area} = \frac{\text{Conc0} - \text{Conc24}}{x \text{ Days} \cdot \ln(\text{Conc0}) - \ln(\text{Conc24})}$$

Where Conc0 is the measured concentration in freshly prepared solutions, and Conc24 is the measured concentration in test solutions after a 24-hour exposure interval, and days is the number of days in the renewal interval.

Time-weighted Means of Test Solutions for Valeraldehyde in mg/L

Nominal Target Concentration	Time-weighted Mean	Percent of Nominal Concentration
Control	<2.0 <sup>1</sup>	NA <sup>2</sup>
Adjuvant Control	<2.0	NA
5.7	2.5	43.9
10.3	3.5	34.0
18.5	9.1	49.2
33.3	18.9	56.8
60.0	34.1	56.8

1: Analytical detection limit for valeraldehyde  
2: Not Applicable

Observations were made for parental mortality in controls and in exposed daphnids in response to exposure to n-valeraldehyde. Mortality was 80% at the highest mean measured concentration tested (34.1 mg/L). (see table below).

Percent Mortality of Parental Daphnids

Mean Concentration	Days					
	1	2	4	7	14	21
Control	0	0	0	0	0	10
Adjuvant Control	0	0	0	0	0	20
2.5	0	0	0	0	0	20
3.5	0	0	0	0	0	50
9.1	0	0	0	0	20	70
18.9	0	0	0	0	30	100
34.1	0	0	10	10	40	80

No dormant eggs were produced in the control groups or any test group. The initial production date (time to first brood) for parental daphnids in controls occurred 9-13 days after the start of the test. Daphnids exposed to the lowest test concentration (2.5 mg/L) had a similar initial production date (9-12 days).



No production was observed in parent daphnids at the two highest concentrations (see table below).

**Time (day) to First Brood Production and Mean Number of Juveniles Produced per Parental Adult**

Mean Concentration (mg/L)	Individual Parental Daphnids										Mean (Days)	Mean (Number of Juveniles)
	1	2	3	4	5	6	7	8	9	10		
Control	9	9	9	10	11	13	9	9	9	9	9.7	77.7
Adjuvant Control	9	9	9	11	9	10	11	10	9	11	9.8	66.6
2.5	9	9	9	9	11	12	9	12	11	11	10.2	67.8
3.5	12	10	9	12	15	>21 <sup>1</sup>	>21	12	9	10	>13	14.0
9.1	12	- <sup>2</sup>	-	>2 1	-	-	16	>2 1	>2 1	-	18	0.0
18.9	-	-	-	-	-	-	-	-	-	-	-	-
34.1	-	-	>2 1	>2 1	-	-	-	-	-	-	>21	0.0

1: no broods were produced during 21-day test interval  
2: parental daphnid dead

The mean cumulative number of offspring per surviving parent daphnid in controls were 77.7 and 66.6; a standard mean minimum of 60 or more offspring is required for a valid test. The mean number of offspring per parent daphnid was 67.5 and 14.0 for the two lowest concentrations (2.5 and 3.5 mg/L). No offspring were observed at higher concentrations.

Based time-weighted mean measured n-valeraldehyde concentrations:  
The LC50 for parent daphnids for the 21-day exposure interval was 4.8 mg/L, with a 95% confidence interval of 1.8-8.2 mg/L.  
The EC50 value for inhibition of propagation was 3.0 mg/L, with a 95% confidence interval of 2.9-3.2 mg/L.  
The concentration which had no effect on the cumulative number of offspring per parent daphnid (NOEC) was 2.5 mg/L.

Reliability: score = 2, valid with restrictions. GLP guideline study which lacks detailed documentation

Reference: Ministry of the Environment (MOE). 1999b. Study of the inhibition of the propagation of water fleas (*Daphnia magna*) by valeric aldehyde. Study number NMMP/E98/3050. Toray Research Center, Nagoya Laboratory, Japan

- (c) Type: Model calculation  
Value: 151.314 mg/L  
Test substance: n-valeraldehyde  
Method: ECOSAR v. 0.99g  
Remark: An acute fish 96-hr LC50 was calculated using the USEPA ECOSAR. The SAR for neutral organics was used. The structure was determined from the CAS RN as stored in the accompanying database of SMILES notations within ECOSAR.  
Reliability: score = 2, valid with restriction; accepted calculation method.

Reference: ECOSAR Model Version 0.99g. EPIWIN (Estimation Program Interface for Windows), Version 3.10. U.S. Environmental Protection Agency, 2000.

#### 4.4 TOXICITY TO BACTERIA

- (a) preferred value reliability score = 2, valid with restriction  
 Type:  
 Species: sewage microorganisms, non-acclimated  
 Unit: mg/l  
 Exposure Period: 16 hour  
 EC0:  
 EC10:  
 EC50: 140  
 Analyt. Monitoring: no data  
 Method other: Test material was evaluated at selected concentrations in a mixture containing 1 ml of a suspension of seed microorganisms, 20 ml dilution water, 4 ml stock buffer solution, 10 ml yeast extract/sodium acetate solution, and 4 ml of an aqueous solution containing the test material. Each mixture was incubated in an 8-ounce narrow-neck round-bottomed bottle for 16 hr on a platform shaker at an ambient temperature of 22 +/- 2 degree C. Seeded control bottles were used to measure growth in control mixtures which did not contain the test material. Bottles were stoppered with cotton plugs during shaking to prevent contamination. Growth inhibition was measured by measuring (optical density 530 nm) the turbidity levels of mixtures containing the test material. Measured optical density values were calculated as a percentage of seeded growth in the control bottles. The percent of control values were then plotted against the log of test sample concentration. The test concentration corresponding to 50% growth inhibition (IC50) was then determined.
- GLP: no data  
 Test substance: n-valeraldehyde (CAS No. 110-62-3), purity not specified  
 Reference: Union Carbide Chemicals and Plastics Company Inc. 1993. Ecological Fate and Effects Testing of UCC&P Products and Wastewaters During 1992. File Report No. 39860, dated February 12, 1993.

#### 4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

##### 4.5.1 CHRONIC TOXICITY TO FISH

No data available.

##### 4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

- (a) Type: semi-static (test solution changed every 24 hours)  
 Test: LC50 (mortality)  
 EC50 (inhibition of propagation)  
 Species: *Daphnia magna* Straus, freshwater invertebrate  
 Unit: mg/L  
 Exposure Period: 21 days  
 LC50: 4.8 (1.8-8.2)  
 EC50: 3.0 (2.9-3.2)  
 NOEC: 2.5  
 Test substance: n-valeraldehyde, purity ≥ 97.0%  
 Analyt Monitoring.: yes  
 Year: 1984  
 GLP: yes

Methods: OECD Guideline for Testing of Chemicals No. 202, *Daphnia sp.*, Acute Swimming Inhibition and Propagation Tests on Water Fleas, 1984.

The test organism, *Daphnia magna* Straus, was originally obtained from National Institute for Environmental Studies and subsequent generations were raised at the test facility. Daphnid instars less than 24 hours old from laboratory-reared cultures were used as the test organism. Daphnid cultures were maintained under room on a 16-hour light/8-hour dark photoperiod at a temperature of  $20 \pm 1$  °C. Daphnids were fed a diet of freshwater green algae (*Chorella regularis*, 0.1-2 µg/day/daphnid). Female adults (raising density no more than 20/L) with larvae in their brood chambers were selected and the larvae which were produced the next day (within 24 hours) were used for the test. Rearing density for immature daphnids was 20-40/L. Dilution water was Elendt M4 as described in Annex 2 of the OECD Revised Guidelines No. 211. The hardness of the dilution water was 226 (converted to mg CaCO<sub>3</sub>/L), and the pH was 7.7.

Definitive testing was conducted in glass beakers with a test solution volume of 80 ml. Additional vessels with no test material added were used as water control. Test vessels were placed in a isothermal tank maintained at water temperature of  $20 \pm 1$  °C. Daphnids were fed a diet of freshwater green algae (*Chorella regularis*, 0.1-2 µg/day/daphnid). Daphnids were observed daily for abnormalities and for births, deaths, and swimming behavior. Dead daphnids were removed. The number of larvae born from the initial daphnids was counted daily and the larvae removed. The incidence of dead larvae, miscarried eggs, and dormant eggs was observed and removed daily.

Because valeraldehyde does not dissolve readily in water, hardened castor oil (HCO-50) was used as a dispersion adjuvant. The test substance was dissolved in HCO-50 which was then filtered-sterilized to make the original test solution. Each test solution was prepared by adding the original test solution to dilution water.

Valeraldehyde nominal test concentrations for the definitive test were selected based on a 48-hour semi-static test which determined an EC<sub>50</sub> for immobility of 31.5 mg/L. Based on this result, the concentrations of the test material selected for the definitive 21-day test the nominal concentrations selected were 0, 5.7, 10.3, 18.5, 33.3, and 60.0 mg valeraldehyde/L. One control vessel contained dilution water with no other additions. An adjuvant control contained dilution water plus 100 mg/L HCO-50. Test solutions were replenished after 24 hours. Test solutions were sampled during preparation, at 0 hr prior to water change, and again at the end of the 24-hr exposure interval at the beginning of the test (day 0), and on day 7 and 15. Analysis of the test solutions demonstrated that nominal test concentrations of 5.7, 10.3, 18.5, 33.3, and 60.0 mg/L were significantly decreased, even in the freshly prepared solutions. The test substance concentrations of in freshly prepared solutions ranged between 48.8 to 79.9% of nominal concentrations, while the test substance concentration in 24-hr old solutions were <1.9 to 55.8% of the nominal target concentrations. The time-weighted mean measured concentrations for each test solution was determined based on the concentration of the test substance at 0-hour and 24-hours (see table below). The time-weighted mean measured concentrations for the 21-day test were 2.5, 3.5, 9.1, 18.9, and 34.1 mg valeraldehyde/L.

Test samples were submitted for analytical confirmation using an a gas chromatograph equipped with a flame ionization detector (FID). The original standard solution was diluted and the standard solution was measured at 5 points, beginning at the limit of detection and including predicted measurement concentrations. Linearity was confirmed. One point on the standard curve was analyzed every measurement day. The GC/FID instrumentation exhibited a linear response over the calibration range of 2.0 to 100 mg valeraldehyde/L.

Statistical analysis: The LC50 for the 21-day exposure and its 95% confidence limits were calculated by the Probit method from the number of deaths of parent fleas and the number of fleas tested (10) for each concentration. Using the mean cumulative number of births (surviving larvae), the 50% inhibition concentration for propagation and its 95% confidence limits were calculated for the 21-day exposure. To calculate the mean number of daphnids used in the test, the mean number of daphnid births of the controls was determined. To calculate the number of live offspring, the mean cumulative number of births at each concentration was determined. The cumulative number of births (surviving larvae) per surviving parent in 21 days was calculated for each test concentration. Bartlett's equal variance test, the Kruskal-Wallis ranking order test, and Dunnett's multi-comparison test were performed for the control group and each test concentration group. The highest concentration which showed no significant difference from the control group was determined to be the 21-day NOEC. For statistical analysis, the EcoTox-Statics (version 1.1), developed by Yashimasa Hoshioka was utilized to calculate the EC50, LC50, and NOEC.

Results: The water temperatures during the 21-day exposure interval ranged between 19.4 and 21 °C; the dissolved oxygen concentrations were between 7.1 and 9.0 mg/L; dissolved oxygen concentrations were maintained at 60% or more in all test and control solutions (at 20°C, 100% saturation occurs at 8.84 mg/L). pH values ranged from 7.4 to 7.4. Total hardness values were in the range of 225 to 234 mg/L (converted to CaCO<sub>3</sub>).

Analysis of freshly prepared test solutions for valeraldehyde and at days 0, 7 and 15 demonstrated mean measured concentrations that ranged from 48.8% to 79.9% of target nominal values. Analysis of test solutions after 24 hours yielded percent of nominal values ranging from <1.9 to 55.8%. Time-weighted means of measured concentrations of valeraldehyde were calculated for all dose levels by averaging the all 0-hour concentrations and all 24-hour solution concentrations for days 0, 7, and 15 (see table and calculations below).

$$\text{Time-weighted mean} = \frac{\text{Total area}}{\text{Total}}$$

$$\text{Area} = \frac{\text{Conc0} - \text{Conc24}}{x \text{ Days } \ln(\text{Conc0}) - \ln(\text{Conc24})}$$

Where Conc0 is the measured concentration in freshly prepared solutions, and Conc24 is the measured concentration in test solutions after a 24-hour exposure interval, and days is the number of days in the renewal interval.

Time-weighted Means of Test  
Solutions for Valeraldehyde in mg/L

Nominal Target Concentration	Time-weighted Mean	Percent of Nominal Concentration
Control	<2.0 <sup>1</sup>	NA <sup>2</sup>
Adjuvant Control	<2.0	NA
5.7	2.5	43.9
10.3	3.5	34.0
18.5	9.1	49.2
33.3	18.9	56.8
60.0	34.1	56.8

1: Analytical detection limit for valeraldehyde  
2: Not Applicable

Observations were made for parental mortality in controls and in exposed daphnids in response to exposure to n-valeraldehyde. Mortality was 80% at the highest mean measured concentration tested (34.1 mg/L). (see table below).

Percent Mortality of Parental Daphnids

Mean Concentration	Days					
	1	2	4	7	14	21
Control	0	0	0	0	0	10
Adjuvant Control	0	0	0	0	0	20
2.5	0	0	0	0	0	20
3.5	0	0	0	0	0	50
9.1	0	0	0	0	20	70
18.9	0	0	0	0	30	100
34.1	0	0	10	10	40	80

No dormant eggs were produced in the control groups or any test group. The initial production date (time to first brood) for parental daphnids in controls occurred 9-13 days after the start of the test. Daphnids exposed to the lowest test concentration (2.5 mg/L) had a similar initial production date (9-12 days). No production was observed in parent daphnids at the two highest concentrations (see table below).

Time (day) to First Brood Production and Mean Number of Juveniles Produced per Parental Adult

Mean Concentration (mg/L)	Individual Parental Daphnids										Mean (Days)	Mean (Number of Juveniles)
	1	2	3	4	5	6	7	8	9	10		
Control	9	9	9	10	11	13	9	9	9	9	9.7	77.7
Adjuvant Control	9	9	9	11	9	10	11	10	9	11	9.8	66.6
2.5	9	9	9	9	11	12	9	12	11	11	10.2	67.8
3.5	12	10	9	12	15	>21 <sup>1</sup>	>21	12	9	10	>13	14.0
9.1	12	- <sup>2</sup>	-	>21	-	-	16	>21	>21	-	18	0.0
18.9	-	-	-	-	-	-	-	-	-	-	-	-
34.1	-	-	>21	>21	-	-	-	-	-	-	>21	0.0

- 1: no broods were produced during 21-day test interval
- 2: parental daphnid dead

The mean cumulative number of offspring per surviving parent daphnid in controls were 77.7 and 66.6; a standard mean minimum of 60 or more offspring is required for a valid test. The mean number of offspring per parent daphnid was 67.5 and 14.0 for the two lowest concentrations (2.5 and 3.5 mg/L). No offspring were observed at higher concentrations.

Based time-weighted mean measured n-valeraldehyde concentrations:  
The LC50 for parent daphnids for the 21-day exposure interval was 4.8 mg/L, with a 95% confidence interval of 1.8-8.2 mg/L.  
The EC50 value for inhibition of propagation was 3.0 mg/L, with a 95% confidence interval of 2.9-3.2 mg/L.  
The concentration which had no effect on the cumulative number of offspring per parent daphnid (NOEC) was 2.5 mg/L.

- Reliability: score = 2, valid with restrictions. GLP guideline study which lacks detailed documentation
- Reference: Ministry of the Environment (MOE). 1999b. Study of the inhibition of the propagation of water fleas (*Daphnia magna*) by valeric aldehyde. Study number NMMP/E98/3050. Toray Research Center, Nagoya Laboratory, Japan

#### 4.6 TOXICITY TO TERRESTRIAL ORGANISMS

No data available.

##### 4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data available.

##### 4.6.2 TOXICITY TO TERRESTRIAL PLANTS

No data available.

##### 4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No data available.

#### 4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data available.

#### 4.8 BIOTRANSFORMATION AND KINETICS

No data available.

#### 4.9 ADDITIONAL REMARKS

None

## 5.1 ACUTE TOXICITY

### 5.1.1 ACUTE ORAL TOXICITY

- (a) Preferred value reliability score = 2, valid with restriction  
 Type: LD50  
 Species: rat  
 Sex: male  
 Number of Animals: 5  
 Vehicle: water  
 Value: 4590 mg/kg bw  
 Method: other  
 Year: 1969  
 GLP: no  
 Test substance: n-valeraldehyde, purity not specified  
 Method: Groups of male Carworth-Wistar rats received increasing dosages of valeraldehyde administered as a 10% aqueous solution by stomach tube. Rats were not fasted prior to dosing. Five rats were included in each group. Animals were observed for signs of toxicity after dosing, and throughout the 14-day observation interval. Animals were weighed prior to dosing and at the end of the observation interval. Animals that died on study were subjected to necropsy; surviving animals were sacrificed at the end of the observation interval and necropsied. Thompson's method of calculating the LD50 was applied to the 14-day mortality data.  
 Result: The peroral LD50 for male Carworth-Wistar rats administered a solution of 10% valeraldehyde by stomach tube was 5.66 ml/kg (4590 mg/kg) body weight.  
 Remark: Animals exhibited signs of narcosis after dosing, and three died within 24 hours of dosing. Other animals died within 4 to 8 days after dosing. Animals that died on study had discolored, mottled lungs, liver, and gastrointestinal tract; visceral organs in contact with the gastrointestinal tract had a "burned" appearance.  
 Reliability score = 2: valid with restriction, test material purity not specified  
 References: Smyth, H.F. et al. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30: 470-476.  
 Union Carbide Corporation. 1957. Unpublished report. Range Finding Tests on n-Valeraldehyde. Report No. 20-110, dated July 30, 1957.
- (b) Type: LD50  
 Species/strain: rat/Carworth-Wistar  
 Value: 3860 mg/kg  
 Method: Groups of five, non-fasted male Carworth-Wistar rats received undiluted valeraldehyde by gavage at dosages arranged in a logarithmic series increasing by a factor of 2. Animals were observed for evidence of toxicity and morbidity immediately after dosing, and throughout the 14 day post-dosing observation interval. The LD50 value was calculated by the moving average method (Thompson, 1947) after the animals had been observed for 14 days for clinical signs and survival.  
 Year: 1962  
 GLP: no

Test substance: valeraldehyde, purity not specified  
 Result: The LC50 for 1-pentanal in male Harlan-Wistar rats (with 95% confidence limits) = 4.76 (3.35-6.75) ml/kg body weight or 3.86 (2.72-5.47) g/kg.  
 Reliability score = 2; valid with restriction, test material purity not specified  
 Reference: Smyth, H.F. et al. 1962. Range-Finding Toxicity Data. Industrial Hygiene J. 23: 95-107.

### 5.1.2 ACUTE INHALATION TOXICITY

- (a) Preferred value reliability score = 2, valid with restriction  
 Type: other  
 Species: rat/Carworth-Wistar  
 Exposure Time: 4 hours  
 Value: 4000 ppm killed 3 of 6  
 Method: Groups of six male rats were exposed to increasing concentrations of dynamically generated valeraldehyde vapor for 4 hours. Rats were observed immediately after exposure and throughout a 14-day post-exposure observation interval. Mortality among each group was recorded and fractional mortality or the LD50 determined at the end of the 14-day observation interval.  
 Year: 1969  
 GLP: no  
 Test material: n-valeraldehyde, purity not specified  
 Result: Among rats exposed to 4000 ppm valeraldehyde for 4 hours, all rats were anesthetized after 1.5 hr exposure; 3 of 6 rats died during the 4-hr exposure interval. There was no mortality among rats exposed to 2000 ppm for 4 hours, and all rats appeared normal during the 14-day observation interval.  
 Remark: 4-hour exposure at 2000 ppm, 0/6 mortality  
 4-hour exposure at 4000 ppm, 3/6 mortality  
 signs of toxicity: anesthesia  
 0.5 hr exposure at approximately 50,000 ppm, 5/6 mortality  
 signs of toxicity: gasping, prostration, anesthesia, evidence of ocular and nasal irritation.  
 Reliability score = 2: valid with restriction, test material purity not specified  
 References: Smyth, H.F. et al. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30: 470-476.  
 Union Carbide Corporation. 1957. Unpublished report. Range Finding Tests on n-Valeraldehyde. Report No. 20-110, dated July 30, 1957.
- (b) Type: other  
 Species: rat/Carworth-Wistar  
 Exposure Time: 4 hours  
 Value: 8000 ppm killed 3 of 6  
 Method: Groups of six male or female rats were exposed to metered vapor concentrations of 1-pentanal for 4 hours. Exposure concentrations were nominal and not analytically verified. Concentrations employed were in a logarithmic series increasing by a factor of two. Rats were observed immediately after exposure and throughout a 14-day post-exposure observation interval. Fractional mortality among each group after 14 days was recorded.  
 Year: 1962



GLP:	no
Test substance:	n-valeraldehyde, purity unknown
Result:	Among rats exposed to 8000 ppm valeraldehyde for 4 hours, 3 of 6 died within the 14 day observation interval.
Reliability	score = 2: valid with restriction, test material purity not specified
Reference:	Smyth, H.F. et al. 1962. Range-Finding Toxicity Data. Industrial Hygiene J. 23: 95-107.
(c) Type:	other: RD50
Species:	mouse (Swiss Webster and B6C3F1)
Sex:	male
Number of Animals:	4
Vehicle:	
Exposure time:	10 minutes
Value:	1121 ppm (Swiss Webster) 1190 ppm (B6C3F1)
Method:	other: see Alarie, Y. Arch. Environ. Health 13: 433-449, 1966.
Year:	1984
GLP:	no
Test substance:	n-valeraldehyde, laboratory grade (Aldrich, usually 97-98%)
Method:	Groups of three or four male mice of each strain were exposed to different concentrations of valeraldehyde vapor in a head-only exposure chamber for 10 minutes. Both B6C3F1 mice and Swiss-Webster mice were used, and their responses compared. Test atmospheres were generated by passing dry nitrogen over valeraldehyde contained in a 100 ml glass impinger. Vaporization rates were controlled by varying the nitrogen flow and/or submerging the impinger in a constant-temperature water bath. Chamber concentrations were attained by regulating chamber air flow, nitrogen flow through the impinger, and the temperature of the water bath. Chamber concentrations were analyzed continuously with an infrared analyzer.
Result:	Sensory irritation was quantified by measuring respiratory rate depression during exposure. Respiratory rates, measured during a 5-min pre-exposure, 10-min exposure, and 5-min recovery interval, were determined by a body plethysmographic method (Y. Alarie, Arch Environ Health 13: 433-449). The average maximum decrease in respiratory rate for 1 min was computed from the response of each group of animals and plotted against the log of the exposure concentration. The RD50 value (concentration eliciting a 50% decrease in respiratory rate) was determined. Concentration-response curves were constructed by the least-squares method for regression and tested for significance by analysis of variance. Valeraldehyde produced a dose-related decrease in respiratory rate in both strains of mice. All concentrations produced a response. The RD50 (95% confidence level) for valeraldehyde in male B6C3F1 mice and male Swiss-Webster mice was 1190 (1109-1283) ppm and 1121 (828-1757) ppm, respectively.
Remark:	Propionaldehyde, butyraldehyde, isobutyraldehyde, and isovaleraldehyde were tested using the same protocol and test conditions.

<u>Aldehyde</u>	RD50 (ppm)	RD50 (ppm)
	B6C3F1	Swiss Webster
Propionaldehyde	2078	2052
Butyraldehyde	1532	1015
Isobutyraldehyde	3016	4167
Valeraldehyde	1190	1121
Isovaleraldehyde	757	1008

The RD data demonstrate that sensory irritation properties within the saturated aldehydes are somewhat comparable, however, there is no clear trend of decreased irritancy with increasing chain length or chain branching.

- Reliability: Score = 2; valid with restriction, purity of test material not verified  
Reference: Steinhagen, W.H. and Barrow, C.S. 1984. Sensory irritation structure-activity study of inhaled aldehydes in B6C3F1 and Swiss-Webster mice. *Toxicol. Appl. Pharmacol.* 75: 495-503.
- (d) Type: other; acute inhalation toxicity  
Species: mouse, guinea pig, rabbit  
Sex: no data  
Number of Animals: mice: 50  
guinea pigs: 20  
rabbits: 5  
Vehicle: air  
Exposure time: 10 hours  
Value: see Results  
Method: In a study of the inhalation toxicity of saturated and unsaturated aldehydes, mice, guinea pigs and rabbits were exposed to 2359 mg/m<sup>3</sup> valeraldehyde aerosol (equivalent to 660 ppm) for 10 hours or until death. Valeraldehyde aerosol was produced by injecting air through an all-metal Collison Spray into a 50 ml valeraldehyde in a glass container. The aerosol was sampled in impingers containing hydroxylamine hydrochloride and the concentration was expressed as mg/m<sup>3</sup>. Animals were exposed in a plate glass exposure chamber with a volume of 1 cubic meter.  
Year: 1960  
GLP: no  
Test substance: n-valeraldehyde, purity not specified  
Results: Particle diameter of the aerosol was 0.7 microns. Mortality among animals during the 10-hour exposure to 2359 mg/m<sup>3</sup> valeraldehyde aerosol was 2/50 mice, 0/20 guinea pigs, and 0/5 rabbits. Two mice and five guinea pigs died after exposure. Total mortality was 4/50 mice, 5/20 guinea pigs, and 0/5 rabbits. Exposure to valeraldehyde caused an initial increase in activity in exposed animals. Animals exhibited signs of irritation, including eye blinking, closed eyes, and rubbing faces with paws. After initial activity, animals became inactive; respirations appeared deep and slow. Mice dying during exposure convulsed just prior to death. At necropsy, all animals were observed to have expanded, edematous, and hemorrhagic lungs. Fluid was observed in the pleural cavity. Distension of alveoli and ruptured alveolar septa were also observed in some animals. Livers appeared enlarged and fluid was observed in the peritoneal cavity. Most lung sections displayed dilated and engorged blood vessels.

Mortality of Test Animals After 10-hour Aldehyde Aerosol Exposure

Aldehyde	mg/m <sup>3</sup>	Mice	Guinea Pigs	Rabbits
Formaldehyde	20	48/50*	1/20	1/5
Valeraldehyde	2359	4/50	5/20	0/5
Isovaleraldehyde	6176	3/50	5/20	0/5

\*Mortality/total number of animals exposed

Remark: Propionaldehyde, butyraldehyde, isobutyraldehyde, and isovaleraldehyde were also testing using the same protocol and similar test conditions. Authors report that increasing chain length resulted in a decreasing order of toxicity for saturated aldehydes. The decreasing order of inhalation toxicities was found to be propionaldehyde, isobutyraldehyde, butyraldehyde, valeraldehyde, and isovaleraldehyde. These saturated aldehydes produced less bronchial irritation than lung irritation.

Reliability: score = 2, purity of test material not specified

Reference: Salem, H. and Cullumbine, H. 1960. Inhalation toxicities of some aldehydes. *Toxicol. App. Pharmacol.* 2: 183-187.

**5.1.3 ACUTE DERMAL TOXICITY**

(a) Preferred value reliability score = 2, valid with restriction

Type: LD50

Species: rabbit

Sex: male

Number of Animals: 4

Vehicle: other: none

Value: 4865 mg/kg

Method: other

Year: 1969

GLP: no

Test substance: valeraldehyde, purity unknown

Method: Groups of male New Zealand rabbits received n-valeraldehyde, applied undiluted to intact, non-abraded skin. Fur was removed from the entire trunk of each rabbit prior to application of the test substance. Four rabbits were included in each dose group. Valeraldehyde was applied to the dorsal surface of the trunk and spread over as large an area as possible. The test material was retained on the skin beneath an impervious plastic film. Rabbits were immobilized during the 24-hr contact interval. After treatment, all wrappings were removed. Animals were observed for signs of toxicity after dosing, and throughout the 14-day observation interval. Animals that died on study were subjected to necropsy; animals sacrificed at the end of the observation interval were also necropsied. Thompson's method of calculating the LD50 was applied to the 14-day mortality data.

Result: The dermal LD50 for male New Zealand rabbits was 6 ml/kg, or 4865 mg/kg body weight.

Remark: Erythema, edema, necrosis, and eschar formation was noted at the application site. Deaths occurred at 24, 48, and 72 hours.

Reliability: score = 2: valid with restriction, test material purity not specified

References: Smyth, H.F. Jr., Carpenter, C.P. and Weil, C.S. et al. 1969. Range-finding toxicity data: List VII. *Am. Ind. Hyg. Assoc. J.* 30: 470-476.

Union Carbide Corporation. 1957. Unpublished report. Range Finding Tests on n-Valeraldehyde. Report No. 20-110, dated July 30, 1957.

- (b) Type: LD50  
 Species: rabbit  
 Sex: male  
 Number of Animals: 4  
 Vehicle: other: none  
 Value: >16,218 mg/kg  
 Method: other  
 Year: 1962  
 GLP: no  
 Test substance: no data  
 Method: Groups of male New Zealand rabbits (2.5-3.5 g) received valeraldehyde, applied undiluted to intact (non-abraded) skin. Fur was removed from the trunk of each rabbit prior to application of the test material. Rabbits were immobilized during the 24-hour skin contact interval. Valeraldehyde was applied to the dorsal surface of the trunk and spread over as large an area as possible. The test material was retained on the skin beneath an impervious plastic film, which was wrapped around the trunk of each animal. After treatment, all wrappings were removed; animals were observed for signs of toxicity after dosing, and throughout the 14-day observation interval. Thompson's method of calculating the LD50 was applied to the 14-day mortality data.  
 Year: 1962  
 GLP: no  
 Test substance: valeraldehyde, purity unknown  
 Result: The dermal LD50 of valeraldehyde for male New Zealand rabbits was > 20 ml/kg, or >16,218 mg/kg body weight.  
 Reliability: score = 2: valid with restriction, test material purity not specified; from collection of data  
 Reference: Smyth, H.F. Jr., Carpenter, C.P., West, C.S., Pozzani, U.C., and Striegel, J.A. 1962. Range-Finding Toxicity Data. *Industrial Hygiene J.* 23: 95-107.
- (c) Remark: Undiluted valeraldehyde was a strong irritant when held in covered contact with the depilated skin of guinea pigs for a period of 24 hours. There was some evidence that it was absorbed directly through the intact skin, since animals in the highest dose groups failed to gain weight during the 14-day observation interval.  
 Reliability: score = 4; insufficient data for assessment  
 Reference: Eastman Kodak Company. 1991. Toxicity and health hazard summary, material data sheet, and toxicity report on pentanal. Eastman Kodak Health and Safety Laboratory. (EPA/OATS Doc # 86-92000053). *Cited in* : National Toxicology Program (NTP). 1996. Chemical Selection Working Group (SCWG). Summary of Data for Chemical Selection. n-Valeraldehyde.

#### 5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

Type: LD50  
 Test material: valeraldehyde

Route: intraperitoneal injection (IP)  
 Species: rat, mouse  
 GLP: no data  
 Results: LD50 (mouse) = 200-400 mg/kg  
 LD50 (rat) = 400-800 mg/kg  
 Reliability: score = 4; insufficient data for assessment  
 Reference: Eastman Kodak Company. 1991. Toxicity and health hazard summary, material data sheet, and toxicity report on pentanal. Eastman Kodak Health and Safety Laboratory. (EPA/OATS Doc # 86-920000053). *Cited in:* National Toxicology Program (NTP). 1996. Chemical Selection Working Group (SCWG). Summary of Data for Chemical Selection. n-Valeraldehyde.

## 5.2 CORROSIVENESS/IRRITATION

### 5.2.1 SKIN IRRITATION/CORROSION

- (a) Preferred value: reliability score = 2, valid with restriction  
 Species: rabbit/New Zealand White  
 Result: necrosis in 2 of 4 rabbits  
 Classification: corrosive  
 Method other: U.S. Department of Transportation Hazardous Materials Regulations Board. Test conducted according to Title 16, Chapter 11, Paragraph 1500.41, Consumer Products Safety Commission.
- Four rabbits (2 male, 2 female) were treated with 0.5 ml undiluted valeraldehyde for a 4-hour period. The dosage was applied to the clipped, intact dorsal skin and then covered. After the 4-hr exposure the dressings were removed, and excess test removed from the skin. Animals were examined for erythema, edema, and other evidence of irritation or skin lesions.
- Year: 1974  
 GLP: no  
 Test substance: n-valeraldehyde, purity not specified  
 Remark: When applied to the skin of four rabbit for a period of 4 hours, n-valeraldehyde produced necrosis in 2 of 4 rabbits.
- Reliability: score = 2: valid with restriction, test material purity not specified  
 Reference: Union Carbide Corporation. 1974. Unpublished report. Title 49-Transportation-Classification of Corrosive Hazards. Report No. 37-54, dated June 14, 1974.
- (b) Species: rabbits  
 Result: slightly irritating  
 Classification:  
 Method other: Five albino rabbits were treated with 0.01 ml of undiluted valeraldehyde for a 24-hour period. The dosage was applied to the clipped, intact skin of the belly and left uncovered. Primary skin irritation was recorded on a 10-grade scale, based upon the severest reaction that developed on each rabbit. Grade 1 indicates no irritation, Grade 2 indicates minimal erythema. Grade 6 indicates necrosis when the test material is applied undiluted.
- Year: 1957  
 GLP: no  
 Test substance: n-valeraldehyde, purity unknown

Remark: When applied uncovered to the clipped belly skin of five rabbits, 0.01 ml of n-valeraldehyde produced no irritation on the skin of 4 of 5 rabbits, and minimal detectable capillary injection on the skin of 1 in 5.

Results: n-valeraldehyde produced Grade 2 irritation (minimal erythema) of the skin on 1/5 rabbits.

Reliability score = 2: valid with restriction, test material purity not specified

References: Union Carbide Corporation. 1957. Unpublished report. Range Finding Tests on n-Valeraldehyde. Report No. 20-110, dated July 30, 1957.

Smyth, H.F. Jr., Carpenter, C.P., West, C.S., Pozzani, U.C., and Striegel, J.A. 1962. Range-Finding Toxicity Data. *Industrial Hygiene J.* 23: 95-107.

### 5.2.2 EYE IRRITATION/CORROSION

(a) Preferred value reliability score = 2, valid with restriction

Species: rabbit

Result: severely irritating

Classification:

Method: Group of rabbits received undiluted n-valeraldehyde which was instilled directed into the eye. The volumes instilled were 0.005 and 0.02 ml. Eyes were not rinsed. Rabbit eyes were examined at regular intervals after instillation for evidence of irritation. Eye irritation was recorded on a 10-grade scale. Grade 1 indicates at most a very small area of corneal necrosis from a flooding dose (0.5 ml). Grade 5 indicates severe corneal injury from a very small dose (0.005 ml).

Year: 1957

GLP: no

Test substance: n-valeraldehyde, purity unknown

Remark: Instillation of 0.005 ml n-valeraldehyde into the rabbit eye resulted in moderate corneal necrosis. Instillation of 0.02 ml resulted in severe corneal necrosis.

Reliability 2: valid with restriction, test material purity not specified

Reference: Union Carbide Corporation. 1957. Unpublished report. Range Finding Tests on n-Valeraldehyde. Report No. 20-110, dated July 30, 1957.

Smyth, H.F. Jr., Carpenter, C.P., West, C.S., Pozzani, U.C., and Striegel, J.A. 1962. Range-Finding Toxicity Data. *Industrial Hygiene J.* 23: 95-107.

### 5.3 SKIN SENSITISATION

(a) Remark: In a standardized skin sensitisation test in guinea pigs, valeraldehyde failed to sensitize any of the five test animals.

Reliability: score = 4; insufficient data for assessment

Reference: Eastman Kodak Company. 1991. Toxicity and health hazard summary, material data sheet, and toxicity report on pentanal. Eastman Kodak Health and Safety Laboratory. (EPA/OATS Doc # 86-920000053). *Cited in:* National Toxicology Program (NTP). 1996. Chemical Selection Working Group (SCWG). Summary of Data for Chemical Selection. n-Valeraldehyde.

- (b) Test substance: Isobutyraldehyde  
 Remark: Isobutyraldehyde is a 4-carbon homolog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as isobutyraldehyde can be valuable in assessing the toxicity of valeraldehyde.  
 Method: Isobutyraldehyde was tested on female B6C3F1 mice by the NTP contact hypersensitivity in the Murine Local Lymph Node Assay.  
 Result: Isobutyraldehyde was applied directly to the shave and abraded ears of mice for 5 consecutive days with and without adjuvant. Doses ranged from 3 to 30% in a solution of four parts acetone to one part olive oil for sensitization, and 30% for challenge. No indication of hypersensitivity was observed.  
 Reliability: score = 4; insufficient data for assessment  
 Reference: National Toxicology Program (NTP). 1990. Assessment of Contact Hypersensitivity of Isobutyraldehyde (CAS NO. 78-84-2) in Female B6C3F1 Mice. Report to the National Toxicology Program. Protocol IBA—0-1-CNM. Studies conducted at Immunotoxicology Program, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA. *Cited in:* Abdo, K.M., Haseman, J.K. and Nyska, A. 1998. Isobutyraldehyde administered by inhalation (whole body exposure) for up to thirteen weeks or two years was a respiratory tract toxicant but was not carcinogenic in F344/N rats and B6C3F1 mice. *Toxicol. Sci.* 42: 136-151.
- (c) Test substances : n-hexanal (C-6 aldehyde)  
 n-octanal (C-8 aldehyde)  
 n-nonanal (C-9 aldehyde)  
 Remark: note: purity of test substances not specified. Human dermal sensitization testing was conducted and the results reported in a series of monographs prepared for the Research Institute Fragrance Materials (RIFM).  
 Method: Hexanal: A maximization test was conducted on 25 human volunteers using a 1% concentration in petrolatum. Octanal: A standard repeated insult patch test was conducted on 40 human subjects using a 0.25% concentration in alcohol (identity of alcohol not specified). Nonanal: A maximization test was conducted on 25 human volunteers using a 1% concentration (vehicle not specified).  
 Result: No case of sensitization was reported for any of the aldehydes tested.  
 Reliability: score = 4, secondary reference, original references not available.  
 References: Opdyke, D.L.J. 1973. Monographys on Fragrance Raw Materials. *Fd. Cosmet. Toxicol.* 11: 95-115. *and* Kligman, A.M. 1972. Report to RIFM, 27 March. Majors, P. 1972. Report to RIFM, 6 May. Kligman, A.M. 1971. Report to RIFM, 27 September.

#### 5.4 REPEATED DOSE TOXICITY

- (a) Preferred result reliability score = 1, valid without restriction, GLP study  
 Test material: isobutyraldehyde

Remark: There are no repeat-dose toxicity studies for valeraldehyde. Isobutyraldehyde is a 4-carbon analog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as isobutyraldehyde can be valuable in assessing the toxicity of valeraldehyde.

Species: rat  
Sex: male/female  
Strain: F344/N  
Route of admin.: inhalation  
Exposure period: 103 weeks  
Frequency of treatment: 6 hr/day, 5 days a week  
Post. obs. period: 3 to 7 days after last day of exposure  
Doses: 0, 500, 1000, 2000 ppm  
Control Group: yes, concurrent  
NOAEC: < 500 ppm (including respiratory effects)  
Year: 1998  
GLP: yes  
Test substance: isobutyraldehyde, 98.6 to 99.1% pure  
Method: Groups of male and female rats (6 weeks old) were distributed randomly into experimental groups of approximately equal weight (50 males and 50 females at each dose) and were housed individually. Animals were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, or 2000 ppm for 6 hours per day, 5 days per week, for 103 weeks. Water was available ad libitum; food was available ad libitum except during exposure. Rats were housed individually during exposure. Clinical observations were recorded once per week. Animals were weighed prior to initiation, and then weekly for 13 weeks, and monthly thereafter until week 92, and every 2 weeks until week 103, and at the end of the study. Necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus were weighed. Visible lesions and tissues masses were subject to microscopic examination. Complete histopathologic examination was performed on all animals.

Aldehyde vapor was dynamically generated by bubbling nitrogen gas through a column of liquid maintained at a constant temperature in a water bath. Diluting air was added to the nitrogen-isobutyraldehyde vapor immediately above the bubbler to prevent condensation of isobutyraldehyde in the manifold or deliver lines when cooled to room temperature. Inhalation chambers (1.15 cubic meters) of the Rochester design were used. Chamber ventilation provided 12 to 15 clean-air (charcoal and HEPA filtered) changes per hour. A small particle detector was used to ensure that aldehyde vapor and not aerosol was produced. Chamber concentrations were monitored 4 times per hour using an 8-port stream select valve with two on-line gas chromatographs (Hewlett Packard Model 5840), which measured the concentration of valeraldehyde present.

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958). The primary statistical method used for the evaluation of tumor incidence was logistic regression analysis (Dinse and Lagakos, 1983; Dinse and Haseman, 1986; McKnight and Crowley, 1984). Additional methods used



Result:	<p>included the life table test appropriate for rapidly lethal neoplasms (Cox, 1972; Tarone, 1975), and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart et al., 1979). Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-related trend.</p> <p>There were no significant differences in survival rates between exposed and control male or female rats. The mean body weights of exposed male and female rats were similar to those of controls throughout the 2-year study. There were no clinical findings that could be attributed to isobutyraldehyde exposure. No increase in the incidence of neoplasms was observed in rats of either sex that could be attributed to isobutyraldehyde exposure. Three primary nasal tumors were observed among exposed animals. One polypoid adenoma was present in the anterior nose section of a male rat exposed to 1000 ppm; one adenoma of the vomeronasal organ was observed in a male exposed to 2000 ppm, and an undifferentiated sarcoma was present in the posterior nasal section of the nose a female exposed to 500 ppm.</p>
Reliability: Reference:	<p>Exposure-related non-neoplastic lesions were limited to the nose and included squamous metaplasia of the respiratory epithelium, degeneration of the olfactory epithelium, and suppurative inflammation. Incidences of minimal to mild squamous metaplasia was significantly increased in male and female rats exposed to 1000 and 2000 ppm, and in females exposed to 500 ppm isobutyraldehyde. The incidences of minimal to mild degeneration of the olfactory epithelium and suppurative inflammation were increased in male and female rats exposed to 2000 ppm.</p> <p>score = 1; valid without restrictions, GLP guideline study</p> <p>Abdo, K.M., Haseman, J.K. and Nyska, A. 1998. Isobutyraldehyde administered by inhalation (whole body exposure) for up to thirteen weeks or two years was a respiratory tract toxicant but was not carcinogenic in F344/N rats and B6C3F1 mice. Toxicol. Sci. 42: 136-151.</p>
(b) Test material: Remark:	<p>isobutyraldehyde</p> <p>There are no repeat-dose toxicity studies for valeraldehyde. Isobutyraldehyde is a 4-carbon analog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as isobutyraldehyde can be valuable in assessing the toxicity of valeraldehyde.</p>
Species:	mouse
Sex:	male/female
Strain:	F344/N
Route of admin.:	inhalation
Exposure period:	104 weeks
Frequency of treatment:	6 hr/day, 5 days a week
Post. obs. period:	3 to 7 days after last day of exposure
Doses:	0, 500, 1000, 2000 ppm
Control Group:	yes, concurrent
NOAEC:	500 ppm (including respiratory effects)
Year:	1998

GLP: yes  
Test substance: isobutyraldehyde, 98.6 to 99.1% pure  
Method: Groups of male and female mice (6 weeks old) were distributed randomly into experimental groups of approximately equal weight (50 males and 50 females at each dose) and were housed individually. Mice were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, or 2000 ppm for 6 hours per day, 5 days per week, for 104 weeks. Water was available ad libitum; food was available ad libitum except during exposure. Mice were housed individually during exposure. Clinical observations were recorded once per week. Animals were weighed prior to initiation, and then weekly for 13 weeks, and monthly thereafter until week 92, and every 2 weeks until week 104, and at the end of the study. Necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus were weighed. Visible lesions and tissues masses were subject to microscopic examination. Complete histopathologic examination was performed on all animals.

Aldehyde vapor was dynamically generated by bubbling nitrogen gas through a column of liquid maintained at a constant temperature in a water bath. Diluting air was added to the nitrogen-isobutyraldehyde vapor immediately above the bubbler to prevent condensation of isobutyraldehyde in the manifold or deliver lines when cooled to room temperature. Inhalation chambers (1.15 cubic meters) of the Rochester design were used. Chamber ventilation provided 12 to 15 clean-air (charcoal and HEPA filtered) changes per hour. A small particle detector was used to ensure that aldehyde vapor and not aerosol was produced. Chamber concentrations were monitored 4 times per hour using an 8-port stream select valve with two on-line gas chromatographs (Hewlett Packard Model 5840), which measured the concentration of valeraldehyde present.

The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958). The primary statistical method used for the evaluation of tumor incidence was logistic regression analysis (Dinse and Lagakos, 1983; Dinse and Haseman, 1986; McKnight and Crowley, 1984). Additional methods used included the life table test appropriate for rapidly lethal neoplasms (Cox, 1972; Tarone, 1975), and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart et al., 1979). Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall dose-related trend.

Result: The survival rates among male mice exposed to 2000 ppm was marginally reduced relative to controls. There were no significant differences in survival rates between exposed and control females. The mean body weights of exposed male mice were similar to those of controls throughout the 2-year study. The mean body weights of female mice exposed to 1000 and 2000 ppm were lower than controls during the second year of the study. There were no clinical findings that could be attributed to isobutyraldehyde exposure. No increase in the incidence of neoplasms was observed in mice of either sex that could be attributed to isobutyraldehyde exposure.

<p>Remark: Reliability: Reference:</p>	<p>Exposure-related non-neoplastic lesions were limited to the nose. There was a significant increase in the incidence of olfactory epithelial degeneration in mice exposed to 1000 and 2000 ppm. Affected olfactory epithelium was characterized by fewer layers of sensory cells, which were often disorganized or irregular in thickness. In some mice, respiratory-like epithelium replaced areas of olfactory epithelium. Necrosis of the olfactory epithelium was observed in 2 mice in both the 1000 and 2000 ppm groups. There was no evidence of squamous metaplasia and suppurative inflammation. No increase in nasal lesions was observed in mice exposed to 500 ppm.</p> <p>The NOAEC for this study in male and female mice is 500 ppm. Score = 1; valid without restrictions, GLP guideline study</p> <p>Abdo, K.M., Haseman, J.K. and Nyska, A. 1998. Isobutyraldehyde administered by inhalation (whole body exposure) for up to thirteen weeks or two years was a respiratory tract toxicant but was not carcinogenic in F344/N rats and B6C3F1 mice. Toxicol. Sci. 42: 136-151.</p>
<p>(c) Test material: Remark:</p>	<p>isobutyraldehyde</p> <p>Isobutyraldehyde is a 4-carbon homolog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as isobutyraldehyde can be valuable in assessing the toxicity of n-valeraldehyde.</p>
<p>Species: Sex: Strain: Route of admin.: Exposure period: Frequency of treatment: Post. obs. period: Doses: Control Group: NOAEC: Year: GLP: Test substance: Method:</p>	<p>rat</p> <p>male/female</p> <p>F344/N</p> <p>inhalation</p> <p>13 weeks</p> <p>6 hr/day, 5 days a week</p> <p>none</p> <p>0, 500, 1000, 2000, 4000, and 8000 ppm</p> <p>yes, concurrent</p> <p>1000 ppm (including respiratory effects)</p> <p>1998</p> <p>yes</p> <p>isobutyraldehyde, 98.6 to 99.1% pure</p> <p>Groups of 10 male and 10 female rats (6 weeks old) were distributed randomly into experimental groups of approximately equal weight and were housed individually. Animals were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, 2000, 4000, and 8000 ppm for 6 hours per day, 5 days per week, for 13 weeks. Water was available ad libitum; food was available ad libitum except during exposure. Rats were housed individually during exposure. Clinical observations were recorded once per week. Animals were weighed prior to initiation, and then weekly and at the end of the study. Necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus were weighed. Visible lesions and tissues masses were subject to microscopic examination. Complete histopathologic examination was performed on control and 4000 ppm male rats, and control and 2000 ppm females.</p>

	Aldehyde vapor was dynamically generated by bubbling nitrogen gas through a column of liquid maintained at a constant temperature in a water bath. Diluting air was added to the nitrogen-isobutyraldehyde vapor immediately above the bubbler to prevent condensation of isobutyraldehyde in the manifold or deliver lines when cooled to room temperature. Inhalation chambers (1.15 cubic meters) of the Rochester design were used.
	Chamber ventilation provided 12 to 15 clean-air (charcoal and HEPA filtered) changes per hour. A small particle detector was used to ensure that aldehyde vapor and not aerosol was produced. Chamber concentrations were monitored 6 to 14 times per exposure interval with an infrared spectrophotometer, which measured total aldehydes present
Result:	All rats exposed to 8000 ppm died before the end of the study. Three male rats and six female rats from the 4000 ppm group, and one female in the 500 ppm group also died. Surviving rats in the 4000 ppm group displayed decreased mean body weights and body weight gains. Clinical observations of exposed animals in the 8000 and 4000 ppm groups included abnormal respiratory sounds, slowed respiration, decreased activity, nasal discharge, and prostration. At necropsy, no visible gross lesions were observed that could be attributed to isobutyraldehyde exposure. No significant organ weight changes were observed. Rats in the 8000 ppm group displayed congestion and severe necrosis of the epithelium of the nasal turbinates, accompanied by acute inflammation and accumulation of serous or fibropurulent exudates within the nasal passages. Rats exposed to 4000 ppm had mild epithelial hyperplasia of the mucosa of the nasal cavity and nasopharynx. Increased incidences of squamous metaplasia and mild acute, suppurative inflammation was note. In addition mild osteodystrophy of the bones of the maxillo- and nasoturbinates, characterized by decreased number of osteoblasts, increased numbers of osteoclasts, decreased bone density, and increased amounts of periosteal connective tissue. These changes were accompanied by inflammation of the overlying mucosa. In rats exposed to 2000 ppm, mild degeneration of the olfactory epithelium characterized by reduced thickness and loss of sensory nuclei. Examination of the trachea and larynx revealed evidence of necrosis in rats exposed to 8000 ppm.
Reliability:	score = 1; valid without restriction, GLP study
Reference:	Abdo, K.M., Haseman, J.K. and Nyska, A. 1998. Isobutyraldehyde administered by inhalation (whole body exposure) for up to thirteen weeks or two years was a respiratory tract toxicant but was not carcinogenic in F344/N rats and B6C3F1 mice. Toxicol. Sci. 42: 136-151.
(d) Test material:	isobutyraldehyde
Remark:	Isobutyraldehyde is a 4-carbon homolog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as isobutyraldehyde can be valuable in assessing the toxicity of valeraldehyde
Species:	mouse
Sex:	male/female
Strain:	B6C3F1

Route of admin.:	inhalation
Exposure period:	13 weeks
Frequency of treatment:	6 hr/day, 5 days a week
Post. observation interval:	none
Doses:	0, 500, 1000, 2000, 4000, and 8000 ppm
Control Group:	yes, concurrent
NOAEC:	500 ppm (including respiratory effects)
Year:	1998
GLP:	yes
Test substance:	isobutyraldehyde, 98.6 to 99.1% pure
Method:	Groups of 10 male and 10 female mice (6 weeks old) were distributed randomly into experimental groups of approximately equal weight and were housed individually. Animals were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, 2000, 4000, and 8000 ppm for 6 hours per day, 5 days per week, for 13 weeks. Water was available ad libitum; food was available ad libitum except during exposure. Mice were housed individually during exposure. Clinical observations were recorded once per week. Animals were weighed prior to initiation, and then weekly and at the end of the study. Necropsy was performed on all animals. The brain, heart, right kidney, liver, lungs, right testis, and thymus were weighed. Visible lesions and tissues masses were subject to microscopic examination. Complete histopathologic examination was performed on control 2000 ppm mice. Aldehyde vapor was dynamically generated by bubbling nitrogen gas through a column of liquid maintained at a constant temperature in a water bath. Diluting air was added to the nitrogen-isobutyraldehyde vapor immediately above the bubbler to prevent condensation of isobutyraldehyde in the manifold or deliver lines when cooled to room temperature. Inhalation chambers (1.15 cubic meters) of the Rochester design were used. Chamber ventilation provided 12 to 15 clean-air (charcoal and HEPA filtered) changes per hour. A small particle detector was used to ensure that aldehyde vapor and not aerosol was produced. Chamber concentrations were monitored 6 to 14 times per exposure interval with an infrared spectrophotometer, which measured total aldehydes present
Result:	No significant clinical observations of exposed mice were reported. With the exception of one male in the 4000 ppm group, all mice exposed to 4000 and 8000 ppm died before the end of the study. One male in the 1000 ppm group also died. Surviving male mice had final mean body weights and mean body weight gains that were comparable to control values. The final mean body weight and mean body weight gain of female mice in the 1000 ppm group were significantly lower than controls. No gross lesions that could be attributed to exposure were observed at necropsy. Absolute and relative kidney weights of males in the 1000 and 2000 ppm groups were greater than controls. Absolute liver weight of 1000 ppm females and relative liver weights of 500 ppm females were lower than controls. Absolute thymus weight of 1000 ppm females and relative and absolute thymus weights of 2000 ppm females were less than control values. No lesions were observed in these organs. Increased incidences of non-neoplastic lesions of the nasal cavity were observed in mice exposed to 1000 and 2000 ppm

	isobutyraldehyde. These lesions included necrosis, inflammation, hyperplasia, and squamous metaplasia of the epithelium. Serous and suppurative exudates within the nasal passages was also observed. Mild osteodystrophy of the bones of the maxillo- and nasoturbinate was also observed characterized by decreased number of osteoblasts, increased numbers of osteoclasts, decreased bone density, and increased amounts of periosteal connective tissue. These changes were accompanied by degeneration of the olfactory epithelium characterized by reduced thickness and loss of sensory nuclei.
Reliability:	(1) valid without restrictions, GLP study
Reference:	Abdo, K.M., Haseman, J.K. and Nyska, A. 1998. Isobutyraldehyde administered by inhalation (whole body exposure) for up to thirteen weeks or two years was a respiratory tract toxicant but was not carcinogenic in F344/N rats and B6C3F1 mice. Toxicol. Sci. 42: 136-151.
(e) Test material:	butyraldehyde, isobutyraldehyde
Remark:	Butyraldehyde and isobutyraldehyde are 4-carbon analogs of valeraldehyde. Information regarding the relative toxicity of these closely related aldehydes can be valuable in assessing the potential toxicity of n-valeraldehyde.
Species:	rat
Sex:	male/female
Strain:	other: Alderley Park SPF
Route of admin.:	inhalation
Exposure period:	2.5 weeks
Frequency of treatment:	6 hr/day, 5 days a week for a total of 12 exposures
Post. obs.period:	no data
Doses:	1000 ppm
Control Group:	other: historical and/or concurrent
NOAEC:	1000 ppm (n-buteraldehyde) < 1000 ppm (isobutyraldehyde – includes respiratory effects)
Year:	1970
GLP:	no
Test substance:	butyraldehyde (purity not specified), isobutyraldehyde (92% pure)
Method:	Groups of 4 male and 4 female Alderley Park SPF rats (average weight 200 g) were exposed to 1000 ppm butyraldehyde or isobutyraldehyde vapor in air for 6 hr/day, 5 days/week, for 12 exposures. Between exposures, animals were returned to their cages where food and water were freely available.
	Aldehyde vapor was dynamically generated by injecting the liquid at a known rate into a metered stream of air were weighed prior to each exposure, and their condition and behavior recorded throughout the exposure interval. Urine was collected overnight after the last exposure day. Urine tests included specific gravity, pH, sugar, bilirubin, and protein. Fasted animals were sacrificed and blood collected by cardiac puncture. Hematology tests included hemoglobin concentration, packed cell volume, white and differential cell counts, platelet count, clotting function, and urea, sodium and potassium concentrations. Each animal was subjected to necropsy; the lungs, liver, kidneys, spleen and adrenals were prepared for histological examination. Historical and/or concurrent

	controls were exposed to air only, using the same exposure regimen. Laboratory tests on controls were performed prior to exposure.
Result:	Rats were exposed to butyraldehyde or isobutyraldehyde vapor in air for 6 hr/day, 5 days/week, for 12 exposures. Rats exposed to butyraldehyde exhibited no signs of toxicity. Rats exposed to isobutyraldehyde exhibited signs of slight nasal irritation. At autopsy, organs appeared normal. Urinalysis and hematology tests were normal. Histological examination of tissues revealed no pathology.
Remark:	Although evidence of slight nasal irritation was noted during exposure, nasal tissues were not examined microscopically for evidence of acute or chronic irritation.
Reliability:	score = 2, valid with restrictions, data from collection of data; purity of test article not specified
Reference:	Gage J.C. 1970. The subacute inhalation toxicity of 109 industrial chemicals. <i>Brit. J. Ind. Med.</i> 27: 1-18.
(f) Test substance:	butyraldehyde
Remark:	Butyraldehyde is a 4-carbon homolog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as butyraldehyde can be valuable in assessing the toxicity of valeraldehyde.
Species:	rat
Sex:	male/female
Strain:	F-344
Route of admin.:	inhalation
Exposure period:	13 weeks
Frequency of treatment:	6 hr/day 5 days a week
Post. obs. period:	none
Doses:	0, 125, 500, or 2000 ppm
Control Group:	air only
NOAEC	< 125 ppm (including respiratory effects)
Method:	Groups of male and female rats were exposed to target concentrations of 0, 125, 500, or 2000 ppm butyraldehyde for 6 hr/day, 5 days/week for 13 weeks.
GLP:	yes
Year:	1979
Result:	Measured concentrations for each group was determined to be 117, 462, and 1852 ppm. Animals at all treatment levels had a significant increase in squamous metaplasia of the nasal cavity. No other treatment-related effects were noted.
Reliability:	score = 2, purity of test article not specified
Reference:	Union Carbide Corporation. 1979. Carnegie-Mellon Institute of Research Report 42-50., dated June 11, 1979.
(g) Test substance:	n-butyraldehyde
Remark:	Butyraldehyde is a 4-carbon homolog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as butyraldehyde can be valuable in assessing the toxicity of valeraldehyde.
Species:	dog
Sex:	not specified
Strain:	Beagle
Route of admin.:	inhalation

Exposure period:	14 weeks
Frequency of treatment:	6 hr/day, 5 days a week
Post. obs. period:	none
Doses:	0, 125, 500, or 2000 ppm
Control Group:	air only
NOAEC:	< 125 ppm (includes respiratory effects)
Method:	Groups of dogs were exposed to 0, 125, 500, or 2000 ppm butyraldehyde for 6 hr/day, 5 days/week for 14 weeks.
GLP:	yes
Year:	1979
Result:	Dogs exposed to 2000 ppm had significant microscopic lesions of the upper respiratory tract, including mucosal cell hyperplasia, inflammation, and squamous metaplasia. Dogs exposed at 125 and 500 ppm had goblet cell hyperplasia within the nasal mucosa. No other treatment-related effects were noted.
Reliability:	score = 2; valid with restriction; purity of test article not specified
Reference:	Union Carbide Corporation. 1979. Carnegie-Mellon Institute of Research Report 42-50., dated June 11, 1979.
(h) Test substance:	butyraldehyde
Remark:	Butyraldehyde is a 4-carbon homolog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as butyraldehyde can be valuable in assessing the toxicity of valeraldehyde
Species:	rat
Sex:	male/female
Strain:	F-344
Route of admin.:	inhalation
Exposure period:	12 weeks
Frequency of treatment:	6 hr/day, 5 days a week
Post. obs. period:	4 weeks
Doses:	0, 1, 10, or 50 ppm
Control Group:	air only
NOAEC:	50 ppm
Method:	Groups consisting of 15 male and 15 female rats were exposed 6 hr/day, 5 days/week for at least 12 weeks to butyraldehyde vapor at target concentrations of 1, 10, and 50 ppm.
GLP:	yes
Year:	1979
Result:	Animals were exposed to measured concentrations of 1.1, 10.3, and 51.3 ppm butyraldehyde for up to 12 weeks. Slight wetness around the nares and urogenital area, with occasional occurrences of reddish-black encrustation around the nares was observed in both males and females at all exposure levels as well as the control group. No treatment-related effects were observed. No adverse effects on the nasal, olfactory, or respiratory epithelial tissues were observed. Lesions encountered in the respiratory tract were compatible with intercurrent infection with Streptococcus pneumonia and Mycoplasma pulmonis and were comparable in frequency and intensity in control and exposed rats.
Remark:	The intercurrent infection of the respiratory tract may have masked any minor irritation effects caused by butyraldehyde to the nasal



<p>Reliability: Reference:</p>	<p>cavity. However, it can be concluded from this study that butyraldehyde, at the concentrations tested, did not induce severe irritation or degeneration of the respiratory tract, and did not potentiate the effects of the infection process already present in rats. score = 2, valid with restriction, purity of test article not specified Union Carbide Corporation. 1980. Unpublished study. Butyraldehyde. Twelve-Week Vapor Inhalation Study in Rats Bushy Run Research Center Report 43-61, dated September 17, 1980.</p>
<p>(i) Test substance: Remark:</p> <p>Species: Sex: Strain: Route of admin.: Exposure period: Frequency of treatment: Post. obs. period: Doses: Control Group: LOAEL: Method:</p> <p>Year: GLP: Test substance: Result:</p> <p>Reliability: Reference:</p>	<p>butyraldehyde Butyraldehyde is a 4-carbon homolog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as butyraldehyde can be valuable in assessing the toxicity of valeraldehyde.</p> <p>rat male/female F344/N oral (gavage) 13 weeks 5 days a week none 0, 0.075, 0.15, 0.3, 0.6, or 1.2 g/kg/day vehicle control 0.075 g/kg/day (includes respiratory effects) Groups of 10 male and 10 female rats received butyraldehyde in corn oil by gavage at dose levels of 0.075, 0.15, 0.3, 0.6, or 1.2 g/kg/day. Animals were dosed 5 days per week for 13 weeks.</p> <p>1987 yes butyraldehyde, purity not specified Treatment-related lesions were noted in the nasal cavity at all dose levels. Stomach lesions were noted at 1.2 and 0.6 g/kg/day. There was decreased body weight gain in animals in the 1.2 g/kg groups. A dose-related increase in mortality was also observed.</p> <p>score = 4; data from abstract; insufficient for assessment Wolfe, C.W. et al. 1987. Thirteen week subchronic toxicity study of butyraldehyde in F344 rats and B6C3F1 mice. The Toxicologist 7.</p>
<p>(j) Test substance: Remark:</p> <p>Species: Sex: Strain: Route of admin.: Exposure period: Frequency of treatment: Post. obs. period: Doses: Control Group:</p>	<p>butyraldehyde Butyraldehyde is a 4-carbon homolog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as butyraldehyde can be valuable in assessing the toxicity of valeraldehyde.</p> <p>mouse male/female B6C3F1 oral (gavage) 13 weeks 5 days a week none 0, 0.075, 0.15, 0.3, 0.6, or 1.2 g/kg/day vehicle control</p>

NOAEL:	0.15 g/kg/day (150 mg/kg/day) (includes respiratory effects)
Method:	Groups of 10 male and 10 female mice received butyraldehyde in corn oil by gavage at dose levels of 0.075, 0.15, 0.3, 0.6, or 1.2 g/kg/day. Animals were dosed 5 days per week for 13 weeks.
Year:	1987
GLP:	yes
Test substance:	butyraldehyde
Result:	Treatment-related lesions were noted in the nasal cavity at 0.3 g/kg/day and above. Stomach lesions were noted at 1.2 g/kg/day. There was decreased body weight gain in animals in the 1.2 g/kg groups. Mortality was also observed only in mice that received 1.2 g/kg/day. Based on these results, the NOEL was 0.15 g/kg/day.
Reliability:	score = 4; data from abstract; insufficient for assessment
Reference:	Wolfe, C.W. et al. 1987. Thirteen week subchronic toxicity study of butyraldehyde in F344 rats and B6C3F1 mice. The Toxicologist 7:

## 5.5 GENETIC TOXICITY IN VITRO

### A. BACTERIAL IN VITRO TEST

(a) Preferred value	reliability score = 2, valid with restrictions
Type:	Ames test
System of testing:	S. typhimurium TA 100, 102, 104
Concentration:	100 - 10000 ug/plate
Metabolic activation:	with and without
Result:	negative
Method:	other: see Maron DM and Ames, B. 1983. Mutat Res 113: 25-34
Year:	1983
GLP:	no data
Test substance:	valeraldehyde, 98+% purity (Fluka)
Method:	Valeraldehyde was tested for mutagenicity in Salmonella typhimurium tester strains TA100, TA102 and TA104 in the presence and absence of Arochlor-induced liver S-9 mix from F344 rats and B6C3F1 mice, at a dose range of 100-10,000 ug/plate. A minimum of three plates per dose were tested using the pre-incubation (Maron and Ames, 1983) protocol. The highest dose was limited by toxicity, which was determined by a thinning of the background lawn, or a reduction in the number of colonies per plate, or both. Liver S-9 was prepared from Arochlor 1254-induced male F344 rats and male B6C3F1 mice. S-9 mix was used at 10 and/or 30%.
	2-Aminoanthracene was used as a positive control for all strains with S-9 added. Without S-9 activation, methyl methanesulfonate, mitomycin C, and formaldehyde or crotonaldehyde were used for tester strains TA100, TA102, and TA104, respectively. Significance of mean revertant counts at individual dose levels was assessed using Dunnett's t-test; dose response effects were analyzed by Wahrendorf ranking and linear regression.
	Responses were considered mutagenic when reproducible, low level increases were obtained, or when both positive and equivocal responses were observed in repeat trials. Responses were considered

**Result:** equivocal when increases in revertants were not reproducible, or were seen only at a single dose. Valeraldehyde was toxic at the high dose of 10000 ug/plate, and scoring was performed on plates within the dose range of 333 to 3333 ug/plate. Valeraldehyde did not produce a mutagenic response, at doses up to 3.3 mg/plate, under all test conditions. There was no increase in the number of revertants produced after exposure to valeraldehyde in tests using the preincubation protocol, both in the presence and absence of S-9 from rats and mice.

**Remark:** Formaldehyde and gluteraldehyde were mutagenic in all strains tested, both in the presence and absence of S-9 metabolic activation. Butyraldehyde and isobutyraldehyde were also tested using the same protocol and under the same conditions, at doses of 10 to 1000 ug/plate and 50 to 5000 ug/plate, respectively. Like valeraldehyde, these aldehydes were also negative in the presence and absence of rat and mouse metabolic activation systems. Propionaldehyde was not mutagenic, even when tested at concentrations up to 3.3% in the vapor phase protocol.

Results of Mutagenicity Testing for Aldehydes

Aldehyde	Concentration tested	w/S9	w/oS9
Propionaldehyde	up to 3.3% in vapor	neg	neg
Butyraldehyde	33-3333 ug/plate	neg	neg
Isobutyraldehyde	50-5000 ug/plate	neg	neg
Valeraldehyde	33-3333 ug/plate	neg	neg

w/S9: with S9 activation from Aroclor-induced mouse and rat S-9s.  
w/oS9: without S9 activation from Aroclor-induced mouse and rat S-9s.

**Reliability:** score = 2, valid with restriction; purity of test article not verified  
**Reference:** Dillon, D., Combes, R. and Zeiger, E. 1998. Effectiveness of Salmonella strains TA 100, TA102 and TA104 for detecting mutagenicity of some aldehydes and peroxides. *Mutagenesis* 134: 19-26.

(b) **Type:** Ames test  
**System of testing:** Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537  
**Concentration:** 3 umol/plate  
**Metabolic activation:** with and without  
**Result:** negative  
**Method:** other: see Ames, B.N. et al.: *Mutation Research* 31, 347-354.  
**Year:** 1975  
**GLP:** no data  
**Test substance:** valeraldehyde, purity at least 97%  
**Remark:** 239 compounds, representing gaseous and semivolatile phases of tobacco smoke were assay for mutagenicity. All compounds were tested with and without metabolic activation, using liver S9 from Aroclor 1254- or methylcholanthrene-induced Sprague Dawley rats. Valeraldehyde was negative when tested in the Ames test. Propionaldehyde, butyraldehyde, isobutyraldehyde, isovaleraldehyde, and hexaldehyde were also tested at 3 umol/plate using the same

<p>Reliability: Reference:</p>	<p>protocol. These aldehydes were also negative in the presence and absence of rat metabolic activation systems. score = 2: valid with restriction; only one dose level tested Florin, I., Rutberg, L., Curvall, M. and Enzell, C.R. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' Test. Toxicology 15: 219-232.</p>
<p>(c) Type: System of testing: Concentration: Metabolic activation: Result: Method: Year: GLP: Test substance: Remark:</p>	<p>Ames test  Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537 100-10,000 ug/plate  with and without negative other: see Ames, B.N. et al.: Mutation Research 31, 347-354. 1996 no data n-valeraldehyde Valeraldehyde was tested in the standard plate incorporation assay with and without metabolic activation, using liver S9 from Aroclor 1254-induced Sprague Dawley rat and Syrian hamsters.</p>
<p>Result: Reliability: References:</p>	<p>Valeraldehyde was negative under all test conditions. score = 4, not assignable; documentation insufficient for assessment NTP. 1996. NTP Results Report, Results, Status, and Publications Information on All NTP Chemicals. National Toxicology Program. Research Triangle Park, NC, dated May 8, 1996.  National Cancer Institute. Short-term Test Program Sponsored by the Division of Cancer Etiology, Dr. David Longfellow, Project Officer. <i>cited in</i> HSDB. Valeraldehyde.. CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.</p>

**B. NON-BACTERIAL IN VITRO TEST**

<p>(a) Preferred result Type: System of testing: Concentration: Metabolic activation: Result: Method:</p>	<p>reliability score = 2, valid with restrictions Sister chromatid exchange (SCE) assay  human lymphocytes 0.002, 0.003 vol%  without negative Human lymphocytes were grown in synthetic medium supplemented with 10% (v/v) calf serum. Incubation time was 5 days. After three days, bromodeoxyuridine (BrDU) was added to each culture at a final concentration of 10E-5. Aldehyde solutions were prepared in a 50% (v/v) ethanol solution; from the stock solution, 10 or 15 ul of the test material solution was added to each culture. Cells were exposed to aldehydes for 24 and 48 hrs. Colcemide (0.8 ug/ml) was added to the cultures 4 hours prior to termination. Control cultures were untreated, solvent controls were exposed to ethanol at concentration of 0.15%. All experiments were performed in duplicate. Positive control cultures were exposed to formaldehyde and acetaldehyde.</p>
---	---

Year: 1979  
 GLP: no data  
 Test substance: n-valeraldehyde, purity not specified  
 Result: Valeraldehyde, at a concentration of 0.002 and 0.003 volume % did not produce a significant increase in the incidence of SCEs in human lymphocytes after 24 or 48 hr incubation.  
 Remark: Propionaldehyde, butyraldehyde, isobutyraldehyde, and isovaleraldehyde were tested using the same protocol and test concentrations. These aldehydes were also negative in the SCE assay using human lymphocytes.

Genotoxicity Testing of Aldehydes

Aldehyde	Concentration	Treatment	Results
Propionaldehyde	0.002 vol %	24 hr	negative
	0/003 vol %	48 hr	negative
	0.003 vol %	48 hr	negative
Butyraldehyde	0.002 vol %	24 hr	negative
	0.002 vol %	48 hr	negative
Isobutyraldehyde	0.002 vol %	24 hr	negative
	0.002 vol %	48 hr	negative
Valeraldehyde	0.002 vol %	24 hr	negative
	0.002 vol %	48 hr	negative
	0.003 vol %	48 hr	negative
Isovaleraldehyde	0.002 vol %	24 hr	negative
	0.002 vol %	48 hr	negative
	0.003 vol %	48 hr	negative

Reliability: score = 2, valid with restriction; purity of test materials not specified  
 Reference: Obe, G. and Beek, B. 1979. Mutagenic activity of aldehydes. Drug Alcohol Depend. 4: 91-94.

(b) Type: DNA repair assay  
 System of testing: human and rat hepatocytes  
 Concentration: 3, 10, and 30 mM (equivalent to 258, 861, and 2580 ug/ml, respectively)  
 Metabolic activation: without  
 Result: weakly positive in rat hepatocytes  
 negative in human hepatocytes  
 Method: other: see Cajelli, E. et al. 1987. Mutat. Res. 190: 47-50.  
 Year: 1994  
 GLP: no data  
 Test substance: valeraldehyde, purity 98% (Merck)  
 Method: Primary rat hepatocytes were isolated from male Sprague Dawley rats by in situ perfusion of the liver with collagenase (see Williams, G. 1977. Cancer Res.97: 1845-1850). Cell suspensions with a viability of less than 80%, as determined by trypan blue exclusion, were not used. Human hepatocytes were prepared from apparently healthy fragments of liver discarded during surgery from one male and one female donor (See Strom, S.C. et al. 1982. J. Natl. Cancer Inst. 68: 771-778). Fragments were checked macro- and microscopically and were devoid of appreciable alterations.

Viability of hepatocytes from the male and female donor was 65% and 83%, respectively. Hepatocytes were suspended in medium and plated in petri dishes coated with rat tail collagen. After a 3 hr attachment interval, dishes were washed and refed with medium containing half-log spaced concentrations of valeraldehyde. There is no mention what solvent was used to prepare test concentrations. Cells were exposed for 20 hours to the test material and 10 uCi/ml [methyl-3H]thymidine, then processed for autoradiographic evaluation of unscheduled DNA synthesis (UDS) or DNA repair (see Williams, 1977). Valeraldehyde was evaluated in two independent experiments using duplicate cultures for each test concentration. Nuclear grain counts were recorded from 50 nuclei per dish. n-Nitrosodimethylamine was used at a dose of 5mM as the positive control. A solvent control was not included. Although two independent tests were performed, the data from both were pooled.

Results: Primary rat hepatocytes exposed to valeraldehyde displayed a slight increase in the incidence of DNA repair (UDS), as measured by the net nuclear grain count. The percentage of cells in repair, (percent cells with net nuclear labeling  $\geq 5$  grains) was increased at all concentrations tested.

UDS in Primary Rat Hepatocytes		
Valeraldehyde (mg/ml) <sup>1</sup>	NNGC <sup>2</sup> (+/- SD)	% repair
untreated control	0.63 +/- 4.76	5
258	2.35 +/- 4.24*	26
861	2.30 +/- 3.78*	23
2580	2.65 +/- 3.88*	22
NDMA <sup>^</sup>	33.41 +/- 23.11*	91

<sup>1</sup>ug/ml dose based on reported test concentrations of 3, 10, 30 mM

<sup>2</sup>net nuclear grain counts +/- standard deviation

<sup>^</sup> positive control (n-nitrosodimethylamine)

\* significant when assessed by Student's t-test (two-tailed)

In contrast, valeraldehyde did not induce an increase in the incidence of DNA repair in primary human hepatocytes.

UDS in Primary Human Hepatocyte		
Valeraldehyde (mg/ml) <sup>1</sup>	NNGC <sup>2</sup> (+/- SD)	% repair
untreated control	0.55 +/- 1.69	1
258	0.85 +/- 2.07	6
861	0.86 +/- 2.63	5
2580	1.09 +/- 3.02	8
NDMA <sup>^</sup>	18.13 +/- 4.95*	90

<sup>1</sup>ug/ml dose based on reported test concentrations of 0, 3, 10, 30 mM

<sup>2</sup>net nuclear grain counts +/- standard deviation

<sup>^</sup> positive control (n-nitrosodimethylamine)

\* significant when assessed by Student's t-test (two-tailed)

Remark: Propionaldehyde, butyraldehyde and hexaldehyde were tested using the same protocol and mM test concentrations. Results obtained from human and rat cells exposed to these aldehydes were very similar to that obtained with valeraldehyde in that they induced a slight increase in the incidence of UDS in primary rat hepatocytes, but not in human hepatocytes.

<p>Reliability: Reference:</p>	<p>score: 2, valid with restrictions; diluent solvent not specified Martelli, A., Canonero, R., Cavanna, M., Ceradelli, M., and Marinari, U.M. 1994. Cytotoxic and genotoxic effects of five n-alkanals in primary cultures of rat and human hepatocytes. <i>Mutat. Res.</i> 323: 121-126.</p>
<p>(c) Type: System of testing: Concentration:</p>	<p>HGPRT assay (forward mutation assay)  Chinese Hamster V79 cells 3, 10, and 30 mM (equivalent to 258, 861, and 2580 ug/ml, respectively)</p>
<p>Metabolic activation: Result: Method: Year: GLP: Test substance: Method:</p>	<p>without positive other: see Cajelli, E. et al. 1987. <i>Mutat. Res.</i> 190: 47-50. 1987 no data valeraldehyde, purity 98% (Merck) Chinese hamster V79 cells were exposed for 60 minutes to 0, 3, 10, 30, or 90 mM valeraldehyde in serum-free medium and in the absence of metabolic activation in a quantitative re-plating assay for induced mutation frequency at the HGPRT locus or the Na/K ATPase locus. After exposure, the medium containing the test article was removed and cells were cultured in fresh medium for a six-day mutant expression interval.</p>
<p>Result:</p>	<p>For selection of mutants at the HGPRT locus, TG (6-thioguanine) was added 2 hr after seeding to give a final concentration of 10 ug/ml. The fraction of TG-resistant cells was determined by counting mutant colonies 8 days after seeding 3 x 10E5 cells per 100 mm petri dish. A total of 10 dishes were evaluated. For selection of mutants at the Na/K ATPase locus, OUA (ouabain) was added 2 days after treatment to give a final concentration of 1 mM. The fraction of OUA-resistant cells was determined by counting mutant colonies after 16-18 days. A total of 18 dishes were evaluated. The relative survival was calculated by determining the ratio of the fraction of viable cells in treated cultures to the fraction of viable cells in control cultures. Negative control cultures were untreated. Cultures were exposed to 8 or 16 mM EMS (ethyl methanesulfonate) or 0.3 and 1.0 mM NMU (N-nitroso-N-methylurea) as positive controls for OUA-resistant and TG-resistant mutagenicity assays, respectively. Mutagenicity potency was defined as the mM concentration of the aldehyde that yielded a mutant frequency three times greater than the spontaneous mutant frequency.</p> <p>There was a dose-dependent decrease in the fraction of surviving cells, and a dose-dependent increase in mutation frequency at the HGPRT locus with TG as the selective agent, at the Na/K ATPase locus, with OUA as the selective agent. Assays were conducted up to maximal concentrations that did not produce severe reductions in plating efficiency. The range of effective concentrations was 10 to 30 mM for valeraldehyde. NMU and EMS, employed as positive controls at doses which produced similar reductions in plating efficiency, yielded higher mutation frequencies. The mutagenic potency of valeraldehyde was determined to be 11.8 mM for TG-</p>

resistance, and 14.6 mM for OUA-resistance. The mutagenicity index for NMU and EMS was 0.39 mM and 2.13 mM, respectively.

Mutagenicity Testing of Aldehydes in V79 Cells

Aldehyde	Dose (mM)	Mutant frequency	% Survival
Negative Control	0	15.1 +/- 0.3	89 +/- 0.04
Propionaldehyde	30	25.9 +/- 9.0	60 +/- 11
Butyraldehyde	30	50.7 +/- 7.5	47 +/- 26
Valeraldehyde	30	66.6 +/- 18.5	56 +/- 26
Hexaldehyde	30	31.7 +/- 4.5	46 +/- 0.8
Positive Control (MNU)	1	106.8 +/- 33.3	64 +/- 0.12

Mutation frequency represents number of TG-resistant colonies per 10E6 viable cells

% Survival = fraction of viable cells in treated cultures/fraction of viable cells in controls x 100

MNU = N-nitroso-N-methylurea

- Remark: Propionaldehyde, butyraldehyde, valeraldehyde, and hexaldehyde, which are formed in the terminal step of biomembrane lipid peroxidation in vivo, were determined to be direct-acting mutagens in V79 Chinese hamster cells when tested in the absence of a mammalian metabolic activation system. All displayed a similar dose-dependent increase in forward mutation frequency.
- Reliability: score = 2, valid with restrictions; metabolic activation not utilized, purity of test article not verified
- Reference: Brambilla, G., Cajelli, E., Canonero, R., Martelli, A., and Marinari, U.M. 1989. Mutagenicity in V79 Chinese hamster cells of n-alkanals produced by lipid peroxidation. *Mutagenesis* 4: 277-279.
- (d) Type: L5178Y/TK<sup>+/+</sup> Mouse Lymphoma Mutagenesis Assay
- System of testing: L5178Y mouse lymphoma cells
- Concentration: 0, 150, 200, 300, 400, 500 ug/ml with metabolic activation  
0, 60, 80, 100, 125, 150 ug/ml without activation
- Metabolic activation: with and without Aroclor 1254-induced rat liver S9
- Result: negative with metabolic activation  
positive in absence of metabolic activation
- Method: according to methods described by:  
Clive, D., Bolcsfoldi, G., Clements, J., Cole, J., Honma, M., Majeska, J., Moore, M., Muller, L., Myhr, B., Oberly, T., Oudelhkim, M., Rudd, C., Shimada, H., Sofuni, T., Thybaud, V. and Wilcox, P. (1995) Consensus agreement regarding protocol issues discussed during the mouse lymphoma workshop: Portland, Oregon, May 7, 1994. *Environ. Molec. Mutagen.* 25:165-168.
- Clive D., Johnson K.O., Spector J.F.S., Batson A.G. and Brown M.M.M. (1979) Validation and characterization of the L5178Y TK<sup>+/+</sup> mouse lymphoma mutagen assay system. *Mutation Res.* 59:61-108.
- Clive, D. and Spector, J.F.S. (1975) Laboratory procedure for assessing specific locus mutations at the TK locus in cultured L5178Y mouse lymphoma cells. *Mutation Res.* 31:17-29.
- Year: 2000
- GLP: yes



Test substance: valeraldehyde, purity not specified in report (tested as a coded material on behalf of study sponsor, the National Institute of Cancer)

Method: L5178Y cells, clone 3.7.2C, were obtained from Patricia Poorman-Allen, Glaxo Wellcome Inc., Research Triangle Park, NC on 15 August 1995. Each lot of cryo-preserved cells was tested using the agar culture and Hoechst staining procedures and found to be free of mycoplasma contamination. Prior to use in the assay, L5178Y cells were cleansed of spontaneous TK<sup>-/-</sup> cells by culturing in a restrictive medium (Clive and Spector, 1975).

Aroclor 1254-induced rat liver S9 was used as the metabolic activation system. The S9 was prepared from male Sprague-Dawley rats induced with a single intraperitoneal injection of Aroclor-1254, 500 mg/kg, five days prior to sacrifice. The S9, lot 1854, was purchased by BioReliance from Moltox and stored at  $\leq -70^{\circ}\text{C}$  until used.

A preliminary toxicity assay was used to establish the optimal concentrations for the mutagenesis assay. L5178Y cells were exposed to the DMSO solvent alone and nine concentrations of test article ranging from 0.5 to 5000  $\mu\text{g/ml}$  n-valeraldehyde in both the absence and presence of S9 activation with a 4-hour exposure and without activation with a 24-hour exposure. The osmolality of the solvent control and the highest soluble concentration in treatment medium were determined.

Cell population density was determined 24 and 48 hours after the initial exposure to the test article. The cultures were adjusted to  $3 \times 10^5$  cells/mL after 24 hours only. Cultures with less than  $3 \times 10^5$  cells/mL were not adjusted. Toxicity was measured as suspension growth of the treated cultures relative to the growth of the solvent control cultures after 48 hours.

The initial mutagenesis assay (using a 4-hour exposure with and without S9 activation) was used to evaluate the mutagenic potential of the test article. L5178Y mouse lymphoma cells were exposed to the solvent alone and at least eight concentrations of test article in duplicate in both the absence and presence of S9. Positive controls, with and without S9 activation, were tested concurrently.

The mutagenesis assay was performed according to a protocol described by Clive and Spector (1975). Treatment was carried out in conical tubes by combining  $6 \times 10^6$  L5178Y/TK<sup>+/+</sup> cells, F<sub>0</sub>P medium or S9 activation mixture, and 100  $\mu\text{L}$  dosing solution of test or DMSO solvent in a total volume of 10 mL. The positive controls were treated with MMS (methyl methane sulfonate, at final concentrations in treatment medium of 10 and 20  $\mu\text{g/mL}$ ) and 7,12-DMBA (7,12dimethylbenz(a)anthracene at final concentrations in treatment medium of 2.5, and 4.0  $\mu\text{g/mL}$ ). Treatment tubes were gassed with  $5 \pm 1\%$  CO<sub>2</sub> in air, capped tightly, and incubated with mechanical mixing for 4 hours at  $37 \pm 1^{\circ}\text{C}$ . The preparation and addition of the test article dosing solutions were carried out under amber lighting and the cells were incubated in the dark during the exposure period. After the treatment period, the cells were washed twice with F<sub>0</sub>P or F<sub>0</sub>P

supplemented with 10% horse serum, 2 mM L-glutamine, 100 U penicillin/mL and 100 µg streptomycin/mL (F<sub>10</sub>P). After the second wash, the cells were resuspended in F<sub>10</sub>P, gassed with 5±1% CO<sub>2</sub> in air and placed on the roller drum apparatus at 37 ± 1°C.

For expression of the mutant phenotype, the cultures were counted using an electronic cell counter and adjusted to 3x10<sup>5</sup> cells/mL at approximately 24 and 48 hours after treatment in 20 and 10 mL total volume, respectively. Cultures with less than 3x10<sup>5</sup> cells/mL were not adjusted.

For expression of the TK<sup>-/-</sup> mutant cells, cells were placed in cloning medium (C.M.) containing 0.22% dissolved Noble agar in F<sub>0</sub>P plus 20% horse serum. Two flasks per culture to be cloned were labeled with the test article concentration, activation condition, and either TFT (trifluorothymidine, the selective agent) or VC (viable count). Each flask was pre-warmed to 37 ± 1°C, filled with 100 mL C.M., and placed in an incubator shaker at 37 ± 1°C until used. The cells were centrifuged at 1000 rpm for 10 minutes and the supernatant was decanted. The cells were then diluted in C.M. to concentrations of 3x10<sup>6</sup> cells/100 mL C.M. for the TFT flask and 600 cells/100 mL C.M. for the VC flask. After the dilution, 1.0 mL of stock solution of TFT was added to the TFT flask (final concentration of 3 µg/mL) and both this flask and the VC flask were placed on the shaker at 125 rpm and 37 ± 1°C. After 15 minutes, the flasks were removed and the cell suspension was divided equally into each of three appropriately labeled petri dishes. To accelerate the gelling process, the plates were placed in cold storage (approximately 4°C) for approximately 30 minutes. The plates were then incubated at 37 ± 1°C in a humidified 5 ± 1% CO<sub>2</sub> atmosphere for the 10-14 days.

After the incubation period, the VC plates were counted for the total number of colonies per plate and the total relative growth determined. The TFT-resistant colonies were then counted for each culture with ≥ 20% total relative growth (including at least one concentration with ≥ 10% but ≤ 20% total growth). The diameters of the TFT-resistant colonies for the positive and solvent controls and, in the case of a positive response, the test article-treated cultures were determined over a range of approximately 0.2 to 1.1 mm. The rationale for this procedure is as follows: Mutant L5178Y TK<sup>-/-</sup> colonies exhibit a characteristic frequency distribution of colony sizes. The precise distribution of large and small TFT-resistant mutant colonies appears to be the characteristic mutagenic "finger-print" of carcinogens in the L5178Y TK<sup>-/-</sup> system. Small colony variants carry chromosome aberrations associated with chromosome 11, the chromosome on which the TK locus is located in the mouse. Large colony mutants received very localized damage, possibly in the form of a point mutation or small deletions within the TK locus, while small colony mutants received damage to collateral loci concordant with the loss of TK activity.

Evaluation of results: The cytotoxic effects of each treatment condition were expressed relative to the solvent-treated control for suspension growth over two days post-treatment and for total growth (suspension growth corrected for plating efficiency at the time of

selection). The mutant frequency (number of mutants per  $10^6$  surviving cells) for each treatment condition was determined by dividing the average number of colonies in the three TFT plates by the average number of colonies in the three corresponding VC plates and multiplying by the dilution factor ( $2 \times 10^{-4}$ ) then multiplying by  $10^6$ . For simplicity, this is described as: (average # TFT colonies / average # VC colonies) x 200 in the tables.

A result was considered positive if a concentration-related increase in mutant frequency was observed and one of the three highest doses exhibited a mutant frequency which was two-fold greater than the background level. All data, including that from cultures with less than 10% total growth, would be used to establish the dose response relationship.

A result was considered weakly positive if there was no dose response but the highest acceptable dose exhibited a two-fold increase in mutant frequency, or if there was a positive dose response but none of the acceptable doses exhibited a two-fold increase in mutant frequency.

A result was considered equivocal if there was no dose response and a dose other than the highest dose exhibited a two-fold increase in mutant frequency over background, or if the results were negative but the toxicity of the doses was inadequate.

A result was considered negative if there was no dose response and none of the test cultures exhibited a two-fold or greater increase in mutant frequency over background.

Criteria for valid study:

Negative Controls: The average spontaneous mutant frequency of the solvent control cultures must be within 20 to 100 TFT-resistant mutants per  $10^6$  surviving cells. The cloning efficiency of the solvent (or vehicle) control group must be greater than 50% but less than 130%.

Positive Controls: At least one concentration of each positive control must exhibit a mutant frequency that is at least twice that of the vehicle control. The colony size distribution for the MMS positive control must show an increase in both small and large colonies.

Test Article-Treated Cultures: A minimum of four analyzable concentrations with mutant frequency data will be required. Ideally, the highest concentration should produce at least 80% toxicity (no more than 20%). The cloning efficiency must be between 10% and 130%. The relative total growth must be greater than 10%.

Results:

The initial toxicity test indicated complete toxicity for non-activated cultures at concentrations greater than 150 ug/ml. There was no cell survival in the presence of metabolic activation in cultures exposed to the test material at concentrations above 500 ug/ml. Based on these data, n-valeraldehyde was tested in the Mouse Lymphoma Assay over a range of concentrations from 15 to 150 ug/ml in the absence of S-9 metabolic activation, and 50 to 500 ug/ml in the presence of activation. After a two-day expression interval cultures were selected for cloning (see Tables below).

Mutant frequencies of cultures treated with the test material in the absence of metabolic activation ranged from 1.3 to 4.6 times greater than that observed in DMSO controls. The total growths of these cultures ranged from 11 to 54% of controls. There was a dose-dependent increase in mutant frequency and toxicity. There was an increase in small, medium, and large colonies in treated cultures relative to controls. Colony size distribution for the MMS positive control cultures also showed an increase in small, medium, and large colonies

Mutant frequencies of cultures treated with the test material in the presence of rat S-9 metabolic activation ranged from 0.9 to 1.6 times the mean mutant frequency observed in DMSO controls. The total growths of these cultures ranged from 18 to 67% of controls. There was a dose-dependent increase in toxicity but no increase mutant frequency. There was an increase in small, medium, and large colonies in treated cultures relative to controls. The 7,12 DMBA positive control cultures displayed an increase in mutant frequency and the expected size distribution for small, medium, and large colonies.

Mouse Lymphoma Mutagenesis Assay With Rat S-9 Metabolic Activation

Valeraldehyde ug/ml	TFT colonies (mean count)	VC colonies (mean count)	Mutant Frequency <sup>1</sup>	Induced mutant frequency <sup>2</sup>	% Total growth <sup>3</sup>
Control A	26 +/- 7	130 +/- 9	0.40	-	-
Control B	36 +/- 1	144 +/- 1	0.50	-	-
150 A	25 +/- 3	127 +/- 9	0.39	- 0.06	64
150 B	24 +/- 6	125 +/- 40	0.39	- 0.06	67
200 A	30 +/- 4	143 +/- 5	0.42	- 0.03	42
200 B	49 +/- 2	134 +/- 27	0.73	0.29	43
300 A	34 +/- 7	135 +/- 24	0.50	0.06	26
300 B	30 +/- 2	143 +/- 8	0.42	- 0.02	25
400 A	40 +/- 1	137 +/- 8	0.59	0.14	21
400 B	41 +/- 12	121 +/- 25	0.68	0.23	18
500 A	44 +/- 7	152 +/- 15	0.57	0.13	21
500 B	41 +/- 8	155 +/- 13	0.53	0.09	19
DMBA <sup>4</sup> 4 ug/ml	197 +/- 6	98 +/- 7	4.01	3.57	39

1: Mutant frequency per 10<sup>4</sup> surviving cells =  $\frac{\text{mean TFT colony count}}{\text{mean VC colony count}} \times 200$

2: Induced mutant frequency per 10<sup>4</sup> surviving cells = mutant frequency – average mutant frequency of controls

3: % Total growth =  $\frac{\% \text{ suspension growth} \times \% \text{ cloning growth}}{100}$

4: DMBA = 7,12 Dimethylbenz(a)anthracene, positive control for activated cultures

Mouse Lymphoma Mutagenesis Assay Without Metabolic Activation

Valeraldehyde ug/ml	TFT colonies (mean count)	VC colonies (mean count)	Mutant Frequency <sup>1</sup>	Induced mutant frequency <sup>2</sup>	% Total growth <sup>3</sup>
Control A	29 +/- 2	138 +/- 24	0.41	-	-

Control B	27 +/- 4	120 +/- 8	0.45	-	-
150 A	36 +/- 6	122 +/- 7	0.59	0.16	48
150 B	43 +/- 7	133 +/- 4	0.65	0.22	54
200 A	41 +/- 8	132 +/- 18	0.62	0.19	39
200 B	34 +/- 17	121 +/- 7	0.55	0.12	41
300 A	47 +/- 6	90 +/- 6	1.05	0.62	24
300 B	55 +/- 7	101 +/- 7	1.09	0.66	26
400 A	55 +/- 4	97 +/- 17	1.14	0.71	15
400 B	69 +/- 3	93 +/- 11	1.48	1.05	14
500 A	79 +/- 8	80 +/- 4	1.99	1.56	11
500 B	76 +/- 6	87 +/- 7	1.74	1.31	11
MMS <sup>4</sup> 10 ug/ml	116 +/- 17	40 +/- 2	5.8	5.37	13

1: Mutant frequency per 10<sup>4</sup> surviving cells =  $\frac{\text{mean TFT colony count}}{\text{mean VC colony count}} \times 200$

2: Induced mutant frequency per 10<sup>4</sup> surviving cells = mutant frequency – average mutant frequency of controls

3: % Total growth =  $\frac{\% \text{suspension growth} \times \% \text{cloning growth}}{100}$

4: MMS = methylmethanesulfonate, positive control for non-activated cultures

Remark:	There was a dose-dependent increase in toxicity but no increase mutant frequency when valeraldehyde was tested in cultures in the presence of a rat S-9 metabolic activation system. There was an increase in toxicity and mutant frequency when tested in the absence of metabolic activation.
Comment:	Isobutyraldehyde, a structural analog of valeraldehyde, was also positive in the absence of metabolic activation when tested by the NTP in the mouse lymphoma assay. Isobutyraldehyde was negative in a two-year chronic inhalation bioassay in mice and rats; the only effects related to treatment were non-neoplastic degenerative lesions of the nasal epithelium. National Toxicology Program (NTP). 1999. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Isobutyraldehyde (CAS No. 78-84-2) in F344/N Rats and B6C3F1 Mice. Appendix E. Genetic Toxicology. NTP TR 472. NIH Publication No. 99-3962.
Reliability:	score = 2, valid with restrictions; purity of test article not specified in report, and atypical test chronology: test material received November 1996; initial toxicity test March 1997, test completed February 1999.
Reference:	BioReliance. 2000. L5178Y/TK <sup>+/+</sup> Mouse Lymphoma Mutagenesis Assay. Test Article Code #77128. Study No. G96CC31.703. Unpublished report dated 8 August 2000.

## 5.6 GENETIC TOXICITY IN VIVO

(a) Preferred result	reliability score = 1, comparable to GLP study
Test material:	n-valeric acid, purity 98.96%
Remark:	Valeraldehyde is metabolized by aldehyde dehydrogenases to form its corresponding 5-carbon acid, valeric acid. Administration of valeraldehyde will result in systemic exposure to valeric acid. Toxicity studies conducted with valeric acid can be useful to identify hazards associated with valeraldehyde exposure. See Section 5.10B for additional information.

System of Testing: In Vivo Mouse Micronucleus Assay  
Test species/strain: mouse/Swiss-Webster  
Concentration: 83, 166, or 266 mg/kg  
Test method: Consistent with USEPA Health Effect Test Guidelines, EPA Report 560/6-83-001, using improved procedures suggested by Schlegel and MacGregor (Mutat. Res. 104: 367-369, 1982).

Range finding: Four-week old male and female Swiss-Webster mice were used for preliminary range-finding tests to select test doses for the definitive assay. Groups of five male and five females were dosed with valeric acid in corn oil by intraperitoneal (IP) injection. Toxicity was assessed by determining the level of mortality produced by dosages of 50 to 400 mg/kg. Control animals received corn oil by IP injection. The LD50 of the n-pentanoic acid was determined from cumulative mortality three days after dosing for males and females separately. The average of the two values was used to set dose levels for the definitive test because of the similarity of the male and female LD50s. To evaluate the potential for bone marrow cytotoxicity, the PCE/NCE (polychromatic/normochromatic erythrocyte) ratio was determined in control animals and for the highest dose group in which at least 30% of the animals survived for 48 hr.

Definitive test: Groups of five-week old male and female Swiss-Webster mice, five per sex per group, were received one IP injection of valeric acid in corn oil at doses of 83, 166, or 266 mg/kg. These doses represent approximately 25%, 50%, and 80% of the average male/female LD50. Three additional males and females were added to the highest dose group because of the potential for high mortality, however, only five animals were evaluated for micronuclei. Vehicle control animals received corn oil (CAS# 8001-30-7) injections. Positive control animals received a dose of 0.3 mg/kg triethylenemelamine (TEM, CAS# 51-18-3). Animals were randomized by weight on the day prior to dosing. Mice outside the range of two standard deviations were not used. Body weights for male mice ranged between 20.2-24.6g, female weights ranged between 15.9 and 21.7g. Five mice/sex/cage were separated by treatment dose and housed in shoe-box type plastic cages with absorbent bedding. Food and water was available ad libitum. Blood samples were taken at three time periods at approximately 30, 48, and 72 hours after dosing. Blood was collected by nicking the tail with a scalpel. One or two blood smear slides were prepared for each animal per sampling time. Slides were stained with Gurr's Giemsa diluted in phosphate buffer. Slides were coded to prevent scoring bias. A minimum of 1000 polychromatic erythrocytes were examined microscopically for each animal per sample time. Micronuclei were identified as darkly-stained, spherical inclusions in polychromatic erythrocytes. The PCE/NCE ratio for approximately 1000 cells was calculated and recorded as an estimate of bone marrow toxicity induced by the test agent.

Evaluation of results: Incidences of micronuclei in test animals were compared to the control group frequencies using the Fisher's Exact Test. A test would be considered positive if there was at least one statistically significant increase ( $p \leq 0.05$ ) above the vehicle

	control with an indication of a dose-effect. A test would be considered inconclusive if only one dose produced a statistically significant increase above the control group value. A test would be considered negative if there was no significant difference between vehicle control and groups treated with n-pentanoic acid.
GLP:	no data
Lowest dose producing toxicity:	N/A
Effect on Mitotic Index or PCE/NCE Ratio:	none
Genotoxic effects:	none
Results:	No remarkable dose-related decreases in the PCE/NCE ratios relative to control values were observed for any of the three sampling intervals. PCE/NCE ratios for the positive control were lower than the vehicle control at all three sampling times. The toxicity of TEM to bone marrow cells was an expected finding. Valeric acid did not produce a treatment-related or significant increase in the incidence of micronuclei in peripheral blood polychromatic erythrocytes of test animals sampled at 30, 48, and 72 hours after dosing.
Remarks:	Range-finding toxicity studies demonstrated an LD50 value of 308 mg/kg for male Swiss-Webster mice, and 356 mg/kg for females; the average LD50 for both sexes for valeric acid in corn oil administered by single IP injection was 332 mg/kg. The PCE/NCE ratio of the vehicle control and the highest test dose with an adequate number of survivors (200 mg/kg) was evaluated for possible bone marrow cytotoxicity. A slight cytotoxic effect was noted in females but not in males. Based on these results, doses of 83, 166, and 266 mg/kg were selected for the definitive assay; these doses represented approximately 25%, 50%, and 80% of the mouse LD50.
Test substance:	valeric acid, purity 98.96%
Reliability:	Score = 1, comparable to GLP study
Reference:	Slesinski, R.S. 1985. Union Carbide Corporation (unpublished report). n-Valeric Acid. In Vivo Mouse Micronucleus Study. Bushy Run Research Center Project Report 48-106, dated September 9, 1985.
(b) Test material:	Isobutyraldehyde, 98% (Aldrich)
Remark:	Isobutyraldehyde is a 4-carbon analog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as isobutyraldehyde can be valuable in assessing the toxicity of valeraldehyde.
Type:	Sex-linked lethal mutation
Test species/strain:	Drosophila melanogaster
Test method:	Assay performed under the auspices of the National Toxicology Program (NTP). Test conducted using the same protocol in three laboratories (see Woodruff, R.C. et al. Environ. Mutagen. 6: 189-202).
	Male Canton-S flies (1 day old) were injected with a freshly prepared solution containing 50,000 ppm isobutyraldehyde in a volume of 0.2-0.3 ul. The test material was dissolved in 0.7% NaCl in distilled water. Injected flies were allowed to recover for 24-48 hours after treatment, then mated with virgin females. For ingestion studies, male

flies (1 day old) were fed 80,000 ppm valeraldehyde in a 5% sucrose solution for three days. Flies were placed into glass shell vials that contained a glass fiber filter disc on the bottom. The disc was soaked with 0.2 - 0.5 ml of the feeding solution. Vials were plugged with rayon or non-absorbant cotton and males were transferred each day, without etherization, to a freshly prepared solution. Palatability was assessed by feeding behavior, amount of excretion, or abdominal size. Mortality was recorded at 24, 48, and 72 hr. After 72 hr, males were removed and mated with virgin females.

Lethal mutation test: treated and control Canton-S males were mated individually with three virgin Basc females to produce three broods at 3 days, 2 days, and 2 days. This mating scheme assesses the effect of treatment primarily on male postmeiotic germ cells. Up to 120 F1 females are then mated to sibling males. F2 progeny are scored for the presence or absence of wild-type males. A reduction or absence of wild-type males indicates a lethal mutation. Immediately after treatment, males were mated with virgin females.

Translocation test: individual F1 heterozygous male progeny from the brood showing the highest frequency of lethal mutations were backcrossed to marker stock Basc females, and F2 progeny were screened for pseudolinkage. This procedure allowed for the recovery of T(2;3), T(y;2), T(Y;3) and T(Y;2;3) events. T(Y;2;3) events were counted as two translocations. Presumptive translocations were re-tested by mating F2 heterozygous males with marker females. A translocation was judged to have occurred only in crosses with total counts of 20 or more progeny.

Remark:

Isobutyraldehyde was tested as a coded chemical, using the same protocol and dosages, in three separate laboratories. Mortality among exposed flies was approximately 30% for both routes of administration. There was no increase in the incidence of sex-linked recessive lethal mutations or reciprocal translocations in *Drosophila* treated with isobutyraldehyde by injection or feeding, as compared to concurrent controls.

Reliability:

score = 2, valid with restriction; purity of test material not verified

Reference:

Woodruff, R.C, Mason, J.M., Valencia, R., and Zimmering, S. 1985. Chemical mutagenesis testing in *Drosophila*. V. Results of 53 coded compounds tested for the National Toxicology Program. Environ. Mutagen. 7: 677-702.

## 5.7 CARCINOGENICITY

Remark:

No carcinogenicity study for valeraldehyde is available. The National Toxicology Program conducted two-year bioassays of a structurally similar aldehyde, isobutyraldehyde, in mice and rats. (See Section 5.4 (a) and (b) of this dossier for robust summaries of these studies).

Male and female rats and mice were exposed to isobutyraldehyde at concentrations of 0, 500, 1000, and 2000 ppm. Animals were exposed for 6 hr per day, 5 days per week, for 2 years.

Among rats, there were no significant differences in survival rates between exposed and control groups; there were no clinical findings



that could be attributed to isobutyraldehyde exposure. No increase in the incidence of neoplasms was observed in either sex that could be attributed to isobutyraldehyde exposure. Non-neoplastic lesions of the nose were observed including olfactory epithelial degeneration, suppurative inflammation, and squamous metaplasia of the respiratory epithelium in rats exposed to 2000 ppm. Minimal to mild squamous metaplasia was noted in male and female rats exposed to 1000 ppm, and female rats exposed to 500 ppm.

Among mice, the survival rate of males exposed to 2000 ppm was significantly reduced. Mean body weights of female mice exposed to 2000 and 1000 ppm were reduced in the second year of the study. The only exposure-related effects observed were non-neoplastic nasal lesions. Degeneration of the olfactory epithelium was observed in mice exposed to 1000 and 2000 ppm. There were no nasal lesions in mice exposed to 500 ppm isobutyraldehyde.

Reference: Abdo, K.M., Haseman, J.K. and Nyska, A. 1998. Isobutyraldehyde administered by inhalation (whole body exposure) for up to 13 weeks or two years was a respiratory tract toxicant but was not carcinogenic in F344 rats and B6C3F1 mice. *Toxicol. Sci.* 42: 136-151.

## 5.8 TOXICITY TO REPRODUCTION

- (a) Preferred result reliability score = 1, valid without restrictions  
 Test substance: isobutyraldehyde, 98.6 to 99.1% pure  
 Remark: Isobutyraldehyde is a 4-carbon analog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as isobutyraldehyde can be valuable in assessing the toxicity of other aldehydes, including valeraldehyde.
- Species: rat  
 Strain: F344  
 Sex: male and female  
 Route of Admin: inhalation  
 Exposure Period: 13 weeks  
 Freq. of Treatment: 6 hr/day, 5 days/week  
 Post Exposure  
 Observation Period: none  
 Doses: 0, 500, 1000, 2000 or 4000 ppm  
 Control Group: yes  
 Method: National Toxicology Program (NTP) Sperm Motility and Vaginal Cytology Examinations (SMVCEs). Rats on test in a 13 week NTP inhalation study [see Section 5.4 (a) for description of study] were screened for potential reproductive effects. For males, body weight, testis, epididymis, and cauda epididymis weights were recorded, and caudal sperm motility and counts were determined. Sperm head morphology was also examined. For females, the average estrous cycle length, relative frequency of different estrous stages, and terminal body weights were determined.
- Year: 1988  
 GLP: yes  
 Results: Males  
 Decreased body weight was noted in rats exposed to 4000 ppm. In male rats, decreased absolute but not relative weight of the right

cauda epididymis and right epididymis was observed in rats exposed to 4000 ppm.

There were no changes in sperm motility, density, or morphology between controls and rats exposed to 2000 and 4000 ppm. Sperm motility decreased in rats exposed to 500 and 1000 ppm.

Based on the variability in sperm motility at low exposure concentrations, and the lack of effect at higher concentrations, the overall effect in male rats was considered negative by Morrissey et al.

Spermatozoal parameters in male rats exposed to isobutyraldehyde

Parameter	Control n = 10	500 ppm n = 10	1000 ppm n = 10	2000 ppm n = 10	4000 ppm n = 7
Motility (%)	78 +/- 6.45	17.3 +/- 3.09 <sup>2</sup>	19.6 +/- 4.47 <sup>2</sup>	79.8 +/- 6.03	64.43 +/- 12.61
Abnormal (%)	1.4 +/- 0.24	1.62 +/- 0.30	1.28 +/- 0.15	1.46 +/- 0.29	2.00 +/- 0.30 <sup>3</sup>
Concentration <sup>1</sup>	348 +/- 60	321 +/- 53	433 +/- 71	342 +/- 54	293 +/- 95

1: 10<sup>6</sup> per gm cauda epididymal tissue

2: significant at p<0.001 from controls by Dunn's test

3: n = 6

#### Females

The length of the estrous cycle in days and estrous stage was evaluated in 10 females from each group. There was significant mortality in the 4000 ppm group, and only 4 females were evaluated; the estrous cycle was unclear in 1 of 4 animals in this group. The length of the estrous cycle was slightly increased in females evaluated in the 4000 ppm group (5.33 ± 0.33 days), as compared to controls (5.00 ± 0.15 days). Among females exposed to up to 2000 ppm isobutyraldehyde, there were no significant differences in the percent of the cycle spent in each estrous stage when compared to controls. Among the 4 remaining females in the 4000 ppm group, it was determined that more time was spent in diestrus and less time in proestrus relative to chamber controls; the differences were significant by Wilk's Criterion, but not by Williams or Dunnett's test

Estrous cycle effects in female rats exposed to isobutyraldehyde

Parameter	Control n = 10	500 ppm n = 10	1000 ppm n = 9	2000 ppm n = 10	4000 ppm n = 4
Estrous cycle (length in days)	5.00 ± 0.15	5.00 ± 0.00	5.00 ± 0.17	4.90 ± 0.23	5.33 ± 0.33 <sup>1</sup>
Estrous stages (% of cycle)					

Diestrus	20.0	18.6	23.8	21.4	32.1 <sup>2</sup>
Proestrus	18.6	11.4	12.7	17.1	0.0 <sup>2</sup>
Estrus	30.0	32.9	22.2	25.7	32.1
Metestrus	30.0	37.1	41.3	34.3	35.7
Uncertain	1.4	0.0	0.0	1.4	0.0

1: estrous cycle duration unclear in 1 of 4 females  
2: only 4 females evaluated; relative length of time spent in estrous stages significantly different by Wilk's criterion (p < 0.05) as compared to controls, but not significant by Williams' or Dunnett's test.

- Reliability: score = 2, valid with restriction; GLP study however, mortality and variability in results make interpretation difficult.
- References: Morrissey, R.E., Schwetz, B.A., Lamb, J.C., IV, Ross, M.D., Teague, J.L., and Morris, R.W. 1988. Evaluation of rodent sperm, vaginal cytology, and reproductive organ weight data from National Toxicology Program 13-week studies. *Fundam. Appl. Toxicol.* 11: 343-358.
- U.S. National Toxicology Program. 1999. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Isobutyraldehyde (CAS No. 78-84-2) in F344/N Rats and B6C3F1 Mice. NTP TR-472, Research Triangle Park, NC.
- (b) Test material: isobutyraldehyde, 98.6 to 99.1% pure  
Remark: Isobutyraldehyde is a 4-carbon analog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as isobutyraldehyde can be valuable in assessing the toxicity of other aldehydes, including valeraldehyde.
- Species: mouse  
Strain: B6C3F1  
Sex: male and female  
Route of Admin: inhalation  
Exposure Period: 13 weeks  
Freq. of Treatment: 6 hr/day, 5 days/week  
Post Exposure  
Observation Period: none  
Doses: 0, 500, 1000, or 2000 ppm  
Control Group: yes  
Method: National Toxicology Program (NTP) Sperm Motility and Vaginal Cytology Examinations (SMVCEs). Mice on test in a 13 week NTP inhalation study [see Section 5.4 (b) for description of study] were screened for potential reproductive effects. For males, body weight, testis, epididymis, and cauda epididymis weights were recorded, and caudal sperm motility and counts were determined. Sperm head morphology was also examined. For females, the average estrous cycle length, relative frequency of different estrous stages, and terminal body weights were determined.
- Year: 1988  
GLP: yes  
Results: There were no changes in reproductive organ weight, sperm motility, density, or morphology in male mice exposed to isobutyraldehyde concentrations up to 2000 ppm. Among females, there was no effect on vaginal cytology.
- Reliability: score = 1, valid without restriction; GLP study

Reference:	Morrissey, R.E., Schwetz, B.A., Lamb, J.C., IV, Ross, M.D., Teague, J.L., and Morris, R.W.1988. Evaluation of rodent sperm, vaginal cytology, and reproductive organ weight data from National Toxicology Program 13-week studies. <i>Fundam. Appl. Toxicol.</i> 11: 343-358. U.S. National Toxicology Program. 1999. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Isobutyraldehyde (CAS No. 78-84-2) in F344/N Rats and B6C3F1 Mice. NTP TR-472, Research Triangle Park, NC.
(c) Test material: Remark:	isobutyraldehyde, 98.6 to 99.1% pure Isobutyraldehyde is a 4-carbon analog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as isobutyraldehyde can be valuable in assessing the toxicity of other aldehydes, including valeraldehyde.
Species:	rat and mouse
Strain:	rat: F344 mouse: B6C3F1
Sex:	male and female
Route of Admin:	inhalation
Exposure Period:	2 years
Freq. of Treatment:	6 hr/day, 5 days/week
Post Exposure	
Observation Period:	none
Doses:	0, 500, 1000, or 2000 ppm
Control Group:	yes
Method	National Toxicology Program Chronic Bioassay See Section 5.7 (a) and 5.7 (b) for details of studies
Year:	1998
GLP:	yes
Test substance:	isobutyraldehyde, 98.6 to 99.1% pure
Remark :	Groups of male and female rats (F344) and mice (B6C3F1) were Exposed to isobutyraldehyde at concentrations of 0, 500, 1000, or 2000 ppm. Animals were exposed 6 hr/day, 5 days/week for 2 years. The survival rate of male mice exposed to 2000 ppm was significantly reduced. There was no effect on survival among female mice, or male and female rats. Mean body weights of females exposed to 1000 and 2000 ppm were lower than those of controls during the second year of the study. There were no other clinical findings that could be attributed to isobutyraldehyde exposure. Organs and tissues examined microscopically at the end of the study included clitoral gland, mammary glands, ovaries, preputial gland, prostate, testes (with epididymis and seminal vesicle), and uterus. All reproductive organs were normal upon gross and microscopic examination.
Reference:	Abdo, K.M., Haseman, J.K. and Nyska, A. 1998. Isobutyraldehyde administered by inhalation (whole body exposure) for up to thirteen weeks or two years was a respiratory tract toxicant but was not carcinogenic in F344/N rats and B6C3F1 mice. <i>Toxicol. Sci.</i> 42: 136-151.
(d) Test material: Remark:	propionaldehyde, purity 99% Propionaldehyde is a 3-carbon analog of valeraldehyde. Information regarding the relative toxicity of a closely related

---

Type:	aldehyde such as propionaldehyde can be valuable in assessing the toxicity of valeraldehyde OECD Screening Information Data Set Combined Repeated Dose/Reproductive Protocol (one generation)
Species:	rat
Sex:	male/female
Strain:	other: CD
Route of admin.:	inhalation
Exposure Period:	52 days (males); 48 days (females)
Frequency of treatment:	6 hr/day, 7 days/week
Premating Exposure Period	
male:	14 days
female:	up to 14 days
Duration of test:	up to 48 days, until day 4 of lactation
Doses:	150, 750, or 1500 ppm (0.36, 1.81 or 3.62 mg/l)
Control Group:	yes, concurrent no treatment
NOAEC:	1500 ppm (reproductive toxicity)
LOAEC:	150 ppm (parental toxicity)
NOAEC:	750 ppm (pup toxicity, based on body weight gain, day 0-4)
Method:	other: OECD Screening Information Data Set Combined Repeated Dose/Reproductive Protocol
Year:	1993
GLP:	yes
Test substance:	propionaldehyde, purity 99%
Method:	Groups of 15 male and 15 female CD rats were exposed to propionaldehyde vapor at concentrations of 150, 750, or 1500 ppm. The purity of the test material was determined to be 99%. Males and females were exposed daily, 6 hr/day, 7 days/week during a pre-mating interval of 14 days, and a mating interval of up to 14 days. Males continued to be exposed after mating until scheduled sacrifice after a total of 52 exposures. Females were exposed daily through day 20 of gestation, and then allowed to deliver and raise their pups until day 4 of lactation. Individual females were exposed for a minimum of 35, and a maximum of 48 consecutive days, depending upon when they were mated. A control group of male and female rats were exposed to filtered air using the same exposure regimen. Animals were observed daily for clinical signs before and after each exposure. Body weights were obtained for all males prior to first exposure and weekly thereafter. Female body weights were obtained weekly during the pre-mating phase, on gestation 0 and weekly thereafter, and on days 0 and 4 of lactation. Food consumption was measured at regular intervals throughout the study. At the end of the 14-day pre-mating interval, rats in each exposure group were randomly mated, one male to one female, to produce the F1 generation. Animals were paired for 7 days; after the first 7 days, females of unsuccessfully mated pairs were randomly assigned to another male from the same exposure group. Gestation day 0 was designated by the observation of copulation plug or the presence of vaginal sperm. Dams were not exposed after gestation day 20, and were allowed to rear their pups until day 4 of lactation. On lactation day 4, F0 females were sacrificed and F1 pups were examined grossly, euthanized, and discarded. F0 males were sacrificed after parturition of the F1 litters.

The following indices were determined for F0: mating index and fertility index for males and females, and the gestation index for females. The live birth index and 4-day survival index were determined for F1 litters. F1 pups were examined on day of birth (day 0) to determine the number of live and stillborn males and females in each litter. Litters were evaluated twice daily for survival and survival indices were calculated on day 0 and 4. All live pups were weighed and examined for physical abnormalities on day 0 and day 4.

Results:

Prior to sacrifice, blood was obtained from F0 males for hematology and clinical chemistry evaluation. Body weights were obtained on all F0 animals on the day of sacrifice. A complete necropsy was performed on all F0 animals; lungs, liver, kidneys, thymus, uterus, testes and epididymides were weighed and retained. The following tissues were also retained: gross lesions, brain, pituitary, upper and lower respiratory tract including nasal turbinates, larynx, trachea, heart, spleen, adrenals, vagina, ovaries, and seminal vesicles. Tissues from high dose and control rats were processed and examined histologically. The nasal cavity from all animals were also examined histologically. Adult males did not display overt signs of toxicity at any time during the study. Body weights, weight gains, food consumption, and clinical observations were similar in all exposure groups and controls. Mating performance and fertility were also unaffected.

Hematology and clinical chemistry analyses revealed elevated erythrocyte counts, corresponding to increases in hemoglobin and hematocrit values, and an increase in monocytes for males in the high dose (1500 ppm) group. At necropsy, kidney weights, as a percentage of finalbody weight, was elevated in high dose males. There were no gross lesions that could be ascribed to propionaldehyde exposure. Microscopic examination revealed an exposure-related effect on the olfactory epithelium in the anterior sections of the nasal cavity. Vacuolization was primarily evident in the low and intermediate dose groups; atrophy was observed in the intermediate and high dose groups. Squamous metaplasia was observed in two males in the 1500 ppm group, and 1 male in the 750 ppm group.

Incidence of Nasal Lesions in Male F0 Rats Exposed to Propionaldehyde Vapor<sup>a</sup>

	Exposure Concentrations in ppm			
	0 (Control)	150	750	1500
Rhinitis	0	0	7	14
Squamous Metaplasia	0	0	1	2
Atrophy, Olfactory Epithelium	0	2	10	15
Vacuolization, Olfactory Epithelium	0	15	15	0
Necrosis, Olfactory Epithelium	0	12	14	2

a: number of individuals affected in each group (number of animals in each dose group = 15)

Adult females did not display any exposure-related clinical signs. Body weight gains and food consumption, however, were

significantly decreased during the first week of exposure in females exposed to 750 and 1500 ppm. During gestation, body weights of high dose females were less than controls on days 0, 7, and 14. Small but consistent decreases in food consumption were noted in females in the 1500 ppm group throughout the study, and in females in the 750 ppm group on gestation days 14-17. On day 0 of lactation, body weights of females in the high and mid-dose groups were significantly less than control, but were within normal limits by day 4. After sacrifice on day 4 of lactation, no gross lesions were noted that could be ascribed to exposure. Microscopic examination of tissues revealed an exposure-related effect on the olfactory epithelium of the nasal cavity. Vacuolization was apparent in the low and mid-dose exposure groups; atrophy was observed primarily at the high dose. Squamous metaplasia was not observed in females. Nasal lesions were less severe in females; this can be attributed to the approximately 6-day recovery interval between cessation of exposures after gestation day 20 and sacrifice on lactation day 4.

Incidence of Nasal Lesions in Female F0 Rats Exposed to Propionaldehyde Vapor<sup>a</sup>

	Exposure Concentrations in ppm			
	0 (Control)	150	750	1500
Rhinitis	0	1	6	1
Squamous Metaplasia	1	1	6	9
Atrophy, Olfactory Epithelium	0	0	2	15
Vacuolization, Olfactory Epithelium	0	15	15	0
Necrosis, Olfactory Epithelium	0	0	0	1

a: number of individuals affected in each group (number of animals in each dose group = 15)

There were no significant effects on any of the reproductive parameters assessed. Litter size and variability were similar among groups. Pup body weights were not affected by exposure, although pup body weight gains between lactation day 0 and 4 were slightly depressed in the high concentration group.

Reproductive Indices in Rats Exposed to Propionaldehyde Vapor

	Exposure Concentrations in ppm			
	0 (Control)	150	750	1500
Mating Index (F0 females)	100	100	100	93.3
Mating Index (F0 males)	100	100	93.3 <sup>a</sup>	93.3
Fertility Index (F0 females)	93.3	100	100	100
Fertility Index (F0 males)	93.3	93.3	100	100
Gestational Index	100	93.3	100	100

a: copulation plug and sperm missed in one female

Litter Indices in Rats Exposed to Propionaldehyde Vapor

	F0 Exposure Concentrations in ppm			
	0 (Control)	150	750	1500
Live Birth Index	98.2 ± 3.66	99.5 ± 1.78	100 ± 0	99.5 ± 2.06
4-Day Survival Index	98.5 ± 2.99	99.5 ± 2.06	96.2 ± 6.78	98.0 ± 4.05

Litter Size, Day 0	14.5 ± 1.87	15.1 ± 1.41	15.0 ± 1.41	14.6 ± 1.09
Litter Size, Day 4	14.0 ± 1.62	14.9 ± 2.79	14.4 ± 1.40	14.2 ± 1.31
Litter Weight (g), Day 0	5.83 ± 0.469	5.94 ± 0.334	5.80 ± 0.614	5.89 ± 0.525
Litter Weight (g), Day 4	9.47 ± 0.885	9.30 ± 0.848	8.91 ± 0.999	8.73 ± 0.980
Litter Body Weight Gain (g) Day 0 to 4	3.63 ± 0.651	3.36 ± 0.642	3.11 ± 0.550	2.84 ± 1.051*

\*Significantly different from control group (p < 0.01)

- Remark: Repeated whole-body inhalation exposure to propionaldehyde vapor at concentrations of 0, 150, 750, or 1500 ppm was associated with minimal toxicity at the two highest concentrations in females; males showed no apparent toxicity. Microscopic examination of the nasal epithelium revealed treatment-related effects at all concentrations in both sexes. Reproductive parameters were not affected at any concentration. A slight decrease in body weight gain in the 1500 ppm offspring was the only finding of possible significance in the neonates.
- The NOAEC for reproductive toxicity is 1500 ppm; the NOAEC for pup toxicity, based on a slight decrease in body weight gain in pups at day 4, is 750 ppm. The LOAEC for parental toxicity is 150 ppm, based on the presence of nasal lesions at 150 ppm, the lowest concentration tested.
- Reliability: score = 1, valid without restriction, GLP guideline study  
Reference: Driscoll, C.D. 1993. Propionaldehyde: Combined Repeated-Exposure Reproductive/Developmental Toxicity Study in CD Rats. Union Carbide Corporation, Bushy Run Research Center Report 91U0086.
- (e) Test substance: butyraldehyde, purity not specified  
Remark: Butyraldehyde is a 4-carbon analog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as butyraldehyde can be valuable in assessing the toxicity of valeraldehyde
- Species: rat  
Sex: male/female  
Strain: F-344  
Route of admin.: inhalation  
Exposure period: 13 weeks  
Frequency of treatment: 6 hr/day 5 days a week  
Post. obs. period: none  
Doses: 0, 125, 500, or 2000 ppm  
Control Group: air only  
Method: Groups of male and female rats were exposed to target concentrations of 0, 125, 500, or 2000 ppm butyraldehyde for 6 hr/day, 5 days/week for 13 weeks.
- GLP: yes  
Year: 1979  
Result: Measured concentrations for each group was determined to be 117, 462, and 1852 ppm. Animals at all treatment levels had a significant



Remark: increase in squamous metaplasia of the nasal cavity. No other treatment-related effects were noted.  
Groups of male and female rats (F344) were exposed to butyraldehyde at concentrations of 0, 117, 462, and 1852 ppm. Animals were exposed 6 hr/day, 5 days/week for 13 weeks. Reproductive organs and tissues examined at the end of the study. All reproductive organs were normal upon gross and microscopic examination.

Reliability: score = 2, valid with restriction; purity of test material not specified

Reference: Union Carbide Corporation. 1979. Carnegie-Mellon Institute of Research Report 42-50, dated June 11, 1979.

### 5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

(a) Preferred value: reliability score = 1, valid without restriction; guideline study

Test material: isobutyraldehyde

Remark: Isobutyraldehyde is a 4-carbon structural analog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as isobutyraldehyde can be valuable in assessing the toxicity of valeraldehyde.

Species: rat

Strain: Wistar

Sex: female

Route of Admin: inhalation

Exposure Period: gestational days (gd) 6 through 15

Freq. of Treatment: 6 hours/day for 10 consecutive days

Duration of Test: dams sacrificed on gd 21

Doses: 0, 1000, 2500, or 4000 ppm

Control Group: yes

NOAEL (Maternal Toxicity): 1000 ppm

NOAEL (Developmental Toxicity): 4000 ppm

Method: OECD Guideline 412; Japan/MAFF Guideline; USEPA FIFRA Guideline 83-3; USEPA TSCA 40 CFR Part 798.2450; EEC Guideline 92/69/EEC. Groups of 25 mated female Wistar rats (75-84 days old) were exposed to target concentrations of 1000, 2500, or 4000 ppm isobutyraldehyde for 6 hours per day, on post-coital day 6 through post-coital day 15. Females were not exposed on post-coital days 16-20. Animals were housed singly in wire cages located within a glass and steel 1.4 cubic meter inhalation chamber and were exposed to air for 5 days before the exposure period. Food and water was not available during exposure. Airflow rates, pressure conditions within the chambers, relative humidity and temperature within the inhalation systems were measured continuously. Clinical examination of animals was performed before, during, and after each exposure. The health of animals was checked at least once per day when animals were not being exposed. Body weights were recorded throughout the study on day 0, 3, 6, 9, 12, 15, 17, and 20. Animals were sacrificed on day 20 and fetuses dissected from the uterus. After sacrifice, dams were subject to necropsy, and the uterus and ovaries removed. The weight of the uterus, number of corpora lutea, number and distribution of implantation sites, number of live fetuses and dead implantations, early resorptions, late resorptions, and dead fetuses were recorded. Fetuses were weighed, sexed, and examined macroscopically for external findings. Viability of each fetus, and the condition of the placenta, umbilical cord, and fetal membranes

	and fluids were also examined. Individual placental weights were also recorded. After fixation, approximately one-half of the fetuses from all groups were subject to soft tissue examination; the skeletons of approximately half the fetuses were stained and examined microscopically for abnormalities.
Year:	1997
GLP:	yes
Test substance:	isobutryaldehyde, purity 99.4% at study initiation, 98.8% upon re-analysis after in-life portion of study was completed.
Result:	Isobutryaldehyde exposure resulted in a dose-related increase in maternal toxicity, as evidenced by a significant decrease in body weight gain in dams exposed to 4000 and 2500 ppm., but not at 1000 ppm. Exposure of dams to isobutryaldehyde had no effect on gestational or litter parameters and did not induce embryofetal toxicity. There was no increase in fetal malformations at any exposure level, up to the highest concentration tested, 4000 ppm.
Remark:	Maternal exposure during organogenesis (gestation day 6-15) to up to 4000 ppm isobutryaldehyde vapor did not produce any effect on reproductive parameters or fetal development. The NOEL for developmental toxicity is 4000 ppm.
Reference:	Garmer, A.O., Hellwig, J. and Hildebrand, B. 1996. Isobutryaldehyde-Prenatal Vapor Inhalation Study in Wistar Rats. BASF Aktiengesellschaft Department of Toxicology Project No. 31R0140/93049. Ludwigshafen, Germany.
(b) Test substance:	propionaldehyde
Remark:	Propionaldehyde is a 3-carbon homolog of valeraldehyde. Information regarding the relative toxicity of a closely related aldehyde such as propionaldehyde can be valuable in assessing the toxicity of valeraldehyde
Species:	rat
Sex:	female
Strain:	Sprague-Dawley
Route of admin.:	other: intraamniotic injection
Exposure period:	gestation day 13
Frequency of treatment:	single injection
Duration of test:	20 days
Doses:	10, 100 and 1000 ug/embryo
Control Group:	other: concurrent, no treatment and saline control
Method:	other
Year:	1985
GLP:	no
Test substance:	propionaldehyde, purity not specified (Aldrich)
Method:	The effect of intraamniotic injection of propionaldehyde on the incidence of resorptions and gross fetal malformations was assessed in rats. Groups of timed-pregnant Sprague-Dawley rats were laparotomized under ether anesthesia on Gestation Day 13. Embryos in one uterine horn received a 10 ul intraamniotic injection of propionaldehyde dissolved in 0.9% NaCl, at a dose of 10, 100, or 1000 ug/embryo. Contralateral embryos were injected with 10 ul of saline or were not injected. The uterus was repositioned in the abdominal cavity and in the incision repaired. Rats were killed on Gestation Day 20; fetuses were removed and the number of dead or resorbed fetuses determined. Live fetuses were examined for

Result:	external malformations, blotted dry, and weighed. Acrolein, known to be teratogenic in rabbits and chickens after intraamniotic injection, was also tested at doses of 0.1-100 ug/embryo. The effect of propionaldehyde treatment was determined by comparison to saline treatment by the Mann-Whitney U Test. The frequency of individual malformations was evaluated by the Fisher exact test. The level of significance for all analyses was $P < 0.05$ . Approximately 24% of saline-injected embryos were resorbed; 6% were malformed. Treatment with propionaldehyde produced a dose-related increase in embryo lethality. The increase in embryo lethality was significant at the highest dose of 1000 ug/embryo when compared to saline-injected controls. Propionaldehyde did not induce an increase in fetal malformations at any dose. Acrolein caused a dose-dependent increase in embryo lethality, and in the incidence of malformations among surviving fetuses.
Remark:	Intramniotic injection of propionaldehyde did not produce an increase in the incidence of fetal malformations, even at doses as high as 1 mg/embryo. The unsaturated 3-carbon analog, acrolein, produced a dose-dependent increase in malformations. The authors suggest that unsaturation of the aldehyde is necessary for teratogenic activity.
Reliability:	score = 2, valid with restriction; purity of test article not specified
Reference:	Slott, V.L. and Hales, B.F. 1985. Teratogenicity and embryo lethality of acrolein and structurally related compounds in rats. <i>Teratology</i> 32: 65-72.
(c) Test material: Remark:	valeric acid, purity >99% In vivo and in vitro studies have demonstrated that alcohols are metabolized by alcohol dehydrogenase (ADH) to form aldehydes, which are in turn metabolized by aldehyde dehydrogenases (ALDH) to form their respective acids. Studies have demonstrated the rapid disappearance of valeraldehyde when injected IP in rats. Additional studies with propanol, isobutanol, butanol, and pentanol have demonstrated that metabolism to the aldehyde and thence to the acid proceeds rapidly in vivo and in vitro. Administration of valeraldehyde will result in systemic exposure to valeric acid. Toxicity studies conducted with valeric acid can be useful to identify hazards associated with valeraldehyde exposure. See Section 5.10B for additional information.
Species:	rat
Strain:	Sprague-Dawley
Sex:	female
Route of Admin:	oral gavage
Exposure Period:	day 6-15 of gestation
Freq of Treatment:	once per day
Duration of Test:	through postnatal day 6
Dose:	0, 50, 100, 200 mg/kg/day
Control Group:	yes
NOAEL Maternal Toxicity:	50 mg/kg
NOAEL Teratogenicity:	Due to severe maternal toxicity, a value could not be determined from this study
Method:	Groups of approximately 24 timed-pregnant female Sprague-Dawley rats received n-valeric acid in corn oil by gavage at doses of 50, 100, and 200 mg/kg/day during organogenesis on gestation days

6 through 15 (day of mating, presence of vaginal sperm, or evidence of copulatory plug = GD0). A control group of 24 females was similarly treated with corn oil only (administered volume for all dose groups was 1 ml/kg bw). Doses were based upon gestation day 6 body weights and remained constant throughout the dosing interval. Prior to treatment initiation, animals were assigned to treatment groups using a nonbiased procedure that assured a homogeneous distribution of body weights among groups. Food and water was available ad libitum except at the time of dosing. Maternal body weights were recorded on gestation days (GD) 6,8,10,13,16, and 20. All rats were examined throughout the study for signs of maternal toxicity. Rats were killed on GD20 by carbon dioxide asphyxiation. Liver and gravid uterine weights were obtained for each dam. For each litter, number of live fetuses per sex, dead fetuses, and resorptions were counted, and the live fetuses were weighed collectively. The number of corpora lutea was also determined for each rat. Approximately half the fetuses from each litter were placed in Bodian's solution for soft tissue examination. The remaining fetuses were fixed and subsequently stained for skeletal examination.

Year:  
GLP  
Test substance:  
Result

1989  
no data  
n-valeric acid; purity > 99% (Aldrich)  
Rales and vocalization were observed in dams at all treatment levels; dyspnea was noted at 100 and 200 mg/kg (see table below). Other clinical observed included salivation after dosing, red discoloration around nose or mouth, and rough hair coat. Mortality occurred in all treatment groups: 1/24 at 50 mg/kg, 3/24 at 100 mg/kg, and 10/24 at 200 mg/kg. Necropsy findings indicated that most deaths were due to congestion of the respiratory tract and/or inflation of the gastrointestinal tract (attributed to dyspnea). The authors suggest that the respiratory effects observed may have been due to gastroesophageal reflux and subsequent aspiration of the irritating dosing solution, which produced airway constriction, pulmonary edema, and, in severe cases, maternal death. Gastric irritation was noted in 6 of the 10 rats that died on study in the 200 mg/kg group. Maternal body weight gains were reduced in all treated groups during the treatment interval (GD 6-15). Body weight gains returned to normal after GD16, however, overall body weight gains and maternal body weights were significantly reduced in the 100 and 200 mg/kg groups. There are no data regarding maternal food and water consumption.

Maternal Data for Rats Gavigated with Valeric Acid on Gestation Days 6-15

Number of Females	Dose Level of Valeric Acid (mg/kg bw/day)			
	0	50	100	200
Treated	24	24	24	24
Died	0	1	3	10
Remaining Pregnant	17	13	18	12
Vocalization upon treatment	0	4	11	14
Rales	0	11	21	19
Dyspnea	0	0	7	11
Body weight gain GD 6-	18.7 ± 1/8	12.9 ± 2.3	4.4 ± 5.1*	4.7 ± 5.5*

10 <sup>1</sup>				
Body weight gain GD 10-16	47.0 ± 1.8	41.9 ± 4.3	18.7 ± 8.0**	18.3 ± 9.3**
Body weight gain GD 16-20	65.3 ± 2.6	67.7 ± 2.6	68.9 ± 5.2	64.3 ± 10.9
Body weight gain GD 6-20	131 ± 4.7	122.5 ± 4.9	92.1 ± 7.6**	87.3 ± 16.5**

1: Mean + SE using number of females remaining pregnant as the sample size

\* Significantly different from control value (p < 0.05)

\*\* Significantly different from control value (p < 0.01)

There were no differences between groups in maternal liver weights, number of corpora lutea, number of implantations, pre-implantation loss, post-implantation loss, or the number of live fetuses per litter. One 200 mg/kg dam had a completely resorbed litter; this dam exhibited severe respiratory distress and weight loss. Fetal weights were significantly reduced at 100 and 200 mg/kg.

Fetal examinations revealed no malformations. Using standard criteria (mean number of pups/litter), there were no significant skeletal variations (see table below). When evaluated on a % litter affected basis, the percent incidence of fetuses with sternebrae that were small, or that had reduced ossification was statistically increased at all dose levels. There are no data on the number of pups per litter affected with reduced ossification, and the threshold criteria used to determine a pup and litter as being affected are not described.

Fetal Skeletal Effects in Rats Receiving Valeric Acid by Gastric Intubation on Gestation Days 6-15

	Dose Level of Valeric Acid (mg/kg bw/day)			
	0	50	100	200
No. Litters Examined	17	13	18	11
No. Fetuses Examined	107	76	107	68
Fetal Body Weight (gm) <sup>1</sup>	4.1 ± 0.1	4.0 ± 1.0	3.7 ± 0.1*	3.8 ± 0.1*
Number Ossified <sup>2</sup>				
Metacarpals	7.5 ± 0.1	7.5 ± 0.2	7.4 ± 0.2	7.2 ± 0.2
Front proximal phalanges	0.9 ± 0.2	0.5 ± 0.3	0.7 ± 0.3	0.3 ± 0.2
Sternebrae	5.9 ± 0.0	5.8 ± 0.1	5.7 ± 0.1	5.7 ± 0.1
Caudal vertebrae	4.3 ± 0.1	4.1 ± 0.2	4.0 ± 0.1	3.8 ± 0.2
Mean % Incidence per Litter <sup>3</sup>				
Calvaria, reduced ossification	21.1 ± 6.2	19.2 ± 7.5	19.9 ± 5.4	11.4 ± 4.8
Supraoccipital, reduced/ irregular	12.3 ± 5.2	15.4 ± 7.2	16.2 ± 6.1	21.2 ± 8.5
Presacral vertebra, extra	0	0	0.8 ± 0.8	0
Ribs, lumbar	11.1 ± 4.3	18.2 ± 5.6	11.2 ± 3.2	4.1 ± 2.8
Ribs, cervical	5.6 ± 2.3	3.8 ± 2.8	1.9 ± 1.9	
Ribs, wavy/callused	0	1.3 ± 1.3	6.3 ± 4.7	1.5 ± 1.5
Sternebrae, small or				

reduced ossification	8.7 ± 7.5	62.7 ± 7.7*	71.3 ± 6.5*	62.5 ± 10.7*
Sternebrae, offset	2.5 ± 1.7	10.6 ± 3.1	7.7 ± 2.2	9.9 ± 3.6

1: Mean ± SE

2: Mean number of pups per litter ± SE

3: Mean ± SE

\* Significantly different from control value (p < 0.05)

Data from Naartosky et al, 1994 and Nartosky and Kavlock, 1989.

No significant fetal visceral effects were observed. An increase in the incidence of dilated ureter was noted; this increase was not dose-related (see table below). The data on the number of pups affected per litter were not presented.

Fetal Visceral Effects in Rats Receiving Valeric Acid by Gastric Intubation on Gestation Day 6-15

	Dose Level of Valeric Acid (mg/kg bw/day)			
	0	50	100	200
No. Litters Examined	17	13	18	11
No. Fetuses Examined	102	79	109	71
Mean % Incidence per Litter <sup>1</sup>				
Hemorrhage	33.8 ± 8.4	17.0 ± 5.3	29.5 ± 7.7	35.2 ± 6.4
Hemorrhage, Intraabdominal	32.1 ± 7.9	15.9 ± 5.2	24.4 ± 6.7	33.4 ± 7.1
Dilated Renal Pelvis	16.0 ± 4.0	22.0 ± 6.2	11.2 ± 3.7	6.9 ± 3.1
Dilated Ureter	28.5 ± 7.8	47.8 ± 7.8*	20.0 ± 5.4	18.2 ± 5.3
Short Kidney	1.2 ± 1.2	2.2 ± 1.5	0	0

1: Mean + SE per litter

\* Marginal significant difference from control value (p ≤ 0.10)

Remarks:

This study demonstrates the difficulties involved when administering a corrosive material by oral gavage. The authors state that the corn oil/valeric acid dosing solution produced respiratory effects upon gastroesophageal reflux into the lungs. There was evidence of gastric and respiratory irritation, and signs of maternal respiratory distress; mortality occurred in all valeric acid treated groups. No data are available for maternal food or water consumption, however, maternal body weight gains were reduced in all valeric acid groups during the dosing interval (GD 6-15). Fetal body weights were reduced at 100 and 200 mg/kg; significant maternal toxicity and mortality were also observed at these doses. There were no fetal malformations; there were no skeletal or visceral variations when evaluated on a mean number of pups per litter basis. When evaluated on a % litter affected basis, there was a non-dose related decrease in fetal sternebrae ossification. The criteria for determining the degree of ossification was not described. The respiratory effects observed may have been due to gastroesophageal reflux and subsequent aspiration of the irritating dosing solution, which produced airway constriction, pulmonary edema, and, in severe cases, maternal death.

Reliability:

score = 2, valid; purity of test article not verified; maternal toxicity precluded ability to make definitive conclusions from this study

References:	<p>Narotsky, M.G., Francis, E.Z., and Kavlock, R.J. 1994. Developmental toxicity and structure-activity relationships of aliphatic acids, including dose-response assessment of valproic acid in mice and rats. <i>Fundam. Appl. Toxicol.</i> 22: 251-265.</p> <p>Narotsky, M.G. and Kavlock, R.J. 1989. Pentanoic Acid Developmental Toxicity Testing. ManTech Environmental Technology, Inc. Contract No. 68-02-4450. Report dated October 10, 1989.</p>
(d) Test material: Remark:	<p>n-valeric acid, purity &gt;99%</p> <p>In vivo and in vitro studies have demonstrated that alcohols are metabolized by alcohol dehydrogenase (ADH) to form aldehydes, which are in turn metabolized by aldehyde dehydrogenases (ALDH) to form their respective acids. Studies have demonstrated the rapid disappearance of valeraldehyde when injected IP in rats. Additional studies with propanol, isobutanol, butanol, and pentanol have demonstrated that metabolism to the aldehyde and thence to the acid proceeds rapidly in vivo and in vitro. Administration of valeraldehyde will result in systemic exposure to valeric acid. Toxicity studies conducted with valeric acid can be useful to identify hazards associated with valeraldehyde exposure. See Section 5.10B for additional information.</p>
Species:	rat
Strain:	Sprague-Dawley
Sex:	female
Route of Admin:	oral gavage
Exposure Period:	day 6-15 of gestation
Freq of Treatment:	once per day
Duration of Test:	through postnatal day 6
Dose:	0, 75, 100 mg/kg/day
Control Group:	yes
NOAEL Maternal Toxicity:	none
NOAEL Teratogenicity:	100 mg/kg
Method:	<p>n-Valeric acid was screened for developmental toxicity using the Chernoff/Kavlock assay, which included skeletal examination of offspring. Groups of 15 timed-pregnant female Sprague-Dawley rats received n-pentanoic acid in corn oil by gavage at doses of 75, or 100 mg/kg/day during organogenesis on gestation days 6 through 15. A control group of 15 females was similarly treated with corn oil only. Doses were based on preliminary range-finding studies; the high dose was expected to produce moderate maternal toxicity. Maternal body weights were recorded on gestation days (GD) 6,8,10,13,16, and 20. All rats were examined throughout the study for clinical signs of toxicity. Beginning on GD 20, dams were examined periodically during the normal workday to determine the time of parturition. Dams were allowed to litter and pups in each litter were examined and counted on postnatal day (PD) 1, 3 and 6. Pups were weighed collectively on PD 1 and 6. After the PD 6 examinations, dams were killed and the number of uterine implantation sites were recorded. Skeletal examinations were conducted on one pup per sex per litter. Pups found dead were preserved and subsequently examined for soft tissue alterations. Externally malformed pups were examined for skeletal and soft tissue alterations.</p>

Year:	1989
GLP	no data
Test substance:	n-valeric acid; purity > 99% (Aldrich)
Result	Two females that in the 100 mg/kg group died on study, possibly due to tracheal intubation; gastric irritation was also noted at necropsy. Clinical signs of toxicity noted in females included rales (13/15 at 75 mg/kg and 11/15 at 100 mg/kg), and dyspnea (3/15 at 100 mg/kg). Mean maternal weight gain was significantly decreased in both the 75 and 100 mg/kg groups for the interval GD 6-10. Maternal weight gains were lower both groups for the entire treatment interval (GD 6 through 20), however the differences were not statistically significant. There were no treatment-related effects on the length of gestation, number of implants, litter size, pup size, or pup viability (postnatal survival). No malformations were observed.
Remarks:	The respiratory effects observed may have been due to gastroesophageal reflux and subsequent aspiration of the irritating dosing solution, which produced airway constriction, pulmonary edema, and, in severe cases, maternal death.
Reliability:	score = 2, valid with restriction; purity of test article not verified
References:	Narotsky, M.G., Francis, E.Z., and Kavlock, R.J. 1994. Developmental toxicity and structure-activity relationships of aliphatic acids, including dose-response assessment of valproic acid in mice and rats. <i>Fundam. Appl. Toxicol.</i> 22: 251-265  Nartosky, M.G. and Kavlock, R.J. 1989. Pentanoic Acid Developmental Toxicity Testing. Report for Contract No. 68-02-4450, dated October 10, 1989.

### 5.10 OTHER RELEVANT INFORMATION

#### A. Specific toxicities

(a) Remark:	Sensory irritation potential of valeraldehyde was measured in male Chinese NIH mice. The RD50 estimate for valeraldehyde was 920 ppm.
Reliability:	score = 4; abstract, data insufficient for assessment
Reference:	Luo, J.E. et al. 1993. Study of sensory irritancy of series of aldehydes and the prediction of safe levels of exposure (TLV). <i>The Toxicologist</i> 13: 263.

#### B. Toxicodynamics, toxicokinetics

(a) Test material:	n-pentyl alcohol, purity not specified
Species:	rat
Route of Admin.	Intraperitoneal (IP) injection
Dose:	1 gm/kg
Method:	Undiluted n-pentyl alcohol was administered to rats by IP injection; rats weighting between 190 and 250 grams received 4 equal doses of 250 mg/kg at 15 minute intervals for a final dose of 1 gm/kg. Blood was drawn for analysis one hour after the first administration and at hourly intervals thereafter. At the end of the study, rats were sacrificed and the availability of residual alcohol in the peritoneum was determined by washing out the abdominal cavity with water and analysis of rinsate.



The concentration of n-pentyl alcohol in expired air was quantitatively determined by the method described by Korenman (Korenman, I.M. Kolorimetrische Bestimmung von Amyl alkohol und Amyl acetal dampfen in der Luft. Arch. F. Hyg. 109: 108, 1932). The concentration of pentyl alcohol in blood and urine was determined by a modification of the furfural method developed by Bassett for the qualitative determination of n-pentyl alcohol in liquids (Basset, H.P. To determine fusel oil in distilled liquors. Indust. Engr. Chem. 2: 389, 1910). Readings were obtained with a Klett colorimeter using a green filter No. 540. Alcohol concentrations were determined after subtracting the background value from normal control samples. The accuracy of the method, as determined from analysis of blood containing known concentrations of n-pentyl alcohol, was +/- 4%.

Expired air was collected into a stream of air and passed through a chamber containing iodine pentoxide heated to 148 degrees C. Iodine liberated in the presence of alcohol was collected in a tube containing a 1% potassium iodide solution and titrated with 0.004 N thiosulfate. Calibration of the system was made against known concentrations of n-pentyl alcohol in air. The tube used to collect liberated iodine was changed at intervals of 15 minutes to 1 hour.

Results:

In a separate series of experiments, n-pentyl alcohol was administered to partially hepatectomized rats in 4 doses of 250 mg/kg every 15 minutes for a final dose of 1 gm/kg. Blood levels of pentyl alcohol were measured to determine the effect of the procedure on alcohol absorption and disposition. Animals demonstrated marked depression after all alcohol had disappeared from the blood; animals appeared sedated but exhibited no other signs of toxicity. Marked irritation of the peritoneum and lungs were noted at sacrifice.

The concentration of n-pentyl alcohol in blood and loss by elimination in expired air and urine was determined in normal rats after receiving IP administration of 1 gm/kg. The peak blood concentration (23 mg per 100 ml blood) for n-pentyl alcohol was noted at the first sampling interval, one hour after administration. Concentrations fell rapidly and were not detectable 3.5 hours after administration. Loss by elimination in expired air consisted of only 0.88% of the administered dose; loss in urine was 0.29%.

Administration of 1 gm/kg n-pentyl alcohol to partially hepatectomized rats resulted a longer uptake interval with a greater peak blood level. Peak blood levels occurred 3.5 hours after administration.

Blood levels\* of n-pentyl alcohol in normal and hepatectomized rats after IP administration

Post-dose interval (hours)	Normal	Hepatectomized
1.0	23	44
2.0	9	70
3.5	n.d**	100

	5.0	n.d.	91
	* blood levels in mg per centileter blood; derived from graphic data **n.d.= non-detectable		
Comment:	The authors suggest that the data support the conclusion that n-pentyl alcohol is rapidly metabolized. In normal rats, uptake from the peritoneum is rapid and peaks within one hour. Only 1.2% of the administered dose was eliminated unchanged in urine and expired air. The remainder was metabolized.		
Reliability:	score = 2, valid with restrictions, purity of test material not specified		
Reference:	Haggard, H.W., Miller, D.P. and Greenberg, L.A. 1945. The amyl alcohols and their ketones: their metabolic fates and comparative toxicities. J. Indus. Hyg. Toxicol. 27: 1-14.		
(b) Test material:	n-pentyl alcohol, purity not specified		
Species:	rat		
Route of Admin.	Intraperitoneal (IP) injection		
Dose:	1 gm/kg		
Method:	In an effort to demonstrate the presence of n-valeraldehyde as a metabolic product of n-pentyl alcohol, undiluted n-pentyl alcohol was administered to rats by IP injection. Rats received 4 equal doses of 250 mg/kg at 15 minute intervals for a final dose of 1 gm/kg.. The concentration of n-valeraldehyde in blood using the method developed by Greenberg and Lester (Greenberg, L.A. and Lester, D. A micromethod for the determination of acetone and ketone bodies. J. Biol. Chem. 154: 177, 1944). This method, although developed to detect ketones, was standardized against valeraldehyde and determined to be highly sensitive. Blood was drawn for analysis 15 minutes after completion of the last IP injection. Using the same protocol, one rat received a total dose of 1 gm/kg valeraldehyde. Blood was drawn at 15 and 45 minutes after the last dose and the concentration of valeraldehyde was determined.		
Results:	<p>To detect the presence of valeraldehyde, expired air of the dosed rat was passed through a 0.5% solution of 2-4-dinitro-phenyl hydrazine in 2N HCl. Air was drawn through the chamber and bubbled through the hydrazine solution for 5 to 20 hours after administration of 1 g/kg n-pentyl alcohol. Precipitated material was separated, washed, recrystallized, and subjected to analysis. Rats received a series of 4 injections of 250 mg/kg n-pentyl alcohol over a 1 hour interval for a total dose of 1 gm/kg. No detectable concentrations of valeraldehyde were detected in expired air.</p> <p>n-Valeraldehyde was detected in the blood 15 minutes after the final IP injection of n-pentyl alcohol. Valeraldehyde blood concentrations were 1.9 mg/100 ml was detected after 15 minutes. When valeraldehyde was administered by IP injection (total dose 1 g/kg), valeraldehyde blood concentratrions were 1.4 mg/100 ml after 15 minutes; 0.78 mg/100 ml was detected in blood 45 minutes after the dose was administered. These data demonstrate that similarly small amounts of valeraldehyde are detected in blood after IP injection of n-pentyl alcohol or valeraldehyde itself.</p>		

Remark:	These data demonstrate that n-valeraldehyde is formed in vivo after IP administration of n-pentyl alcohol. The data also demonstrates the extremely transient nature of valeraldehyde in vivo.
Comment:	The authors suggest that n-pentyl alcohol is metabolized to valeraldehyde which in turn is rapidly converted to valeric acid. The authors postulate that valeric acid is responsible for the persistent sedation displayed by rats which received n-pentyl alcohol and valeraldehyde; marked sedation persisted long after blood alcohol and aldehyde concentrations had decreased to non-detectable levels. IP injection of rats with 1 gm/kg sodium valerate (the sodium salt of valeric acid) also resulted in marked sedation of animals which persisted for several hours.
Reliability:	Score = 2; valid with restrictions: purity of test material not specified
Reference:	Haggard, H.W., Miller, D.P. and Greenberg, L.A. 1945. The amyl alcohols and their ketones: their metabolic fates and comparative toxicities. <i>J. Indus. Hyg. Toxicol.</i> 27: 1-14.
(c) Species:	rat
Strain:	Sprague-Dawley
Sex:	male
Route of Admin:	inhalation
Exposure Period	90 minutes
Freq. of Treatment:	Single
Duration of Test	90 minutes
Exposure Concentration:	2600 ppm (the chamber is charged with a target concentration of 2600 ppm amyl alcohol mixture (approximately 1650 ppm n-pentanol and 950 ppm 2-methylbutanol) and the concentration drops as the rat inhales the test article. Loss to chamber equipment and external surface of the rat is corrected for.
Control Group:	None (biological samples taken prior to exposure). The amount inhaled by the rat (versus deposited on chamber equipment surfaces) is corrected for.
Method:	In an effort to understand the respiratory bioavailability of aliphatic alcohols and esters, a whole-body plethysmograph was installed in a gas-uptake chamber. The rat has an indwelling jugular cannula implanted prior to study start and is placed in the plethysmograph. The plethysmograph (containing the rat) is then placed in the gas-uptake chamber. The leads from the plethysmograph and the venous catheter are exteriorized from the chamber for sample and data collection. The chamber is charged with the amyl alcohol mixture (described above) and the chamber concentration decay curve is followed by gas chromatography. In addition, venous blood samples are taken at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes. The whole-body plethysmograph is designed to measure (non-invasively) ventilatory movements on conscious rats. By collecting data on ventilatory movements, and chamber and venous blood n-pentanol and 2-methylbutanol concentrations, respiratory bioavailability determinations can be calculated. Blood samples from five animals were analyzed for n-pentanol, valeric acid, 2-methylbutanol, and 2-methylbutyric acid concentrations.
Year:	2004
GLP:	no (conducted in spirit of GLP, but not specifically)
Test substances:	amyl alcohol mixture (approximately 63% n-pentanol and 37% 2-methylbutanol)

Purity:  
Result:

Spectroscopic grade (>99.9%)  
The blood concentrations of n-pentanol, valeric acid, 2-methylbutanol, and 2-methylbutyric acid during the exposure period are reported below. The presence of valeric acid following n-pentanol inhalation exposure clearly demonstrates that valeric acid is the major metabolite of n-pentanol metabolism. Blood levels of n-pentanol reached peak blood concentrations of 451  $\mu$ M at 20 minutes into the exposure. Valeric acid achieved peak concentration (7  $\mu$ M) at 20 minutes into the exposure. Chamber concentrations of n-pentanol decline from time zero, both due to loss to chamber equipment surfaces as well as uptake by the rat (data not shown). These data clearly demonstrate that valeric acid is the major metabolite present following n-pentanol exposures. The presence of 2-methylbutyric acid following 2-methylbutanol inhalation exposures clearly demonstrates that 2-methylbutyric acid is the major metabolite of 2-methylbutanol metabolism. Blood levels of 2-methylbutanol reached peak blood concentrations of 217  $\mu$ M at 20 minutes into the exposure. Peak levels of 2-methylbutyric acid in the blood (25  $\mu$ M) were found 20 minutes into the exposure. Chamber concentrations of 2-methylbutanol decline from time zero, both due to loss to chamber equipment surfaces as well as uptake by the rat (data not shown). These data clearly demonstrate that 2-methylbutyric acid is the major metabolite present following 2-methylbutanol exposures.

n-Pentanol and valeric acid blood levels found following n-pentanol inhalation.

Sampling Time (minutes)	n-Pentanol	Valeric acid
0	0	0
5	239	3
10	337	4
15	376	6
20	451	7
25	332	5
30	281	5
40	315	5
50	327	5
60	193	4
90	190	4

\*mean  $\mu$ M whole blood

2-Methylbutanol and 2-methylbutyric acid blood levels found following 2-methylbutanol inhalation.

Sampling Time (minutes)	2-Methylbutanol	2-Methylbutyric acid
0	0	0
5	103	5
10	164	9
15	182	17
20	217	25
25	171	21
30	148	20

40	164	23
50	162	20
60	120	17
90	107	13

\*mean  $\mu$ M whole blood

- Reference: Poet, T. 2004a. Unpublished data on Primary Amyl Alcohol (mixture of n-pentanol and 2-methylbutanol). Battelle, Pacific Northwest National Laboratory, US Dept. of Energy. For Oxo-Process Panel, Chemstar, American Chemistry Council, Arlington, VA, 22209.
- (d) Species: rat  
 Strain: Sprague-Dawley  
 Sex: male  
 Route of Admin: inhalation  
 Exposure Period: 90 minutes  
 Freq. of Treatment: Single  
 Duration of Test: 90 minutes  
 Exposure Concentration: 3500 ppm (the chamber is charged with a target concentration of 3500 ppm amyl acetate mixture (approximately 2300 ppm n-pentyl acetate and 1200 ppm 2-methylbutyl acetate) and the concentration drops as the rat inhales the test article. Loss to chamber equipment and external surface of the rat is corrected for.
- Control Group: None (biological samples taken prior to exposure). The amount inhaled by the rat (versus deposited on chamber equipment surfaces) is corrected for.
- Method: In an effort to understand the respiratory bioavailability of aliphatic alcohols and esters, a whole-body plethysmograph was installed in a gas-uptake chamber. The rat has an indwelling jugular cannula implanted prior to study start and is placed in the plethysmograph. The plethysmograph (containing the rat) is then placed in the gas-uptake chamber. The leads from the plethysmograph and the venous catheter are exteriorized from the chamber for sample and data collection. The chamber is charged with the amyl acetate mixture (described above) and the chamber concentration decay curve is followed by gas chromatography. In addition, venous blood samples are taken at 0, 5, 10, 15, 20, 25, 30, 40, 50, 60, and 90 minutes. The whole-body plethysmograph is designed to measure (non-invasively) ventilatory movements on conscious rats. By collecting data on ventilatory movements, and chamber and venous blood n-pentyl acetate and 2-methylbutyl acetate concentrations, respiratory bioavailability determinations can be calculated. Blood samples from five animals were analyzed for n-pentyl acetate, n-pentanol, valeric acid, 2-methylbutyl acetate, 2-methylbutanol, and 2-methylbutyric acid concentrations.
- Year: 2004  
 GLP: no (conducted in spirit of GLP, but not specifically)  
 Test substances: amyl acetate mixture (approximately 66% n-pentyl acetate and 34% 2-methylbutyl acetate)  
 Purity: Spectroscopic grade (>99.9%)  
 Result: The blood concentrations of n-pentyl acetate n-pentanol, valeric acid, 2-methylbutyl acetate, 2-methylbutanol, and 2-methylbutyric acid during the exposure period are reported below. The presence

of n-pentanol and valeric acid following n-pentyl acetate inhalation exposure clearly demonstrates that n-pentanol and valeric acid were the major metabolites of n-pentyl acetate metabolism. The presence of 2-methylbutanol and 2-methylbutyric acid following 2-methylbutyl acetate inhalation exposures clearly demonstrates that 2-methylbutanol and 2-methylbutyric acid were the major metabolites of 2-methylbutyl acetate metabolism. Blood levels of n-pentanol exceeded those of n-pentyl acetate at the first time point measured (5 minutes into the exposure) with blood concentrations of 36  $\mu\text{M}$ . At the next time point (10 minutes into exposure), the levels of n-pentanol in the blood was approximately 2-fold higher (55  $\mu\text{M}$ ) than the blood levels of n-pentyl acetate. n-Pentyl acetate levels peaked at 10 minutes (32  $\mu\text{M}$ ) and declined over the remaining 80 minutes. Chamber concentrations decline from time zero, both due to loss to chamber equipment surfaces as well as uptake by the rat (data not shown). Blood n-pentanol levels were approximately 1-3-fold higher than blood n-pentyl acetate levels from 10 to 25 minutes after the start of the exposure. Valeric acid levels reached levels of 3  $\mu\text{M}$  and were maintained throughout the exposure. These data clearly demonstrate that n-pentanol and valeric acid are the major toxicants present following n-pentyl acetate exposures. Blood levels of 2-methylbutanol exceeded those of 2-methylbutyl acetate at the first time point measured (5 minutes into the exposure) with blood concentrations of 28  $\mu\text{M}$ . At the next time point (10 minutes into exposure), the levels of 2-methylbutanol in the blood was approximately 4-fold higher (41  $\mu\text{M}$ ) than the blood levels of 2-methylbutyl acetate. 2-Methylbutyl acetate levels peaked at 10 minutes (10  $\mu\text{M}$ ) and declined over the remaining 80 minutes. Chamber concentrations decline from time zero, both due to loss to chamber equipment surfaces as well as uptake by the rat (data not shown). Blood 2-methylbutanol levels were approximately 4-5-fold higher than blood 2-methylbutyl acetate levels from 10 to 25 minutes after the start of the exposure. 2-Methylbutyric acid levels reached up to 17  $\mu\text{M}$  at 25 minutes after the start of the exposure. These data clearly demonstrate that 2-methylbutanol and 2-methylbutyric acid are the major toxicants present following 2-methylbutyl acetate exposures.

n-Pentyl acetate, n-pentanol, and valeric acid blood levels found following n-pentyl acetate inhalation.

Sampling Time (minutes)	n-Pentyl acetate*	n-Pentanol	Valeric acid
0	0	0	0
5	25	36	2
10	32	55	3
15	28	54	3
20	28	59	3
25	25	55	3
30	25	52	3
40	19	48	2
50	21	40	2
60	23	34	2
90	20	24	1

\*mean  $\mu\text{M}$  whole blood

2-Methylbutyl acetate, 2-methylbutanol, and 2-methylbutyric acid blood levels found following 2-methylbutyl acetate inhalation.

Sampling Time (minutes)	2-Methylbutyl acetate*	2-Methylbutanol	2-Methylbutyric acid
0	0	0	0
5	8	28	5
10	10	41	10
15	9	44	14
20	9	47	15
25	9	46	17
30	8	44	17
40	7	39	17
50	7	35	15
60	8	32	14
90	7	23	7

\*mean  $\mu$ M whole blood

Reference: Poet, T. 2004b. Unpublished data on Primary Amyl Acetate (mixture of n-pentyl acetate and 2-methyl butyl acetate). Battelle, Pacific Northwest National Laboratory, US Dept. of Energy. For Oxo-Process Panel, Chemstar, American Chemistry Council, Arlington, VA, 22209.

- (e) Test substance: n-pentyl alcohol, analytical grade  
 Species: rat  
 Strain: Wistar  
 Sex: male  
 Route of Admin: inhalation  
 Exposure Period: 7 to 14 weeks  
 Freq. of Treatment: 6 h/day, 5 days/week  
 Post Exposure  
 Observation Period: none  
 Doses: 0, 100, 300, or 600 ppm  
 Control Group: yes  
 NOEL: NA  
 LOEL: NA  
 Method: Male Wistar rats (254 +/- 54 g) were assigned to 3 groups of 10 rats each and exposed to n-pentyl alcohol at target concentrations of 100, 300, and 600ppm for 6 hours per day, 5 days per week for 7 or 14 weeks. Ten control rats (253 +/- 22 g) were exposed to air only. Five animals in each group were killed by decapitation after 7 or 14 weeks. Rats were dynamically exposed in a 1 m<sup>3</sup> chamber; concentrations were continuously monitored by infrared spectrophotometry. Animals were weighed prior to exposure and prior to sacrifice. Blood and brain (left cerebral hemisphere) was collected and prepared for determination of n-pentyl alcohol and valeraldehyde levels by gas chromatography. The right cerebral hemisphere and left gluteal muscle were analyzed for acetylcholinesterase activity. Liver and kidneys were collected for microsomal cytochrome 450 content and ethoxycoumarin O-deethylase activity, and cytosolic n-pentanol dehydrogenase activity.  
 Year: 1985

GLP:	no
Test substance:	n-pentyl alcohol, analytical grade
Remark:	No valeraldehyde was found in the blood while n-pentyl alcohol concentrations in blood and brain were linearly correlated to exposure levels at both 7 and 14 weeks. Brain levels of n-pentyl alcohol at week 14 were lower than that observed at 7 weeks. Valeraldehyde was found in the brain only in animals exposed to the highest dose, 600 ppm. Hepatic and renal alcohol dehydrogenase activities, cytochrome P-450 levels, and o-deethylase activities in exposed animals were unchanged or lower than controls. Brain acetylcholinesterase activity was increased in exposed animals at 7 weeks but not at 14 weeks.
Reliability:	score = 2, valid with restriction; purity of test material not specified
Reference:	Savolainen, H., Pfaffli, P., and Elovaara, E. 1985. Blood and brain n-pentanol in inhalation exposure. <i>Acta Pharmacol. Toxicol.</i> 56: 206-264.
(f) Test material:	isobutyl alcohol, purity not specified
Species:	human
Strain:	not applicable
Sex:	not available
Route of Admin:	oral
Exposure Period	2 hours
Freq. of Treatment:	single
Duration of Test:	11 hours
Exposure Conc.:	Isobutanol and ethanol were administered in water to produce a blood isobutanol level of 4 µmol/L at end of dosing interval.
Control Group:	None (biological samples taken prior to exposure)
Method:	In an effort to understand the elimination kinetics of aliphatic alcohols found in alcoholic beverages, human test subjects consumed isobutanol in a ethanol/water vehicle over a two hour time interval. Blood and urine samples were collected prior to consumption, at the end of the two-hour consumption period, and at one, two, eight (urine only), and nine hours after the end of the exposure period. Similar experiments resulted in an oral dose of approximately 5 mg/kg isobutanol. Each blood and urine sample was homogenized, treated with β-glucuronidase, deproteinated, and esterified with methanol or ethanol to detect the acid or aldehyde “down-stream” metabolites. Blood concentration-time curves were constructed for isobutanol, isobutyraldehyde, and isobutyric acid. Urine concentration-time curves were constructed for isobutanol, isobutyraldehyde, isobutyric acid, propionaldehyde, propionic acid, and succinic acid. The last three metabolites (propionaldehyde, propionic acid, and succinic acid) are the known metabolites of isobutyric acid.
Year:	1983
GLP:	no
Test substances:	isobutyl alcohol, ethyl alcohol
Purity:	not specified
Result:	The blood concentrations of isobutyl alcohol, isobutyraldehyde, and isobutyric acid were approximately 4, 4, and 17 µmol/L at the end of the consumption period. These data demonstrate that isobutyric acid is the major metabolite of isobutyl alcohol metabolism. Addition of ethanol to the test beverage resulted in competitive inhibition and altered the rate of isobutanyl alcohol metabolism. The presence of ethanol, however, did not affect how isobutyl alcohol was



metabolized. Blood levels of isobutyl alcohol decreased over the next two hours while the isobutyraldehyde levels slowly increased in the blood. Isobutyric acid levels also decreased after the end of the consumption period.

Urinary concentrations of isobutyl alcohol peaked at the one-hour post-exposure time point. Urinary levels of isobutyraldehyde peaked at the eight-hour post-exposure time point. Urinary levels of isobutyric acid peaked at the end of the two-hour exposure period. Urinary levels of propionaldehyde roughly followed those for isobutyraldehyde with peak levels of approximately 8 µmol/L. Urinary levels of propionic acid rose after the exposure period ended with plateau levels between 2 and 8 hours of approximately 60 µmol/L. Urinary levels of succinic acid roughly followed the propionic acid urinary elimination curve with peak levels of approximately 30 µmol/L. The authors diagrammatically describe further metabolism of isobutyric acid, ending with propionic acid.

Blood levels\* of isobutanol and metabolites in humans following isobutanol administration.

Sampling time (hr)	Isobutanol	Isobutyraldehyde	Isobutyric acid
Beginning of dosing	0	0	0
End of dosing (2 hr)	4	4	17
1 hr post dosing	2	4	14
2 hr post dosing	1	5	13
9 hr post dosing	0	5	10

\*mean µmol/L whole blood; Values derived from graphs provided in the paper.

Urine levels\* of isobutanol and metabolites in humans following isobutanol administration.

Sampling time (hr)	Isobutanol	Isobutyraldehyde	Isobutyric acid
Beginning of dosing	0	0	0
End of dosing (2 hr)	30	4	80
1 hr post dosing	125	6	70
2 hr post dosing	100	6	70
8 hr post dosing	50	7	40
9 hr post dosing	10	6	30

\*mean µmol/L urine; Values derived from graphs provided in the paper.

Remark: These data demonstrate that isobutanol is metabolized in humans to isobutyraldehyde, which in turn is metabolized to isobutyric acid. The data also demonstrates the transient nature of isobutyraldehyde, which is rapidly converted to isobutyric acid.

Reliability: score = 2, valid with restriction; purity of test material not specified

Reference: Rudell, E. von, Bonte, W., Sprung, R., and Kuhnholz, B. 1983. Zur Pharmakokinetik der holheren aliphatischen Alkohole. Beitr. Gerichtl. Med.. 41: 211-218.

(g) Test material: Isobutyl alcohol  
 Species: Human  
 Test system: liver isozyme from human donors  
 Sex: not specified

Route of Admin:	N/A (in vitro)
Exposure Period	10 minutes
Freq. of Treatment:	Single
Duration of Test:	10 minutes
Exposure Conc.: 100 µM	
Control Group:	compared to 2.5 to 10 mM ethanol
Method:	The roles of different isozymes of alcohol dehydrogenase (ADH) in the metabolism of aliphatic alcohols were investigated. Human liver ADH isoenzymes were prepared from two healthy tissue donors that succumbed to sudden death. Class I, II, and III ADH isoenzymes were isolated using DEAE-cellulose chromatography with affinity chromatography as the final separation step. The enzymes were assayed at 25°C in 50 mM sodium phosphate buffer at pH 7.4 containing 1.5 mM NAD and the respective alcohols. 50 mM semicarbazide was used to prevent the further reaction of the aldehydes to the corresponding acids. The reaction was initiated by the addition of the isoenzyme and stopped by the addition of ortho-phosphoric acid. The addition of the acid also liberated the respective aldehydes that were then analysed in the vial headspace by gas chromatography. All runs were assayed in triplicate. The reaction time was such that the aldehyde increased linearly with isoenzyme concentration. An additional check was to correlate the concentration of the aldehyde with the increase in NADH concentration (determined spectrophotometrically). Kinetic constants were estimated from the initial rate equations using a simplex algorithm with standard deviations estimated using Monte Carlo sensitivity analysis.
Year:	1988
GLP:	no
Test substance:	isobutyl alcohol, purity not specified
Result:	Class I ADH had a Km of 33 µM and a Vmax of 0.19 IU/mg protein for isobutanol. The resulting Class I activity (IU/mg) was 0.14 while the Class II ADH activity was 0.0004. Class III activity was below the limit of detection.
Remark:	These results demonstrate that the Class I ADH activity is primarily responsible for the oxidation of isobutanol in the human liver, and that isobutyraldehyde is the product of the reaction.
Remark:	score = 2, valid with restriction; purity of test material not specified
Reference:	Ehrig, T., Bohren, K.M., Wermuth, B., and von Wartburg, J-P. (1988) Degradation of Aliphatic Ethanol and Pharmacokinetic Implications. Alcoholism: Clinical and Experimental Research 26: 789-794.
(h) Test Substance:	n-butyl acetate
Species:	rat
Strain:	Sprague-Dawley
Sex:	male
Route of Admin:	intravenous
Exposure Period:	bolus injection into indwelling catheter
Freq. of Treatment:	single
Duration of Test:	Intravenous blood sampling occurred from immediately post dosing until approximately 6 hours after bolus injection
Exposure Concentration:	0.28 mmol/kg
Control Group:	yes, concurrent vehicle

Method:	Preliminary studies were conducted to select dose levels, dose formulations, and sampling times for the definitive studies. n-Butyl acetate in saline with 1% Tween 20 was administered individually to five animals via an indwelling femoral vein catheter. Serial blood samples were collected from an indwelling jugular vein catheter and immediately deproteinized to halt enzymatic activity. Concentrations of n-butyl acetate as well as down stream metabolites (n-butanol, n-butyraldehyde, n-butyric acid) were assayed by an internal standard GC-MS selected ion monitoring method.
Year:	2001
GLP:	yes
Result:	Following intravenous administration of n-butyl acetate, target blood collection times were 0, 0.5, 1.0, 1.5, 2.5, 5, 10, and 30 minutes post dosing. Analysis of these blood samples demonstrated a very rapid hydrolysis of n-butyl acetate to form n-butyl alcohol. Peak n-butyl acetate levels were found at 0.5 minutes, the earliest time point tested. N-Butyl acetate levels were at or below the limit of quantitation by ten minutes. n-Butyl alcohol was present in the 0.5 minute sample; peak levels were found at the one minute sampling time. n-Butyric acid was also found in the initial 0.5 minute sample and peak levels were noted at the 1 minute time point. This study demonstrates a very rapid hydrolysis of n-butyl acetate, with a half-life measured in seconds. It also demonstrates the rapid appearance and disappearance of the down stream metabolites, n-butanol and n-butyric acid. Studies with direct intravenous injection demonstrated the extremely transient nature of the metabolite, n-butyraldehyde.
Remark:	These data demonstrate that butyl alcohol is metabolized in rats to butyraldehyde, which in turn is metabolized to butyric acid. The data also demonstrate the transient nature of butyraldehyde, which is rapidly converted to butyric acid.
Reliability:	score = 1; valid without restriction
Reference:	Deisinger, P.J. and English, J.C. Pharmacokinetics of n-Butyl Acetate and Its Metabolites in Rats After Intravenous Administration. Toxicological Health Sciences Laboratory, Health and Environment Laboratory, Eastman Kodak Company, Rochester, NY. Report TX-2000-277, for the Oxo-Process Panel, CHEMSTAR, American Chemistry Council, Arlington, VA, Ref. OXO-49.0-Kodak-Butyl Acetate, as presented in Deisinger, et al., Family Approach PBPK Modelling of n-Butyl Acetate and Its Metabolites in Male Rats, Abstract #699, The Toxicologist, Vol. 60, No. 1, March 2001.
(i) Type:	In vitro oxidation of n-pentyl alcohol
Test material:	1-pentyl alcohol
Test system:	male rat hepatic and pulmonary cytosolic preparations
Concentration:	0.001 to 1.0 mM for liver 0.01 600 mM for lung
Control Group:	None, background activity measured prior to addition of alcohol
Remark:	Studies with ethyl alcohol have demonstrated that metabolism via alcohol dehydrogenase (ADH) results in the formation of acetaldehyde. Removal of acetaldehyde is catalyzed by an enzyme with a very low Km, which results in low concentrations, even when substrate levels are relatively high. An increase in NADH

Method: concentration (measured spectrophotometrically) has been shown to correlate with aldehyde formation (Ehrig, T. et al. 1988)  
 In an effort to understand the role of alcohol dehydrogenase (ADH) in the metabolism of n-pentyl alcohol and other alcohols, the activity of ADH as influenced by pH and substrate concentration was measured in lung and liver cytosolic preparations. Adult male Sprague Dawley rats were killed by decapitation and livers and lungs removed immediately homogenized in 4 volumes of 0.5 M HEPES buffer containing 0.5 mM dithiothreitol at pH 8.4. The initial homogenates were centrifuged at 10,000 g for 20 min, and the resulting supernatant centrifuged at 105,000 g for 60 min at 4 °C to obtain the cytosolic fraction. The cytosols were partially purified using Sephadex G-50 columns equilibrated in buffer (10 mM Tris-HCl buffer, pH 8, and 1 mM ethylenediamine tetracetic acid) containing 0.1 mM NaCl. Cytosolic preparations were assayed spectrophotometrically for ADH activity at 37 °C by following NADH formation at 340 nm after addition of alcohol substrate. The incubation mixture contained 0.5 M Tris-HCl buffer, 2.8 mM NAD<sup>+</sup>, and 0.05 ml of cytosolic fraction containing approximately 0.5 to 1.4 mg cytosolic protein. Selection of appropriate concentrations of alcohol substrates was based on range-finding studies. Apparent k<sub>M</sub> and V<sub>max</sub> values for lung and liver were calculated using Lineweaver-Burk plots from determinations using 4 to 7 rats, with values given as mean +/- standard error.

Year: 1995  
 GLP: no  
 Test substance: 1-pentyl alcohol  
 Purity: purity not specified  
 Result: Hepatic oxidation of 1-pentyl alcohol by liver cytosolic ADH activity was measured. The k<sub>m</sub> value was slightly lower at pH 10.0 than at pH 7.2 and 9.0. Similar results were obtained with the propyl and butyl alcohol, the 3- and 4-carbon structural analogs of 1-pentyl alcohol.

Hepatic Alcohol Metabolism by ADH in Male Rats

	pH	V <sub>max</sub> <sup>1</sup>	K <sub>m</sub> <sup>2</sup>
1-pentyl alcohol	7.2	24.1 +/- 3.4	0.291 +/- 0.121
	9.0	25.3 +/- 4.5	0.324 +/- 0.137
	10.0	23.9 +/- 4.7	0.105 +/- 0.065
1-butyl alcohol	7.2	13.2 +/- 1.5	0.159 +/- 0.085
	9.0	15.9 +/- 6.9	0.136 +/- 0.051
	10.0	9.2 +/- 1.1	0.045 +/- 0.013
1-propyl alcohol	7.2	21.3 +/- 2.4	0.114 +/- 0.031
	9.0	28.8 +/- 1.4	0.013 +/- 0.002
	10.0	39.1 +/- 2.9	0.079 +/- 0.017

1: nM/min/mg protein 2: mM

For all alcohols studied, pulmonary ADH V<sub>max</sub> rates at pH 10 were not appreciably different than those obtained for the liver. However, maximal activity required a higher pH in cytosolic fractions derived from the lung. The apparent pulmonary K<sub>m</sub> values at pH 10 were 180, 430, and 520 times higher than the corresponding hepatic K<sub>m</sub> values for 1-pentyl, 1-butyl, and 1-propyl alcohol, respectively. These results indicate that all three alcohols

are substrates for alcohol dehydrogenases derived from liver and lung.

Pulmonary Alcohol Metabolism by ADH in Male Rats

	pH	Vmax <sup>1</sup>	Km <sup>2</sup>
1-pentyl alcohol	7.2	ND <sup>3</sup>	ND
	9.0	ND	ND
	10.0	19.3 +/- 2.7	19.0 +/- 5.5
1-butyl alcohol	7.2	ND <sup>3</sup>	ND
	9.0	ND	ND
	10.0	20.2 +/- 2.1	19.4 +/- 7.4
1-propyl alcohol	7.2	3.8 +/- 0.8	1792 +/- 1414
	9.0	8.0 +/- 1.1	62.6 +/- 22.0
	10.0	11.6 +/- 1.4	41.2 +/- 10.2

1: nM/min/mg protein 2: mM

3: Not determined due to low activity

The authors report that studies with ethyl alcohol have also demonstrated that rat pulmonary ADH activity is pH dependent, whereas rat hepatic alcohol metabolism displayed little pH dependence. These differences in pH dependence suggest that different ADH isozymes may be present in the lung. Studies with human ADH have demonstrated genetically distinct ADH isoenzymes, which have different kinetic properties and pH optimums. The pH optimums for individual human ADH isoenzymes are 7.0, 8.5, and 10.0.

Remark: These data indicate that 1-pentyl alcohol is oxidized in the liver and lung by ADH; the product of aliphatic alcohol oxidation is the the corresponding aldehyde.

Reliability: score = 2, reliable with restriction; purity of test substances not specified

Reference: Carlson, G.P., Olson, R.M.C. 1995. Comparison of the metabolism of alcohols by rat hepatic and pulmonary alcohol dehydrogenase. *Biochem Mol. Biol.* 37: 65-71.

(j) Remark: The authors present evidence that straight-chain and branched aldehydes are oxidized to their respective acids. A mitochondrial suspension system was used which represented 250 mg of fresh original rat liver tissue. Experiments were carried out for 60 minutes at 38 °C with air as the gas phase. Aldehydes used were commercial products that were distilled prior to use. The authors report that a variety of aldehydes are oxidized by rat liver mitochondrial aldehyde dehydrogenase, including formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, isobutyraldehyde, hexaldehyde, and heptaldehyde (see table below). With the exception of formaldehyde, oxidation of aldehydes to their respective fatty acids was not inhibited by high substrate concentrations. Experiments with longer-chain length aldehydes that were insoluble in water were conducted with the aldehydes in suspension, which did not appear to affect results. Like their corresponding acids, most aldehydes yielded acetoacetate upon incubation in the mitochondrial suspension system.

Oxidation of Some Aldehydes by Rat Liver Mitochondria

Substrate			
Aldehyde	mM	O <sub>2</sub> Uptake (uM)	Acetoacetate (uM)
None (control)		3.00	0.40
Formaldehyde (C1)	1.0	4.06	NR <sup>2</sup>
Acetaldehyde (C2) <sup>1</sup>	1.0	8.0	NR
Propionaldehyde (C3)	5.0	8.58	0.60
Butyraldehyde (C4)	10.0	11.50	4.55
Isobutyraldehyde (C4)	5.0	9.10	NR
Hexaldehyde (C6)	1.0	11.20	1.52
Heptaldehyde (C7)	1.0	7.73	1.08
2-Ethyl hexaldehyde (C8)	2.0	3.08	0.35

1: number of carbons in aldehyde

2: not reported; test reports "...no appreciable accumulation of acetoacetate..."

The authors report that numerous experiments (data not shown) have demonstrated that the sole product of acetaldehyde oxidation by mitochondria is acetic acid. It was determined that the oxygen consumption corresponded to the amounts of acetic acid isolated, and there was no appreciable accumulation of acetoacetate. Similar results were obtained with formaldehyde and propionaldehyde.

To obtain additional information on the oxidation of aldehydes by rat liver mitochondria, a comparison of the rate of oxygen consumption and acetoacetate formation was made between butyraldehyde and butyric acid. Rates of oxygen consumption and acetoacetate production were similar for both materials. These results suggest that oxidation of the acid is at least as rapid as the aldehyde, and that the overall reaction is not limited by either step.

Oxidation of Butyraldehyde and Butyric Acid by Rat Mitochondria Suspensions<sup>1</sup>

Time (min)	Substrate					
	Control		Butyraldehyde (2.0 mM)		Butyric Acid (2.0 mM)	
	O <sub>2</sub> uptake	acetoacetate	O <sub>2</sub> uptake	acetoacetate	O <sub>2</sub> uptake	acetoacetate
10	0.28	NR <sup>2</sup>	2.28	1.65	2.98	1.75
20	1.21	NR	4.71	2.82	5.02	2.82
30	1.78	NR	6.10	3.53	6.58	3.80
60	3.27	0.36	8.36	3.68	9.18	4.91

1: Oxygen and acetoacetate values are in uM

2: None reported

The authors report that similar results were obtained with rat kidney and pigeon liver mitochondria (data not shown). These results suggest that the mitochondrial enzyme acts directly on the aldehyde and the oxidation product is the corresponding acid.

Reference:

Walkenstein, S.S. and Weinhouse, S. 1953. Oxidation of aldehydes by mitochondria of rat tissues. *J. Biol. Chem.* 200: 515-523.

(k) Remark:

Human liver aldehyde dehydrogenase (ALDH) activity was

measured in a series of 13 samples of normal human liver obtained at autopsy. Case history and pathological examination were used to demonstrate the lack of disease in each liver sample. ALDH activity ranged from 0.8 to 4.4 units/g wet weight (average 2.3 units/g). The enzyme was purified approximately (detailed procedure described by authors) and the enzyme activity adsorbed onto DEA-cellulose column (2 cm x 35 cm) and equilibrated with 10 mM potassium phosphate, pH 6.0. Enzyme activity was eluted by a linear salt gradient (10 to 80 mM potassium phosphate, pH 6.0. Fractions selected were pooled and concentrated by precipitation with solid ammonium sulfate. This procedure resulted in approximately 20-fold purification of the ALDH enzyme obtained from 13 human liver samples.

It was determined that aldehydes are oxidized when  $\text{NAD}^+$ , but not  $\text{NADP}^+$ , is the electron acceptor. Maximal activity for the partially purified ALDH enzyme was between pH 9 and 10. A variety of aldehydes served as substrates for human ALDH (see table below). Half-maximal activity with acetaldehyde was estimated to be on the order of 1.0  $\mu\text{M}$ . Kinetic characterization of the aldehydes was complicated by the low concentrations at which activity occurred and their volatility. Accordingly,  $K_m$  and  $V_{max}$  values were not calculated. The authors do report, however, that for simple aliphatic aldehydes, concentrations giving half-maximal activity (i.e. the apparent  $K_m$ ) were in the micromolar range.

Relative rates of oxidation of aldehydes by partially purified aldehyde dehydrogenase (ALDH) from human liver<sup>1</sup>

Substrate	Aldehyde Concentration		
	0.05 mM	0.3 mM	3.0 mM
Acetaldehyde	0.82	0.92	1.0 <sup>2</sup>
Propionaldehyde	0.90	1.0	1.1
Butyraldehyde	0.81	0.95	1.1
Valeraldehyde	0.93	1.0	1.0

1: Control reactions with enzyme omitted were conducted (data not shown); activities shown in table are for enzyme in presence of substrate minus activity recorded in absence of enzyme.

2: Rate with 3.0 mM acetaldehyde set equal to 1.0 as relative standard.

These results suggest that valeraldehyde and other short-chain aldehydes are readily oxidized, and that the relative rates of oxidation are similar when tested at substrate concentrations between 0.5 and 3.0 mM using partially purified human liver aldehyde dehydrogenase. The rate of oxidation for C3 to C5 aldehydes was comparable to acetaldehyde.

Reference:

Blair, A.H. and Bodley, F.H. 1969. Human liver aldehyde dehydrogenase: partial purification and properties. *Can. J. Biochem.* 47: 265-272.

(1) Remark:

Oxidation of aldehydes to their corresponding acids occurs via aldehyde dehydrogenases (ALDHs), a rather large group of enzymes. ALDH activity has been found in liver, erythrocytes, kidney, heart,

and placenta. Mitochondrial ALDH has also been characterized. The metalloenzymes, aldehyde oxidase and xanthine oxidase also oxidase aldehydes including propionaldehyde, butyraldehyde, and valeraldehyde. The acid oxidation products of aldehydes may be either excreted or condensed with Coenzyme A to produce the acyl-CoA derivative.

Reference: Brabec, M.J. 1993. Aldehydes and Acetals. *in*: Clayton, G.D., Clayton, F.E. (Eds.). *Patty's Industrial Hygiene and Toxicology*, New York, NY: John Wiley & Sons.

(m) Remark: Aldehyde dehydrogenase (ALDH) is a ubiquitous enzyme that has been measured in many tissues. ALDH acts to detoxify aldehydes. Human liver mitochondrial ALDH showed similar affinity (Km) toward C4 to C8 aldehydes.

Reference: Mukerjee, N. and Pietruszko, R. 1992. Human mitochondrial aldehyde dehydrogenase substrate specificity: comparison of esterase with dehydrogenase reaction. *Arch. Biochem. Biophys.* 299: 23-29. *cited in*: Guth, D.J. 1996. Dose-response assessment of non-cancer effects of propionaldehyde based on comparative toxicity with other short-chained aldehydes. *Human Ecol. Risk Assess.* 2: 580-590.

(n) Remark: Aldehyde dehydrogenase (ALDH) is a tetrameric enzyme present in the cytosol and mitochondria. ALDH is found in the liver and lung as well as in the respiratory and olfactory epithelium of the nose; it is also found in the nasal epithelial mucosa.

References: Carlson, G.P. and Olson, R.M. 1995. Comparison of the metabolism of alcohols by rat hepatic and pulmonary dehydrogenase. *Biochem. Mol. Biol. Int.* 37: 65-71.

Morris, J.B., Hassett, D.N. and Blanchard, K.T. 1993. A physiologically based pharmacokinetic model for nasal uptake and metabolism of nonreactive vapors. *Toxicol. Appl Pharmacol.* 123: 120-129.

**C. Other**

(a) Remark: The log oil/water partition coefficients and log RD50s (sensory irritation potency in mice) for butyraldehyde, isobutyraldehyde, valeraldehyde, and isovaleraldehyde are very similar:

<u>Aldehyde</u>	<u>log RD50</u>	<u>Log O/W</u>
Butyraldehyde	3.006	2.30
Isobutyraldehyde	3.620	2.15
Valeraldehyde	3.050	2.82
Isovaleraldehyde	3.003	2.59

All four aldehydes were found to have similar log oil-water partition coefficients, as well as similar log RD50s. Interestingly, other chemical-physical properties, including excess molar refraction, chemical depolarity/polarizability, and hydrogen bond acidity/basicity were also very similar.

Reference: Alarie, Y., Schaper, M., Nielsen, G.D. and Abraham, M.H. 1998. Structure-activity relationships of volatile organic chemicals as sensory irritants. *Arch. Toxicol.* 72: 125-140.



- (b) Remark: The effect of valeraldehyde on calf brain microtubular protein assembly: tubulin preparations (2 mg/ml) was investigated by incubating valeraldehyde with preparations at 37 degree C for 30 minutes. Valeraldehyde concentrations were 0, 0.1, 0.25, 0.50, and 1.0 mM. Valeraldehyde inhibited microtubule assembly at all concentrations tested. The inhibition produced was proportional to the concentration; low concentrations had negligible effect while 1 mM caused 40% inhibition. Colchicine binding of tubulin after incubation with valeraldehyde was also studied in order to determine if molecular integrity was preserved. Colchicine binding increased with increasing aldehyde concentrations. The authors hypothesise that a stoichiometric reaction occurs between the aldehyde and microtubular protein. Addition of excess SH groups did not protect against this reaction, the authors suggest that the aldehyde reacts with other functional groups such as amino groups. Intracellular lipo-oxidation products such as valeraldehyde may attack cytoskeletal structures and may inhibit cell functions.
- Reference: Miglietta, A., Gabriel, L., and Gadoni, E. 1987. Cell Biochem. Function 5: 189-194.

#### 5.11 EXPERIENCE WITH HUMAN EXPOSURE

- (a) Remarks: The odor threshold for aqueous aldehyde solutions for normal and anosmic individuals for aldehydes is presented in tabular form:

Odor Threshold in Normal and Anosmic Human Subjects

Aldehyde	(Normal, ppb)	(Anosmic, ppb)
Butyraldehyde	37.3	217
Valeraldehyde	60.6	154
Isobutyraldehyde	2.30	1190
Isovaleraldehyde	2.02	18

- Reference: Amooore, J.E., Forrester, L.J. and Pelosi, P. 1976. Specific anosmia to isobutyraldehyde: the malty primary odor. Chem. Senses Flavor 2: 17-25.
- (b) Test material: valeraldehyde  
Remark: Three Asian subjects who reported experiencing severe facial flushing in response to ethanol ingestion were subjects of patch testing to aliphatic alcohols and aldehydes. An aqueous suspension of 75% (v/v) of each alcohol and aldehyde was prepared and 25 uL was used to saturate ashless grade filter paper squares which were then placed on the forearm of each subject. Patches were covered with Parafilm and left in place for 5 minutes when the patches were removed and the area gently blotted. Sites showing erythema during the next 60 minutes were considered positive. All three subjects displayed positive responses to ethyl, propyl, butyl, and pentyl alcohols. Intense positive reactions, with variable amounts of edema, were observed for all the aldehydes tested (valeraldehyde as well as acetaldehyde, propionaldehyde, and butyraldehyde). The irritation potential of the test materials were not discussed. The authors suggest that an accumulation of aldehydes is caused by

- Reference: decreased aldehyde reductase activity in Oriental subjects which provokes flushing after consumption of alcohol.  
Wilkin, J.K. and Fortner, G. 1985. Ethnic contact urticaria to alcohol. *Contact Dermatitis* 12: 118-120.
- (c) Test material: isovaleraldehyde  
Remark: Several chemists exposed to isovaleraldehyde developed signs of chest discomfort, nausea, vomiting, and headaches. Exposure levels were not measured, however the odor was very pronounced. All recovered within a few days without residual after effects.  
Reference: Wilkinson, J.F. 1940. *J. Hyg.* 40: 555. *cited in*: Brabec, M.J. 1993. *Aldehydes and Acetals. in*: Clayton, G.D., Clayton, F.E. (Eds.). *Patty's Industrial Hygiene and Toxicology*, New York, NY: John Wiley & Sons.

- Abdo, K.M., Haseman, J.K. and Nyska, A. 1998. Isobutyraldehyde administered by inhalation (whole body exposure) for up to 13 weeks or two years was a respiratory tract toxicant but was not carcinogenic in F344 rats and B6C3F1 mice. *Toxicol. Sci.* 42: 136-151.
- Alarie, Y., Schaper, M., Nielsen, G.D., and Abraham, M.H.. 1998. Structure-activity relationships of volatile organic chemicals as sensory irritants. *Arch. Toxicol.* 72: 125-140.
- Aldrich Chemical Company. 1996. Aldrich Flavors and Fragrances. Milwaukee, WI.
- American Conference Governmental Industrial Hygienists (ACGIH). 2005. 2005 TLVs® and BEIs®. ACGIH, Inc.: Cincinnati, OH.
- American Conference Governmental Industrial Hygienists (ACGIH). 2005. 2005 Guide to Occupational Exposure Values. ACGIH, Inc.: Cincinnati, OH.
- Amoore, J.E., Forrester, L.J. and Pelosi, P. 1976. Specific anosmia to isobutyraldehyde: the malty primary odor. *Chem. Senses Flavor* 2: 17-25.
- AOPWIN. Version 1.91. Atmospheric Oxidation. EPIWIN (Estimation Program for Windows) Version 3.12. U.S. Environmental Protection Agency, 2005.
- Atkinson, R. 1989. Kinetics and mechanisms of the gas-phase reactions of the hydroxyl radical with organic compounds. *J. Phys. Chem. Ref. Data. Monograph No 1.*
- Barton, H.A., Deisinger, P.J., English, J.C., Gearhart, J.M., Faber, W.D., Tyler, T.R., Banton, M.I., et al. 2000. Family approach for estimating reference concentrations/doses for series of related organic chemicals. *Toxicol. Sci.* 54: 251-261.
- BASF Aktiengesellschaft Ludwigshafen. Safety Data Sheet. CAS No. 110-62-3. Version 5.00. Revised 10.09.97.
- BCFWIN. Version 2.15. BCF Estimate from Log Kow. EPIWIN (Estimation Program Interface for Windows). Version 3.10. U.S. Environmental Protection Agency, 2000.
- Bizzari, S.N., Fenelon, S. and Ishikawa-Yamaki, M. 1999. CEH Marketing Research Report, dated May 1999.
- Blair, A.H. and Bodley, F.H. 1969. Human liver aldehyde dehydrogenase: partial purification and properties. *Can. J. Biochem.* 47: 265-272.
- Brabec, M.J. 1993. Aldehydes and Acetals. *in: Clayton, G.D., Clayton, F.E. (Eds.). Patty's Industrial Hygiene and Toxicology*, New York, NY: John Wiley & Sons.
- Brambilla, G., Cajelli, E., Canonero, R., Martelli, A., and Marinari, U.M. 1989. Mutagenicity in V79 Chinese hamster cells of n-alkanals produced by lipid peroxidation. *Mutagenesis* 4: 277-279.
- Budavari, S.B. (ed.). 1996. The Merck Index. An Encyclopedia of Chemicals, Drugs, and Biologicals, 12<sup>th</sup> Edition. Whitehouse Station, NJ: Merck & Co., Inc.
- Buttery, R.G. et al. 1969. *J. Agric. Food Chem.* 17: 385-389.
- Carlson, G.P. and Olson, R.M. 1995. Comparison of the metabolism of alcohols by rat hepatic and pulmonary dehydrogenase. *Biochem. Mol. Biol. Int.* 37: 65-71.

Chou, C-C. and Que-Hee, S.S. 1994. Saliva-available carbonyl compounds in some chewing tobaccos. *J. Agric. Food Chem.* 42: 2225-2230.

Chun, H.N. and Kim, Z.U. 1992. Evaluation of vegetable oil rancidity by headspace gas chromatographic analysis. *Han'guk Nonghwa Hakhoechi* 35: 36-41.

Collins, D.W. and Richey, F.A., Jr. 1992. Synthetic organic chemicals. In: Kent, J.A. (Ed). *Riegel's Handbook of Industrial Chemistry*, 9<sup>th</sup> Edition. New York: Van Nostrand Reinhold.

Colombo, A. et al. 1990. *Sci. Total Environ.* 91: 237-249.

Dahl, A.R., Miller, S.C. and Petridou-Fischer, J. 1987. Carboxylesterases in the respiratory tracts of rabbits, rats and Syrian hamsters. *Toxicology Letters* 36: 129-136.

Daubert, T.E. and Danner, R.P. 1989. *Physical and Thermodynamic Properties of Pure Chemicals: Data Compilation*. New York, NY: Hemisphere Publishing Corp.

Davis, J.W. and Marty, G.T. 2004. Valeraldehyde: Evaluation of ready biodegradability according to OECD Guideline 301D: Closed Bottle Test (unpublished study). *Toxicology & Environmental Research and Consulting*. Study ID 031115. The Dow Chemical Company, Midland, MI.

DeBortoli, M. et al. 1986. *Environ. Internat.* 12: 343-350.

Deener, J.W., Seinen, W. and Hermens, J.L.M. 1988. The acute toxicity of aldehydes to the guppy. *Aquatic Toxicol.* 12: 185-192.

Deisinger, P.J. and English, J.C. 2000. Pharmacokinetics of n-Butyl Acetate and Its Metabolites in Rats After Intravenous Administration. *Toxicological Health Sciences Laboratory, Health and Environment Laboratory, Eastman Kodak Company, Rochester, NY*. Report TX2000-277, prepared for the OxoProcess Panel, Chemstar, American Chemistry Council, Arlington, VA.

Deisinger, P.J. and J. C. English. 2001. The *In Vivo* Pharmacokinetics of n-Butyl Acetate in Rats After Intravenous Administration. *Toxicological Health Sciences Laboratory, Health and Environment Laboratory, Eastman Kodak Company, Rochester, NY*. Lab. Proj. ID 94-0306BT01, for the Oxo-Process Panel, CHEMSTAR, Chemical Manufacturers Association, 1300 Wilson Blvd., Arlington, VA, Ref. OXO-22.0-BA-Kodak, as presented in Deisinger, et al., Family Approach PBPK Modelling of n-Butyl Acetate and Its Metabolites in Male Rats, Abstract #699, *The Toxicologist*, Vol. 60, No. 1, March 2001.

Dillon, D., Combes, R. and Zeiger, E. 1998. Effectiveness of Salmonella strains TA 100, TA102 and TA104 for detecting mutagenicity of some aldehydes and peroxides. *Mutagenesis* 134: 19-26.

Driscoll, C.D. 1993. Propionaldehyde: Combined Repeated-Exposure Reproductive/Developmental Toxicity Study in CD Rats. Union Carbide Corporation, Bushy Run Research Center Report 91U0086.

Eastman Kodak Company. 1991. Toxicity and health hazard summary, material data sheet, and toxicity report on pentanal. Eastman Kodak Health and Safety Laboratory. (EPA/OATS Doc # 86-92000053). *Cited in:* National Toxicology Program (NTP). 1996. Chemical Selection Working Group (SCWG). Summary of Data for Chemical Selection. n-Valeraldehyde.

Ehrig, T., Bohren, K.M., Wermuth, B., and von Wartburg, J-P. 1988. Degradation of Aliphatic Ethanol and Pharmacokinetic Implications. *Alcoholism: Clinical and Experimental Research*, Vol. 26, No. 6, pp. 789-794.

EPISuite Version 3.12. U.S. Environmental Protection Agency, 2004.

Erickson M.D. and Pellizzari, E.D. 1978. Analysis of organic Air Pollutants in the Kanawha Valley, WV and the Shenandoah Valley VA USEPA-903/9-78-007

Falbe, J. Lappe, P. and Weber, J. 1985. Aldehydes, aliphatic and araliphatic. *Cited in: Ullmann's Encyclopedia of Industrial Chemicals*, 5<sup>th</sup> Edition. Volume A-1.

Flick, E.W. 1991. *Industrial Solvents Handbook*, 4<sup>th</sup> Edition. Park Ridge, NJ: Noyes Data Corp.

Florin, I., Rutberg, L., Curvall, M. and Enzell, C.R. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' Test. *Toxicology* 15: 219-232.

Frankel, E.N., Selke, E., Neff, W.E., and Miyashita, K. 1992. Autoxidation of polyunsaturated triacylglycerols. IV. Volatile decomposition products from triacylglycerols containing linoleate and linolenate. *Lipids* 27: 442-446.

Fugacity Model Level III. EPISuite Version 3.12. U.S. Environmental Protection Agency, 2004.

Furia, T.E. (Ed). 1972. *CRC Handbook of Food Additives*. Cleveland, OH: CRC Press.

Gage J.C. 1970. The subacute inhalation toxicity of 109 industrial chemicals. *Brit. J. Ind. Med.* 27: 1-18.

Garmer, A.O., Hellwig, J. and Hildebrand, B. 1996. Isobutyryaldehyde-Prenatal Vapor Inhalation Study in Wistar Rats. BASF Aktiengesellschaft Department of Toxicology Project No. 31R0140/93049. Ludwigshafen, Germany.

Geiger, D.L., Northcott, C.E., Call, D.J., and Brooke, L.t. (eds). 1985. *Acute Toxicities of Organic Chemicals to Fathead Minnows (Pimephales promelas)*. Volume II. Center for Lake Superior Environmental Studies. University of Wisconsin-Superior.

Geiger, D.L., Poirier, S.H., Brooke, L.T., Call, D.J. (Eds.). 1986. *Acute Toxicities of Organic Chemicals to Fathead Minnows (Pimephales promelas)*. Vol. III. Center for Lake Superior Environmental Studies, University of Wisconsin-Superior

Gerhold, R.M. and Malaney, G.W. 1966. Structural determinants in the oxidation of aliphatic compounds by activated sludge. *J. Water Pollut. Control Fed.* 38: 562-579.

Graedel, T.E. et al. 1986. *Atmospheric Chemical Compounds*. NY: Academic Press

Grosjean, D. 1988. *Atmos. Environ.* 22: 1637-1648.

Guicherit, K. and Schulting, F.L. 1985. *Sci. Total Environ.* 43: 193-219.

Guth, D.J. 1996. Dose-response assessment of non-cancer effects of propionaldehyde based on comparative toxicity with other short-chained aldehydes. *Human Ecol. Risk Assess.* 2: 580-590.

Haggard, H.W., Miller, D.P. and Greenberg, L.A. 1945. The amyl alcohols and their ketone: their metabolic fates and comparative toxicities. *J. Indus. Hyg. Toxicol.* 27: 1-14.

Hancock, G.A., McClymont, E.L., and Staley, J.L. 2003. n-Valeraldehyde: Growth Inhibition Test with the Freshwater Green Algae, *Pseudokirchnerilla subcapitata* (unpublished study). Toxicology & Environmental Research and Consulting, Study ID 031086. The Dow Chemical Company, Midland, MI.

Hazardous Substance Data Bank (HSDB). No. 851, Valeraldehyde (Pentanal) CASRN 110-62-3, complete update on 11/08/2002.

HENRYWIN. Version 3.10. Henry's Law Constant. EPIWIN (Estimation Program Interface for Windows). Version 3.10. U.S. Environmental Protection Agency, 2000.

International Technical Information Institute (ITII). 1988. Toxic and Hazardous Industrial Chemicals Safety Manual. ITT, Tokyo, Japan.

James, J.T.J. 2000. C3 to C8 Aliphatic Saturated Aldehydes. Spacecraft Maximum Allowable Concentrations for Selected Airborne Contaminants. Washington, DC: National Academy of Science.

Jonsson, A., Persson, E.A., and Grigoriadis, V. 1985. Measurements of some low-molecular-weight oxygenated, aromatic, and chlorinated hydrocarbons in ambient air and in vehicle emissions. *Environ. Intl.* 11: 383-392.

Keith, L.H. et al. 1976. Identification Analysis of Organic Pollutants in Water. Ann Arbor, MI: Ann Arbor Press.

KOWWIN, Version 1.66. Log Octanol-Water Partition Coefficient. EPIWIN (Estimation Program for Windows) Version 3.10. U.S. Environmental Protection Agency, 2000.

Lewis, R.L., Sr. 1993. *Hawley's Condensed Chemical Dictionary*, 12<sup>th</sup> ed. New York: Van Nostrand Reinhold.

Lide, D.R. (ed) *CRC Handbook of Chemistry and Physics*, 76<sup>th</sup> ed. Boca Raton, FL: CRC Press Inc., 1995-1996.

Lipari, F. et al. 1984. *Environ. Sci. Technol.* 18: 326-330.

Lloyd, A.C. 1978. *Tropospheric Chemistry of Aldehydes*. National Bureau of Standards. Washington, DC.

Luo, J.E. et al. 1993. Study of sensory irritancy of series of aldehydes and the prediction of safe levels of exposure (TLV). *The Toxicologist* 13: 263.

Lyman, W.J. et al. 1982. *Handbook of Chemical Property Estimation Methods*. NY: McGraw Hill Book Company.

Marino, T.A, McClymont, E.L., and Yaroch, A.M. 2003a. n-Valeraldehyde: An Acute Toxicity Study with the Rainbow Trout, *Oncorhynchus mykiss* Walbaum (unpublished study). Toxicology & Environmental Research and Consulting, Study ID 031104. The Dow Chemical Company, Midland, MI.

Marino, T.A, McClymont, E.L., and Yaroch, A.M.. 2003b. n-Valeraldehyde: An Acute Toxicity Study with the Daphnid, *Daphnia magna* Straus (unpublished study). Toxicology & Environmental Research and Consulting, Study ID 031103. The Dow Chemical Company, Midland, MI.

Martelli, A., Canonero, R., Cavanna, M., Ceradelli, M., and Marinari, U.M. 1994. Cytotoxic and genotoxic effects of five n-alkanals in primary cultures of rat and human hepatocytes. *Mutat. Res.* 323: 121-126.

Mattheis, J.P. et al. 1991. *J. Agric. Food. Chem.* 39: 1902-1906.

Merck-Schuchardt. Safety Data Sheet. Pentanal for synthesis. 04.2000. The Merck Chemical Database-online: <http://www.merck.de> (accessed October 16, 2000).

Meylan, W.M. and Howard, P.H. 1995. Atom/fragment contribution method for estimating octanol-water partition coefficients. *J. Pharm. Sci.* 84: 83-92.

- Miglietta, A., Gabriel, L., and Gadoni, E. 1987. *Cell Biochem. Function* 5: 189-194.
- Miller, W.E., Green, J.C., and Shiroyama, T. 1978. The *Selenastrum capricornutum* Printz Algal Assay Bottle Test. EPA-600/9-78-018.5.
- Morris, J.B., Hassett, D.N. and Blanchard, K.T. 1993. A physiologically based pharmacokinetic model for nasal uptake and metabolism of nonreactive vapors. *Toxicol. Appl Pharmacol.* 123: 120-129.
- Morrissey, R.E., Schwetz, B.A., Lamb, J.C., IV, Ross, M.D., Teague, J.L., and Morris, R.W. 1988. Evaluation of rodent sperm, vaginal cytology, and reproductive organ weight data from National Toxicology Program 13-week studies. *Fundam. Appl. Toxicol.* 11: 343-358.
- Mukerjee, N. and Pietruszko, R. 1992. Human mitochondrial aldehyde dehydrogenase substrate specificity: comparison of esterase with dehydrogenase reaction. *Arch. Biochem. Biophys.* 299: 23-29.
- Muller, W.J. and Black, M.S. 1995. Sensory irritation in mice exposed to emissions from indoor products. *Am. Ind. Hyg. Assoc. J.* 56: 794-803.
- Narotsky, M.G. and Kavlock, R.J. 1989. Pentanoic Acid Developmental Toxicity Testing. ManTech Environmental Technology Inc. Report No. 68-02-4450. Report dated October 10, 1989.
- Narotsky, M.G., Francis, E.Z., and Kavlock, R.J. 1994. Developmental toxicity and structure-activity relationships of aliphatic acids, including dose-response assessment of valproic acid in mice and rats. *Fundam. Appl. Toxicol.* 22: 251-265.
- National Cancer Institute. Short-term Test Program Sponsored by the Division of Cancer Etiology, Dr. David Longfellow, Project Officer. *cited in: HSDB. Valeraldehyde (Pentanal). CASRN 110-62-3. Hazard Substance Data Bank (HSDB) No. 851, complete update on 11/08/2002.*
- NFPA. 2002. National Fire Protection Association. Fire Protection Guide to Hazardous Materials. 13th edition. NFPA. Quincy, MA.
- NIOSH. 1990. NIOSH Occupational Exposure Survey (NOES) as of 12/06/90. National Institute for Occupational Safety and Health (NIOSH), Cincinnati, OH.
- NIOSH. 1997. NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) Publication 97-140.
- Noma, E. et al. 1988. *Atmos. Environ.* 22: 451-460.
- National Toxicology Program (NTP). 1990. Assessment of Contact Hypersensitivity of Isobutyraldehyde (CAS No. 78-84-2) in Female B6C3F1 Mice. Report to the National Toxicology Program. Protocol IBA—0-1-CNM. Studies conducted at Immunotoxicology Program, Medical College of Virginia, Virginia Commonwealth University, Richmond, VA.
- NTP. 1996. NTP Results Report, Results, Status, and Publications Information on All NTP Chemicals. National Toxicology Program. Research Triangle Park, NC, dated May 8, 1996.
- NTP. 1999. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Isobutyraldehyde (CAS No. 78-84-2) in F344/N Rats and B6C3F1 Mice. Appendix E. Genetic Toxicology. NTP TR 472. NIH Publication No. 99-3962.
- Obe, G. and Beek, B. 1979. Mutagenic activity of aldehydes. *Drug Alcohol Depend.* 4: 91-94.
- Onstot, J.D. et al. 1987. Characterization of HRGC/MS Unidentified Peaks from the Broad Scan Analysis of the FY82 NHATS Composites. Volume 1. USEPA 68-02-4252.

- Opdyke, D.L.J. 1973. Monographs on Fragrance Raw Materials. *Fd. Cosmet. Toxicol.* 11: 95-115.
- Opdyke, D.L. 1979. Monographs on fragrance raw materials. n-Valeraldehyde. *Cosmet. Toxicol.* 17 (Suppl.): 919-921.
- Oswald, A.A., Jermsen, T.G., Westner, A.A., and Huang, I.D., 1987. Selective hydroforylation process using alkyl diaryl phosphine rhodium carbonyl hydride catalysts. Exxon Research and Engineering Co. (Patent No. US4687874 A). *Cited in:* National Toxicology Program (NTP). 1996. Chemical Selection Working Group (SCWG). Summary of Data for Chemical Selection. n-Valeraldehyde.
- PCKOCWIN. Version 1.66. Soil Adsorption Coefficient. EPIWIN (Estimation Program Interface for Windows). Version 3.10. U.S. Environmental Protection Agency, 2000.
- Pellizzari, E.D. 1982. Analysis for organic vapor emissions near industrial and chemical waste disposal sites. *Sci. Total Environ.* 16: 781-785.
- Pellizzari, E.D., Hartwell, T.D., Harris, B.S., Waddell, R.D., Whitaker, D.A., and Erickson, M.D. 1982. Purgeable organic compounds in mother's milk. *Bull. Environ. Contam. Toxicol.* 28: 322-328.
- Poet, T. 2004a. Unpublished data on Primary Amyl Alcohol (mixture of n-pentanol and 2-methylbutanol). Battelle, Pacific Northwest National Laboratory, U.S. Dept. of Energy. Sponsored by the Oxo-Process Panel, Chemstar, American Chemistry Council, Arlington, VA, 22209.
- Poet, T. 2004b. Unpublished data on Primary Amyl Acetate (mixture of n-pentyl acetate and 2-methyl butyl acetate). Battelle, Pacific Northwest National Laboratory, U.S. Dept. of Energy. Sponsored by the Oxo-Process Panel, Chemstar, American Chemistry Council, Arlington, VA, 22209.
- Rekker, R.F. 1977. *The Hydrophobic Fragment Constant*. Amsterdam: Elsevier.
- Rogers, J.A. 1981. Oils, Essential. *In:* Grayson, M. and Eckroth, D. eds., *Kirk-Othmer Encyclopedia of Chemical Technology*, 3<sup>rd</sup> Edition. Volume 16. New York: John Wiley & Sons.
- Rudell, E. von, Bonte, W., Sprung, R., and Kuhnholz, B. 1983. Zur Pharmakokinetik der holheren aliphatischen Alkohole. *Beitr. Gerichtl. Med.* 41: 211-218.
- Salem, H. and Cullumbine, H. 1960. Inhalation toxicities of some aldehydes. *Toxicol. App. Pharmacol.* 2: 183-187.
- Savolainen, H., Pfaffli, P., and Elovaara, E. 1985. Blood and brain n-pentanol in inhalation exposure. *Acta Pharmacol. Toxicol.* 56: 206-264.
- Sax, I.N. and Lewis, R.J., Sr. (eds). *Hawley's Condensed Chemical Dictionary*, 11<sup>th</sup> Edition. New York, NY: Van Nostrand Reinhold Company, 1987.
- Shibamoto, T. 1990. A new analytical method for low-molecular weight aldehydes. *In:* Charalamboris, G. (Ed.). *Developments in Food Science, Flavors and Off-Flavors*. Amsterdam: Elsevier Science Publishers.
- Slesinski, R.S. 1985. Union Carbide Corporation (unpublished report). n-Valeric Acid. In Vivo Mouse Micronucleus Study. Bushy Run Research Center Project Report 48-106, dated September 9, 1985.
- Slott, V.L. and Hales, B.F. 1985. Teratogenicity and embryoletality of acrolein and structurally related compounds in rats. *Teratology* 32: 65-72.
- Smyth, H.F. Jr., Carpenter, C.P., West, C.S., Pozzani, U.C., and Striegel, J.A. 1962. Range-Finding toxicity data: List VI. *Industrial Hygiene Journal* 23: 95-107.



Smyth, H.F. Jr., Carpenter, C.P. and Weil, C.S. et al. 1969. Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30: 470-476.

Snyder, J.M. 1995. Volatile analysis of oxidized oils by direct supercritical fluid extraction method. J. Food Lipids 2: 25-33.

Steinhagen, W.H. and Barrow, C.S. 1984. Sensory irritation structure-activity study of inhaled aldehydes in B6C3F1 and Swiss-Webster mice. Toxicol. Appl. Pharmacol. 75: 495-503.

Swann, R.L., Laskowski, D.A., McCall, P.J., Vander Kuy, K., and Dishburger, H.J. 1983. A rapid method for the estimation of the environmental parameters octanol/water partition coefficient, soil sorption constant, water to air ratio, and water solubility. Res.Rev. 85: 17-28.

Union Carbide Chemicals and Plastics Company Inc. 1993. Ecological Fate and Effects Testing of UCC&P Products and Wastewaters During 1992. File Report No. 39860, dated February 12, 1993.

Union Carbide Corporation. Material Safety Data Sheet # 5422: Valeraldehyde. Effective date 06/26/2000. Union Carbide Chemicals and Plastics Technology Corporation, The Dow Chemical Company, Danbury, CT.

Union Carbide Corporation. 1979. Unpublished study. Carnegie-Mellon Institute of Research Report 42-50., dated June 11, 1979.

Union Carbide Corporation. 1980. Unpublished study. Butyraldehyde. Twelve-Week Vapor Inhalation Study in Rats Bushy Run Research Center Report 43-61, dated September 17, 1980.

Urbach, G. 1987. Dynamic headspace gas chromatography of volatile compounds in milk. J. Chromatography 404: 163-174.

U.S. Department of Transportation (U.S.DOT). 1996. North American Emergency Response Guidebook. A Guidebook for First Responders During the Initial Phase of a Hazardous Material/Dangerous Goods Incident. U.S.DOT Research and Special Programs Administration, Washington, DC.

U.S. Environmental Protection Agency (USEPA). 2003. Experimental water solubility and vapor pressure values reported by EPI Suite software, Version 3.11. USEPA, Office of Pollution Prevention and Toxics, Washington, DC. Available at: <http://www.epa.gov/loppt/exposure/docs/episuiteldl.htm>

U.S. National Toxicology Program. 1999. NTP Technical Report on the Toxicology and Carcinogenesis Studies of Isobutyraldehyde (CAS No. 78-84-2) in F344/N Rats and B6C3F1 Mice. NTP TR-472, Research Triangle Park, NC.

Van Netten, C. et al. Bull. Environ. Contam. Toxicol. 40: 672-7.

Verschueren, K. 2001. Handbook of Environmental Data on Organic Chemicals, 4<sup>th</sup> Edition. New York, NY: John Wiley & Sons, Inc.

Walkenstein, S.S. and Weinhouse, S. 1953. Oxidation of aldehydes by mitochondria of rat tissues. J. Biol. Chem. 200: 515-523.

Walker, J. 1995. Communication transmitted from Executive Director, TSCA Interagency Testing Committee, U.S. Environmental Protection Agency. Cited in: National Toxicology Program (NTP). 1996. Chemical Selection Working Group (SCWG). Summary of Data for Chemical Selection. n-Valeraldehyde.

Wilkin, J.K. and Fortner, G. 1985. Ethnic contact urticaria to alcohol. Contact Dermatitis 12: 118-120.

Wilkinson, J.F. 1940. *J. Hyg.* 40: 555. *cited in*: Brabec, M.J. 1993. Aldehydes and Acetals. *in*: Clayton, G.D., Clayton, F.E. (Eds.). *Patty's Industrial Hygiene and Toxicology*, New York, NY: John Wiley & Sons.

Wolfe, C.W. et al. 1987. Thirteen week subchronic toxicity study of butyraldehyde in F344 rats and B6C3F1 mice. *The Toxicologist* 7:

Woodruff, R.C, Mason, J.M., Valencia, R., and Zimmering, S. 1985. Chemical mutagenesis testing in *Drosophila*. V. Results of 53 coded compounds tested for the National Toxicology Program. *Environ. Mutagen.* 7: 677-702.

WSKOW. Version 1.37. Water Solubility Estimate from Log Kow. EPIWIN (Estimation Program for Windows) Version 3.10. U.S. Environmental Protection Agency, 2000.

Yalkowsky, S.H. and Dannenfelser, R.M. 1992. *The Aquasol Database of Aqueous Solubility*, 5<sup>th</sup> Edition. University of Arizona, College of Pharmacy, Tucson, AZ.