FOREWORD INTRODUCTION

ISOBUTANAL

CAS N°: 78-84-2

SIDS Initial Assessment Report

For

SIAM 5

Belgirate, Italy, 28-30 October 1996

(Revised September, 2004)

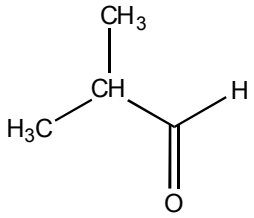
1. Chemical Name:	Isobutanal
2. CAS Number:	78-84-2
3. Sponsor Country:	United States SIDS Contact Point in Sponsor Country: Mr. Oscar Hernandez Director, Risk Assessment Division U.S. Environmental Protection Agency Office of Pollution Prevention and Toxics (7403M) 1200 Pennsylvania Ave, N.W. Washington, D.C. 20460 Telephone: (202) 564-7641
4. Shared Partnership with:	-
5. Roles/Responsibilities of the Partners:	-
• Name of industry sponsor /consortium	-
• Process used	-
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme ?	SIDS Dossier and Testing Plan were discussed at the 1st SIDS Review Meeting, November 1990. This chemical was discussed at SIAM 4, and at the meeting it was agreed that no further testing was needed. Results of analogues (CAS No. 123-38-6 [SIAM 3], 123-72-8 [SIAM 5], and 590-86-3 [SIAM 10]) as well as more recent results have been included for an update (September 2004; see comments below)
7. Review Process Prior to the SIAM:	
8. Quality check process:	
9. Date of Submission:	27 August 1996
10. Date of last Update:	September 2004
11. Comments:	Based on structure-activity considerations, information on the isobutanal analogs butyraldehyde (CAS No.123-72-8),

propionaldehyde (CAS No. 123-38-6) and isovaleraldehyde (CAS No. 590-86-3) were incorporated into this SIDS evaluation to provide a more complete evaluation of acute toxicity, repeated dose toxicity and developmental and reproductive toxicity. An NTP carcinogenicity study on isobutanal was published in 1999 and the results of this study have been included in this revised SIAR.

New information on the genotoxicity of isobutanal, as summarized in NTP (1999), indicates that, contrary to the conclusions presented in the earlier draft of the SIAR and in the current SIAP, there is a strong weight of evidence that isobutanal is mutagenic in mammalian cell systems. This information has been added to the SIDS Documents.

Aquatic PEC calculations for several sites, as provided by OECD reviewers, is included in an Addendum to this SIAR.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	78-84-2
Chemical Name	Isobutanal
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Analog justification

Based on structure-activity considerations, data on the isobutanal analogs butyraldehyde (CAS No. 123-72-8), propionaldehyde (CAS No. 123-38-6) and isovaleraldehyde (CAS No. 590-86-3) were incorporated into the SIAR and SIDS Dossier to provide a more complete evaluation of the toxicity of isobutanal.

Human Health

Studies have been conducted that identify tissues and organs most sensitive to the effects of isobutanal. Direct contact produced an irritant response, and repeated inhalation exposure to 500 ppm and higher can lead to lesions of the tissues of the nasal mucosa. A developmental toxicity study indicated that isobutanal does not pose a hazard to developing fetuses at exposure concentrations up to 4000 ppm. Effects on male reproductive organs occurred at 4000 ppm and were accompanied by significant toxicity and mortality. Sperm motility after repeated exposure to rats was significantly decreased at 500 and 1000 ppm but was comparable to the controls at 2000 and 4000 ppm, with an overall conclusion that the effect of isobutanal on sperm motility was negative. There is *in vitro* and *in vivo* evidence that isobutanal causes mutagenic and genotoxic effects in mammalian cells. NTP carcinogenicity studies in rats and mice did not reveal any carcinogenic activity for isobutanal.

Environment

Isobutanal is a liquid at ambient temperatures with a melting point of -66 ^{o}C. It is soluble in water (25 g/L at 20 ^{o}C, 89 g/L at 25 ^{o}C), has a high vapor pressure (18.4 kPa at 20 ^{o}C; 172 mm Hg or 22.9 kPa at 25 ^{o}C) and a low octanol water partition coefficient (Log Kow = 0.77 at 25 ^{o}C). Isobutanal oxidizes slowly upon exposure to air, forming isobutyric acid; peroxides or peracids may also form. It is considered a highly flammable liquid which can easily be ignited by heat, sparks or flame. Its flashpoint is less than –18 ^{o}C. The flammability limits are 1.6% (lower) to 10.6% (upper).

Based on Level III distribution modeling, the majority of isobutanal released into the environment would partition into the water (64.8%), soil (27.4%) and air (7.72%). Measured and calculated concentrations in surface waters are below prediced no-effect concentrations. Modeling predicts that isobutanal is biodegradable and is not expected to accumulate in the environment.

For isobutanal, a static test with fathead minnows (P*imephales promelas*) was reported to give a 96-hour LC_{50} of 23 mg/L. With *Daphnia magna* Strauss, the reported 48 h EC_{50} was 277 mg/L. The isobutanal toxicity to algae was tested with *Scenedesmus subspicatus* to give a 72-hour LC_{50} of 84 mg/L.

Exposure

The worldwide production of isobutanal in 1993 *ca.*700 807 metric tonnes (1545 million pounds);of this,

258,500 metric tonnes (*ca.* 570 million pounds), are produced in the US. This chemical finds sole use as a chemical intermediate. It is produced and used exclusively in closed systems and transport is by bulk carrier.

Toxics Release Inventory data reported for 1999 show that in the U.S., 118.6 metric tonnes (261,000 pounds) were released to the environment. The vast majority of this material, 118.0 metric tonnes (260,000 pounds), was released to the air, whereas 0.55 metric tonnes (1,200 pounds) were released into water. In addition to direct releases, 297.7 metric tonnes (656,000 pounds) were transferred to publicly owned treatment facilities and another 328.9 metric tonnes (725,000 pounds) to other off-site locations giving a total off-site waste transfer of approximately 626.6 metric tonnes (1,382,000 pounds).

In view of its primary use as a chemical intermediate, its low persistence in the environment, its low potential for adverse environmental impacts, and the unlikely occurrence of human exposure except in occupation situations, isobutanal is considered to be of low priority for further work.

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

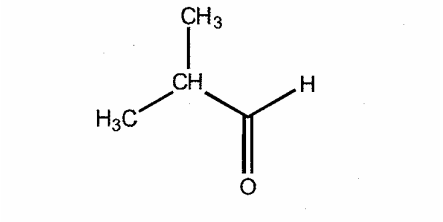
Isobutanal is currently of low priority for further work for human health and the environment.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 78-84-2
IUPAC Name: Isobutanal
Molecular Formula: C_4H_8O
Structural Formula:



Molecular Weight: 72.11
Synonyms: Propanal, 2-methyl-; isobutyraldehyde

1.2 Purity/Impurities/Additives

Degree of Purity: 99.6%
Major Impurity: 1-Butanal

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference
Melting point	-66 ºC	Union Carbide, MSDS
Boiling point	64.1º C	Union Carbide, MSDS
Vapour pressure	18.4 kPa (138 mm Hg) at 20 °C 22.9 kPa (172 mm Hg) at 25 ºC	Union Carbide, MSDS Howard and Meylan, 1997
Water solubility	75 g/L at 20 °C 89 g/L at 25 °C	BASF AG, 1993 Howard and Meylan, 1997
Partition coefficient n-octanol/water (log value)	0.77 at 25 °C (measured)	BASF AG, 1987

Isobutanal is a liquid at ambient temperatures. It is very soluble in water (75 g/L at 20°C, 89 g/L at 25 °C), has a relatively high vapor pressure (138 mm Hg or 18.4 kPa at 20 ºC; 172 mm Hg or 22.9 kPa at 25 °C) and a very low octanol water partition coefficient (log Pow = 0.77 at 25 °C). Isobutanal oxidizes slowly upon exposure to air, forming isobutyric acid; hazardous peroxides or peracids may also be formed (AIHA, 2002). It is considered to be a highly flammable liquid which can easily be ignited by heat, sparks or flame. Its flash point is less than –18 ºC; its flammability limits are 1.6 % (lower) to 10.6% (upper) (Union Carbide, MSDS; National Fire Protection Association, 2002).

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The estimated worldwide production volume of isobutanal in 1993 was 700,807 metric tonnes (1545 million pounds); of this, approximately 258,550 metric tonnes (570 million pounds) are produced in the United States. It is believed that a major portion of the worldwide production is used as an internal plant chemical intermediate in the production of downstream chemicals.

Isobutanal is manufactured as a coproduct with normal butanal (butyraldehyde) by catalytic hydroformylation of propylene. The propylene, carbon monoxide and hydrogen reaction is carried out under pressure in closed systems. The isobutanal/butanal mix is stripped of dissolved gasses and heavies and either hydrogenated to 1-butanol and isobutanol, or the aldehyde mix is further refined to separate the isobutanal and butanal. Typically, process vents from reactors, columns and storage tanks are collected into the plant fuel system. Many plants in the U.S. are now operating under the "New Source Performance Standards (NSPS)" rule which requires fugitive emission monitoring of all size valves on a quarterly basis and all pumps and compressors on a monthly basis.

Isobutanal is stored in pressured tanks or tanks equipped with internal floating roofs with a nitrogen blanket over the floating roof, this minimizing evaporative losses. The aldehyde is shipped in bulk by tank truck or tank car (rail cars). Properly designed stations allow for loading into closed tanks of the trucks or cars. Vapor emitted during these operations is collected and routed through a vent collection system to an incinerator where isobutanal vapor is destroyed.

Isobutanal’s major use is as a chemical intermediate. The major use is the in-plant conversion to isobutanol. In addition, the aldehyde may also be oxidized to isobutyric acid. Isobutanal is also converted through aldol condensation to a dimer, which is hydrogenated to 2,2,4-trimethyl-1,3-pentanediol. Other major uses include the manufacture of esters and specialty chemicals. Fifteen percent of isobutanal production is converted to neopentyl glycol by condensation with formaldehyde and hydrogenation (Kirk-Othmer, 4th ed., vol. 4, p. 736).

According to information submitted to OECD, isobutanal is used in Finland in the production of softeners.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Isobutanal appears on the U.S. EPA's Emergency Planning and Right-To-Know Act (EPCRA), Superfund Amendments and Reauthorization Act (SARA) Section 313 Toxic Chemical List. This requires U.S. facilities that manufacture or process 11.34 metric tonnes (25,000 pounds) or more, or facilities who otherwise use 4.54 metric tonnes (10,000 pounds) or more isobutanal to make yearly reports on releases to the environment. The most recent report available is for 1999. In that year, facilities reported a total of 118.6 metric tonnes (261,000 pounds) released to the environment. The vast majority of this material, 118.0 metric tonnes (260,000 pounds), was released to the air, 0.55 metric tonnes (1,200 pounds) were released into water. In addition to direct releases, 297.7 metric tonnes (656,000 pounds) were transferred to publicly owned treatment facilities and another 328.9 metric tonnes (725,000 pounds) to other off-site locations giving a total off-site waste transfer of approximately 626.6 metric tonnes (1,382,000 pounds). A similar pattern of release would be expected for worldwide production and use.

Isobutanal is natural-occurring component of many foods. It is present in beans, beef fat, black currents, bread, green vegetables, butter, carrots, cauliflower, cheese, coffee, tea, potatoes, peanuts,

tomatoes, wine, and whisky (Food Chemical Codes, 1972). Reported average concentrations of isobutanal in food range from 5.0 ppm in alcoholic beverages to 0.5 to 1.0 ppm in baked good, 0.67 ppm in candy, 0.25 to 0.50 ppm in ice cream, and 0.3 ppm in non-alcoholic beverages (Furia, T.E., and Bellanca, N., 1975).

Very little monitoring data are available for isobutanal. The chemical was identified at a concentration of 1 ppb in 1 of 204 samples collected from 14 heavily industrialized river basins in the U.S. between August, 1975 and September, 1976 (Ewing et al., 1977; as cited in HSDB, 2002).

Based upon its physical and chemical properties, isobutanal is unlikely to persist as an environmental contaminant. The aldehyde is soluble in water and has an octanol/water partition coefficient of less than 10. Isobutanal is typical of aldehydes in that it readily oxidizes to isobutyric acid. Isobutyric acid is a bacterial degradation product of the essential amino acid valine.

Results for the Mackay Level III fugacity model were calculated using EPIWIN v3.10 (model run on February 8, 2002, see Table 1). Input values (Phys-prop data base) were as follows: Water Solubility = 89 g/L at 25 °C; Boiling Point = 64.5 °C; Melting Point = -65.9 °C; Vapor Pressure = 172 mm Hg at 25 °C; Henry' Law Constant 0.00069 atm-m^3/mole; and predicted Log Kow = 0.74 at 25 °C (KowWin program).

Table 2 Results of Mackay Level III Fugacity Model (EPIWIN v3.10)

	Percent in each compartment	**Half-life (hr)**	**Emissions (kg/hr)**
AIR	7.72	9.76	1000
WATER	64.8	360	1000
SOIL	27.4	360	1000
SEDIMENT	0.113	1440	0
Persistence Time: 115 hr			

Assuming equal emissions to air, water, and soil, results of the fugacity modeling indicate that isobutanal will partition primarily to water and soil.

2.2.2 Photodegradation

2.2.3 Stability in Water

The calculated Henry's Law Constant for isobutanal ranges from 1.8 x 10^{-4} to 6.9 x 10^{-4} atm-m^3/mole, indicating that the compound is somewhat volatile from aqueous media. The compound is expected to have a short residence time in water. EPIWIN v3.10 modeling predicts a half-life of 88.5 hr from a model lake (depth 1 m, wind velocity 0.5 m/sec, and current velocity 0.05 m/sec), and 1.6 hr from a model river (depth 1 m, wind velocity 5 m/sec, and current velocity 1 m/sec).

2.2.4 Transport between Environmental Compartments

Isobutanal released to the atmosphere is not expected to remain intact for an appreciable length of time. Calculations indicate the aldehyde has a half-life in air of 5.5 hours (AOP Program v1.9 in EPIWIN v3.10).

2.2.5 Biodegradation

BIOWIN v4.0 (EPIWIN v3.10) modeling predicts that isobutanal is degradable, with rates of degradation on the order of days to weeks. Experimental studies indicate that the 5-day aerobic Biological Oxidation Demand (BOD_5) is 66 percent of the Theoretical Oxygen Demand (ThOD) and 72 percent of the Chemical Oxidation Demand (COD) (Verschueren, 1996). Biodegradation rates for activated sludge samples ranged from 72 to >95 percent after 5 days to 81- 99 percent after 13 days under aerobic conditions (Hoechst AG, 1979; BASF AG, 1976, 1977).

2.2.6 Bioaccumulation

Although experimental data are not available, isobutanal is not expected to bioaccumulate in the environment, based on the predicted log BCF of 0.5 (BCFWIN v2.14 in EPIWIN 3.10).

2.3 Human Exposure

2.3.1 Occupational Exposure

In the U. S., no OSHA Permissible Exposure Limit (PEL) has been established for isobutanal. A WEEL (Workplace Environmental Exposure Level) of 25 ppm has been established by the American Industrial Hygiene Association (AIHA). The 8-hour TWA (time-weighted average) WEEL value represents the workplace exposure level to which it is believed all employees could be exposed repeatedly without adverse health effects (AIHA, 2003). When establishing the WEEL, the AIHA determined that the primary use of isobutanal is as a reactive intermediate, and that manufacturing and transportation practices minimize workplace exposure (AIHA, 2002).

In one production site, some industrial hygiene monitoring was conducted in the 1990 to 1995 time frame in order to establish an exposure baseline to this material. A total of 27 samples were collected; the bulk of the results were less than 0.010 ppm. Two samples yielded results with measurable exposure concentrations, 12 and 18 ppm based on an 8-hour time weighted average. Similar data have been collected in a European production facility. A total of 217 personal monitoring samples were collected between 1979 and 1996. Of these, 193 were in the production units, 12 were associated with storage and filling operations, 8 with research activities and 4 with maintenance operations. Results are listed in the following table:

Total		**Production**	**Storage/Filling**	**Research**	**Maintenance**
n	217	193	12	8	4
Average	0.2 ppm	0.2 ppm	0.1 ppm	0.1 ppm	3.4 ppm
Range	0 - 7 ppm	0 - 7 ppm	0.02 -0.3 ppm	0 - 0.3 ppm	3 - 3 .7 ppm

Fugitive emissions monitoring is being conducted on valves, pumps and flanges in some units (as required by some federal and state regulations in the U.S.). Regulations have allowable "leak" limits, which range from 500 to 10,000 ppm. Under some regulations, repairs must be attempted as early as 5 days after detection of leaks exceeding the allowable limit, but with proper reporting may be extended until the next scheduled 24-hour shutdown.

According to information submitted to OECD, occupational and environmental exposures to isobutanal in Finland are as follows:

Source	Workplace Concentration (mg/m3)
Emissions in handling PVB films	1.9
Manufacture of pesticides	0.02-0.08
Use of hotmelt gluing machine	0.01-0.07
Scarving laminated glass plates	0.01-0.07

2.3.2 Consumer Exposure

Because isobutanal is used primarily as a chemical intermediate, exposure to the general public is not expected to be significant. However, according to information submitted to OECD by Finland, the general public may be exposed to isobutanal as a result of emissions from car exhaust. A concentration of 0.002 mg/m^3 has been reported.

Isobutanal is also a naturally-occurring component of many foods, and public exposure to minimal concentrations may occur by this route. Reported concentrations of isobutanal in food range from 5.0 ppm in alcoholic beverages to 1.0 ppm or less in baked goods, candy, ice cream, and non-alcoholic beverages (Furia, T.E., and Bellanca, N., 1975).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

Analog justification

Based on structure-activity considerations, data on the isobutanal analogs butyraldehyde (CAS No. 123-72-8), propionaldehyde (CAS No. 123-38-6) and isovaleraldehyde (CAS No. 590-86-3) were included to provide a more complete evaluation of the toxicity of isobutanal.

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies on the rate of uptake of isobutanal through the skin are not available; however, dermal uptake is suggested by the reported congestion and hemorrhage of the lungs of rabbits exposed to the substance in occluded skin patch tests (Union Carbide, 1952).

Isobutanal, like other simple aliphatic aldehydes, is subject to oxidation in animals by ubiquitous aldehyde dehydrogenase enzymes. The oxidation product, isobutyric acid, is rapidly metabolized to CO_2 through conversion to the isobutyral coenzyme A complex and subsequent oxidation by the malate-pyruvate and oxaloacetic-phosphoenol pyruvate pathways (DiVincenzo and Hamilton, 1979).

3.1.2 Acute Toxicity

Studies in Animals

Isobutanal is slightly to moderately toxic following oral, dermal or inhalation exposure. Oral LD_{50} values for rats range from 1.6 to 3.7 g/kg body weight (Brabec, 1981; Union Carbide, 1952). Exposure to a measured concentration of 16000 ppm for 4 hours killed 6 of 6 rats; exposure to 8000 ppm for 4 hr killed 1 of 6 rats (Union Carbide, 1952). The vapor concentration required to elicit a

50% decrease in respiratory rate (RD_{50}) was 3016 ppm for B6C3F1 mice and 4167 ppm for Swiss-Webster mice (Steinhagen and Barrow, 1984).

In percutaneous studies conducted on guinea pigs, the 4-hr LD_{50} was found to be greater than 20 g/kg (Brabec, 1981). In occluded percutaneous tests conducted on New Zealand white rabbits, the 24-hr LD_{50} was 7.1 mL/kg (Union Carbide, 1952).

Studies in Humans

No irritation was experienced by 15 male volunteers exposed to 210 ppm (620 mg/m^3) isobutanal vpor for 30 minutes; nausea was noted by some subjects, however, and one subject vomited (Sim, V.M. and Pattle, R.E. 1957).

Isobutanal has a potent odor that offers warning of exposure. The odor threshold in normal individuals is > 2 ppb and in anosmic individuals > 1 ppm (Amoore et al., 1976).

3.1.3 Irritation

Studies in Animals

Isobutanal produces moderate to severe skin irritation and burns, as well as severe eye irritation on direct contact in the rabbit. Isobutanal would be considered corrosive at sufficiently high concentrations.

Application of 0.01 mL of undiluted isobutanal to the uncovered clipped skin of rabbits resulted in marked erythema at the site of contact in one of six test animals (Union Carbide, 1952).

Instillation of 0.02 mL of undiluted isobutanal into the inferior conjunctival sac of rabbit eyes resulted in severe damage to the cornea of all treated eyes (Union Carbide, 1952). Instillation of 0.005 mL caused moderate injury to the cornea.

3.1.4 Sensitisation

Studies in Animals

There was no indication of sensitization in mice in an NTP-sponsored test for irritancy and contact hypersensitivity. Isobutanal was applied directly to shaved and abraded ears of mice for 5 consecutive days with and without adjuvant. Doses of isobutanal ranged from 3% to 30% in 4:1 solution of acetone and olive oil for sensitization tests, and 30% for challenge tests (NTP, 1990).

3.1.5 Repeated Dose Toxicity

Studies in Animals

A number of studies have been conducted in which rats or mice were repeatedly exposed to isobutanal vapor. The results of these studies are summarized in Table 1. In a 13-week inhalation study, minimal to mild degeneration of the olfactory epithelium was observed in male rats exposed to 2000 and 4000 ppm (NTP, 1999). Increased incidences of squamous metaplasia and mild osteodystrophy of the turbinate bone were observed in male and female rats exposed to 4000 ppm. Spermatozoal motility was significantly reduced in the 500 and 1000 ppm groups; sperm motility was comparable to controls in rats exposed to 2000 and 4000 ppm. Because of variability between groups, Morrissey et al (1988) determined that the overall response of sperm motility in male rats to isobutanal was negative (personal communication with NTP, 2004). The time female rats spent in

estrous stage was shorter in controls (5.00 +/- 0.15 days) than in the four surviving females exposed at 4000 ppm (5.33 +/- 0.33 days). Significance for the difference in the length of the estrous cycle was achieved only by Wilk's Criterion; there was no statistical significance by Dunn's Test (NTP, 1999).

In a 13-week study conducted on mice, increased incidences of nonneoplastic lesions of the nasal cavity occurred in males and females exposed to 1000 ppm or higher (NTP, 1999). Body weight and body weight gain of females in the 1000 ppm group was significantly reduced, and absolute and relative kidney weights of males in the 1000 and 2000 ppm groups were significantly increased. Clinical findings included decreased activity, tremors, prostration, and slower and labored respiration.

Complementary studies carried out with a close structural analog of isobutanal, butyraldehyde, lend support to the idea that nasal turbinates is the most sensitive target organ (see Table 1). In a 12-week inhalation study conducted on rats, a clear NOEL of 50 ppm (highest dose tested) was identified for butyraldehyde. A respiratory infection may have masked minor irritation, but no other toxic effects were observed. Based on the results of all studies, it is reasonable to anticipate that 50 ppm would be a conservative estimate of the NOEL for isobutanal in subchronic exposures.

Table 3 Repeated Inhalation Toxicity of Isobutanal and Butyraldehyde in Experimental Animals

Species	Exp. protocol	Critical Effects	Reference
Isobutanal			
Rat	6-hr/day for 10 days; 1000, 2500, and 4000 ppm; pregnant animals	Hyperplasia of the transitional epithelium of the anterior part of the lateral wall of the nasal cavity was observed in 8/10 animals exposed to 4000 ppm, 6/10 animals exposed to 2500 ppm and 0/10 animals exposed to 1000 ppm. One animal exposed to 4000 ppm exhibited moderate focal atrophy of the olfactory epithelium in the dorsal meatus.	Garmer et al., 1995
Rat	10 exposures; 6-hr/day, 5 days/wk 500, 1000, 2000, 4000, and 8000 ppm	Eight rats exposed to 8000 ppm died, all after the first exposure. There was a suggestion of weight change in the kidneys of males exposed to 8000 ppm. RBCs decreased in males exposed to 500 and 1000 ppm. Pulmonary interstitial inflammation occurred at 4000 and 8000 ppm.	Eastin, 1990
Rat	12 exposures, 6-hr/day to 1000 ppm	Evidence of slight nasal irritation, but no evidence of systemic toxicity.	Gage, 1970
Rat	6-hr/day, 5 days/wk for 13 wk. 500, 1000, 2000, 4000, and 8000 ppm	100% mortality at 8000 ppm, 45% mortality at 4000 ppm. Minimal to mild degeneration of the olfactory epithelium in males exposed to 2000 and 4000 ppm. Squamous metaplasia and mild osteodystrophy of the turbinate bone were observed in male and female rats exposed to 4000 ppm. Spermatozoal motility significantly reduced at 500 and 1000 ppm but not at 2000 and 4000 ppm. Time females spent in estrous stage different from controls (5.00 days) at 4000 ppm (5.33 days).	NTP, 1999
Mice	6-hr/day, 5 days/wk for 13 wk. 500, 1000, 2000, 4000, and 8000 ppm	100% mortality at 8000 ppm, 95% mortality at 4000 ppm. Increased incidences of non-neoplastic lesions of the nasal cavity in males and females at 1000 ppm or higher. Body weight and body weight gain of females in the 1000 ppm group significantly reduced. Absolute and relative kidney weights of males in the 1000 and	NTP, 1999

		2000 ppm groups significantly increased. Clinical findings included decreased activity, tremors, prostration and slower and labored respiration.	
Butyraldehyde			
rat mouse, guinea pig, rabbit, dog	9 exposures; 6-hr/day; 2000, 3100, and 6400 ppm	Definite signs of eye and respiratory irritation, and statistically significant decreases in body weight gain were observed in most species at concentrations of 3100 and 6400 ppm. Other signs observed in most animals at 6400 ppm included coordination loss, anesthesia and death. At 3100 ppm these effects were observed only in the dog. In some animals exposed to 2000 ppm decreased weight gain was observed. Scattered organ weight differences were also noted in rats exposed to 2000 and 3100 ppm. No pathologically significant treatment related gross lesions were found among animals exposed to 3100 or 2000 ppm.	Union Carbide, 1978
dog	6-hr/day, 5 days/wk for 14 wk; 125, 500, and 2000 ppm	Exposure to 2000 ppm resulted in microscopic lesions of the upper respiratory tract. Significant levels of goblet cell hyperplasia in the nasal mucosa observed at 125 and 500 ppm.	Union Carbide, 1979
rat	6-hr/day, 5 days/wk for 13 wk; 125, 500, and 2000 ppm	A concentration dependent increase in the incidence of squamous cell metaplasia of the nasal cavities was observed in rats in all exposure groups.	Union Carbide, 1979
rat	6-hr/day, 5 days/wk for 12 wk; 1, 10, and 50 ppm	NOEL = 50 ppm (highest dose tested).	Union Carbide, 1980

3.1.6 Mutagenicity

Isobutanal has been investigated for genotoxic activity using *in vitro* bacterial assays (Ames Test), *in vitro* mammalian cell mutagenicity and genetic toxicity assays, *in vivo* mammalian cell assays, andan *in vivo* Drosophila sex-linked recessive lethal mutation assay, and *in vivo* Micronucleus Assays in rats and mice (see Table 2). Negative results were obtained for *S. typhimurium* tester strains TA 97, TA98, TA102, and TA 1537, and TA 1538 (McMahon et al., 1979; Florin et al., 1980; Mortelmans et al., 1986; Aeschbacher et al., 1989; Zeiger et al, 1992). In the one bacterial study where mutagenic activity was noted, it occurred without metabolic activation in *S. typhimurium* strains G-46 and TA-100, and in *Escherichia coli* strains WP2 and *WP2 uvrA*$^-$ (McMahon et al., 1979*)*. All four strains detect base substitution mutagens. In four other studies in *S. typhimurium* strain TA-100, negative results were obtained. Because TA-100 has a very high spontaneous mutation rate (McMahon et al., 1976), slight increases in frequency over background may be difficult to detect. However, negative results were also reported for TA-1535, another strain capable of detecting base substitution mutations.

Isobutanal gave positive results when tested *in vitro* for chromosomal aberrations in Chinese hamster ovary (CHO) cells in the absence of metabolic activation, and also in an assay for sister chromatid exchanges in CHO cells (NTP, 1985; 1999).

Isobutanal gave positive results for gene mutations when tested *in vitro* in the absence of metabolic activation in the L5178Y TK$^{+/-}$ mouse lymphoma assay (NTP, 1986; 1999). Isobutanal gave negative results in *in vivo* erythrocyte micronucleus assays conducted on mice and rats (NTP, 1999). In a sex-linked recessive lethal assay conducted on *Drosophila*, there was no evidence of mutagenic activity (Woodruff et al., 1985). Isobutanal was positive at one concentration in an in vivo mouse chromosomal aberration assay (NTP, 1999).

Although most Ames assays and the micronucleus tests gave negative results, the evidence indicates that isobutanal may result in base substitution mutations in bacteria when tested in the absence of metabolic activation, and that it also causes mutagenic and genotoxic effects in mammalian cells when tested *in vitro* in several different types of assays. Negative results were obtained in three of four *in vivo* genotoxicity tests.

Table 4. Results of genetic toxicity tests with isobutanal

Test	Test System	Result	Reference
Ames	*S. typh*. (strains G46, TA100)	Positive without metabolic activation in both strains	McMahon et al., 1979
Ames	*S. typh.* (strains TA1535, C3076, TA1537, D3052, TA1538, TA98)	Negative with and without metabolic activation	McMahon et al., 1979
Ames	*S. typh*. (strains TA100, TA1535, TA1537, TA-98)	Negative with and without metabolic activation	Mortelman et al., 1986
Ames	*S. typh*. (strains TA98; TA100, TA1535, TA1537)	Negative with and without metabolic activation	Florin et al., 1980
Ames	*S. typh*. (strains TA98; TA100)	Negative with and without metabolic activation	Sasaki and Endo, 1978
Ames	*S. typh*. (strains TA98; TA100, TA102)	Negative with and without metabolic activation	Aeschbacher et al., 1989
Ames	*S. typh*. (*strains TA97, TA98; TA100, TA102 TA1535, TA1537*)	Negative with and without S9 in all strains except TA 104. Equivocal in TA104 with S9.	NTP, 1999
Ames	*E. coli (strains WP2, WP2 uvrA⁻)*	Positive without metabolic activation in both strains	McMahon et al., 1979
Gene mutations	*L5178Y TK$^{+/-}$ mouse lymphoma cells*; in vitro	Positive without metabolic activation	NTP, 1986, 1999
Chromosomal aberrations	*Chinese hamster ovary cells*; in vitro	Positive without metabolic activation	NTP, 1985, 1999
Chromosomal aberrations	*Mouse, bone marrow;* in vivo	Positive	NTP, 1999
Sister chromatid exchanges	*Chinese hamster ovary cells*; in vitro	Positive with and without metabolic activation	NTP, 1985, 1999
Erythrocyte micronucleus assay	*Rat, bone marrow;* in vivo	Negative	NTP, 1999
Erythrocyte micronucleus assay	*Mouse, bone marrow*; in vivo	Negative	NTP, 1999
Gene mutations	Drosophila melanogaster; in vivo	Negative	Woodruff et al., 1985

3.1.7 Carcinogenicity

Isobutanal has been investigated for carcinogenic potential in inhalation oncogenicity studies carried out by the U. S. National Toxicology Program (NTP, 1999). In one study, groups of 50 male and 50 female F344/N rats were exposed to 0, 500, 1,000, or 2,000 ppm isobutanal by inhalation, 6 hours per day, 5 days per week, for 105 weeks. No differences were found in survival

rates between exposed and control animals. The mean body weights of male and female rats were generally similar to those of the controls throughout the study. There was no increase in neoplasm incidence that could be attributed to exposure to isobutanal in either sex. Nonneoplastic lesions related to isobutanal exposure were limited to the nose and consisted of squamous metaplasia of the respiratory epithelium, degeneration of the olfactory epithelium, and suppurative inflammation. Incidences of minimal to mild squamous metaplasia were greater than control values in males and females exposed to 1,000 and 2,000 ppm and in females exposed to 500 ppm. Minimal to mild degeneration of the olfactory epithelium occurred in both males and females exposed to 2,000 ppm. The incidences of suppurative inflammation (rhinitis) were increased in male and female rats exposed to 2,000 ppm.

In a 2-yr NTP inhalation study conducted on $B6C3F_1$ mice, groups of 50 males and 50 females were exposed to 0, 500, 1,000, or 2,000 ppm, 6 hours per day, 5 days per week, for 105 weeks (NTP, 1999). There was an exposure-related decrease in survival of male mice. The survival of males exposed to 2,000 ppm was marginally lower than that of the chamber controls. The mean body weights of female mice exposed to 1,000 or 2,000 ppm were lower than those of the chamber controls during the second year of the study. No neoplasms that could be attributed to isobutanal exposure were observed. Nonneoplastic lesions related to isobutanal exposure were limited to the nasal cavity. The incidences of olfactory epithelial degeneration in males and females exposed to 1,000 and 2,000 ppm were significantly greater than controls.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

The effects of isobutanal on selected reproductive parameters were evaluated in a 13-week NTP inhalation toxicity study on rats and mice. The results of this study were reported by NTP (1999) and also summarized earlier by Morrissey et al. (1988). Male and female F344/N rats were exposed to 500, 1000, 2000 and 4000 ppm isobutanal 6 hr/day, 5 days/week for 13 weeks**.** Decreased body weight and body weight gains were observed in males exposed to 4000 ppm (NTP, 1999). NTP (1999) reported that spermatozoal motility was significantly reduced in the 500 and 1000 ppm exposure groups, but not in rats exposed to 2000 and 4000 ppm. Because of the variability in sperm motility observed between groups, Morrissey et al (1988) determined that the overall response of sperm motility in male rats to isobutanal was negative (personal communication with NTP, 2004). There was no effect of exposure on sperm density or sperm morphology (Morrissey et al, 1988; NTP, 1999). The relative time that females exposed to 4000 ppm spent in estrous stages was different from controls. The estrous cycle was assessed in only 4 surviving females in the 4000 ppm exposure group. The difference in the length of the estrous cycle (5.00 +/- 0.15 days in control females and 5.33 +/- 0.33 days in 4000 ppm females) was significant only by Wilk's Criterion and was *not* significant by Dunn's Test (NTP, 1999).

In reviewing selected reproductive parameters evaluated in NTP 13-week studies, Morrissey et al. (1988) reported decreased absolute but not relative weight of right cauda epididymis, and decreased absolute and relative weight of right epididymis in the remaining male rats exposed to 4000 ppm (NTP, 1999). This effect was seen only a concentration which elicited significant toxicity and mortality. There was no significant weight change of the right testes in rats exposed to isobutanal, (Morrissey et al., 1988; NTP, 1999).

In an NTP inhalation study conducted on male and female $B6C3F_1$ mice, the test animals were exposed to 500, 1000, and 2000 ppm isobutanal 6 hr/day, 5 days/week for 13 weeks (NTP, 1999, see also Morrissey et al., 1988). No changes in weight of male reproductive organs or effects on

sperm were observed in any of the exposed groups. The NOAEL for indices of male reproductive effects was 2000 ppm, the highest concentration tested.

Reproductive toxicity of isobutanal can also be assessed using information on the chemical analog propionaldehyde. In tests conducted on Sprague-Dawley rats, males and females were exposed to 0, 150, 750, or 1500 ppm propionaldehyde 6 hr/day for 52 consecutive days. Females were exposed prior to and during mating and through gestation day 20. No significant effects were noted for any reproductive parameters. External examination of the offspring was unremarkable. A reproductive and developmental NOAEL of 1500 ppm (highest exposure tested) was indicated for propionaldehyde (Union Carbide, 1992).

Developmental Toxicity

The potential for isobutanal to effect the embryo and fetal development has been assessed in an OECD developmental toxicity guideline inhalation study (Garmer et al., 1996). Rats were exposed to concentrations of 1000, 2500 or 4000 ppm isobutanal 6 hours per day on days 6 through 15 of gestation. For maternal animals, a clear NOAEL of 1000 ppm was established; decreased body weight gain and lesions of nasal mucosa occurred in the higher exposure groups. The NOAEL for developmental effects was 4000 ppm, the highest concentration tested.

3.2 Initial Assessment for Human Health

Studies have been conducted that identify tissues and organs most sensitive to the effects of isobutanal. Direct contact with this aldehyde produces an irritant response; repeated inhalation exposure of 500 ppm led to lesions of the tissues of the nasal mucosa. This observation is consistent with the known irritant effects of other short chain aliphatic aldehydes. A developmental toxicity study conducted for the OECD/SIDS program demonstrated no adverse effects on the developing fetus. Observations of effects on indices of sperm viability r after repeated exposure to rats were variable and the overall response was considered negative. Slight reductions in male rat reproductive organ weights were observed at 4000 ppm, and were accompanied by significant reductions in body weight gain as well as mortality. No reproductive effects were observed in mice. Although most bacterial assays gave negative results, the weight of evidence indicates that isobutanal is a base substitution mutagen in bacteria when tested in the absence of metabolic activation, and that it also causes mutagenic and genotoxic effects in mammalian cells when tested *in vitro* in several different types of assays. Three of four In vivo genetic toxicity tests were negative. NTP carcinogenicity studies in rats and mice did not reveal any carcinogenic activity for isobutanal.

4 HAZARDS TO THE ENVIRONMENT

Analog justification

Based on structure-activity considerations, data on the isobutanal analogs butyraldehyde (CAS No. 123-72-8), propionaldehyde (CAS No. 123-38-6) and isovaleraldehyde (CAS No. 590-86-3) were included to provide a more complete evaluation of the toxicity of isobutanal.

4.1 Aquatic Effects

Studies indicate that isobutanal is moderately toxic to fish. LC_{50}'s of >25 mg/L were obtained in 4-day and 14-day acute toxicity studies with fathead minnows and guppies, respectively (Waggy and Payne 1974; Deneer et al., 1988). Isobutanal was found to be of low toxicity to *Daphnia* (48-hr EC_{50} = 277 mg/L) (BASF

AG, unpublished) as was a close structurally related analog, isovaleraldehyde (48-hr EC_{50} = 180 mg/L) (BASF AG, unpublished). The aldehydes were moderately toxic to algae (*Scenedesmus subspicatus*) in a 72-hr study, EC_{50} values of 84 and 80 mg/L were obtained for butanal and isovaleraldehyde, respectively (BASF AG, unpublished).

Potential aquatic effects of isobutanal have also been evaluated by SAR analysis (EPIWIN V 3.10). The analysis was based on an aldehyde SAR (chemical class: aldehyde-C4), molecular weight 72.11, water solubility = 89,000 mg/L at 25 ºC, Kow = 0.74 at 25 ºC. The resulting predicted toxicity values were as follows

Fish 96 hr LC_{50}	= 15.0 mg/L
Daphnid 48-hr LC_{50}	= 22 mg/L
Algal 96 hr EC_{50}	= 467 mg/L
Fish chronic value	= 3.5 mg/L
Algal chronic value	= 22.5 mg/L

4.2 Terrestrial Effects

No information is available.

4.3 Other Environmental Effects

Isobutanal is acutely toxic to bacteria (EC_{50} of 468 mg/1) and at concentrations released from production and processing units would not disrupt the operation of sewage treatment facilities.

4.4 Initial Assessment for the Environment

Isobutanal is a liquid at ambient temperatures with a melting point of -66 ^{o}C and a boiling point of 64.1 ^{o}C (at 101.3 kPa). It is soluble in water (25 g/L at 20 ^{o}C, 89 g/L at 25 ^{o}C), has a high vapor pressure (18.4 kPa at 20 ^{o}C; 172 mm Hg or 22.9 kPa at 25 ^{o}C) and a low octanol water partition coefficient (Log Pow = 0.77 at 25 ^{o}C). Isobutanal oxidizes slowly upon exposure to air, forming isobutyric acid: peroxides or peracids may also form. It is considered a highly flammable liquid which can easily be ignited by heat, sparks or flame. Its flashpoint is less than –18 ^{o}C. The flammability limits are 1.6% (lower) to 10.6% (upper).

Based on Level III distribution modeling, the majority of isobutanal released into the environment would partition into the water (64.8%), soil (27.4%) and air (7.72%). Modeling predicts that isobutanal is biodegradable and is not expected to accumulate in the environment. For isobutanal, a static test with fathead minnows (P*imephales promelas*) was reported to give a 96-hour LC_{50} of 23 mg/L. With *Daphnia magna* Strauss, the reported 48 h EC_{50} was 277 mg/L. The isobutanal toxicity to algae was tested with *Scenedesmus subspicatus* to give a 72-hour LC_{50} of 84 mg/L.

Information on the concentration of isobutanal in surface waters is limited to one report identifying the chemical at a concentration of 1 ppb in a heavily industrialized river basin in the U.S. (Ewing, 1977, as cited in HSDB, 2002; see also Section 2.1.1.).

5 RECOMMENDATIONS

In view of its primary use as a chemical intermediate, its low persistence in the environment, its low potential for adverse environmental impacts, the unlikelihood of human exposure except in occupational situations, isobutanal is considered to be of low priority for further work.

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ANNEX

Aquatic PEC Estimates

Local PECs were estimated for three production sites in Germany (J. Ahlers, Umweltbundesamt, Berlin, pers. com.). Based on local production data and using a generic exposure scenario (Emissions Scenario Document, TGD) with the following assumptions (1% emission factor for production and processing; a 300 day per year duration, a sewage treatment plant elimination rate of 92% (according to the model SIMPLETREAT) and a site specific flow rate of 10%ile or a default value of 60 m^3/s), the PEC_{local} values for the three sites were estimated to be 1.36 µg/L, 0.091 µg/l and 7.7 µg/L, respectively.

If it is assumed that total releases of 10400 lb (4.7 metric tonnes, as reported in TRI) are to a single treatment plant, the daily release would be 16 kg/day, and the resulting PEC_{local} would be 0.25 µg/L (L. Musset, Ministere de l'Environnement, Paris, pers. com.).

[NOTE: These calculations may not apply to any specific U.S. site].

Summary of Responses to the OECD Request for
Available Data on HPV Chemicals
(revised July, 2004)

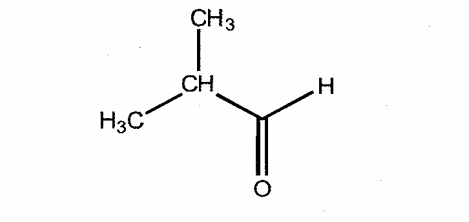
1.01 Substance Information

CAS Number: **78-84-2**

Name: Isobutanal

Molecular Formula: **C_4H_8O**

Structural Formula:



Molecular Weight: **72.11**

1.02 OECD Information

Sponsor Country: **United States of America**

Contact Point:

Mr. Oscar Hernandez
Director, Risk Assessment Division
U.S. Environmental Protection Agency
Office of Pollution Prevention and Toxics (7403M)
1200 Pennsylvania Ave, N.W.
Washington, D.C. 20460
Telephone: (202) 564-7641

Lead Organization: **U.S. Environmental Protection Agency**

Name of Responder:

Barbara Francis
American Chemistry Council
1500 Wilson Boulevard
Arlington, VA 22209
703-741-5609
Barbara_Francis@americanchemistry.com

1.1 General Substance Information

Type of Substance: **Organic**

Physical State: **Liquid**

Purity: **99.6 % by weight**

1.2 Common Synonyms

Isobutyraldehyde
2-Methylpropanal
Isobutyl aldehyde
Propanal, 2-methyl
Isobutyric aldehyde
2-Methyl-l-propanal
2-methylpropianaldehyde
Valine aldehyde
Isopropylformaldehyde
UN2045
OHS11740

1.3 Identity of Major Impurities

1-Butanal

1.4 Essential Additives.

None

1.5 Quantity

Estimated worldwide annual production (1993) of *ca*.700,807 metric tonnes (*ca* 1545 million pounds).

Estimated U.S. total annual production (1993) of *ca.*258,550 metric tonnes (*ca* 570 million pounds).

This chemical is solely used as a chemical intermediate and is produced and used exclusively in closed systems. Transport is primarily by bulk carrier.

Reference: **Union Carbide plant experience**

Manufacturing Process

Isobutanal is manufactured as a coproduct with normal butanal (n-butyraldehyde) by catalytic hydroformylation of propylene. The propylene, carbon monoxide and hydrogen reaction is carried out under pressure in closed systems. The isobutanal/butanal mix is stripped of dissolved gasses and heavies and either hydrogenated to 1-butanol and isobutanol, or the aldehyde mix is further refined to separate the isobutanal and butanal. Typically, process vents from reactors, columns and storage tanks are collected into the plant fuel system. Many plants in the U.S. are now operating under the "New Source Performance Standards (NSPS)" rule which requires fugitive emission monitoring of all size valves on a quarterly basis and all pumps and compressors on a monthly basis.

Distribution

The aldehyde is shipped in bulk by tank truck or tank car (rail cars). Properly designed stations allow for loading into closed tanks of the trucks or cars. Vapor emitted during these operations is collected and routed through a vent collection system to an incinerator where isobutanal vapor is destroyed.

References: **Union Carbide plant experience**

1.6 Labelling and Classification

1.7 Use Pattern

Industrial

Isobutanal finds sole use as a chemical intermediate. The major use is the in-plant conversion to isobutanol. In addition, the aldehyde may also be oxidized to isobutyric acid. Isobutanal is also converted through aldol condensation to a dimer, which is hydrogenated to 2,2,4-trimethyl-1,3-pentanediol. Other major uses include the manufacturer of esters and specialty chemicals. Fifteen percent of isobutanal production is converted to neopentyl glycol by condensation with formaldehyde and hydrogenation (Kirk-Othmer, 4th ed., vol. 4, p. 736).

According to information submitted to OECD, isobutanal is used in Finland in the production of softeners.

Consumer Uses/Exposures

Isobutanal is natural component of many foods. It is present in beans, beef fat, black currents, bread, green vegetables, butter, carrots, cauliflower, cheese, coffee, tea, potatoes, peanuts, tomatoes, wine, and whisky.

Reference: **Food Chemical Codex, 1972. *Cited in*: 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 4472, Research Triangle Park, NC.

Reported average concentrations of isobutanal range from 5.0 ppm in alcoholic beverages to 0.5 to 1.0 ppm in baked good, 0.67 ppm in candy, 0.25 to 0.50 ppm in ice cream, and 0.3 ppm in non-alcoholic beverages.

Reference: **Furia, T.E., and Bellanca, N. (eds). Fenaroli's Handbook of Flavor Ingredients, 2nd Edition, Volume 2. CRC Press, Cleveland, OH..**
Not identified.

1.8 Occupational Exposure Limit Values

In the U.S. no OSHA Permissible Exposure Limit (PEL) has been established for isobutanal.

A WEEL (Workplace Environmental Exposure Level) of 25 ppm has been established by the American Industrial Hygiene Association (AIHA). The AIHA WEEL value represents the workplace exposure level to which it is believed all employees could be exposed repeatedly without adverse health effects.

Reference: **American Industrial Hygiene Association (AIHA). (2003) The AIHA 2003 Emergency Response Planning Guidelines and Workplace Environmental Exposure Level Guides Handbook. American Industrial Hygiene Association, Fairfax, VA.**

Isobutanal's primary use is as a reactive intermediate. Most isobutanal is consumed captively in chemical manufacturing. Production and conversion to other chemicals necessarily takes place in closed systems because of the volatile and flammable nature of isobutanal. It is transported by bulk carrier. These manufacturing and transportation practices minimize workplace exposure.

Reference: **American Industrial Hygiene Association (AIHA). (2002) AIHA Workplace Environmental Exposure Level Guide for Isobutyraldehyde. American Industrial Hygiene Association, Fairfax, VA.**

1.9 Sources of Exposure

Fugitive Emissions

Fugitive emissions monitoring is being conducted on valves, pumps and flanges in some units (as required by some federal and state regulations in the U.S.). Regulations have allowable "leak" limits, which range from 500 to 10,000 ppm. Under some regulations, repairs must be attempted as early as 5 days after detection of leaks exceeding the allowable limit, but with proper reporting may be extended until the next scheduled 24-hour shutdown.

Occupational Exposures

In one production site, some industrial hygiene monitoring was conducted in the 1990 to 1995 time frame in order to establish an exposure baseline to this material. A total of 27 samples were collected; the bulk of the results were less than 0.010 ppm. Two samples yielded results with measurable exposure concentrations, 12 and 18 ppm based on an 8-hour time weighted average. Similar data have been collected in a European production facility. A total of 217 personal monitoring samples were collected between 1979 and 1996. Of these, 193 were in the production units, 12 were associated with storage and filling operations, 8 with research activities and 4 with maintenance operations. Results are listed in the following table:

Total		Production	Storage/Filling	Research	Maintenance
N	217	193	12	8	4
Average	0.2 ppm	0.2 ppm	0.1 ppm	0.1 ppm	3.4 ppm
Range	0 - 7 ppm	0 - 7 ppm	0.02 -0.3 ppm	0 - 0.3 ppm	3 - 3 .7 ppm

According to information submitted to OECD, occupational and environmental exposures to isobutanal in Finland are as follows:

Source	Workplace Concentration (mg/m^3)
Emissions in handling PVB films	1.9
Manufacture of pesticides	0.02-0.08
Use of hotmelt gluing machine	0.01-0.07
Scarving laminated glass plates	0.01-0.07

1.10 Additional Remarks

Options for Disposal

Incineration in the event of spill.

2.1a Melting or Decomposition Point

-66 °C

Method (e.g. OECD, other): ASTM D2386/D1177

GLP: YES [ ]
NO [X]

Comments: **Freezing point**

Reference: **Union Carbide Chemicals and Plastics Co., Solvents & Coatings Materials Division, Material Safety Data Sheet**

2.1b Melting or Decomposition Point

-65.9°C

Method (e.g. OECD, other): no data

GLP: YES [ ]
NO [X]

Comments: **Freezing point**

Reference: **Budavari, S (Ed) (1989) The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals, 11th Edition. Merck Research Laboratories, Rahway, NJ.**

2.2a Boiling Point

64.1°C at 101.3 kPa (760 Torr)

Method (e.g., OECD, other): **ASTM E1719-95**

GLP: Yes [ ]
No [X]

Comments:

Reference: **Union Carbide Chemicals and Plastics Co., Solvents & Coatings Materials Division, Material Safety Data Sheet**

2.2b Boiling Point

64 °C at 101.3 kPa (760 Torr)

Method (e.g., OECD, other): no data

GLP: Yes [ ]
No [X]

Comments:

Reference: **Budavari, S (Ed) (1989) The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals, 11th Edition. Merck Research Laboratories, Rahway, NJ.**

2.3 Density

0.79 g/ml (20ºC/4ºC)

Method (e.g., OECD, other): ASTM D4052

GLP: Yes [ ]
No [ ]

Comments:

Reference: **Budavari, S. ed. (1989) The Merck Index, An Encyclopedia of Chemicals, Drugs and Biologicals, 11th Edition. Merck Research Laboratories, Rahway, NJ**

2.4 Vapour Pressure

a) 18.4 kPa at 20°C (= 138 mm Hg)
b) 172 mm Hg at 25ºC (experimental)

Method (e.g. OECD, other): **ASTM E1719-95**

GLP: YES [ ]
NO [X]

Comments:

Reference: **a) Union Carbide Chemicals and Plastics Co., Solvents & Coatings Materials Division, Material Safety Data Sheet**

b) Howard, P.H. and W. M. Meylan (ed.) (1997) Handbook of Physical Properties of Organic Chemicals. Lewis Pub. New York, p. 72.

2.5a Partition Coefficient (n-Octanol/water)

log P_{ow} = 0.89

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method:

Comments:

Reference: **Calculated from water solubility based on procedure of Verschueren, K. (1983) *Handbook of Environmental Data on Organic Chemicals,* 2nd ed. p. 24.**

2.5b Partition Coefficient n-Octanol/water

log P_{ow} = 0.77 at 25°C

Method: calculated [ ]
measured [X]

GLP: YES [ ]
NO [X]

Analytical Method: **OECD Guide-line 107 "Partition Coefficient (n-octanol/water Flaskshaking Method"**

Comments:

Reference: **BASF AG, Analytisches Labor; unveroeffentlichte Untersuchung (J.Nr. 124659/10 vom 10.12.1987)**

2.5c Partition Coefficient (n-Octanol/water)

log P_{ow} = 0.74

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method:

Comments: **at 25 °C**

Reference: **Howard, P.H. and W. M. Meylan (ed.) (1997) Handbook of Physical Properties of Organic Chemicals. Lewis Pub. New York, p. 72.**

2.6a Water Solubility

6.5 wt% at 20 °C

Method (e.g., OECD, others):

GLP: YES [ ]
NO [X]

Analytical Method:

Comments:

Reference: **Union Carbide Chemicals and Plastics Co., Solvents & Coatings Materials Division, Material Safety Data Sheet.**

2.6b Water Solubility

75 g/L at 20°C

Method (e.g., OECD, others):

GLP: YES [ ]
NO [X]

Analytical Method:

Comments: **pH 7**

Reference: **BASF AG, Sicherheitsdatenblatt Isobutyaldehyd (19.11.1993)**

2.6c Water Solubility

89 g/L at 25°C

Method (e.g., OECD, others): **Experimental**

GLP: YES [ ]
NO [ ]

Analytical Method:

Comments

Reference: **Howard, P.H. and W. M. Meylan (ed.) (1997) Handbook of Physical Properties of Organic Chemicals. Lewis Pub. New York, p. 72.**

2.6d pH in Water

pH 7 at 85 mg/L (water)

Method (e.g., OECD, other):

GLP: YES [ ]
NO [X]

Comments:
Reference: **Waggy, G. T. and J. R. Payne (1974) "Environmental Impact Analysis - Acute Aquatic Toxicity Testing". Project Report 910F44, Union Carbide Corporation, South Charleston Technical Center, South Charleston, WV.**

2.7a Flash Point (liquids)

< -18 °C (closed cup)
-10 °C (open cup)

Method (e.g., OECD, other): **Tag, ASTM D56, ASTM D1310**

GLP: YES [ ]
NO [X]

Comments:

Reference: **Union Carbide Chemicals and Plastics Co., Solvents & Coatings Materials Division, Material Safety Data Sheet**
National Fire Protection Association (2002) Fire Protection Guide to Hazardous Materials, 13th Edition. National Fire Protection Association (NFPA), Quincy, MA.

2.7b Flash Point (liquids)

-40 °C

Method (e.g., OECD, other including reference to the standard used):

GLP: YES [ ]
NO [ ]

Comments:

Reference: **Kirk-Othmer Encyclopedia of Chemical Technology (1991) 4th ed. vol. 4, p. 476. John Wiley and Sons, New York.**

2.8 Auto Flammability (solid/gases)

196 °C

GLP: YES [ ]
NO [X]

Comments: **385 °F, autoignition temperature**

Reference: **National Fire Protection Association (2002) Fire Protection Guide to**
Hazardous Materials, 13th Edition. National Fire Protection Association (NFPA), Quincy, MA.

2.9 Flammability (solid/gases)

Method (e.g., OECD, others):

GLP: YES [ ]
NO [X]

Test results:

Lower 1.6 % by volume
Upper 10.6 % by volume

Comments:

Reference: **Union Carbide Chemicals and Plastics Co., Solvents & Coatings Materials Division, Material Safety Data Sheet**

National Fire Protection Association (2002) Fire Protection Guide to Hazardous Materials, 13th Edition. National Fire Protection Association (NFPA), Quincy, MA.

2.10 Explosive Properties

2.11 Oxidising Properties

Comment: **Oxidizes slowly upon exposure to air, forming isobutyric acid. Oxidation can also cause formation of hazardous peroxides or peracids.**

Reference: **American Industrial Hygiene Association (2002).** ***AIHA Workplace Environmental Exposure Guide for Isobutyraldehyde*****. AIHA, Fairfax, VA.**

2.12 Oxidation-Reduction Potential

2.13 Other Data

a) Log_{10} Henry's Constant = -3.16 atm-m^3/mole (calc. = 6.9 x 10^{-4} atm-m^3/mole)

b) Henry's Law Constant = 1.8 x 10^{-4} atm-m^3/mole (calc. from VP and WSOL)

Comments:

References:

a) QSAR Database, Technical Database Services, Inc. (Based on Thomas, R. G. (1982) Handbook of Chemical Properties Estimations.)

b) Howard, P.H. and W. M. Meylan (ed.) (1997) Handbook of Physical Properties of Organic Chemicals. Lewis Pub. New York, p. 72.

3.1 Stability

3.1.1 Photodegradation

Test substance: **Isobutanal**

Test method or estimation method (e.g., OECD, others): **Experimental determination based upon reaction rate with OH^- in air**

GLP YES [ ]
NO [X]

Test results: **Rate Constant = 26.3 x 10^{-12} cm^3/molecule/second**
$T_{1/2}$ = 5.5 hours

Reference: **Meylan, W. M. and P. H. Howard (1992) *Atmospheric Oxidation Program*. Lewis Publishing Co., Boca Raton, FL**

3.1.2 Stability in Water

No data

3.1.3 Stability in Soil

No data

3.2 Monitoring Data:

Comment: **1 ppb in 1 of 204 samples collected from 14 heavily industrialized river basins in the U.S.**

Reference: **Ewing, B.B., et al. 1977. Monitoring to detect previously unrecognized pollutants in surface waters. Appendix, Organic Analysis Data, USEP 560/6-77-015, Washington, DC. (As cited in Hazardous Substance Data Base, on-line file, National Library of Medicine, 2002)**

3.3 Transport and Distribution between Environmental Compartments

Method: **EPIWIN 3.1, Mackay Level III Fugacity Model**

Results:

	Concentration (%)	Half-life (hr)	Emissions (kg/hr)
AIR	7.72	9.76	1000
WATER	64.8	360	1000
SOIL	27.4	360	1000
SEDIMENT	0.113	1440	0
Persistence Time: 115 hr			

Comments: **Input values were as follows: Water Solubility = 89 g/L at 25 ºC; Boiling Point = 64.5°C; Melting Point = -65.9°C; Vapor Pressure = 172 mm Hg at 25 ºC; Henry' Law Constant 0.00069 atm-m^3/mole; and predicted Log Kow = 0.74 at 25 ºC (KowWin program).**

Reference: **EPIWIN 3.10 (program run on Feb. 8, 2002)**

3.4 Identification of Main Mode of Degradability in Actual Use

No Data

3.5a Biodegradation

Test substance: **Isobutanal**

Test type, aerobic [X], anaerobic [ ]

Test medium: **Activated Sludge, Industrial, Non-Adapted**

Test method (e.g., OECD, ISO, others): OECD Guideline 302 B

GLP: YES[ ]
NO [X]

Test results: > 95% after 5 days

Comments: **"Inherent biodegradability: Modified Zahn-Wellens Test". Eliminierung durch nicht biologische Vorgaenge < 10%**

Reference: **Hoechst AG (1979), unveroeffentlichte Untersuchung (RWL 26.02.79)**

3.5b Biodegradation

Test substance: **Isobutanal**

Test type, aerobic [X], anaerobic [ ]

Test medium:

Test method (e.g., OECD, ISO, others): DIN 38409, Teil 51

GLP: YES [ ]
NO [X]

Test results: **72% after 5 days**

Comments: **BSBx-Bestimmung, DEV H5 DIN 38409, Teil 51, Deutsche Einheitsverfahren zur Wasser-, Abwasser- and Schlammunt ersuchung, Bestimmung des biochemischen Sauerstoffbedarfs**

Reference: **BASF AG (1977) Labor Oekologie; unveroeffentlichte untersuchung**

3.5c Biodegradation

Test substance: **Isobutanal**

Test type, aerobic [X], anaerobic [ ]

Test medium: **Activated Sludge**

Test method (e.g., OECD, ISO, others): **MITI-Test (BOD of THOD)**

GLP:YES [ ]
NO [X]

Test results: **81% after 14 days**

Comments: **Concentration = 100 mg/L related to Test Substance. Concentration of Sludge: 30 mg/L**

Reference: **Biodegradation and Bioaccumulation Data of Existing Chemicals Based on Japan, edited by Chemicals Inspection & Testing Institute Japan, Published by Japan Chemical Industry Ecology-Toxicology & Information Center, October 1992.**

3.5d Biodegradation

Test substance: **Isobutanal**

Test type, aerobic [X], anaerobic [ ]

Test medium: **Activated Sludge from Three Treatment Plants (2500 mg/L Sludge Solids)**

Test method (e.g., OECD, ISO, others): **Warburg-Test (Respirometer)**

GLP: YES[ ]
NO [X]

Test results: **24.3% in 24 hours at 20°C**

Comments: **500 mg/L test substance concentration**

Reference: **Gerhold, R. M., Malaney, G.W. (1966) Structural determinants in the oxidation of aliphatic compounds by activated sludge. *Jour. Water Pollution Control Fed*. 38, 562-579.**

3.5e Biodegradation

Test substance**: Isobutanal**

Test type, aerobic [X], anaerobic [ ]

Test medium: **Activated Sludge, Non-adapted**

Test method (e.g., OECD, ISO, others):

GLP: YES [ ]
NO [X]

Test results: **99% after 13 days**

Comments: **400 mg/L Test Substance, Standversuch (TOC)**

Reference: **BASF AG (1976) Labor Oekologie; unveroeffentlichte untersuchung**

3.5f Biodegradation

Test substance: **Isobutanal**

Test type, aerobic [ ], anaerobic [X]

Test medium: **Digester Sludge**

Test method (e.g., OECD, ISO, others):

GLP: YES [ ]
NO [X]

Test results: **71% after 10 days**

Comments: **Contact digestion; influent, effluent analysis, average of 12 samples; 39 ºC; parameter type: biolog treat. sim.; analysis method: GC; Chemical Concentration: 102 ppm; Retention Time: 144-240 hours**

Reference: **Hovious, J.C., et al. (1972) "Anaerobic Treatment of Synthetic Organic Wastes", EPA 12020 DIS 01/72, USEPA, Washington, DC, p 202.**

3.5g Biodegradation

Test substance: **Isobutanal**

Test type, aerobic [ ], anaerobic [X]

Test medium: **Digester Sludge**

Test method (e.g., OECD, ISO, others):

GLP: YES [ ]
NO [X]

Test results: **76% after 100 days**

Comments: **Semi-pilot lagoon; Photosynthesis; aerobic process occur at surface; Wind and wave mixing; Thermal turn overs; 3 foot depth; Influent, effluent analysis; Parameter type: biological treatment Sam.; Analysis method: C02, CH_4 GC; Retention Time: 240-2400 hours; Chemical Concentration: 210ppm; 15 °C**

Reference: **Hovious, J.C., et al. (1972) "Anaerobic Treatment of Synthetic Organic Wastes", EPA 12020 DIS 01/72, USEPA, Washington, DC,p. 202.**

3.6 BOD5, COD or Ratio BOD5/COD

Test substance: **Isobutanal**

Test type, aerobic [X], anaerobic [ ]

Test medium: **Waste Water Treatment**

Test method (e.g., OECD, ISO, others):

GLP YES [ ]
NO [X]

Test results:

BOD_5 **66% of ThOD**
72% of COD

Comments:

Reference: **Verschueren, K. (1996)** ***Handbook of Environmental Data on Organic Chemicals*****, 3rd ed. pp. 1154-1155.**

3.7 Bioaccumulation

Test substance: **Isobutanal**

Method: **EPIWIN 3.10, BCFWIN v2.14**

Results: **Predicted log BCF = 0.5**

Comments: **Estimated from log Kow of 0.74 at 25 ºC, MW = 72.11, Water sol. = 8.9 x 10^4 mg/L at 25 ºC.**

Reference: **EPIWIN 3.10 (program run on Feb. 8, 2002)**

3.8 Additional Remarks

Sewage Treatment (information on treatability of the substance)

Test results: **No data submitted**

4.1 Acute/Prolonged Toxicity to Fish

4.1a Results of Acute Tests

Test substance: **Isobutanal**

Test species: ***Poecilia reticulata*** **(guppy)**

Test method (e.g., OECD, others):

Type of test: static [ ], semi-static [X], flow-through [ ] Other (e.g., field test) [ ]

GLP YES [ ]
NO [X]

Test results: **LC_{50} = 27 mg/L (14-day)**

Comments: **log LC_{50} = 2.57 when LC_{50} in units of umoles/liter**

Reference: **Deneer, J. W., Seinen, W. and J. L. M. Hermens (1988) The acute toxicity of aldehydes to the guppy. *Aqu. Tox*. 12:185-192.**

4.1b Results of Acute Tests

Test substance: **Isobutanal**

Test species: ***Pimephales promelas*** **(fathead minnow)**

Test method (e.g., OECD, others):

Type of test: static [X] , semi-static [ ], flow-through [ ] , Other (e.g., field test) [ ]

GLP: YES [ ]
NO [X]

Test results:

LC_{50} = 51 mg/1 (24 hr);
24 mg/1 (48 hr);
23 mg/1 (96 hr).

Comments:

Reference: **Waggy, G. T. and J. R. Payne (1974) "Environmental Impact Analysis -Acute Aquatic Toxicity Testing". *Project Report* 910F44, Union Carbide Corporation, South Charleston Technical Center, South Charleston, WV.**

4.1c Results of Acute Tests

Test substance: Isobutanal

Test species: ***Leuciscus idus*** **(fish, fresh water)**

Test method (e.g., OECD, others): **DIN 38412 part 15**

Type of test: static [X] , semi-static [ ], flow-through [ ], Other (e.g., field test) [ ]

GLP YES [ ]
NO [X]

Test results:

LC_{50} = 86 mg/L

Comments: **48-hr exposure**

Reference: **Huels Study (unpublished) zitiert im Schr. der Huels AG vom 27.04.1994.**

4.1d Results of Acute Tests

Test substance: **Isobutanal**

Test Method: **EPIWIN 3.10, ECOSAR v.0.99g**

Results: **96 hr LC_{50} = 15.0 mg/L**

Comments: **Based on aldehyde SARs (ecotoxicity class aldehyde C-4). Estimated from log Kow of 0.74 at 25 ºC, MW = 72.11, Water sol. = 8.9 x 10^4 mg/L at 25 ºC.**

Reference: **EPIWIN 3.10 (program run on Feb. 8, 2002)**

4.2 Acute Toxicity to Aquatic Invertebrates

4.2.1a Daphnia

Test substance: **Isobutanal**

Test species: ***Daphnia magna* Strauss**

Test method (e.g., OECD, others): **EC Directive 84/449/EEC, C.2 "Acute Toxicity for Daphnia"**

GLP: YES [ ]
NO [X]

Test results:

EC_0 (24 hr) = 125 mg/L
EC_{50} (24 hr) = 308 mg/L
EC_{100} (24 hr) = 500 mg/L

Comments:

Reference: **BASF AG, Ecology Laboratory Project Report No. 0080/88 (unpublished data)**

4.2.1b. Test substance: **Isobutanal**

Test species: ***Daphnia magna* Strauss**

Test method (e.g., OECD, others): **EC Directive 84/449/EEC, C.2 "Acute Toxicity for Daphnia"**

GLP: YES [ ]
NO [X]

Test results:

EC_0 (48 hr) = 125 mg/L
EC_{50} (48 hr) = 277 mg/L
EC_{100} (48 hr) = 500 mg/L

Comments:

Reference: **BASF AG, Ecology Laboratory Project Report No. 0080/88 (unpublished data)**

4.2.1c.Test substance: I**sovaleraldehyde**

Test species: ***Daphnia magna* Strauss**

Test method (e.g., OECD, others): **EC Directive 79/831 EEC Annex V C.2.**

GLP: YES [ ]
NO [X]

Test results:

EC_0 (24/48 hr) = 125/125 mg/L
EC_{50} (24/48 hr) = 210/180 mg/L

Comments: **Results of ecotoxicity studies on isovaleraldehyde should be considered applicable to isobutyraldehyde based on structure activity considerations.**

Reference: **BASF AG, Ecology Laboratory Project Report No. 1023/88 (unpublished data)**

4.2.1d. Test substance: **Isobutanal**

Test Method: **EPIWIN 3.10, ECOSAR v. 0.99g**

Results: **48-hr LC_{50} = 22 mg/L**

Comments: **Based on aldehyde SARs (ecotoxicity class aldehyde C-4). Estimated from log Kow of 0.74 at 25 ºC, MW = 72.11, Water sol. = 8.9 x 10^4 mg/L at 25 ºC.**

Reference: **EPIWIN 3.10 (program run on Feb. 8, 2002)**

4.2.2a Toxicity to Other Aquatic Organisms

Test substance: **Isobutanal**

Test species: ***Aedes aegypti* larvae (mosquito)**

Test method (e.g., OECD, others):

Type of test: static [X], semi-static [ ], flow-through [ ], Other (e.g., field test) [ ]

GLP YES [ ]
NO [X]

Test results: **LC_{50} = 0.25% (v/v)**

Comments: **Test substance reagent grade or better. No details given as to concentrations used. Percentage death determined after 4 hours and the value represents the average of three separate experiments agreeing within +/- 10%.**

Reference: **Kramer, V. C., Schnell, D. J. and K. W. Nickerson (1983) Relative toxicity of organic solvents to *Aedes aegypti* larvae. *J. Invert. Path.* 42:285-287.**

4.3a Toxicity to Aquatic Plants (algae)

Test substance: **Isobutanal**

Test species: ***Scenedesmus subspicatus***

Test method (e.g., OECD, others): **Scenedesmus-Zellvermehrungs-Hemmtest, DIN 38412 Teil 9 Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Gruenalgen**

GLP YES [ ]
NO [X]

Test results:

EC_{20} (72 hr) = 51 mg/L
EC_{50} (72 hr) = 84 mg/L
EC_{90} (72 hr)= 147 mg/L

Comments: **Technical Grade Test Substance**

Reference: **BASF AG, Ecology Laboratory Project Report No. 1012/88 (unpublished data)**

4.3b Toxicity to Aquatic Plants (algae)

Test substance: **Isovaleraldehyde**

Test species**:** ***Scenedesmus subspicatus***

Test method (e.g., OECD, others): **DIN 38412 L9**

GLP: YES [ ]
NO [X]

Test results:

EC_0 (72/96 hr) = 33 / 38 mg/L
EC_{50} (72/96 hr) = 80 / 78 mg/L

Maximum concentration at which no effect was observed within the period of the test

Minimum concentration at which no effect was observed within the period of the test

Comments: **Results of ecotoxicity studies on isovaleraldehyde should be considered applicable to isobutyraldehyde based on structure activity considerations**

Reference: **BASF AG, Ecology Laboratory (1988) (unpublished data)**

4.3c. Toxicity to Aquatic Plants (algae)

Test substance: **Isobutanal**

Test Method: **EPIWIN 3.10, ECOSAR v.0.99g**

Results: **Algal 96 hr EC_{50} = 467 mg/L**
Algal chronic value = 22.5 mg/L

Comments: **Based on aldehyde SARs (ecotoxicity class aldehyde C-4). Estimated from log Kow of 0.74 at 25 ºC, MW = 72.11, Water sol. = 8.9 x 10^4 mg/L at 25 ºC.**

Reference: **EPIWIN 3.10 (program run on Feb. 8, 2002)**

4.4a Toxicity to Bacteria

Test substance: **Isobutanal**

Test species: ***Pseudomonas putida***

Test method (e.g., OECD, others): **DIN 38412 Teil 8**

o Type of test
o Other (e.g., field observation) [ ]

GLP YES [ ]
NO [X]

Test results:

EC_{10} = 337 mg/L
EC_{50} = 468 mg/L
EC_{90} = 599 mg/L

Comments: **Technical Grade**

Reference: **BASF AG, Ecology Laboratory Project Report No. 1012/88, (1988) (unpublished data)**

4.4b Toxicity to Bacteria

Test substance: **Isobutanal**

Test species: **Other bacteria: Belebtschlamm aus kommunalen Abwaessern**

Test method (e.g., OECD, others): **ETAD Gaerroebrchentest "Bestimmung der Schadwirkung gegen Abwasserbakterien nach dem Gaerroehrchentest"**

o Type of test
o Other (e.g., field observation) [ ]

GLP: YES [ ]
NO [X]

Test results: **Schaedlichkeitsgrenze = 500 mg/L**

Comments:

Reference: **Hoechst** AG, (9179) unveroeffentlichte Untersuchung (RWL 26.02.79)

4.4c Toxicity to Bacteria

Test substance: **Isovaleraldehyde**

Test species: ***Pseudomonas putida***

Test method (e.g., OECD, others): **DIN 38412 L 8**

o Type of test
o Other (e.g., field observation) [ ]

GLP YES [ ]
NO [X]

Test results: **EC_0 = 310 mg/L**

Comments: **Results of microbiological studies on isovaleraldehyde should be considered applicable to isobutyraldehyde based on structure activity considerations**

Reference: **BASF AG, Ecology Laboratory Project Report No. 330168, (1988) (unpub. data)**

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Test substance: **Isobutanal**

Test Method: **EPIWIN 3.10, ECOSAR v.0.99g**

Results: **Chronic value = 3.5 mg/L**

Comments: **Based on aldehyde SARs (ecotoxicity class aldehyde C-4). Estimated from log Kow of 0.74 at 25 ºC, MW = 72.11, Water sol. = 8.9 x 10^4 mg/L at 25 ºC.**

Reference: **EPIWIN 3.10 (program run on Feb. 8, 2002)**

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Test substance: **Isobutanal**

No data submitted

4.6 Toxicity to Terrestrial Organisms

4.6.1 Toxicity to Soil Dwelling Organisms

No data submitted

4.6.2 Toxicity to Terrestrial Plants

No data submitted

4.6.3 Toxicity to Other Non Mammalian Terrestrial Species

No data submitted

4.7 Biological Effects Monitoring (including Biomagnification)

No data submitted

4.8 Biotransformation and kinetics in environmental species

No data submitted

(Toxicity- oral, dermal and inhalation, as appropriate. Where observation on humans are available, e.g., irritation, these should be entered in the appropriate "Comments" section.)

5.1 Acute Toxicity

5.1.1a Acute Oral Toxicity

Test substance: **Isobutanal**

Test species/strain: **Carworth Wistar female rats 90-120 g in weight.**

Test method (e.g., OECD, EC, limit test): **Gavage**

GLP YES [ ]
NO [X]

Test results: [LD_{50} or other measure of acute toxicity (e.g. in case of fixed dose test)]

Oral LD_{50} = 3.73 g/kg (95% confidence interval 2.7-5.2 g/kg)

Comments: **Administered to non-fasted rats as a 20% aqueous dispersion; groups of 5 rats per dose; dose levels administered were 2.0, 3.98, and 7.95 g/kg body weight.**

Reference: **Union Carbide Corporation, Mellon Institute of Industrial Research Report 15-55 dated June 30, 1952.**

5.l.lb Acute Oral Toxicity

Test substance: **Isobutanal**

Test species/strain: **Rat.**

Test method (e.g., OECD, EC, limit test): **Gavage**

GLP YES [ ]
NO [X]

Test results: [LD50 or other measure of acute toxicity (e.g. in case of fixed dose test)]

Oral LD_{50} = 1.6 to 3.7 g/kg

Comments: **IP LD_{50} - 1.6 to 3.2 g/kg in the rat.**

Reference: **Brabec, M. J. (1981) " Aldehydes and Acetals". in *Patty's Industrial Hygiene and Toxicology*, 3rd rev. ed., vol. 2A, chapter 37, Clayton, G. D. and F. E. Clayton (eds). John Wiley & Sons, New York. p. 2643.**

5.1.2a Acute Inhalation Toxicity

Test substance: **Isobutanal**

Test species/strain: **Rat/ Carworth Wistar**

Test method (e.g., OECD, EC, limit test): **Whole body exposure**

GLP YES [ ]
NO [X]

Test results: **Dynamically generated substantially saturated vapor killed 0 of 6 rats in 15 minutes, and 4 of 6 rats in 20 minutes. Exposure to a measured concentration of 16,000 ppm for 4 hours killed 6 of 6 rats, 8,000 ppm killed 1 of 6 rats.**

Reference: **Union Carbide Corporation, Mellon Institute of Industrial Research Report 15-55 dated June 30, 1952.**

5.1.2b Acute Inhalation Toxicity

Test substance: Isobutanal

Test species/strain: **B6C3F1 & Swiss-Webster mice**

Test method (e.g., OECD, EC, limit test): **Alarie, Y. (1966) *Arch. Environ. Health* 13:433-449.**

GLP YES [ ]
NO [X]

Test results: **The vapor concentration required to elicit a 50% decrease in respiratory rate (RD_{50}) of B6C3F1 mice was 3016 ppm (95% confidence interval 2568 to 3610 ppm), and in Swiss-Webster mice was 4167 ppm (95% confidence interval 3258 to 5671 ppm).**

Reference: **Steinhagen, W. H. and C. S. Barrow (1984) Sensory irritation structure-activity study of inhaled aldehydes in B6C3F1 and Swiss-Webster mice. *Toxicol. Appl. Pharmacol.* 72:495-503**.

5.1.3a Acute Dermal Toxicity

Test substance: **Isobutanal**

Test species/strain: **Male New Zealand rabbits 3 to 5 months in age.**

Test method (e.g., OECD, limit test): **24-hr occluded skin contact.**

GLP: YES [ ]
NO [X]

Test results: **Percutaneous LD_{50} = approximately 7.1 mL/kg**

Comments: **Erythema, edema and necrosis of the skin at the site of contact, with congestion and hemorrhage of the lungs in rats dying on study . Approximate LD50 is based on 4/5 mortality at 10 g/kg and 2/5 at 5 g/kg.**

Reference: **Union Carbide Corporation, Mellon Institute of Industrial Research Report**

15-55 dated June 30, 1952.

5.1.3b Acute Dermal Toxicity

Test substance: **Isobutanal**

Test species/strain: **Guinea pig.**

Test method (e.g., OECD, limit test): 4 hours (no details given)

GLP YES [ ]
NO [X]

Test results: **Percutaneous LD_{50} greater than 20 g/kg**

Comments:

Reference: **Brabec, M. J. (1981) " Aldehydes and Acetals". in *Patty's Industrial Hygiene and Toxicology*, 3rd rev. ed., vol. 2A, chapter 37, Clayton, G. D. and F. E. Clayton (eds). John Wiley & Sons, New York. p. 2643.**

5.2 Corrosiveness/Irritation

5.2.1 Skin Irritation

Test substance: **Isobutanal**

Test species/strain: **Rabbit/male/Nw Zealand White**

Test method (e.g., OECD, others): **0.01 mL of undiluted isobutyraldehyde applied to uncovered clipped skin of the rabbit belly**

GLP YES [ ]
NO [X]

Comments: **Produced marked erythema at the site of contact on one of six rabbits**

Reference: **Union Carbide Corporation, Mellon Institute of Industrial Research Report 15-55 dated June 30, 1952.**

5.2.2 Eye Irritation

Test substance: **Isobutanal**

Test species/strain: **Male New Zealand Rabbits**

Test method (e.g., OECD, others): **0.02 mL of undiluted isobutyraldehyde instilled into the inferior conjunctival sac of rabbit eyes**

GLP**:** YES [ ]
NO [X]

Comments: **Produced severe damage to the cornea of all treated eyes. Instillation of 0.005 mL caused moderate injury to the cornea.**

Reference: **Union Carbide Corporation, Mellon Institute of Industrial Research Report 15-55 dated June 30, 1952.**

5.3 Skin Sensitisation

Test substance: **Isobutanal**

Test species/sex/strain: **Mouse/female/B6C3F1**

Test method (e.g. OECD, others): **Murine Ear Swelling Test/Local Lymph Node Assay.**

Comments: **Mice received 20 ul isobutanal applied directly to shaved and abraded ears for 5 consecutive days with and without adjuvant in an NTP-sponsored test for irritancy and contact hypersensitivity. Doses of isobutanal ranged from 3% to 30% in a solution of four parts acetone to one part olive oil for sensitization tests, and 30% for challenge tests**.

GLP YES [ ]
NO [X]

Test results: **Negative; no indication of irritation or hypersensitivity observed**

Reference: **National Toxicology Program (1990) Assessment of Contact Hypersensitivity to Isobutyraldehyde in female B6C3F1 Mice (IBA-0-1-CNM). National Toxicology Program, Studies Conducted at Immunotoxicology Program, Medical College of Virginia, Virginia Commonwealth University, Richmond VA.**

5.4a Repeated Dose Toxicity

Test substance: **Isobutanal**

Test species/strain: **Alderley Park specific-pathogen-free rats**

Test method (e.g., OECD, others): **Isobutyraldehyde liquid injected at a known rate into a metered stream of air by means of a controlled, fluid-free atomizer.**

GLP YES [ ]
NO [X]

Test results: **Evidence of slight nasal irritation but no evidence of systemic toxicity in 4 rats of each sex receiving 12, 6-hour exposures to 1000 ppm.**

Dose or concentration at which no toxic effects were observed: 1000 ppm

Comments: **At autopsy, organs normal (organs examined macroscopically and microscopically included the lungs, liver, kidneys, spleen and adrenals).**

Reference: **Gage, J. C. *(1970)* The subacute inhalation toxicity of 109 industrial chemicals. *Brit. J. Indust. Med. 27:1-18.***

5.4b Repeated Dose Toxicity

Test substance: **Isobutanal**

Test species/strain: **Female Wistar Rats (10 pregnant animals per exposure concentration)**

Test method (e.g., OECD, others): **Rats were exposed to air concentrations of 1000, 2500 and 4000 ppm, 6 hours/day for 10 consecutive days. This study was designed as a concentration finding study for a definitive developmental toxicity study. At necropsy, the last day of exposure, tissues of the nasal cavities were examined by light microscopy**

GLP YES [X]
NO [ ]

Test results: **Hyperplasia of the transitional epithelium of the anterior part of the lateral wall of the nasal cavity was observed in 8/10 animals exposed to 4000 ppm, 6/10 animals exposed to 2500 ppm and 0/10 animals exposed to 1000 ppm. One animal exposed to 4000 ppm exhibited moderate focal atrophy of the olfactory epithelium in the dorsal meatus**

Dose or concentration at which no toxic effects were observed: **1000 ppm**

Comments:

Reference: **Garmer, A. O., Hellwig, J and B. Hildebrand (1995) "Brief Report on the Maternal Inhalation Toxicity of Isobutyraldehyde as a vapor in Pregnant Wistar Rats" BASF Aktiengesellschaft Department of Toxicology Project No.: 11R0140/93019. Ludwigshafen, Germany.**

5.4c Repeated Dose Toxicity

Test substance: **Isobutanal**

Test species/strain: **Fischer 344 Rats (number per exposure concentration not given)**

Test method (e.g., OECD, others): **Rats were exposed to air concentrations of 500, 1000, 2000, 4000 and 8000 ppm 6 hours/day, 5 days/week for a total of 10 exposures. Observations for mortality and clinical signs were made along with measurements of body weight change, organ weights, hematology, clinical chemistries, and histology.**

GLP: YES [ ]
NO [X]

Test results: **Eight rats exposed to 8000 ppm died, all after the first exposure. There was a suggestion of weight change in the kidneys of males exposed to 8000 ppm, decreases in RBCs of males exposed to 500 and 1000 ppm. No significant effects**

were noted in other indices of toxicity. Pulmonary interstitial inflammation at the two highest exposure concentrations.

Dose or concentration at which no toxic effects were observed:

Comments: **Data obtained from NTP summary, details lacking.**

Reference: **Eastin, W. (1990) "Thirteen-Week Subchronic Study in F344 Rats: Isobutyraldehyde" National Toxicology Program (Letter to Mr. T. J. Cawley, Union Carbide Corporation, dated November 29, 1990).**

5.4d Repeated Dose Toxicity

Test substance: **Isobutanal**

Test species/strain: **Fischer 344 Rats (10/sex/exposure concentration)**

Test method (e.g., OECD, others): **Rats were exposed to air concentrations of 500, 1000, 2000, 4000 and 8000 ppm 6 hours/day, 5 days/week for 13 weeks. Observations for mortality and clinical signs were made along with measurements of body weight change, organ weights, hematology, clinical chemistries, and histology.**

GLP YES [X]
NO [ ]

Test results: **100% mortality at 8000 ppm, 45% mortality at 4000 ppm (3/10 males, 6/10 females). Minimal to mild degeneration of the olfactory epithelium was observed in males in the 2000 and 4000 ppm groups. Increased incidences of squamous metaplasia of the nasal epithelium and mild osteodystrophy of the turbinate bone were observed in male and female rats exposed to 4000 ppm. Spermatozoal motility was significantly reduced in males in the 500 and 1000 ppm groups, but not at 2000 and 4000 ppm. Time females spent in estrous stage was shorter in controls than in the 4 surviving females exposed to 4000 ppm (5.00 days in controls, 5.33 days in remaining females from the 4000 ppm group).**

Dose or concentration at which no toxic effects were observed:

Comments: **The estrous cycle was assessed in only 4 surviving females in the 4000 ppm exposure group. The difference in the length of the estrous cycle (5.00 +/- 0.15 days in control females and 5.33 +/- 0.33 days in 4000 ppm females) was significant only by Wilk's Criterion and was *not* significant by Dunn's Test (NTP, 1999).**

Reference: **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 4472, Research Triangle Park, NC.**

5.4e Repeated Dose Toxicity

Test substance: **Isobutanal**

Test species/strain: B6C3F1 mice (10/sex/exposure concentration)

Test method (e.g., OECD, others): **Mice were exposed to air concentrations of 500, 1000, 2000, 4000 and 8000 ppm, 6 hours/day, 5 days/week for 13 weeks. Observations for mortality and clinical signs were made along with measurements of body weight change, organ weights, hematology, clinical chemistries, and histology.**

GLP YES [X]
NO [ ]

Test results: **100% mortality at 8000 ppm, 95% mortality at 4000 ppm. Increased incidences of non-neoplastic lesions of the nasal cavity occurred in males and females exposed to 1000 ppm or higher. Body weight and body weight gain of females in the 1000 ppm group significantly reduced. Absolute and relative kidney weights of males in the 1000 and 2000 ppm groups significantly increased. Clinical findings included decreased activity, tremors, prostration and slower and labored respiration.**

Dose or concentration at which no toxic effects were observed:

Comments:

Reference: **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 4472, Research Triangle Park, NC.**

5.4f Repeated Dose Toxicity

Test substance: **Butyraldehyde**

Test species/strain: **Rats, Mice, Guinea Pigs, Rabbits and Dogs**

Test method (e.g., OECD, others): **Animals were exposed to air concentrations of 2000, 3100 and 6400 ppm, 6 hours/day, 5 days/week for a total of 9 exposures.**

GLP YES [ ]
NO [X]

Test results: **Definite signs of eye and respiratory irritation, and statistically significant decreases in body weight gain were observed in most species at concentrations of 3100 and 6400 ppm. Other signs observed in most animals at 6400 ppm included coordination loss, anesthesia and death. At 3100 ppm these effects were observed only in the dog. In some animals exposed to 2000 ppm decreased weight gain was observed. Scattered organ weight differences were also noted in rats exposed to 2000 and 3100 ppm. No pathologically significant treatment related gross lesions were found among animals exposed to 3100 or 2000 ppm.**

Dose or concentration at which no toxic effects were observed:

Comments: **Based on structure activity relationships, results of mammalian test data on butyraldehyde should be applicable for hazard identification of isobutyraldehyde**

Reference: **Union Carbide Corporation (1978) Carnegie-Mellon Institute of Research, Chemical Hygiene Fellowship Project Report 41-39.**

5.4g Repeated Dose Toxicity

Test substance: **Butyraldehyde**

Test species/strain: **Male Beagle Dogs, Male and Female Sprague-Dawley Rats**

Test method (e.g., OECD, others): **Animals were exposed to air concentrations of 125, 500 and 2000 ppm (340, 1360, and 5440 mg/m^3) 6 hours/day, 5 days/week for up to 14 and 13 weeks respectively. Indices of toxicity included body and organ weights, urinalysis, blood chemistries, histopathology, ophthalmologic and hematological examinations.**

GLP: YES [X]
NO [ ]

Test results: **A concentration dependent increase in the incidence of squamous cell metaplasia of the nasal cavities was observed in rats of all exposure groups. Dogs exposed to 2000 ppm had significant microscopic lesions of the upper respiratory tract. Exposure concentration related goblet cell hyperplasia within the nasal mucosa was seen in dogs exposed to 125 and 500 ppm. No other significant lesions, at any of the exposure concentrations, in either species, could be attributed to butyraldehyde vapor.**

Dose or concentration at which no toxic effects were observed:

Comments: **Based on structure activity relationships, results of mammalian test data on butyraldehyde should be applicable for hazard identification of isobutyraldehyde.**

Reference: **Union Carbide Corporation (1979) Carnegie-Mellon Institute of Research, Chemical Hygiene Fellowship Project Report 42-50.**

5.4h Repeated Dose Toxicity

Test substance: **Butyraldehyde**

Test species/strain: **Male and Female Fischer 344 Rats (15/sex/group)**

Test method (e.g., OECD, others): **Rats were exposed to air concentrations of 1, 10 and 50 ppm (3.2, 30, and 50 mg/m^3) 6 hours/day, 5 days/week for at least 12 weeks. Indices of toxicity included body weights, food**

consumption, kidney and liver weights, serum chemistries, histopathology, ophthalmologic and neurological examinations.

GLP YES [X]
NO [ ]

Test results: **Histopathologic findings indicated no specific adverse effects could be attributed to exposure to butyraldehyde vapor at concentrations up to 50 ppm. An intercurrent infection in the respiratory tract may have masked any minor irritation effect due to exposure. It was concluded that the test material did not induce any severe irritation to the respiratory tract. No evidence of neurologic effects in a functional observational battery (Irwin Screen).**

Dose or concentration at which no toxic effects were observed: **50 ppm**

Comments: **Based on structure activity relationships, results of mammalian test data on butyraldehyde should be applicable for hazard identification of isobutyraldehyde.**

Reference: **Union Carbide Corporation (1980) Carnegie-Mellon Institute of Research, Chemical Hygiene Fellowship Project Report 43-61.**

5.5 Genetic Toxicity In Vitro

5.5.1a Bacterial Test

Test substance: **Isobutanal**

Test species/strain: ***S. typhimurium*** **strains G-46 & TA-100, TA-1535, C3076, TA-1537, D3052, TA-1538, and TA-98.**

Test method (e.g., OECD, others): **Bacterial forward gene mutation assay in *Salmonella typhimurium* (Ames Test)**

GLP YES [ ]
NO [X]

Test results: **Ambiguous**

Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: **Not reported**
without metabolic activation: **Not reported**

Concentration of test compound resulting in precipitation: **Not reported**

Genotoxic effects

	+	?	–
with metabolic activation:	[ ]	[ ]	[ ]
without metabolic activation:	[ ]	[ ]	[ ]

Comments: **Positive in both G-46 and TA-100 (base substitution mutagens). Negative in TA-1535 (base substitution mutagen) and negative in the frame shift mutagens C3076, TA-1537, D3052, TA-1538, and TA-98. Plate counts not given in original publication.**

Reference: **McMahon, R. E., Cline, J. C. and C. Z. Thompson *(1979)* Assay of 855 test chemicals in ten tester strains using a new modification of the Ames test for bacterial mutagens. *Cancer Res.* 39:683-693.**

5.5.1b Bacterial Test

Test substance: **Isobutanal**

Test species/strain: ***S. typhimurium* strains TA-100, TA-1535, TA-1537 & TA-98.**

Test method (e.g., OECD, others): **Bacterial forward gene mutation pre-incubation assay in *Salmonella typhimurium* (Ames Test)**

GLP YES [ ]
NO [X]

Test results: **Negative**

Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: **no toxicity observed up to 10,000 ug/plate**
without metabolic activation: **no toxicity observed up to 10,000 ug/plate**

Concentration of test compound resulting in precipitation:

Genotoxic effects:

	+	?	–
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: **Five concentrations used ranging between 100 and 10000 :ug/plate (100, 333, 1000, 3333, and 10,000 ug/plate). Both rat liver S9 and hamster liver S9 used for metabolic activation system**

Reference: **Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B. and E. Zeiger (1986) *Salmonella* mutagenicity tests: II. Results from the testing of 270 chemicals. *Environ. Mut.* 8 (suppl.7): 1-119.**

5.5.1c Bacterial Test

Test substance: **Isobutanal**

Test species/strain: ***S. typhimurium* strains TA-98, TA-100, TA-1535 & TA-1537**

Test method (e.g., OECD, others): **Bacterial forward gene mutation assay in *Salmonella typhimurium* (Ames Test)**

GLP: YES [ ]
NO [X]

Test results: **Negative**

Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:
without metabolic activation:

Concentration of test compound resulting in precipitation:

Genotoxic effects:

	+	?	–
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: **Maximum dose tested 3 umole (216 ug)/plate**

Reference**:** **Florin, I., Rutberg, L., Curvall, M. and C. R. Enzell (1980) Screening of tobacco constituents for mutagenicity using the Ames test. *Toxicol*. 18:219-232.**

5.5.1d Bacterial Test

Test substance: **Isobutanal**

Test species/strain: ***S. typhimurium*** **strains TA-100 and TA-98.**

Test method (e.g., OECD, others): **Bacterial forward gene mutation assay in *Salmonella typhimurium* (Ames Test)**

GLP YES [ ]
NO [X]

Test results: **Negative**

Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:
without metabolic activation:

Concentration of test compound resulting in precipitation:

Genotoxic effects:

	+	?	–
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: **No plate counts given in abstract**.

Reference: **Sasaki, Y. and R. Endo (1978) Mutagenicity of aldehydes in *Salmonella. Mut. Res.* 54:251-252.**

5.5.le Bacterial Test

Test substance: Isobutanal

Test species/strain: **S. *typhimurium* strains TA-98, TA-100 and TA-102**

Test method (e.g., OECD, others): **Bacterial forward gene mutation assay in *Salmonella typhimurium* (Ames Test)**

GLP YES [ ]
NO [X]

Test results: **Negative**

Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:
without metabolic activation:

Concentration of test compound resulting in precipitation:

Genotoxic effects:

	+	?	–
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: **No plate counts given. Tested at concentrations between 1.1 nmoles and 0.11mmoles per plate.**

Reference: **Aeschbacher, H. U., Wolleb, U., Loliger, J., Spadone, J. C. and R. Liardon (1989) Contribution of coffee aroma constituents to the mutagenicity of coffee". *Fd. Chem. Toxic*. 27:227-232.**

5.5.1f Bacterial Test

Test substance: **Isobutanal**

Test species/strain: ***Escherichia coli* strains WP2 and WP2 uvrA⁻.**

Test method (e.g., OECD, others): **Bacterial forward gene mutation assay in *Escherichia coli***

GLP YES [ ]
NO [ ]

Test results: **Positive**

Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: **Not reported**
without metabolic activation: **Not reported**

Concentration of test compound resulting in precipitation: **Not reported**

Genotoxic effects

	+	?	–
with metabolic activation:	[ ]	[ ]	[ ]
without metabolic activation:	[X]	[ ]	[ ]

Comments: **Positive in both WP2 and WP2 uvrA⁻ (base substitution mutagens).**

Reference: **McMahon, R. E., Cline, J. C. and C. Z. Thompson (1979) Assay of 855 test chemicals in ten tester strains using a new modification of the Ames test for bacterial mutagens. Cancer Res. 39:683-693.**

5.5.1g Bacterial Test

Test substance: **Isobutanal**

Test species/strain: ***S. typhimurium*** **strains TA-97, TA-98, TA-100, TA-102, TAS-104, TA-1535 and TA-1537**

Test method (e.g., OECD, others): **Bacterial forward gene mutation assay in *Salmonella typhimurium* (Ames Test)**

GLP YES [ ]
NO [ ]

Test results: **Negative in strains TA-97, TA-98, TA-100, TA-102, TA-1535 & TA-1537 with and without rat and hamster liver S9; equivocal in strain TA-104 but only with rat liver S9.**

Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: **3333 ug/plate**
without metabolic activation: **1600 ug/plate**

Concentration of test compound resulting in precipitation: **Not applicable**

Genotoxic effects

	+	?	–
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: **Tested in presence of 10% and 30% S9 preparations from both rat and hamster**

Reference: **Zeiger, E., Anderson, B., Haworth, S., Lawlor, T. and Mortelmans, K. (1992) Salmonella mutagency tests: V. Results from the testing of 311 chemicals. Environ Molec Mutagen 19 (Suppl 21): 2-141.**

5.5h Non-Bacterial In Vitro Test

Test substance: **Isobutanal**

Test species/strain: **Mouse**

Test method (e.g., OECD, others): **Mouse lymphoma gene mutation assay**

GLP YES [ ]
NO [ ]

Test results: **Positive**

Minimum concentration of est substance at which toxicity was observed: **1000 ug/mL**

Genotoxic effects

	+	?	–
with metabolic activation:	[ ]	[ ]	[ ]
without metabolic activation:	[X]	[ ]	[ ]

Comments: **Tested only in the absence of S9 metabolic activation. Concentrations tested: 0 (ethanol vehicle), 62.5, 125, 250, 500, 1000, and 1500 ug/mL**

Reference: **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.**

5.5i Non-Bacterial In Vitro Test

Test substance: **Isobutanal**

Test species/strain: **Hamster/Chinese, ovary cells**

Test method (e.g., OECD, others): **Sister chromatid exchange**

GLP YES [ ]
NO [ ]

Test results: **Positive**

Minimum concentration of test substance at which toxicity was observed:

with metabolic activation: **1600 ug/mL**
without metabolic activation: **500 ug/mL**

Genotoxic effects

	+	?	–
with metabolic activation:	[X]	[ ]	[ ]
without metabolic activation:	[X]	[ ]	[ ]

Comments: **A total of 50 cells scored for each concentration tested. Dose levels without metabolic acitivation: 0 (DMSO vehicle), 5, 16, 50, 160, 500 ug/mL; without metabolic activation: 0 (DMSO vehicle), 16, 50, 160, 500, 1600 ug/mL**

Reference: **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.**

5.5j Non-Bacterial In Vitro Test

Test substance: **Isobutanal**

Test species/strain: **Hamster/Chinese, ovary cells**

Test method (e.g., OECD, others): **Chromosomal aberrations**

GLP YES [ ]
NO [ ]

Test results: **Positive**

Minimum concentration of test substance at which toxicity was observed:

with metabolic activation: **3000 ug/mL**
without metabolic activation: **3000 ug/mL**

Genotoxic effects

	+	?	–
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[X]	[ ]	[ ]

Comments: **Induction of chromosomal aberrations in Chinese hamster ovary (CHO) cells was noted only in the absence of S9 metabolic activation. Concentrations tested with and without metabolic activation: 0 (DMSO vehicle), 16, 50, 160, 500, 1500, 3000, 4000 ug/mL.**

Reference: **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.**

5.6a Genetic Toxicity in Vivo

Test substance: **Isobutanal**

Test species/strain: **Mouse/B6C3F1, bone marrow cells**

Test method (e.g., OECD, others): **Bone Marrow Chromosomal Aberration Test**

GLP YES [ ]
NO [ ]

Test results: **2000 mg/kg a lethal dose; extent of mortality observed at lower doses not reported.**

Genotoxic effects: **Positive at highest concentration (1750 mg/kg) that did not produce complete lethality; negative at lower concentrations.**

Comments: **Induction of chromosomal aberrations in mouse bone marrow cells. Isobutanal in corn oil was injected intraperitoneally into mice at doses of 500, 1000, 1200, 1500, 1750, and 2000 mg/kg. Femoral bone marrow cells were harvested 17 hours after dosing. A total of 50 first-division metaphase cells were scored from each animal (10 animals per exposure group).**

Reference: **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.**

5.6b Genetic Toxicity In Vivo

Test substance: **Isobutanal**

Test species/strain: **Mouse/B6C3F1, bone marrow cells**

Test method (e.g., OECD, others): **Erythrocyte Micronucleus Test**

GLP YES [ ]
NO [ ]

Test results: **20% (1/5) mortality at 1250 mg/kg**

Genotoxic effects:
Negative

Comments: **Isobutanal in corn oil was injected intraperitoneally three times into mice at 24-hour intervals at 0 (corn oil vehicle), 39, 78, 156, 312, 652, and 1250 mg/kg (5 animals per exposure group). Blood smears were collected from femurs 24 hours after the 3rd injection. A total of 2000 polychromatic erythrocytes (PCEs) were scored for frequency of micronucleated cells for each animal.**

Reference: **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.**

5.6c Genetic Toxicity In Vivo

Test substance: **Isobutanal**

Test species/strain: **Rat, bone marrow**

Test method (e.g., OECD, others): **Erythrocyte micronucleus assay**

GLP YES [ ]
NO [ ]

Test results: **20% (1/5) mortality at 1250 mg/kg**

Genotoxic effects:
Negative

Comments: **Isobutanal in corn oil was injected intraperitoneally three times into rats at 24-hour intervals at 0 (corn oil vehicle), 312, 652, and 1250 mg/kg (5 animals per exposure group). Blood smears were collected from femurs 24 hours after the 3rd injection. A total of 2000**

polychromatic erythrocytes (PCEs) were scored for frequency of micronucleated cells for each animal.

Reference: **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.**

5.6d Genetic Toxicity In Vivo

Test substance: **Isobutanal**

Test species/strain: ***Drosophila melanogaster***

Test method (e.g., OECD, others): **Induction of sex-linked recessive lethal mutations in meiotic and post meiotic germ cell stages of Canton-S males by injection and feeding**

GLP YES [ ]
NO [X]

Test results: **Negative**

Lowest dose producing toxicity:

Effect on Mitotic Index or P/N Ratio:

Genotoxic effects:	+	?	–
	[ ]	[ ]	[X]

Comments: **50,000 ppm in saline used in injection study, 80,000 ppm in 5% sucrose in water used in feeding study. Concentrations selected induced approximately 30% mortality after 72 hours of feeding or 24 hours after injection.**

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. Mut.* 7:677-702.**

5.7a Carcinogenicity

Test substance: **Isobutanal**

Test species/strain: **Rat/ F344/N.**

Test method (e.g., OECD, others): **NTP. Groups of 50 male and 50 female F344/N rats were exposed to 0, 500, 1000, or 2000 ppm isobutyraldehyde by inhalation, 6 hours per day, 5 days per week, for 105 weeks**

GLP:YES [X]
NO [ ]

Test results:

Survival and Body Weights

No differences in survival rates between exposed and chamber control rats were found. The mean body weights of male and female rats were generally similar to those of the chamber controls throughout the study.

Pathology Findings

No increase in neoplasm incidences that could be attributed to exposure to isobutyraldehyde was observed in male or female rats. Non-neoplastic lesions related to isobutyraldehyde exposure were limited to the nose and consisted of squamous metaplasia of the respiratory epithelium, degeneration of the olfactory epithelium, and suppurative inflammation. Incidences of minimal to mild squamous metaplasia in 1000 and 2000 ppm males (10/49 and 44/50, respectively) and females (9/49 and 44/50, respectively) and in 500 ppm females (11/50) were significantly greater than those in the chamber controls (1/50, 1/49). Minimal to mild degeneration of the olfactory epithelium occurred in the 2000 ppm males and females (44/50 and 45/50, respectively, vs. no occurrences in controls). Incidences of suppurative inflammation (rhinitis) in both sexes exposed to 2000 ppm were increased (15/50 and 11/50, respectively) compared to controls (5/50 and 2/49).

Comments: **Study conducted for U.S. National Toxicology Program**

Reference: **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 4472, Research Triangle Park, NC.**

5.7b Carcinogenicity

Test substance: **Isobutanal**

Test species/strain: **B6C3F1 mice**.

Test method (e.g., OECD, others): **NTP. Groups of 50 male and 50 female B6C3F1 mice were exposed to 0, 500, 1000, or 2000 ppm isobutyraldehyde, 6 hours per day, 5 days per week, for 105 weeks.**

GLP:YES [X]
NO [ ]

Test results:

Survival and Body Weights

There was an exposure-related decrease in survival of male mice, and the survival of males exposed to 2000 ppm was marginally lower than that of the chamber controls. The mean body weights of female mice exposed to 1000 or 2000 ppm were lower than those of the chamber controls during the second year of the study.

Pathology Findings

No neoplasms that could be attributed to isobutyraldehyde exposure were observed in either males or females. Non-neoplastic lesions related to isobutyraldehyde exposure were limited to the nose. The incidences of olfactory epithelial degeneration in 1000 and 2000 ppm males (11/50, 45/50) and females (27/50, 49/50) were significantly greater than in the chamber controls (0/50, 1/50).

Comments: **Study conducted for U.S. National Toxicology Program**

Reference: **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 4472, Research Triangle Park, NC.**

5.8a Toxicity to Reproduction

Test substance: **Isobutanal**

Test species/strain: Fischer 344 rats

Test method (e.g., OECD, others): **Evaluation of sperm cytology and male reproductive organ weight data from National Toxicology Program 13-week inhalation study. The data evaluated were for rats exposed to 500, 1000, 2000 and 4000 ppm.**

GLP:YES [X]
NO [ ]

Test results: **Decreased body weight and body weight gains observed in males exposed to 4000 ppm (NTP, 1999). Spermatozoal motility was significantly reduced in rats exposed to 500 and 1000 ppm; sperm motility was comparable to controls in rats exposed to 2000 and 4000 ppm (NTP, 1999).**

Comment: **Because of the variability in sperm motility observed between groups, Morrissey et al (1988) determined that the overall response of sperm motility in male rats to isobutanal was negative (personal communication with NTP, 2004). For the same data set, Morrissey et al. (1988) reported no effects on sperm density or morphology, and no significant weight change of the right testis. , There was, however, a decrease in the absolute but not relative weight of right cauda epididymis, and a decrease in the absolute and relative weight of right epididymis in rats exposed to 4000 ppm.**

Reference: **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 4472, Research Triangle Park, NC.**

Morrissey, R., E., Schwetz, B. A., Lamb, J. C. IV, Ross, M. D., Teague, J. L. and R. W. Morris. (1988) Evaluation of rodent sperm, vaginal cytology, and reproductive organ weight data from National Toxicology Program 13-week studies. *Fund. Appl. Toxicol.* 11:343-358

5.8b Toxicity to Reproduction

Test substance: **Isobutanal**

Test species/strain: **B6C3F1 mice.**

Test method (e.g., OECD, others): **Evaluation of sperm cytology and male**

reproductive organ weight data from National Toxicology Program 13-week inhalation study. The data evaluated were for mice exposed to 500, 1000 and 2000 ppm.

GLP:YES [X]
NO [ ]

Test results: **Changes in absolute or relative weight of reproductive organs and effects on sperm were not observed in male mice exposed to vapor concentrations up to 2000 ppm.**

Reference: **Morrissey, R.. E., Schwetz, B. A., Lamb, J. C. IV, Ross, M. D., Teague, J. L. and R. W. Morris. (1988) Evaluation of rodent sperm, vaginal cytology, and reproductive organ weight data from National Toxicology Program 13-week studies. *Fund. Appl. Toxicol.* 11:343-358**

U.S. National Toxicology Program, (1999) NTP Technical Report on theToxicology and Carcinogenesis Studies of Isobutyraldehyde (CAS No. 78-84-2) in F344/N Rats and B6C3F1 Mice. NTP TR 4472, Research Triangle Park, NC.

5.8c Toxicity to Reproduction

Test substance: **Propionaldehyde**

Test species/strain: Sprague-Dawley rats.

Test method (e.g., OECD, others): **OECD combined repeated dose/reproductive toxicity study (one generation). Inhalation exposure to 0, 150, 750, 1500 ppm, 6 hr/day for 52 consecutive days for males and females prior to and during mating and through gestation day 20 in females.**

GLP:YES [X]
NO [ ]

Test results: **No significant effects were noted for any reproductive parameters. External examination of the offspring was unremarkable. A reproductive and developmental NOAEL of >1500 ppm (highest exposure tested) was indicated.**

Reference: **Union Carbide Corporation. 1992. Bushy Run Research Center Report 91U0086. Draft. June 17.**

5.9 Developmental Toxicity/Teratogenicity

Test substance: **Isobutanal**

Test species/strain: **Wistar Rats (25 mated females per exposure concentration)**

Test method (e.g., OECD, others): **OECD Guideline 412; Japan/MAFF Guideline; U.S. EPA TSCA 40 CFR §798.2450; EEC Guideline 92/69/EEC. Rats were exposed to concentrations of 1000, 2500 or 4000 ppm 6-hours a day on days 6 through 15 of gestation.**

GLP YES [X]
NO [ ]

Test results: **NOAEL for maternal animals: 3 mg/L (1000 ppm)**
NOAEL for offspring: 12 mg/L (4000 ppm)

Maternal general toxicity: **Decreased body weight gain; Lesions of nasal mucosa**

Pregnancy and litter data: **No substance related effects up to and including highest exposure concentration**

Foetal data (live/dead, sex, external defects, soft tissue and skeletal defects): **No substance related effects up to and including highest exposure concentration**

Comments: **Study conducted for OECD/SIDS Program**

Reference: **Garmer, A. O., Hellwig, J and B. Hildebrand (1996) "Isobutyraldehyde – Prenatal vapor inhalation Toxicity Study in Wistar Rats" BASF Aktiengesellschaft Department of Toxicology Project No.: 31R0140/93049. Ludwigshafen, Germany.**

5.10 Other Relevant Information

A. Specific Toxicities (Neurotoxicity, immunotoxicity etc.)

No data submitted

B. Toxicodynamics, Toxicokinetics

No data submitted

5.11a Experience with Human Exposure (give full description of study design, effects of accidental or occupational exposure, epidemiology)

Comment: **Odor threshold of aqueous solutions for normal individuals, 2.3 ppb, for anosmic individuals, 1190 ppb.**

Reference: **Amoore, J. E., Forrester,, L. J. and P. Pelosi (1976) Specific anosmia to isobutyraldehyde: The malty primary odor". *Chem. Senses Flavor* 2:17-25.**

5.11b Comment: **No irritation was experienced by 15 males exposed to 210 ppm (620 mg/m^3) of isobutyraldehyde for 30 minutes, however, nausea was noted by some subjects and one subject vomited.**

Reference: **Sim, V.M. and Pattle, R.E. (1957) Effect of possible smog irritants on human subjects. *J. Amer. Med. Assoc*. 165: 1908-1913. cited in: American Industrial Hygiene Association (2002) *Workplace Environmental Exposure Level Guide for Isobutyraldehyde*. American Industrial Hygiene Association, Fairfax, VA.**

6. RECOMMENDED PRECAUTIONS, CLASSIFICATION (use and/or transportation) and Safety Data Sheets.

MSDS available

7. AVAILABILITY AND REFERENCE (S) FOR EXISTING REVIEW

Available