

[FOREWORD](#)

[INTRODUCITON](#)

**3-METHYLBUTANAL**  
**CAS N°:590-86-3**

**SIDS Initial Assessment Report  
for SIAM 10  
(10-17 March 2000, Tokyo, Japan)**

**Chemical Name:** 3-Methyl butanal  
**CAS No:** 590-86-3  
**Sponsor Country:** Germany

**National SIDS Contact Point in Sponsor Country**

**Name of lead organization:** Umweltbundesamt  
**Contact person:** Dr Jan Ahlers  
**Address:** Postfach 330022  
14191 Berlin

**History:** The substance was selected in 1991. A testing plan was agreed in 1992 in conjunction with the chemical isobutyraldehyde (CAS 78-84-2). The SIAR was discussed at SIAM 9 and 10. Post-SIDS testing was considered necessary (mouse-micronucleus test). The revised SIAR including the new test results was agreed in 2001.

**Comments:**

## SIDS INITIAL ASSESSMENT PROFILE

<b>CAS No.</b>	590-86-3
<b>Chemical Name</b>	3-Methylbutanal (Isovaleraldehyde)
<b>Structural Formula</b>	$\text{CH}_3\text{-CH}(\text{CH}_3)\text{-CH}_2\text{-CHO}$
<b>RECOMMENDATIONS</b>	
The chemical is currently of low priority for further work.	
<b>SUMMARY CONCLUSIONS OF THE SIAR</b>	
<b>Human Health</b>	
<p>Isovaleraldehyde is an irritating fluid of unpleasant odor, which at excessive doses may be absorbed into the body via all routes of exposure (oral, dermal and inhalation). Under practical conditions the irritation potential and chemical reactivity, however, would preclude significant systemic absorption. Biotransformation occurs through the usual oxidative pathway, mediated by aldehyde dehydrogenase to isovaleric acid, which may be incorporated into the intermediary metabolism. Furthermore, isovaleric acid and – transiently - also isovaleraldehyde may arise from isovaleric alcohol (3-methylbutanol). For that reason, toxicity data from this alcohol and also from isovaleric acid may help in the assessment of potential systemic effects of isovaleraldehyde (i.e. this part of toxicity which is not mediated by the protein-reactive aldehyde function).</p> <p>Isovaleraldehyde is low in general acute toxicity after oral, dermal or inhalation exposure, is clearly irritating to the eyes and is strongly irritant to the skin under occlusive conditions. The material is not regarded as a potent sensitizer which is a common experience for aliphatic aldehydes with a single aldehyde function in the molecule supported by the negative animal data from the structural analogous aldehydes n-butyraldehyde, n-valeraldehyde and 2-methylbutanal. Studies with repeated exposure in animals (subchronic toxicity) do not exist with isovaleraldehyde. However, the relatively uniform toxicity profiles of aldehydes allow an estimation of these endpoints on the basis of data and results, which have been obtained during the investigation of other structurally related aldehydes, such as propionaldehyde, n-butyraldehyde and isobutyraldehyde. For systemic effects in the tested aldehydes the NOAEL for oral uptake is 300 mg/kg in rats, with effects on blood at &gt;600 mg/kg bw (n-butyraldehyde). For inhalation, the NOAELs with respect to systemic toxicity are <math>\geq 150</math> ppm. Effects observed were reduced food consumption in female rats at 750 ppm (propionaldehyde); no systemic effects were found up to the highest concentration of 2,000 ppm in rats (n-butyraldehyde). At 4,000 and 8,000 ppm body weight depression and mortality were observed in 13-week and 2-year studies in rats (isobutyraldehyde). In the metabolic precursor (3-methylbutanol-1) the only effects at the highest dose of 1,250 mg/kg (drinking water, rats) were blood effects. With respect to irritation, there is a clear dependency on molecule size, water solubility and LogPow, indicating a NOAEL for isovaleraldehyde of &gt; 51 ppm; butyraldehydes show a distinct lower irritating potential than propionaldehyde. The genotoxicity of isovaleraldehyde was investigated in-vitro with negative results in the Ames test and questionable results on SCE-rate in human lymphocytes. The substance did not show DNA-damaging activity in a Bacillus subtilis study (Rec-Assay). A mouse micronucleus test after intraperitoneal administration in doses up to 100 mg/kg body weight was clearly negative with respect to clastogenicity and impairment of chromosome distribution in the course of mitosis. Thus, there is no concern with respect to genotoxicity. At present, there is no concern for carcinogenic effects of isovaleraldehyde. The experiments with isobutyraldehyde indicate a LOAEL for non-neoplastic effects of 500 ppm with weak local effects in female rats. Prenatal toxicity investigations have been carried out with propionaldehyde in rats and isobutyraldehyde in rats and 3-methylbutanol-1 in rats and rabbits. In these studies no prenatal defects and no high systemic toxicity was observed; hence, also isovaleric</p>	

acid is not expected to exert prenatal toxicity. Isovaleric acid is, furthermore, also physiologically formed during the catabolism of leucine.

The NOAELs derived from the toxicological endpoints show no concern for the workplace, consumers and in relation to direct and indirect exposure from the environment.

#### **Environment**

3-Methylbutanal has a log Kow of 1.3, a water solubility of 20 g/l and a vapour pressure of 61 hPa. Based on the high vapour pressure of the substance isovaleraldehyde tends to pass from water to air. The compound does not tend to adsorb on sediment/soil or accumulate in biota. According to Mackay I the target compartment for this substance is the atmosphere.

It can be concluded that 3-methylbutanal is biologically readily degradable from a BOD5/COD ratio > 60 %.

Short-term tests with fish, daphnids and algae are available. For *Daphnia magna* EC50-values of 210 mg/l (24 h) and 177 mg/l (48 h) based on nominal concentrations were found. For *Scenedesmus subspicatus* a EC50 of 80 mg/l and a EC10 of 33 mg/l based on nominal concentrations was obtained in a 72h test. In a flow-through study with *Pimephales promelas* a 96h-LC50 of 3.25 mg/l was found based on measured concentrations. With an assessment factor of 1000 a PNEC<sub>aqua</sub> of 3.3 µg/l was derived.

#### **Exposure**

The production level of 3-methylbutanal (isovaleraldehyde) in Germany is in the range of 1000 - 5000 t/a. A certain amount is exported (no data about volumes). There is no information about import volumes. The chemical is used as an intermediate for pharmaceuticals, pesticides, solvents and softeners. Consumer exposure is not expected.

#### **NATURE OF FURTHER WORK RECOMMENDED**

No recommendation.

## FULL SIDS SUMMARY

CAS-NO.:590-86-3		SPECIES	PROTOCOL	RESULTS
PHYSICAL CHEMICAL				
2.1	Melting Point		NA	ca. -51 °C
2.2	Boiling Point		DIN 51 751	91 - 93°C (at 1013 hPa)
2.3	Density		NA	0.798 kg/m <sup>3</sup>
2.4	Vapour Pressure		NA	6100 Pa at 20°C
2.5	Partition Coefficient (Log Pow)		NA	1.318
2.6 A	Water solubility		NA	20 g/l at 20°C
ENVIRONMENTAL FATE / BIODEGRADATION				
3.1.1	Photodegradation		calc. (Atkinson)	In air T <sub>1/2</sub> = 0.6 days
3.3	Transport and Distribution		calculated (fugacity level 1 type)	in air: 90.06 % In water 9.91 % in soil 0.02 % in sediment 0.01 %
3.5	Biodegradation		BOD <sub>5</sub> /COD	readily biodegradable
ECOTOXICOLOGY (lowest effect concentrations only)				
4.1	acute/prolonged toxicity to fish	<i>Pimephales promelas</i>	NA	LC <sub>50</sub> (96hr) = 3.25 mg/l
4.2	acute/prolonged toxicity to aquatic invertebrates (daphnia)	<i>Daphnia magna</i>	84/449/EEC, C.2	EC <sub>50</sub> (48hr) = 177 mg/l
4.3	toxicity to aquatic plants e. g. algae	<i>Scenedesmus subspicatus</i>	DIN 38412 part 9	EC <sub>50</sub> (72 hr) = 80 mg/l
4.4	toxicity to microorganisms	<i>Pseudomonas putida</i>	NA	TGK (16 hr) =310 mg/l
TOXICOLOGY				
5.1.1	acute oral toxicity	Rat	Other	LD <sub>50</sub> > 5000 mg/kg
		Mouse	Other	LD <sub>50</sub> = 4750 mg/kg
5.1.2	acute inhalation toxicity	Rat	Other	LC <sub>50</sub> = 91000 mg/m <sup>3</sup> (vapor)
		Rat	Other	LC <sub>50</sub> < 57000 mg/m <sup>3</sup> (4 h) (vapor)

CAS-NO.:590-86-3		SPECIES	PROTOCOL	RESULTS
5.1.3	acute dermal toxicity	Mouse	Other	LC <sub>50</sub> = 51000 mg/m <sup>3</sup> (vapor)
		Rabbit	Other	LD <sub>50</sub> > 5000 mg/kg
5.4	repeated dose toxicity	Rabbit	Other	LD <sub>50</sub> 2730 mg/kg
		Rat	Close to OECD 413 (inhalation)	NOAEL: 51 ppm (12 weeks) (n-Butyraldehyde)
5.5	genetic toxicity in vitro  A) bacterial test (gene mutation)	Mice, rat	Close to OECD 408 (gavage)	300 mg/kg NOAEL's (90 days; systemic and irritative) (n-Butyraldehyde)
		Mice, rat	Close to OECD 413 (inhalation)	LOAEL (weak effects): 500 ppm (2 years) (Isobutylaldehyde)
		Rat	OECD 408 (drinking water)	NOAEL (3 months): males: 4000 ppm = 295 mg/kg females: 16000 ppm = 1430 mg/kg (2-Methyl-1- propanol)
		Salmonella typhimurium	Other	with/without metabolic activation: negative / negative
5.5	B) non-bacterial in vitro test (chromosomal aberrations)		Other	with/without metabolic activation: negative / negative
			Other	with/without metabolic activation: equivocal / equivocal
			no data	
5.5	C) other	Bacillus subtilis	Recombination Assay	with/without metabolic activation: negative / negative
		Human lymphocytes	SCE	with/without metabolic activation: not tested / equivocal
		5.6	genetic toxicity in vivo	Mouse
5.8	toxicity to reproduction	Rat	Close to OECD 413 (inhalation)	No effect on sex organs (12 weeks) (n-Butyraldehyde)

CAS-NO.:590-86-3		SPECIES	PROTOCOL	RESULTS
5.9	developmental toxicity / teratogenicity	Rat	OECD 408 (drinking water)	No effect on sex organs at 1068 (males) and 1431 (females) mg/kg (3 months) (3-Methyl-1-propanol)
		Rat	Close to OECD 413 (inhalation)	No effect on sex organs at 4000 ppm (m) and 2000 ppm (f) (13 weeks) (Isobutyraldehyde)
		Rat	Screening	LOAEL: 500 ppm (13 weeks) (Isobutyraldehyde)
		Rat	OECD 422	NOAEL: 1,500 ppm (Propionaldehyde)
		Rat	OECD 414 (inhalation)	NOAEL (fetal) 4000 ppm (= 12 mg/l)  NOAEL (maternal) 1000 ppm (Isobutyraldehyde)
		Rat, rabbit	OECD 414 (inhalation)	NOAEL (fetal): 10 mg/l (3-Methylbutanol-1)
5.11	experience with human exposure		OECD 422	NOAEL: 1,500 ppm (Propionaldehyde)
			no data	

## **SIDS Initial Assessment Report**

### **1. Identity**

Name: Butanal, 3-methyl-

Cas-No.: 590-86-3

Empirical formula:  $C_5H_{10}O$

Structural formula:  $CH_3-CH(CH_3)-CH_2-CHO$

Synonyms: 3-Methylbutanal  
Isovaleraldehyde  
Isoamylaldehyde

## 2. General Information on Exposure

The production level of isovaleraldehyde in Germany is in the range of 1000 - 5000 t/a. A certain amount is exported (no data about volumes). There is no information about import volumes.

Data on production volumes in other countries are not available.

The compound is produced and used in closed systems. It is used as an intermediate for pharmaceuticals, pesticides, solvents and softeners.

Isovaleraldehyde being an intermediate, exposure would happen at production and processing sites.

According to the German manufacturer, all exhaust gases are burnt in an incinerator. There is no information about waste water emissions.

The compound also occurs as natural aroma component in fruits, vegetables and beverages (0.02 up to 8.3 ppm; Arctander, 1969. and Maarse, H., 1991). Only very small amounts (0.1%) of total production are used as aroma components in food, which might have a total concentration of 0.5 –5 ppm.

Though isovaleraldehyde is allowed in cosmetic products (EU, 1996), there is no detailed information on its actual use.

### 3. Environment

#### 3.1 Environmental Exposure

##### 3.1.1 General Discussion

Isovaleraldehyde is soluble in water at 20,000 mg/l (20°C) and has a vapour pressure of 6100 Pa at 20°C. Based on these data a Henry-constant of  $26.3 \text{ Pa}\cdot\text{m}^3\cdot\text{mol}^{-1}$  is calculated.

Its measured log Pow of 1.31 indicates that there is no considerable potential for bio- or geoaccumulation.

Based on these physico-chemical properties, the preferred environmental compartment is the atmosphere (Mackay I: 90.06 %) The compound does not tend to adsorb on sediment/soil or accumulate in biota.

From a BOD<sub>5</sub>/COD ratio of > 60 % it can be concluded that isovaleraldehyde is biologically readily degradable. Although it was not possible to validate the test result, it is assumed for the risk assessment that isovaleraldehyde is readily biodegradable. One reason for this assumption is that the structural analogue isobutyraldehyde has been shown to be readily biodegradable in several tests. In addition because of the high vapour pressure of the substance volatilization plays a significant role for elimination in a sewage treatment plant. Hydrolytic degradation or direct photodegradation in the hydrosphere are not to be expected. According to the model SIMPLETREAT, in waste water treatment plants a removal rate of 89 % is predicted.

The half-life due to photochemical-oxidative degradation in the atmosphere is between 13 and 20 hours.

##### 3.1.2 Predicted Environmental Concentration

Because there is no information about waste water emissions during production and processing, we would consider the following worst case scenario according to the EU Technical Guidance Documents:

For chemicals only used as intermediates, a release fraction of 1% of the production volume into the waste water is assumed for production and processing. Based on a maximum production volume of 5,000 t/a, a total amount of 50 t/a is emitted into the sewage. With an elimination factor of 89% in the treatment plant, 5.5 t/a are emitted into the river Rhine (near the site). In this model a flow of 734 m<sup>3</sup>/s (10%-ile) for the river Rhine is used.

Assuming production/processing during 300 d/a, the predicted environmental concentration is

$$\text{PEC} = \frac{5.5 \cdot 10^6 \text{ g}}{1.9 \cdot 10^{13} \text{ l}} = 0.29 \text{ } \mu\text{g/l}$$

## 3.2 Effects on the Environment

### 3.2.1 Aquatic effects

#### Available data

The following ecotoxic effect concentrations, corresponding to the aquatic compartment, are available:

#### a) toxicity to fish

<i>Pimephales promelas</i>	96h-LC <sub>50</sub>	3.25 mg/l	(Geiger et al. 1984/85)
(flow-through, measured concentration)			
<i>Leuciscus idus</i>	96h-LC <sub>50</sub>	53 mg/l	(BASF 1989a)
(static, nominal concentration)			
<i>Poecilia reticulata</i>	14d-LC <sub>50</sub>	13.3 mg/l	(Deneer et al. 1988)
(semi-static, measured concentration)			

#### b) toxicity to crustaceans

<i>Daphnia magna</i>	24h-EC <sub>50</sub>	210.0 mg/l	(BASF 1989b)
"	48h-EC <sub>50</sub>	176.8 mg/l	
(nominal concentration, effect: immobilization)			

#### c) toxicity to algae

<i>Scenedesmus subspicatus</i>	72h-E <sub>b</sub> C <sub>10</sub>	33.0 mg/l	(BASF 1989c)
"	96h-E <sub>b</sub> C <sub>10</sub>	38.0 mg/l	
"	72h-E <sub>b</sub> C <sub>50</sub>	80.0 mg/l	
"	96h-E <sub>b</sub> C <sub>50</sub>	78.0 mg/l	
(nominal concentration, effect: growth inhibition)			

#### d) toxicity to bacteria

<i>Pseudomonas putida</i>	16h-EC <sub>10</sub>	310 mg/l	(BASF 1989d)
(nominal concentration, effect: growth inhibition)			

#### Determination of PNEC<sub>aqua</sub>

According to the EU Technical Guidance Document, the value of the assessment factor F is to be determined to 1000 for the aquatic compartment, as data from short-term toxicity tests with species from 3 trophic levels are available. Applying this factor on the effect value derived for the most sensitive species (*Pimephales promelas*, 96h-LC<sub>50</sub> = 3.25 mg/l) the following PNEC is calculated:

$$\text{PNEC} = 3,250 \mu\text{g/l} / 1000 = \mathbf{3.25 \mu\text{g/l}}$$

### 3.2.2 Terrestrial organisms

There are no data available on terrestrial organisms.

### 3.3 Initial Assessment for the Environment

The following PEC/PNEC ratio for the German production and processing site can be calculated:

$$0.29 \mu\text{g/l} / 3.25 \mu\text{g/l} = 0.089$$

As the ratio is lower than 1, isovaleraldehyde represents presently no significant hazard for the aquatic compartment.

The use pattern of isovaleraldehyde does not suggest an exposure of the terrestrial compartment. Therefore a significant hazard to the terrestrial compartment is presently not to be expected.

## 4. Human Health

### 4.1 Effects on Humans

#### 4.1.1 Acute toxicity

Several studies on oral, inhalation and dermal administration route are available, mostly only in tabular (summarized) form. Description and documentation of these mostly fairly old investigations do not comply with today's GLP requirements; e.g. purity of test substance and concentrations administered were rarely reported; details on strain, number of animals and dose groups were mostly missing.

Signs and symptoms, as far as reported, appear to be sequels of gastric ulceration, peritoneal inflammation and exsiccosis.

##### 4.1.1.1 Acute oral toxicity

The following LD<sub>50</sub> values were reported:

- LD<sub>50</sub> rat > 3,200 mg/kg bw (Patty, 1994)
- LD<sub>50</sub> rat > 5,000 mg/kg bw (Ford, 1988)
- LD<sub>50</sub> rat 6,200 mg/kg bw (7,200 µl/kg) in 2 – 30% aqueous emulsion (BASF, 1973)
- LD<sub>50</sub> rat 7,660 mg/kg bw (8,910 µl/kg; Carpenter et al., 1974)
- LD<sub>50</sub> guinea pig 2,950 mg/kg bw (Safronkina et al., 1987)
- LD<sub>50</sub> mouse 4,750 mg/kg bw (Safronkina et al., 1987)

##### 4.1.1.2 Acute inhalation toxicity

The following LC<sub>50</sub> data were reported:

- LC<sub>50</sub> rat 91 mg/l; exposure duration unclear (Safronkina et al., 1987)
- LC<sub>50</sub> mouse 51 mg/l (exposure time?): Safronkina et al., 1987)
- LC<sub>50</sub> mouse approx. 6.2 mg/l/10 h (Salem and Cullumbine, 1960)
- LC<sub>50</sub> guinea pigs approx. 6.2 mg/l/10 h (Salem and Cullumbine, 1960)
- LC<sub>50</sub> rabbit > 6.2 mg/l/10 h (Salem and Cullumbine, 1960)
- LC<sub>50</sub> rat < 16,000 ppm/l/4 h (Carpenter et al., 1974)
- IRT\* rat: no mortality after 15-minute exposure towards saturated vapor concentrations; mortality after longer exposure times (Carpenter et al., 1974)
- IRT\* rat, 30 min.: no mortality after 10 minutes; mortality after longer exposure times (BASF, 1974)

Sensoric irritation (50% decrease of respiration rate; 10 min.) in B6C3F1 und Swiss-Webster mice was reported as RD<sub>50</sub> concentrations of 2.7 and 3.6 mg/l (Steinhagen and Barrow, 1984).

---

\* IRT = Inhalation risk test; results depending on toxicity and volatility

#### 4.1.1.3 Acute dermal toxicity

The following LD<sub>50</sub> data were reported:

- LD<sub>50</sub> rabbit 2,730 mg/kg (3,180 µl/kg; (Carpenter et al., 1974)
- LD<sub>50</sub> rabbit > 5,000 mg/kg (Ford, 1988)
- LD<sub>50</sub> guinea pig > 10 ml/kg (Patty, 1994)

#### 4.1.1.4. Experience in humans:

Wilkinson (1940) reported an instance in which several persons distilling isovaleraldehyde experienced chest discomfort, nausea, vomiting and headaches. The odor of the material was very pronounced, exposure was supposed to be high; all persons recovered completely in the subsequent days.

#### Conclusion:

In summary, acute toxicity is low.

### 4.1.2 Corrosiveness and irritation

#### 4.1.2.1 Skin

Isovaleraldehyde (in concentrated form) was found to be strongly irritant to rabbit skin after 24-hour occlusive dermal administration (BASF, 1973; Ford, 1988).

In earlier reports on studies in rabbits (Carpenter et al., 1974) and guinea pigs (Patty, 1994) slight to moderate irritation was found; however, due to the poor description of test substance and experiments, it is not clear whether the material was allowed to evaporize.

According to Bagley et al. (1996), isovaleraldehyde (> 98.5%) was tested in rabbits for 4 hours under semiocclusive conditions under OECD guideline 404 and evaluated with a primary irritation index of 2.83.

#### 4.1.2.2 Eye irritation

The material was found to be irritating to eyes according to Draize scoring (4/10) in rabbits (Carpenter et al., 1974). Marked irritation was also found in another experiment (BASF, 1973).

#### Conclusion:

Isovaleraldehyde is clearly irritating to the eyes.

Isovaleraldehyde is strongly irritant to the skin under occlusive conditions. The irritation potential under semiocclusive conditions (OECD 404) is slight to moderate.

### 4.1.3 Sensitization

No animal experiments of sensitization are available.

Dermal sensitization was examined in 29 volunteers in a maximization test with a 1% solution in petrolatum. Under those conditions, there was no dermal sensitization. This may not totally preclude a hazard of sensitization of the concentrated material after repeated exposure; however, the material is not regarded as a potent sensitizer which is a common experience for aliphatic aldehydes with a single aldehyde function in the molecule.

From structural analogues there are negative data: A Buehler test in guinea pigs was negative for **n-butyraldehyde** (see Annex 1), for **n-valeraldehyde** there is a negative maximization test in guinea pigs (see Annex 1) and for the isomer **2-methylbutanal** there is a negative maximization test in humans (see Annex 1).

#### 4.1.4 Repeated dose toxicity

No studies exist with isovaleraldehyde.

General comment:

In 1990 (SIAM) it was decided that aldehydes are to be considered as a class in which one (or several closely related) chemical(s) may serve as a surrogate. In 1991 OECD decided that concerning isobutyraldehyde and isovaleraldehyde a developmental toxicity by inhalation route on isobutyraldehyde was sufficient. According to the OECD SIAM group on existing chemicals in 02/1994 it was pointed out that "a DE-US joint combined testing for both of these chemicals (isovaleraldehyde and isobutyraldehyde) has been developed. This followed the philosophy of the SIDS Manual, where reduced test requirements can be applied for closely related homologous and relevant precursors.

Aldehydes have a consistent profile of the aldehyde function due to electronegativity, decreasing with increasing chain length. Protein binding is due to this electronegativity and the resulting cytotoxicity. Water solubility and Log Pow are of similar orders of magnitude and with regard to similar molecular size, the conclusion that toxicity data can be cross-read is supported, especially for butyraldehydes (n- and iso-) (Annex 1).

**Propionaldehyde** showed a NOAEL for systemic toxicity of 150 ppm in a combined OECD/SIDS study (No. 422); at 750 ppm, only decreased food consumption in females was seen (SIAR).

For irritation (nasal damage) the LOAEL was 150 ppm.

There are two subchronic gavage studies on **n-butyraldehyde** available (Hazleton, 1986), which were peer-reviewed (NTP, 1987). The test material was administered to rats and mice at dose levels of 75, 150, 300, 600 and 1,200 mg/kg bw/d over 13 weeks. Increased lethality was observed throughout all dose groups (in rats 100% at 1,200 mg/kg bw/d), yet the deaths were regarded as gavage-related. Gastric ulceration was a frequent finding, furthermore, inflammatory lesions in the nasal cavity, both lesions resulting from a direct effect of the (irritating) compound on the mucosal epithelium of both tissues. An increase of alanine aminotransferase (male animals) and a decrease in the alkaline phosphatase levels (female animals) were found at 600 mg/kg bw/d. An increase in reticulocyte count, absolute reticulocyte and alkaline phosphatase levels was recorded only at 75 mg/kg bw/d in male mice; these findings, however, are regarded as incidental findings since at high doses no respective effect could be detected. With respect to systemic and local irritative effects, the NOAEL was 300 mg/kg bw/d for both male and female rats. In mice the NOAEL with respect to systemic effects was 600 mg/kg bw/d, taking into account also local irritative effects the NOAEL is 300 mg/kg bw/d.

Male and female Sprague-Dawley rats were exposed 6h/day, 5 d/week for 13 weeks to **n-butylaldehyde** vapor in concentrations of 125, 500 and 2,000 ppm (0.34, 1.36, 5.44 mg/l). There was a full investigation with respect to body and organ weights, urinalysis, blood chemistry, pathology and hematological examinations. Rats of all concentrations had a significant incidence of squamous metaplasia of mucosal epithelium, rhinitis and initial goblet cell atrophy followed by goblet cell hyperplasia. These alterations were more severe in rats sacrificed after 6 weeks of exposure than in those sacrificed after 13 weeks of exposure. The changes are indicative of a response to repeated upper respiratory tract irritation. In none of the other parameters investigated or organs any significant differences were found between test and control groups which could be related to inhalation of n-butylaldehyde vapor concentrations, i.e. no systemic toxicity was found (Ballantyne et al., 1986). Thus, the NOAEL with respect to systemic toxicity is > 2,000 ppm, with respect to irritative effects < 125 ppm.

A follow-up study with 51.3, 10.3 and 1.1 ppm (151, 30, 3.2 mg/m<sup>3</sup>) in 15 male and female rats with a similar study design was performed in order to find also a NOAEL for effects on the upper respiratory tract. Histopathological findings indicated that no specific adverse effects could be attributed to **n-butylaldehyde**. A NOAEL of 51 ppm was therefore be derived from this study for irritation (Ballantyne et al., 1986).

In a similar study (125, 500 and 2,000 ppm; **n-butylaldehyde**; s. a.) with dogs over 14 weeks besides analogous responses to the upper respiratory tract no systemic effects were found in any dose group (Ballantyne et al., 1986).

**Isobutylaldehyde** was administered by inhalation (whole-body exposure) to rats and mice up to 13 weeks or 2 years in concentrations of 0; 500; 1,000; 2,000; 4,000 or 8,000 ppm; complete necropsy and histopathological examinations were performed. In the 13-week studies substance-related body weight depressions and deaths occurred in rats and mice at 4,000 and 8,000 ppm. At 2,000 ppm the rats showed lesions in the nose (olfactory epithelium degeneration), at 4,000 ppm in addition hyperplasia (epithelium), squamous metaplasia, osteodystrophy of turbinate bone and inflammation and severe necrosis at 8,000 ppm in respiratory tract. No other effects in organs/tissues were detected. Data on clinical chemistry/ hematology were not given. In mice increased incidences of non-neoplastic lesions of the nasal mucosa and nasal turbinate bone were observed at 500 ppm (only minor effects) and at the higher concentrations. Other singular effects (organ weights of liver, kidney, thymus) were not regarded as substance-related due to lack of dose response and the absence of a histopathological correlate.

In the course of a prenatal study in rats (s. chapter 4.1.7) 1,000 ppm did not show adverse effects.

Thus, a NOAEL of 1,000 ppm can be derived for rats and a LOAEL of 500 ppm with only weak effects in female mice (Abdo et al., 1998). **3-methylbutanol-1** is a metabolic precursor of isovaleraldehyde and is biotransformed in an oxidative pathway to isovaleraldehyde and readily further oxidized to isovaleric acid. This means that isovaleraldehyde and 3-methylbutanol-1 have the same common metabolite which is inherently assessed in the 3-methylbutanol-1 study. For the intermediary isovaleraldehyde no high bioavailability is assumed.

For estimation of the systemic toxicity of metabolic sequel products of isovaleraldehyde, a 3-month drinking water study with the precursor **3-methylbutanol-1** in rats is available. Though there are no quantitative kinetic data in this case, the mechanism of the oxidative metabolism from alcohols to aldehydes is well known.

A 3-month drinking water study (OECD 408) was performed with **3-methylbutanol-1** with doses of 16,000 ppm (1,250 mg/kg bw/d); 4,000 ppm (340 mg/kg bw/d) and

1,000 ppm (about 80 mg/kg bw/d). In the highest dose group the only effects were increase in red blood cells (males) and decrease in the mean corpuscular volume and mean corpuscular hemoglobin (males). The NOAEL of 340 mg/kg bw/d was established (BASF, 1991; Schilling et al., 1997).

### **Conclusion:**

For systemic effects in the tested aldehydes the NOAEL for oral uptake is 300 mg/kg bw/d.

For inhalation, the NOAELs with respect to systemic toxicity are  $\geq 150$  ppm. With respect to irritation, there is a clear dependency on molecule size, water solubility and Log Pow, indicating a NOAEL for isovaleraldehyde of  $> 51$  ppm; butyraldehydes show a distinct lower irritating potential than propionaldehyde.

It appears reasonable to postulate a similar profile for isovaleraldehyde as for n-butyraldehyde and isobutyraldehyde with nasal irritation as critical effect in the lower dose range. In analogy to n-butyraldehyde one may assume a NOAEL for isovaleraldehyde in the same order of magnitude (ca. 50 ppm). Furthermore, isovaleraldehyde is slightly less electrophilic and less chemically reactive than n-butyraldehyde and therefore also considered to exert less irritating properties.

## **4.1.5 Genetic toxicity in vitro**

### **4.1.5.1 In vitro investigations**

Three Ames test results with isovaleraldehyde are available, conducted with and without metabolic activation:

Florin et al. (1979) tested isovaleraldehyde in *S. typhimurium* strains TA 98, 100, 1535, 1537 in concentrations of 0.03, 0.3, 3 and 30  $\mu\text{mol}/\text{plate}$ ; no increase in the number of revertants were found.

Aeschbacher et al. (1989) tested isovaleraldehyde in *S. typhimurium* strains TA 98, 100, 102 in concentrations of 0,01 - 1,000  $\text{nmol}/\text{plate}$ ; there was no increase in the number of revertants.

Kamiya and Ose (1989) found equivocal results in a poorly described experiment in *S. typhimurium* strains TA 98, 100, 104.

In a *Bacillus subtilis* study (Rec-Assay), Matsui et al. (1989) did not find DNA-damaging activity in concentrations of 1.03 - 1.99  $\text{mg}/\text{l}$ , with and without metabolic activation.

A sister chromatid exchange study in human lymphocytes gave equivocal results (Obe and Beck, 1979). The concentrations were 0.002 - 0.003%; no metabolic activation was employed.

### **4.1.5.2 In vivo investigations**

In a mouse micronucleus test after single intraperitoneal administration according to OECD No. 474 isovaleraldehyde does not have any chromosome-damaging (clastogenic) effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis. The test substance was administered once to male animals at dose levels of 25  $\text{mg}/\text{kg}$  bw, 50  $\text{mg}/\text{kg}$  bw and 100  $\text{mg}/\text{kg}$  bw. The administration of the test substance

led to evident signs of toxicity (piloerection, squatting posture, poor general state) (BASF 2001).

**Conclusion:**

Since isovaleraldehyde was clearly negative in the Ames test and in an in vivo mouse micronucleus test there is no concern with respect to genotoxicity.

**4.1.6 Carcinogenicity**

No data are available with isovaleraldehyde.

However, a 2-year inhalation study in rats and mice with **isobutyraldehyde** is published employing 500, 1,000 and 2,000 ppm for the chronic exposure regimen (Abdo et al., 1998). No biologically significant increase in tumors was observed in this study. At 500 ppm there was still a slight nasal metaplasia among the female rats. In the subchronic studies (4.1.4) female mice showed a decrease of relative liver weights at 500 ppm; this was not recorded in the chronic experiment.

**Conclusion:**

At present, there is no concern for carcinogenic effects of isovaleraldehyde. The experiments with isobutyraldehyde indicate a LOAEL for non-neoplastic effects of 500 ppm with weak local effects in female rats.

**4.1.7 Developmental toxicity**

No data are available with isovaleraldehyde.

According to the decision of SIAM (1990) structurally related substances can be used, especially "that concerning isobutyraldehyde and isovaleraldehyde a developmental toxicity study by inhalation route on isobutyraldehyde was sufficient" (see general comment 4.1.4.).

Data are available for **propionaldehyde** and **isobutyraldehyde**:

**Propionaldehyde** "does not have specific adverse effects on the reproductive capabilities of either male or female rats and does not produce specific adverse effects on the developing offspring of laboratory animals". It showed a NOAEL in a OECD/SIDS combined study (No. 422) of 1,500 ppm (SIAR).

A prenatal toxicity study (OECD 414) with **isobutyraldehyde** in Wistar rats was carried out after inhalation exposure towards 1,000, 2,500 and 4,000 ppm (3, 7.6 and 12 mg/l; 6 h/day; day 6 – 15 p.c., 25 pregnant animals per group). In the two higher exposure groups there were some signs of maternal toxicity, i.e. reduced body weights. No other findings were recorded during the course of this study. The fetal NOAEL was evaluated as 4,000 ppm; the NOAEL for maternal toxicity is 1,000 ppm (BASF; 1995).

A prenatal toxicity study of a metabolic precursor of isovaleraldehyde, **3-methylbutanol-1**, may be used as a further surrogate for the following reason:

3-methylbutanol-1 is biotransformed in an oxidative pathway to isovaleraldehyde and readily further oxidized to isovaleric acid. Though there are no quantitative kinetic data in this case, the mechanism of the oxidative metabolism from alcohols to aldehydes is well

known. This means that isovaleraldehyde and 3-methylbutanol-1 have the same common ultimate metabolite which is inherently assessed in the 3-methylbutanol-1 study. For the intermediary isovaleraldehyde no high bioavailability is assumed. 3-methylbutanol-1 caused no prenatal toxicity in rats and rabbits and no other form of unexpected systemic toxicity at inhalation exposure levels up to 10 mg/l (OECD guideline 414; BASF, 1988/1990; Klimisch und Hellwig, 1995). This implies that 3-methylbutanol-1 is devoid of selective fetal toxicity.

Furthermore, isovaleric acid is also physiologically formed during the catabolism of leucine and occurs naturally in many edible plants (Patty, 1994).

### **Conclusion:**

From the data of the structurally related propionaldehyde and isobutyraldehyde it is concluded that isovaleraldehyde is highly unlikely to cause selective fetal toxicity. The metabolic sequel product of isovaleraldehyde, isovaleric acid, is also assumed to be devoid of prenatal toxicity. This conclusion may be derived from studies with 3-methylbutanol-1 in rats and rabbits. No additional investigations are necessary.

NOAEL > 1,500 ppm (propionaldehyde) in OECD/SIDS combined inhalation study (No. 422) and the fetal NOAEL as 4,000 ppm and maternal NOAEL as 1,000 ppm for isobutyraldehyde (OECD No. 414).

#### **4.1.8 Effects on fertility**

No data are available with isovaleraldehyde.

(see general comments 4.1.4.).

For **propionaldehyde** a NOAEL in a OECD/SIDS combined study (No. 422) of 1,500 ppm was established (SIAR).

Subchronic and chronic investigations with **isobutyraldehyde** (Morrissey et al., 1988; Abdo et al., 1998) did not indicate testicular or ovarian toxicity. In one study (Morrissey et al., 1988) epididymal weight was adversely affected at high dose levels, but this may have been a secondary, stress-related phenomenon.

Furthermore, the studies available on **n-butyraldehyde** and **3-methylbutanol-1** (see chapter 4.1.4 Repeated dose toxicity) did not record toxic effects on sex organs.

### **Conclusion:**

There is at present no concern for adverse effects of isovaleraldehyde on fertility.

## **4.2 Risk characterization**

### **4.2.0 General aspects**

Isovaleraldehyde is an irritating fluid of unpleasant odor, which at excessive doses may be absorbed into the body via all routes of exposure (oral, dermal and inhalation). Under practical conditions the irritation potential and chemical reactivity, however, would preclude significant systemic absorption.

Biotransformation occurs through the usual oxidative pathway, mediated by aldehyde dehydrogenase to isovaleric acid, which may be incorporated into the intermediary metabolism.

Furthermore, isovaleric acid and - transiently - also isovaleraldehyde may arise from Isovaleric alcohol (**3-methylbutanol**). For that reason, toxicity data from this alcohol may help in the assessment of potential systemic effects of isovaleraldehyde (i.e. this part of toxicity which is not mediated by the protein-reactive aldehyde function).

Isovaleric aldehyde is low in general acute toxicity and shows an irritation potential to skin and mucous membranes.

Dermal sensitization was examined in 29 volunteers in a maximization test with a 1% solution in petrolatum. Under those conditions, there was no dermal sensitization. This may not totally preclude a hazard of sensitization of the concentrated material after repeated exposure, however, the material is not regarded as a potent sensitizer which is a common experience for aliphatic aldehydes with a single aldehyde function in the molecule.

Studies with repeated exposure in animals (subchronic toxicity) do not exist with isovaleraldehyde. However, the relatively uniform toxicity profiles of aldehydes allow an estimation of these endpoints on the basis of data and results, which have been obtained during the investigation of other structurally related aldehydes, such as **propionaldehyde**, **n-butyraldehyde** and **isobutyraldehyde**:

Prenatal toxicity investigations have been carried out with **propionaldehyde** in rats and **isobutyraldehyde** in rats and **3-methylbutanol-1** in rats and rabbits. In these studies no prenatal defects and no high systemic toxicity was observed; hence, also isovaleric acid is not expected to exert prenatal toxicity. Isovaleric acid is, furthermore, also physiologically formed during the catabolism of leucine.

The genotoxicity of isovaleraldehyde was investigated in-vitro with negative results in the Ames test and questionable results on SCE-rate in human lymphocytes. The material did not show DNA-damaging activity in a *Bacillus subtilis* test (Rec-Assay). Isovaleraldehyde was clearly negative in an in vivo mouse micronucleus test. Thus, there is no concern for genotoxicity.

Carcinogenicity data are only available with **isobutyraldehyde**. At present, there is no concern for carcinogenic effects of isovaleraldehyde.

#### 4.2.1 Workers

##### 4.2.1.1 Critical toxicity in the case of dermal exposure

Isovaleraldehyde is a dermal irritant and may cause irritation to the skin after exposure to higher concentrations of the material, especially when repeated. No systemic effects are to be expected from this administration route under practical work conditions, due to the irritation potential. Uncontrolled dermal exposure is to be avoided.

##### 4.2.1.2 Critical toxicity due to inhalation exposure

In order to convert these data into a human health risk assessment in the workplace, the NOAEL of 50 ppm may be combined with a default factor of 5 (resulting from a factor of 2 - 3 in order to extrapolate for subchronic to chronic exposure and of 2 for potential intra-species variations). 10 ppm are therefore considered as a safe level.

An inter-species extrapolation factor in order to compensate for the different metabolic rates of rats and humans is not necessary, since in the course of inhalation exposure experiments, small rodents inhale more material per kg bw than humans, due to their higher respiratory rate which is related to the higher metabolic rate of smaller animal.

#### **Conclusion for risks due to inhalation exposure:**

Inhalation exposure appears to be the most important route. As has been shown with other aldehydes, the rat model appears to be sufficiently conservative for humans in order to protect against the local (nasal) toxicity, allowing to derive from a NOAEL of 50 ppm for a safe level of 10 ppm.

Under practical conditions, the workplace today it is not expected to offer such exposure levels unless for short moments. This is also suggested by current values of exposure measurements.

#### **4.2.2 Consumers**

Consumer exposure from food and possibly via cosmetics is very low (order of micro g/kg bw/d) and with respect to the NOAELs derived there is no concern for consumers.

#### **4.2.3 Man exposed indirectly via the environment**

The total exposure via air, drinking water and fruits is estimated to be lower than that of acetic aldehyde, which occurs in ambient air (indoor) and in fruit and vegetable nutrients. The reactivity of isovaleraldehyde is regarded to be lower than that of acetaldehyde. This difference is equivalent to a kind of safety margin for this material when compared to levels of acetic aldehyde. The ratios expected from environmental exposure levels and the no adverse effect levels in animal studies already exhibit high margins of safety.

Isovaleraldehyde is of no concern in relation to indirect exposure from the environment. There is at present no need for further investigations, for further testing of specific risk reduction measures beyond those which have been applied already.

## 5. Conclusions and Recommendations

### 5.1 Conclusions

#### Environment:

The risk assessment for the aquatic compartment showed that the calculated PEC/PNEC ratio is lower than 1. On the whole, isovaleraldehyde is of low concern to the environment.

#### Human Health:

Isovaleraldehyde is low in general acute toxicity after oral, dermal or inhalation exposure, is clearly irritating to the eyes and is strongly irritant to the skin under occlusive conditions. The material is not regarded as a potent sensitizer which is a common experience for aliphatic aldehydes with a single aldehyde function in the molecule supported by the negative animal data from the structural analogous aldehydes n-butylaldehyde, n-valeraldehyde and 2-methylbutanal. Studies with repeated exposure in animals (subchronic toxicity) do not exist with isovaleraldehyde. However, the relatively uniform toxicity profiles of aldehydes allow an estimation of these endpoints on the basis of data and results, which have been obtained during the investigation of other structurally related aldehydes, such as propionaldehyde, n-butylaldehyde and isobutylaldehyde: For systemic effects in the tested aldehydes the NOAEL for oral uptake is 300 mg/kg bw/d (n-butylaldehyde). For inhalation, the NOAELs with respect to systemic toxicity are  $\geq 150$  ppm. With respect to irritation, there is a clear dependency on molecule size, water solubility and Log Pow, indicating a NOAEL for isovaleraldehyde of  $> 51$  ppm; butylaldehydes show a distinct lower irritating potential than propionaldehyde. The genotoxicity of isovaleraldehyde was investigated in-vitro with negative results in the Ames test and questionable results on SCE-rate in human lymphocytes. The material did not show DNA-damaging activity in a Bacillus subtilis test (Rec-Assay). An in vivo micronucleus study (mouse) which was performed to clarify the genotoxic potential of isovaleraldehyde is clearly negative: Isovaleraldehyde did not show any chromosome-damaging (clastogenic) effects and did not show indications of any impairment of chromosome distribution in the course of mitosis. Thus, there is no concern with respect to genotoxicity. At present, there is no concern for carcinogenic effects of isovaleraldehyde. The experiments with isobutylaldehyde indicate a LOAEL for non-neoplastic effects of 500 ppm with weak local effects in female rats. Prenatal toxicity investigations have been carried out with propionaldehyde in rats and isobutylaldehyde in rats and 3-methylbutanol-1 in rats and rabbits. In these studies no prenatal defects and no high systemic toxicity was observed; hence, also isovaleric acid is not expected to exert prenatal toxicity. Isovaleric acid is, furthermore, also physiologically formed during the catabolism of leucine.

The NOAELs derived from the toxicological endpoints show no concern for the workplace, consumers and in relation to direct and indirect exposure from the environment.

### 5.2 Recommendations

No recommendation.

## 6. References

- Abdo, K.M. et al., *Toxicol. Sci.* 42, 136-151, 1998
- Aeschbacher, H.U. et al., *Food Chem. Toxicol.* 27, 217 - 232, 1989
- Arctander, S.; *Perfume and flavor chemicals*; Montclair, N.J., 1969
- Bagley, D.M. et al., *Toxicol. in Vitro* 10, 1 – 6, 1996
- Ballantyne, B. et al., *The Toxicologist* 6, 59, 1986
- BASF AG, Isovaleraldehyd – Gewerbetoxikologische Vorprüfung (Reports XXIII/198 and 533), 1973/1974
- BASF AG, studies (88/56) for BG Chemie, Heidelberg (1988/1990)
- BASF AG 1989a: unpublished data
- BASF AG 1989b: unpublished data
- BASF AG 1989c: unpublished data
- BASF AG 1989d: unpublished data
- BASF AG, study (88/56) for BG Chemie, Heidelberg (1991)
- BASF AG, 1995: unpublished data
- BASF AG 2001: unpublished data
- Biodynamics Inc. (1979): Report to Monsanto, available as TSCAT-OTS Doc. 0517382
- Carpenter, C.P. et al., *TAP* 28, 313 - 319, 1974
- Deneer, J.W. et al., *Aquatic Toxicology* 12, 185-192, 1988
- Dupont (1978/1992): Reports to EPA, available under TSCATs OTS 0517708 and 0571318
- Florin, J. et al., *Toxicol.* 15, 119 - 132, 1979
- Ford, R.F., *Food and Chem. Toxicol.* 26, 273 – 417, 1988
- Geiger D.L. et al. 1984/85: Acute toxicities of organic chemicals to fathead minnows (*Pimephales promelas*), Vols. I and II, Center for Lake Superior Environmental Studies, University of Wisconsin-Superior, Superior, Wisconsin, 414, 326 pp (cited in Protic M., Sabljic A. 1989: Quantitative structure-activity relationships of acute toxicity of commercial chemicals on fathead minnows: effect of molecular size, *Aquatic Toxicology* 14, 47-64)
- Hazleton Laboratories America Inc. (1986): Reports to NTP

- Kamiya, A. and Ose, Y., *Sci. Total Environment* 78, 131 - 145, 1989
- Klimisch, H.J. and Hellwig, J., *Fund. Appl. Toxicol.* 27, 77 – 89, 1995
- Maarse, H. et al., *Volatile compounds in food; Qualitative and quantitative data; Supplement 2 and cumulative index.* TNO, The Netherlands, 1991
- Matsui, S. et al., *Wat. Sci. Techn.* 21, 875 - 887, 1989
- Morrissey, R.E. et al., *Fund. Appl. Toxicol.* 11, 343 – 358, 1988
- NTP, National Toxicology Program (USA), TSCAT OTS 0516688, 1987 Obe, G. and Beek, B., *Drug and Alcohol Depend.* 4, 91 - 94, 1979
- Opdyke, D.L.J., Letizia, C., *Food Chem. Toxic.* 20, 739-740, 1982
- Patty's Ind. Hyg. Tox., Vol. II, John Wiley & Sons, New York, p. 303; p. 3545, 1994
- Safronkina, E.J. et al., *Gig. Truda i Prof. Zabol.* 31, 53, 1987 and 27, 60 - 61, 1983
- Salem, H. and Columbine, H., *Toxicol. Appl. Pharmacol.* 2, 183 – 187, 1960
- Schilling, K. et al., *Human & Experim. Toxicol.* 16, 722 – 726, 1997
- Steinhagen, W.H. and Barrow, C.D., *Tox. Appl. Pharmacol.* 72, 495, 1984
- Technical Guidance Documents in Support of the Commission Directive 93/67/EEC on the Risk Assessment for New Notified Substances and the Commission Regulation (EC) 1488/94 on Risk Assessment for Existing Substances (1996)
- Wilkinson, D.W., *J. Hyg.* 40, 55, 1940
- Wolfe, G.W. et al., *The Toxicologist* 7, 1, 209, 1987

Annex IIsovaleraldehyde**SAR's (Aldehydes C<sub>3</sub> – C<sub>6</sub>) and Precursor**

	propionaldehyde		n-butyraldehyde		iso-butyraldehyde		Isovaleraldehyde		n-valeraldehyde		2-methylbutanal		n-hexanal		3-methylbutanal	
	CAS No.	123-38-6	123-72-8	78-84-2	590-86-3	110-62-3	96-17-3	66-25-1	123-51-3							
Water solubility	22% at 20°C	11.8% at 20°C	6.7% at 20°C (weakly acidic) 7.5% at 20°C (neutral)	2% at 20°C	1.4% at 20°C	1.3% at 20°C	0.5% at 20°C	∅								
Partition coefficient	Log Pow = 0.83 at 20°C	Log Pow = 0.8; 0.88	Log Pow = 0.77 at 25°C	Log Pow = 1.3 at 25°C	Log Pow = 1.3	Log Pow = N	Log Pow = 1.78 at 25°C	∅								
Repeated dose	OECD 422 inhal. r: NOAEL: 150 ppm (systemic toxicity) LOAEL: < 150 ppm (irritation) Effects at > 750 ppm: FC? ( ? )	12 w inhal. r: NOAEL (systemic): > 2000 ppm NOAEL (irrit.): 51 ppm; 90 d r and m p.o.: NOAEL's 300 mg/kg bw/d (systemic and irrit.) Effects at ≥ 600 mg/kg bw/d: blood toxicity	Inhal., 90 d, r and m: NOAEL (r): 1000 ppm (syst) LOAEL (m): 500 ppm (irrit.) Effects: > 4000 ppm: body weight depression; mortality	N	N	N	N	OECD 408 90d drinking water rat NOAEL: 340 mg/kg bw/d								
	OECD 422 (s.a.) (inhal., r): NOAEL > 1500 ppm	No toxic effects on repro. organs up to 1200 mg/kg bw/d r + m in 90-d study (s.a.)	Inhal., 90 d, r and m: NOAEL (r): 4000 ppm NOAEL (m): 2000 ppm	N	N	N	N	No toxic effects on reproorg. up to the highest dose (1250 mg/kg bw/d in 90 d								

Develop. Toxicity/ Teratogenicity	OECD 422 (s.a.): NOAEL > 1500 ppm	N	OECD 414 inhal., r: (mat.) NOAEL 1000 ppm NOAEL (fetal): 4000 ppm	N	N	N	N	s.a.) OECD 414 Inhal. r + rbt: no fetal tox. up to highest dose (10 mg/l ? 2780 ppm)
	Sensit. (skin)	N	Buehler test (guinea pig): -	N	Max. test (guinea pig): -	Max. test (human): -	test (human): -	Patch test (human): -

N = No data available; + = positive; - = negative; r = rat; m = mouse; rbt = rabbit; + = and; Ø = not relevant; FC? = reduced food consumption

# I U C L I D D a t a S e t

Existing Chemical ID: 590-86-3  
CAS No. 590-86-3  
EINECS Name isovaleraldehyde  
EC No. 209-691-5  
Molecular Formula C5H10O

## Producer Related Part

Company: BASF AG  
Creation date: 17-FEB-2000

## Substance Related Part

Company: BASF AG  
Creation date: 17-FEB-2000

Memo: OECD SIAM 10

Printing date: 11-JUN-2002  
Revision date: 16-FEB-2000  
Date of last Update: 11-JUN-2002

Number of Pages: 42

Chapter (profile): Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10  
Reliability (profile): Reliability: without reliability, 1, 2, 3, 4  
Flags (profile): Flags: without flag, confidential, non  
confidential, WGK(DE), TA-Luft (DE), Material  
Safety Dataset, Risk Assessment, Directive  
67/548/EEC, SIDS, BPD Notification

---

## 1. General Information

---

### **1.0.1 Applicant and Company Information**

### **1.0.2 Location of Production Site, Importer or Formulator**

### **1.0.3 Identity of Recipients**

### **1.0.4 Details on Category/Template**

#### **1.1.0 Substance Identification**

##### **1.1.1 General Substance Information**

Substance type: organic  
Physical status: liquid  
Purity: >= 98 - % w/w

##### **1.1.2 Spectra**

#### **1.2 Synonyms and Tradenames**

.beta.-Methylbutanal  
3-Methyl-1-butanal  
3-Methylbutanal  
3-Methylbutyraldehyde  
Butanal, 3-methyl- (9CI)  
Butyraldehyde, 3-methyl- (7CI)  
iso-Valeraldehyde  
Isoamylaldehyde  
Isopentanal  
Isovaleral  
Isovaleraldehyd  
Isovaleraldehyde (8CI)  
Isovaleric aldehyde

#### **1.3 Impurities**

---

## 1. General Information

---

### 1.4 Additives

### 1.5 Total Quantity

### 1.6.1 Labelling

**Labelling:** provisionally by manufacturer/importer  
**Symbols:** (F) highly flammable  
(Xi) irritating  
**R-Phrases:** (11) Highly flammable  
(36/38) Irritating to eyes and skin  
**S-Phrases:** (16) Keep away from sources of ignition - No smoking  
(23) Do not breathe vapour

(1)

### 1.6.2 Classification

**Classified:** provisionally by manufacturer/importer  
**Class of danger:** highly flammable  
**R-Phrases:** (11) Highly flammable

(1)

**Classified:** provisionally by manufacturer/importer  
**Class of danger:** irritating  
**R-Phrases:** (36/38) Irritating to eyes and skin

(1)

### 1.6.3 Packaging

### 1.7 Use Pattern

#### 1.7.1 Detailed Use Pattern

#### 1.7.2 Methods of Manufacture

### 1.8 Regulatory Measures

#### 1.8.1 Occupational Exposure Limit Values

**Type of limit:** MAK (DE)  
**Remark:** no MAK value available

(2)

#### 1.8.2 Acceptable Residues Levels

---

## 1. General Information

---

### 1.8.3 Water Pollution

**Classified by:** KBwS (DE)  
**Labelled by:** KBwS (DE)  
**Class of danger:** 1 (weakly water polluting)

### 1.8.4 Major Accident Hazards

**Legislation:** Stoerfallverordnung (DE)  
**Substance listed:** yes

**Remark:** No 2 "highly flammable liquids"

(3)

### 1.8.5 Air Pollution

### 1.8.6 Listings e.g. Chemical Inventories

### 1.9.1 Degradation/Transformation Products

### 1.9.2 Components

### 1.10 Source of Exposure

**Remark:** Isovaleraldehyde is probably not used in perfumes. It finds considerable use in flavor compositions, mainly for imitation Butter, Chocolate, Cocoa, Nut, Coffee, Caramel, etc. and in many fruit complexes. The concentration in finished products will be as low as 0.5 ppm up to 4 ppm or 5 ppm.

(4)

**Remark:** Concentrations in ppm found in following researched food:  
Kohlrabi 0.02; tomato 0.4 - 0.9; carrot 0.04 - 0.2; bourbon  
whiskey 8.3; brandy 4.2 - 6

(5)

### 1.11 Additional Remarks

### 1.12 Last Literature Search

### 1.13 Reviews

### 2.1 Melting Point

**Value:** < -60 degree C

**Remark:** Pourpoint

**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (6)

**Value:** = -51 degree C

**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (1)

### 2.2 Boiling Point

**Value:** = 90.4 degree C

**Reliability:** (4) not assignable  
Secondary quotation (7)

**Value:** = 91 - 93 degree C

**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (1)

**Value:** = 93 degree C at 1013 hPa

**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (6)

### 2.3 Density

**Type:** density

**Value:** = .795 - .799 g/cm<sup>3</sup> at 20 degree C

**Test substance:** isovaleraldehyde > 98%

**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (6)

**Type:** density

**Value:** ca. .798 g/cm<sup>3</sup> at 20 degree C

## 2. Physico-chemical Data

Substance Id: 590-86-3

**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (1)

**2.3.1 Granulometry****2.4 Vapour Pressure**

**Value:** = 61 hPa at 20 degree C

**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (1)

**Value:** = 70.04 hPa at 24.3 degree C

**Method:** other (measured): dynamic with Argon

**Result:** temperature (°C) / vapour pressure (hPa): 24.26/70.04;  
31.55/99.80; 57.57/300.4; 71.52/500.6; 81.41/700.5;  
92.51/1000.4

**Test substance:** isovaleraldehyde 96.8%

**Reliability:** (2) valid with restrictions  
Discrepancy between documented test parameters and  
standard methods, but scientifically acceptable. (8)

**2.5 Partition Coefficient**

**log Pow:** = 1.31 at 25 degree C

**Method:** other (measured)

**Test substance:** isovaleraldehyde 99.22% (GC)

**Reliability:** (2) valid with restrictions  
Discrepancy between documented test parameters and  
standard methods, but scientifically acceptable. (9)

**2.6.1 Solubility in different media**

**Value:** = 20 g/l at 20 degree C

**Remark:** pH value: neutral

**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (1)

## 2. Physico-chemical Data

Substance Id: 590-86-3

**Value:** = 15 g/l at 20 degree C

**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (6)

**Value:** = 1.9 other: weight% at 24 degree C

**Method:** other: visual observation of cloud point and  
gas-chromatographic analysis of saturated phases

**Test substance:** isovaleraldehyde 97.9 area% (GC)

**Reliability:** (2) valid with restrictions  
Discrepancy between documented test parameters and  
standard methods, but scientifically acceptable. (10)

**2.6.2 Surface Tension**

**Value:** = 28 mN/m at 0 degree C

**Remark:** = 24 mN/m at 40 °C  
= 20 mN/m at 80 °C

**Reliability:** (4) not assignable  
Secondary quotation (7)

**2.7 Flash Point**

**Value:** = -5 degree C

**Method:** other: DIN 51 755

**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (6)

**Value:** = -4.5 degree C

**Type:** closed cup

**Method:** other: DIN 51 755

**Test substance:** isovaleraldehyde crude 6806

**Reliability:** (2) valid with restrictions  
Discrepancy between documented test parameters and  
standard methods, but scientifically acceptable. (11)

**Value:** = 0 degree C

**Method:** other: DIN 51 755

## 2. Physico-chemical Data

Substance Id: 590-86-3

**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (1)

**2.8 Auto Flammability**

**Value:** = 175 degree C  
**Method:** other: DIN 51 794  
**Remark:** Autoignition temperature  
**Reliability:** (1) valid without restriction  
National standard specification (12)

**Value:** = 210 degree C  
**Method:** other: DIN 51794  
**Remark:** ignition temperature  
**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (1)

**Value:** = 240 degree C  
**Method:** other: DIN 51 794  
**Remark:** Autoignition temperature  
**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (6)

**2.9 Flammability**

**Result:** highly flammable  
**Reliability:** (4) not assignable  
Manufacturer / producer data without proof (1)

**2.10 Explosive Properties**

**Result:** not explosive  
**Remark:** because of chemical structure  
**Reliability:** (2) valid with restrictions  
Expert judgement (13)

**2.11 Oxidizing Properties**

**Result:** no oxidizing properties

**Remark:** because of chemical structure

**Reliability:** (2) valid with restrictions

Expert judgement

(13)

**2.12 Dissociation Constant****2.13 Viscosity****2.14 Additional Remarks**

**Remark:** Explosive limits: 1.7 - 6.8 Vol.%

Hazardous reactions: Risk of self-ignition when a large surface area is produced due to fine dispersion.

**Reliability:** (4) not assignable

Manufacturer / producer data without proof

(1)

**Result:** Explosion limits: 1.0 - 5.0 Vol.%

**Reliability:** (1) valid without restriction

Test procedure in accordance with generally accepted standard methods.

(12)

**3.1.1 Photodegradation**

Type: air  
 INDIRECT PHOTOLYSIS  
 Sensitizer: OH  
 Conc. of sens.: 5000 molecule/cm<sup>3</sup>  
 Rate constant: = .0000000000274 cm<sup>3</sup>/(molecule \* sec)

Remark: Rate Constant obtained at 25 Deg C. Half-life = 0.6 days  
 (calculated).

Reliability: (2) valid with restrictions

(14)

**INDIRECT PHOTOLYSIS**

Sensitizer: OH  
 Conc. of sens.: 500000 molecule/cm<sup>3</sup>  
 Rate constant: = .0000000000295221 cm<sup>3</sup>/(molecule \* sec)  
 Degradation: = 50 % after 13 hour(s)

Method: other (calculated): AOP (v1.87)

Reliability: (1) valid without restriction

(15)

Type: other

Remark: K=2.89E-11 cm<sup>3</sup>/mol\*s; calculated with AOP according to  
 Meylan at 298 K  
 K=2.58E-11 cm<sup>3</sup>/mol\*s; calculated with AOP according to  
 Meylan at 298 K  
 K=1.86E-11 cm<sup>3</sup>/mol\*s; calculated with AOP according to  
 Meylan at 298 K

Reliability: (4) not assignable

(14) (16)

**3.1.2 Stability in Water****3.1.3 Stability in Soil****3.2.1 Monitoring Data (Environment)**

Medium: food

Remark: Isovaleraldehyd occurs in orange, lemon, eucalyptus and  
 other oils.

(17)

**3.2.2 Field Studies****3.3.1 Transport between Environmental Compartments**

**3.3.2 Distribution****3.4 Mode of Degradation in Actual Use****3.5 Biodegradation**

**Type:** aerobic  
**Inoculum:** other bacteria: BASF-Belebtschlamm  
**Degradation:** = 99 % after 10 day(s)  
**Result:** other: gut eliminierbar aus Wasser  
**Kinetic:** 1 day(s) = 5 %  
 3 day(s) = 11 %  
 7 day(s) = 98 %  
 10 day(s) = 99 %

**Method:** OECD Guide-line 302 B "Inherent biodegradability:  
 Modified Zahn-Wellens Test"  
**GLP:** no

**Remark:** About 20 -30 % of the elimination was due to  
 strippingStudy was completed in 1987, not in 1978

**Reliability:** (2) valid with restrictions (18)

**Type:** aerobic  
**Inoculum:** other bacteria: sludge from aeration tank of waste  
 water system of HOECHST AG, not adapted  
**Concentration:** 300 mg/l related to DOC (Dissolved Organic Carbon)  
**Degradation:** > 95 % after 10 day(s)

**Method:** OECD Guide-line 302 B "Inherent biodegradability:  
 Modified Zahn-Wellens Test"  
**GLP:** no

**Remark:** Adsorption on activated sludge within 3 hours after  
 Start of the test amounts 30%.  
 Degree of elimination amounts 86% in 5 days, >95% in  
 10 days. A calculation of biological degradation is  
 not possible, because isovaleraldehyde can be  
 eliminated by stripping because of its volatility.

**Reliability:** (2) valid with restrictions (19)

**3.6 BOD5, COD or BOD5/COD Ratio**

**Method:**  
**Year:**  
**GLP:** no

**R A T I O B O D 5 / C O D**

**BOD5/COD:** = .75  
**Method:**  
**Remark:** BOD5= 1423 mg/g; COD= 1908 mg/g  
TOC = 701 mg/g  
**Reliability:** (4) not assignable

(20)

**3.7 Bioaccumulation****3.8 Additional Remarks**

**AQUATIC ORGANISMS****4.1 Acute/Prolonged Toxicity to Fish**

**Type:** semistatic  
**Species:** Poecilia reticulata (Fish, fresh water)  
**Exposure period:** 14 day(s)  
**Unit:** mg/l **Analytical monitoring:** yes  
**LC50:** = 13.3  
  
**Method:** other: according to Alabaster, J.S. and Abrams, F.S.H.:  
 Adv.  
 Water Poll. Res., Proc. 2nd Int. Conf. Tokyo, Vol 1,  
 Pergamon  
 Press, Oxford (1964)  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
  
**Remark:** Fish, freshwater. Original quotation of LC50; log LC50 =  
 2.19 umol/l  
**Reliability:** (2) valid with restrictions  
(21)

**Type:** static  
**Species:** Leuciscus idus (Fish, fresh water)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:** yes  
**NOEC:** 22  
**LC0:** 22  
**LC50:** ca. 53  
**LC100:** 100  
  
**Method:** other: after DIN 38 412, test procedure with aquatic  
 organism Group L, Part L15  
**Year:** 1982  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4  
  
**Remark:** Fish, fresh water  
**Reliability:** (1) valid without restriction  
(22)

**Species:** Pimephales promelas (Fish, fresh water)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:** yes  
**LC50:** = 3.25  
  
**Method:** other: no data  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
  
**Remark:** Fish, fresh water  
**Reliability:** (2) valid with restrictions  
(23) (24)

**4.2 Acute Toxicity to Aquatic Invertebrates**

**Species:** Daphnia magna (Crustacea)  
**Exposure period:** 24 hour(s)  
**Unit:** mg/l **Analytical monitoring:**  
**EC0:** = 125  
**EC50:** = 210  
**EC100:** = 500  
  
**Method:** Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"  
**GLP:** no  
  
**Reliability:** (1) valid without restriction (25)

**Species:** Daphnia magna (Crustacea)  
**Exposure period:** 48 hour(s)  
**Unit:** mg/l **Analytical monitoring:**  
**EC0:** = 125  
**EC50:** = 177  
**EC100:** = 250  
  
**Method:** Directive 84/449/EEC, C.2 "Acute toxicity for Daphnia"  
**GLP:** no  
  
**Reliability:** (1) valid without restriction (25)

**Species:** other: Chaetogammarus marinus  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:**  
**EC50:** = 170  
  
**GLP:** no  
  
**Remark:** Test solutions were almost saturated with oxygen  
 Throughout exposure.  
 Gammarid length=5mm; LC50 based on nominal  
 concentration.  
  
**Test condition:** pH-value: 8.00; purity: 97.0%  
 Temperature: 15.0 deg C; salinity: 28 o/oo  
**Reliability:** (4) not assignable  
 no raw data were presented (26)

**4.3 Toxicity to Aquatic Plants e.g. Algae**

**Species:** Scenedesmus subspicatus (Algae)  
**Exposure period:** 72 hour(s)  
**Unit:** mg/l **Analytical monitoring:**  
**EC10:** = 33  
**EC50:** = 80

## 4. Ecotoxicity

**Method:** other: Scenedesmus Cell Multiplication Inhibition Test,  
DIN 38412 part 9 (draft)  
**GLP:** no

**Reliability:** (1) valid without restriction (25)

**Species:** Scenedesmus subspicatus (Algae)  
**Exposure period:** 96 hour(s)  
**Unit:** mg/l **Analytical monitoring:**  
**EC10:** = 38  
**EC50:** = 78

**Method:** other: Scenedesmus Cell Multiplication Inhibition Test,  
DIN 38412 part 9 (draft)  
**GLP:** no

**Reliability:** (1) valid without restriction (25)

**4.4 Toxicity to Microorganisms e.g. Bacteria**

**Type:** aquatic  
**Species:** Pseudomonas putida (Bacteria)  
**Unit:** mg/l **Analytical monitoring:**  
**TGK :** = 310

**Method:** other: Cell Multiplication Inhibition Test  
**GLP:** no

**Remark:** Start of inhibition at a concentration of 310 mg/l.

**Reliability:** (2) valid with restrictions (27)

**Type:** aquatic  
**Unit:** mg/l **Analytical monitoring:**  
**EC20 :** = 250

**Method:** other: Gas Production Test (Fermentation Tube Test), not  
standardized  
**GLP:** no

**Reliability:** (2) valid with restrictions (28)

**4.5 Chronic Toxicity to Aquatic Organisms****4.5.1 Chronic Toxicity to Fish****4.5.2 Chronic Toxicity to Aquatic Invertebrates**

**TERRESTRIAL ORGANISMS****4.6.1 Toxicity to Sediment Dwelling Organisms****4.6.2 Toxicity to Terrestrial Plants****4.6.3 Toxicity to Soil Dwelling Organisms****4.6.4 Toxicity to other Non-Mamm. Terrestrial Species****4.7 Biological Effects Monitoring****4.8 Biotransformation and Kinetics****4.9 Additional Remarks**

## **5.0 Toxicokinetics, Metabolism and Distribution**

### **5.1 Acute Toxicity**

#### **5.1.1 Acute Oral Toxicity**

**Type:** LD50  
**Species:** rat  
**Value:** = 7660 mg/kg bw

**Method:** other: no data  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** Original quotation: LD50 = 8910 ul/kg  
**Reliability:** (2) valid with restrictions (29)

**Type:** LD50  
**Species:** rat  
**Value:** > 3200 mg/kg bw

**Method:** other: no data  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4

**Reliability:** (3) invalid (30) (31)

**Type:** LD50  
**Species:** rat  
**Value:** ca. 6200 mg/kg bw

**Method:** other: BASF test  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** Original quotation: LD50 ca. 7200 ul/kg  
**Reliability:** (2) valid with restrictions (32)

**Type:** LD50  
**Species:** rat  
**Value:** = 5600 mg/kg bw

**Method:** other: no data  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Reliability:** (4) not assignable (33)

## 5. Toxicity

**Type:** LD50  
**Species:** rat  
**Value:** > 5000 mg/kg bw

**Method:** other: no data  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Reliability:** (4) not assignable (34)

**Type:** LD50  
**Species:** mouse  
**Value:** = 4750 mg/kg bw

**Method:** other: no data  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Reliability:** (4) not assignable (35) (36)

**Type:** LD50  
**Species:** guinea pig  
**Value:** = 2950 mg/kg bw

**Method:** other: no data  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Reliability:** (4) not assignable (37) (38)

**5.1.2 Acute Inhalation Toxicity**

**Type:** LC50  
**Species:** rat  
**Value:** = 91 mg/l

**Method:** other: no data  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Reliability:** (3) invalid (39) (40)

**Type:** other  
**Species:** rat  
**Exposure time:** 4 hour(s)  
**Value:** = 57 mg/l

**Method:** other: no data  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

## 5. Toxicity

**Remark:** Original quotation: 1600 ppm cor. 57 mg/l, 4 hours; 5/6 lethal

**Reliability:** (2) valid with restrictions

(29)

**Type:** other: IRT  
**Species:** rat  
**Exposure time:** 15 minute(s)

**Method:** other: no data  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** No mortality after 15 minutes exposure time (saturated vapour resp. enriched with vapour in atmosphere, at 20 degree Celsius (room temperature)). Deaths occurred at a longer exposure time.

**Reliability:** (2) valid with restrictions

(29)

**Type:** other: IRT  
**Species:** rat  
**Exposure time:** 30 minute(s)

**Method:** other: BASF test  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** No mortality after 10 minutes exposure time (saturated vapour resp. enriched vapour atmosphere, at 20 degree Celsius). Lethality after a longer exposure time.

**Reliability:** (2) valid with restrictions

(41)

**Type:** LC50  
**Species:** mouse  
**Value:** = 51 mg/l

**Method:** other: no data  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Reliability:** (4) not assignable

(42) (40)

**Type:** other  
**Species:** mouse  
**Exposure time:** 10 hour(s)  
**Value:** = 6.2 mg/l

**Method:** other: according to Salem, H.: Dissertation, Univ. of Toronto, Canada (1958)  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4

## 5. Toxicity

Substance Id: 590-86-3

**Remark:** 10 hours, lethal at 3/5 mice; aerosole: mean concentration of substance was 6.176 mg/l.  
**Reliability:** (4) not assignable (43)

**Type:** other: RD50 (50 % decrease of respiration rate)  
**Species:** mouse  
**Exposure time:** 10 minute(s)  
**Value:** 2.7 - 3.6 mg/l

**Method:** other: according to Alarie, Y.: Arch. Environ. Health 13, 433-449 (1966)  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** Sensoric irritation RD50 757-1008 ppm; B6C3F1, Swiss Webster, decrease of respiration rate to 50 %.  
**Reliability:** (3) invalid (44)

**Type:** other  
**Species:** rabbit  
**Exposure time:** 10 hour(s)  
**Value:** = 6.2 mg/l

**Method:** other: according to Salem, H.: Dissertation, Univ. of Toronto  
Canada (1958)  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** 10 hours, lethal 0/5 rabbits, aerosol: mean concentration of substance was 6.176 mg/l.  
**Reliability:** (4) not assignable (43)

**Type:** other  
**Species:** guinea pig  
**Exposure time:** 10 hour(s)  
**Value:** = 6.2 mg/l

**Method:** other: according to Salem, H.: Dissertation, University of Toronto, Canada (1958)  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** 10 hours, lethal 5/20 guinea pigs, aerosol: mean concentration of substance was 6.176 mg/l.  
**Reliability:** (4) not assignable (45)

## 5. Toxicity

**5.1.3 Acute Dermal Toxicity**

**Type:** LD50  
**Species:** rabbit  
**Value:** = 2730 mg/kg bw

**Method:** other: no data  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** Original quotation: LD50 = 3180 ul/kg  
**Reliability:** (2) valid with restrictions

(29)

**Type:** LD50  
**Species:** rabbit  
**Value:** > 5000 mg/kg bw

**Method:** other: no data  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Reliability:** (3) invalid

(46)

**Type:** LD50  
**Species:** guinea pig  
**Value:** > 8600 mg/kg bw

**Method:** other: no data  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** Original quotation: LD50 = 10 000 ul/kg  
**Reliability:** (3) invalid

(47)

**5.1.4 Acute Toxicity, other Routes**

**Type:** LD50  
**Species:** mouse  
**Route of admin.:** i.p.  
**Value:** ca. 237 mg/kg bw

**Method:** other: BASF test  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** Original quotation: LD50 ca. 275 ul/kg  
**Reliability:** (2) valid with restrictions

(41)

**Type:** other  
**Species:** rat

---

5. Toxicity

---

Route of admin.: i.p.  
Value: = 800 mg/kg bw

Method: other: no data  
GLP: no data  
Test substance: as prescribed by 1.1 - 1.4

Remark: Lethal concentration 800 mg/kg (no further information).  
Reliability: (4) not assignable

(48)

**5.2 Corrosiveness and Irritation****5.2.1 Skin Irritation**

Species: rabbit  
Result: irritating

Method: other: BASF test  
GLP: no  
Test substance: as prescribed by 1.1 - 1.4

Reliability: (2) valid with restrictions

(41)

Species: rabbit  
Result: irritating

Method: other: occlusive, 24 hours  
GLP: no data  
Test substance: as prescribed by 1.1 - 1.4

Remark: Framework to determination of LD50  
Reliability: (3) invalid

(46)

Species: rabbit  
Result: not irritating

Method: other: Smyth Carpenter  
GLP: no  
Test substance: as prescribed by 1.1 - 1.4

Remark: Degree 2/10  
Reliability: (2) valid with restrictions

(29)

Species: guinea pig  
Result: irritating

Method: other: no data  
GLP: no  
Test substance: as prescribed by 1.1 - 1.4

Remark: Quotation originates from a tabular review. Irritation

effect is described as "moderate".  
**Reliability:** (3) invalid (49) (31)

### 5.2.2 Eye Irritation

**Species:** rabbit  
**Result:** irritating  
**Method:** other: Smyth Carpenter  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** Degree 4/10  
**Reliability:** (2) valid with restrictions (29)

**Species:** rabbit  
**Result:** irritating  
**Method:** other: BASF test  
**GLP:** no  
**Test substance:** as prescribed by 1.1 - 1.4  
**Reliability:** (2) valid with restrictions (41)

### 5.3 Sensitization

**Type:** other: maximization test  
**Species:** human  
**Result:** not sensitizing  
**Method:** other: according to Kligman, A.M.: J. Invest. Derm. 47, 393 (1966) and Kligman, A.M. and Epstein, W.: Contact Dermatitis 1, 231 (1975)  
**Year:** 1975  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4  
**Remark:** Tested were 29 probands, substance was dissolved (1 %) in petroleum  
**Reliability:** (3) invalid (50)

### 5.4 Repeated Dose Toxicity

## 5. Toxicity

**5.5 Genetic Toxicity 'in Vitro'**

**Type:** Ames test  
**System of testing:** Salmonella typhimurium TA98, TA100, TA1535, TA1537  
**Concentration:** 0.03, 0.3, 3 and 30 umol/plate  
**Metabolic activation:** with and without  
**Result:** negative

**Method:** other: according to Ames, B.N. et al.: Mutation Research 31, 347-364 (1975)  
**Year:** 1975  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** Result originates from a summary.  
**Reliability:** (2) valid with restrictions

(51)

**Type:** Ames test  
**System of testing:** Salmonella typhimurium TA98, TA100 and TA104  
**Concentration:** no data  
**Metabolic activation:** with and without  
**Result:** ambiguous

**Method:** other: according to Kamiya, A. and Ose, Y.: Sci. Total Environ. 65, 109-120 (1987)  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** Not to evaluate, tested were fractions of water leakage, no data for single components, in case of isovaleraldehyde only reference to a slight, positive effect.  
**Reliability:** (2) valid with restrictions

(52)

**Type:** Ames test  
**System of testing:** Salmonella typhimurium TA98, TA100 and TA102  
**Concentration:** 0.01-1000 nmol  
**Metabolic activation:** with and without  
**Result:** negative

**Method:** other: according to Yahagi, T.: Mutation Research 48, 121 (1977)  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** Only at TA98 (+S9) were found a slight, not significant mutation factor of 1.4.  
**Reliability:** (2) valid with restrictions

(53)

**Type:** Bacillus subtilis recombination assay  
**System of testing:** Bacillus subtilis H17, M45  
**Concentration:** 1.03-1.99 g/l

## 5. Toxicity

**Metabolic activation:** with and without  
**Result:** negative

**Method:** other  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** In this trial isovaleraldehyde even generates an reverse effect.

**Reliability:** (3) invalid

(54)

**Type:** Sister chromatid exchange assay  
**System of testing:** human lymphocytes  
**Concentration:** 0.002-0.003 %  
**Metabolic activation:** without  
**Result:** ambiguous

**Method:** other  
**GLP:** no data  
**Test substance:** as prescribed by 1.1 - 1.4

**Remark:** Result, ambiguous positive, tested were only 20-62 metaphases. No dose dependence was found.

**Reliability:** (3) invalid

(55)

**5.6 Genetic Toxicity 'in Vivo'**

**Type:** Micronucleus assay  
**Species:** mouse **Sex:** male  
**Strain:** NMRI  
**Route of admin.:** i.p.  
**Exposure period:** single injection  
**Doses:** 0, 25, 50, 100 mg/kg bw  
**Result:** negative

**Method:** OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"  
**Year:** 1997  
**GLP:** yes  
**Test substance:** other TS: Isovaleraldehyde, purity: 99.3 % (GC)

**Method:** In this study, the ability of the test substance to induce chromosomal damage (clastogenicity) and to induce spindle poison effects (aneugenic activity) was investigated.  
 The test substance was dissolved in DMSO  
 Administration volume: 4 ml/kg bw.  
 5 animals / dose group.

Negative control: DMSO  
 Positive controls: cyclophosphamide (20 mg/kg bw), vincristine (0.15 mg/kg bw).  
 The animals were sacrificed and the bone marrow of the

---

**5. Toxicity**

---

Two femora was prepared 24 and 48 hours after administration in the highest dose group of 100 mg/kg body weight and in the vehicle controls. In the test groups of 50 mg/kg and 25 mg/kg body weight and in the positive control groups, the 24-hour sacrifice interval was investigated only. After staining of the preparations, 2,000 polychromatic erythrocytes were evaluated per animal and investigated for micronuclei. The normocytes with and without micronuclei occurring per 2,000 polychromatic erythrocytes were also registered.

**Result:**

The administration of the test substance led to evident Signs of toxicity:

- 25 mg/kg bw: squatting posture
- 50 mg/kg bw: squatting posture and poor general state
- 100 mg/kg bw: squatting posture, piloerection, poor general state

There was no increase in the number of polychromatic erythrocytes containing either small or large micronuclei.

The rate of microneuclei was nearly the range of the concurrent negative control in all dose groups and within the range of the historical control data.

No inhibition of erythropoiesis, determined from the ratio of polychromatic to normochromatic erythrocytes, was detected.

The test substance had no chromosome-damaging (clastogenic) effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis (aneugenic activity) in bone marrow cells in vivo.

Both of the positive control chemicals, i.e. cyclophosphamide for clastogenic effects and vincristine for induction of spindle poison effects, induced the expected increases in the rate of polychromatic erythrocytes containing small or large micronuclei. The result for the negative control was within the historical control range.

**Reliability:**

(1) valid without restriction

11-JUN-2002

(56)

**5.7 Carcinogenicity****5.8.1 Toxicity to Fertility****5.8.2 Developmental Toxicity/Teratogenicity****5.8.3 Toxicity to Reproduction, Other Studies**

## 5.9 Specific Investigations

### 5.10 Exposure Experience

**Remark:** A group of seven chemists were accidentally exposed To isovaleraldehyde leaking from a laboratory apparatus for several days. Toxic effects were mainly tightness in the chest, irriatationof the upper respiratory tract, cough, dyspnoea, marked loss of energy and weakness, dizziness, headahes, profuse perspiration, tachcardia, nausea, vomiting, dirrhoea, anorexia, somnolence, sometimes insomnia, and in one case a partial pneumothorax. All recovered rapidly after removing the exciting cause. Isovaleraldehyde was detected in the air by aspirating it through a solution containing dinitrophenylhydrazine. Odor was descriebed as pungent but no informations on actual air concentrations were given.

**Reliability:** (2) valid with restrictions  
basic data given, acceptable restrictions (57)

**Remark:** The mean plasma isovaleraldehyde concentration in non-fasting patients with hepatic encephalopathy, 0.244 µmol/litre (range 0-1.30) was not significantly different from the mean value in controls, 0.116 µmol/litre (o-0.349). Oral leucine feeding (a total of 9.5 g) resulted in significant increases in plasma isovaleraldehyde in both control subjects (mean 1.61 µmol/litre, range 0.767-2.09 µmol/litre) and patients with cirrhosis (mean 1.09 µmol/litre, 0.791-1.326 µmol/litre).

**Reliability:** (2) valid with restrictions basic data given, acceptable restrictions (58)

**Remark:** A maximization test according to Kligman was carried out on 29 volunteers. The material was tested at a concentration of 1 % in petrolatum and produced no sensitization reactions.

**Reliability:** (1) valid without restriction  
Method and performance conform to standard (59)

### 5.11 Additional Remarks

**Type:** Biochemical or cellular interactions

**Remark:** The oxidative metabolism (noradrenaline-induced respiration)from "brown fat" tissue cells of hamsters was decreased to 55 % at concentration of 1 mM isovaleraldehyde. (60)

- Type:** Biochemical or cellular interactions
- Remark:** The membrane permeability of human lung fibroblasts was increased up to 25 % (after incubation with 25 mM test substance = isovaleraldehyde, dissolved in Tris-buffered NaCl solution ). Incubation time, 30 minutes. (61)
- Type:** Biochemical or cellular interactions
- Remark:** The incubation with 5 mM isovaleraldehyde for a time of 60 minutes did not lead to a decrease of the ciliar activity intrachea-cell cultures of chicks embryos. (62)
- Type:** Biochemical or cellular interactions
- Remark:** The test substance (isovaleraldehyde) led to a significant inhibition of the acetaldehyde oxidation in rat liver and showed itself as a very potent inhibitor of the oxidation of different mitochondrial substrates. (63)
- Type:** Cytotoxicity
- Remark:** Isovaleraldehyde inhibited cell growth of Ascites sarcoma BP8 cells about 13 % (87 % growth were found), concentration: 0.1 mM. At a concentration of 1 mM no cell growth was observed. (64)
- Type:** Metabolism
- Remark:** Degradation of higher aliphatic alcohols among other things showed isovaleraldehyde. (65)
- Type:** other
- Remark:** Skin irritation: reference chemicals data bank (66)
- Type:** other: RD50
- Remark:** Evaluation of the sensory irritation test for the assessment of occupational health risk. RD50: The concentration that induces a 50 % decrease in the respiratory rate.  
Mouse: Smith Webster; RD50: 1.008 (1008?) ppm (10 minutes exposure); mouse: B6C3F1; RD50: 757 ppm (10 minutes exposure). (67)
- Type:** other: summarizing reports
- Remark:** Summarizing reports (isovaleraldehyde) (68)

## 6. References

- (1) BASF AG, safety data sheet isovaleraldehyde, 16.03.1999
- (2) TRGS 900 of 10/1996 and 905 of 4/1995
- (3) Stoerfall-Verordnung of 20.09.1991
- (4) Actander, Steffen, Perfume and Flavor Chemicals (Aroma Chemicals) Vol. II, 1969, Montclair, N.J.(U.S.A.)
- (5) TNO, Biotechnology and Chemistry, Volatile Compounds in Food, Qualitative and Quantitative Data, Supplement 2
- (6) Hoechst AG, Firmenschrift Aldehyde, Alkohole, Ester, Acetale/Ether, Business Line Amine/Oxo-Derivate
- (7) BASF AG, Verfahrenstechnik, unveröffentlichte Untersuchung, Bericht 185.0552.2, 18.12.1985
- (8) BASF AG, Mischphasenthermodynamik, unveröffentlichte Untersuchung, Bericht BRU 94.322, 10.08.1994
- (9) BASF AG, Analytisches Labor, unveröffentlichte Untersuchung, Bericht zu J.Nr.: 130239/02, 28.10.1988
- (10) BASF AG, Physikalisch-chemische Konstanten, unveröffentlichte Untersuchung, Bericht BRU 73.82, 05.09.1973
- (11) BASF AG, Sicherheitstechnische Kenndaten, unveröffentlichte Untersuchung, SIK-Nr. 76/0984, 08.12.1976
- (12) BASF AG, Sicherheitstechnische Kenndaten, unveröffentlichte Untersuchung, SIK-Nr. 78/0066, 16.02.1978
- (13) BASF AG, Sicherheitstechnik, interne Mitteilung, 15.09.1999
- (14) Atkinson, R., J. Phys. Chem. Ref. Data, Monograph 1 (1989)
- (15) BASF AG, department of ecology, unpublished calculation, 22.11.1999
- (16) Meylan, W., Howard, P., Atmospheric Oxidation Programme Version 1.5. Syracuse Research Corporation, New York (1993)
- (17) Merck Index, 10.ed., 5076; (1983)
- (18) BASF AG, Laboratory of Ecology and Environmental Analytics, unpublished data (1987)
- (19) HOECHST AG, Abt. UWS, Abwasserforschung, REPRINT OF AN EXISTING TEST REPORT from 1979, (22.05.92)
- (20) BASF AG, Laboratory of Ecology and Environmental Analytics, unpublished data (1978)

## 6. References

- (21) Deneer, J.W. et al.: Aquatic Toxicol. 12, 185-192 (1988)
- (22) BASF AG, Department of Toxicology, unpublished data (88/712) 28/5/1989
- (23) Geiger, D.L. et al.: Acute Toxicity of Organic Chemicals to Fathead Minnows (*Pimephales promelas*), Vol 2, Center for Lake Superior Environmental Studies, Univ. of Wisconsin, Superior (1985).  
quoted in: Protic, M. and Sabljic, A.: Aquatic Toxicol. 14, 47-64 (1989)
- (24) Geiger, D.L. et al.: Acute Toxicity of Organic Chemicals to Fathead Minnows (*Pimephales promelas*), Vol. 2, Center for Lake Superior Environmental Studies, Univ. of Wisconsin, Superior (1985)
- (25) BASF AG, Laboratory of Ecology and Environmental Analytics, unpublished data (1023/88)
- (26) Adema, D.M.M., Tests and desk studies carried out by MT-TNO during 1980-1981 for Annex II of Marpol, Report CL82/14; (1982); zitiert in ECDIN 09/1993
- (27) BASF AG, Analytical Laboratory, unpublished data (330168)
- (28) HOECHST AG, Abt. UWS, Abwasserforschung-Biologie, REPRINT OF AN EXISTING TEST REPORT from 1978, (27.02.92)
- (29) Carpenter, C.P. et al.: Toxicol. Appl. Pharmacol. 28, 313-319 (1974)
- (30) Fassett, D.W.: S. 1968 in: Industrial Hygiene and Toxicology, Ed. Patty F.A. New York-London-Sidney 1962
- (31) TSCATS: OTS 012345, Doc. I.D. 86-920000088, Eastman Kodak Company 10/29/1991
- (32) BASF AG, Department of Toxicology, unpublished data (XXIII/533), 10/3/1974
- (33) RTECS, update 8912: Gig. Truda i Prof. Zabol. 31(12), 53 (1987)
- (34) Moreno, O.M.: Report to RIFM (1980); quoted in: Ford, R.A. et al.: Fd. Chem. Toxic. 26, 273-416 (1988)
- (35) RTECS, update 8912: Gig. Truda i Prof. Zabol. 27(5), 60 (1983)
- (36) Safronkina, E.I. et al.: Gig. Truda Prof. Zabol. 27(5), 60-61 (1983)
- (37) RTECS, update 8912: Gig. Truda. i Prof. Zabol. 27(5), 60 (1983)

## 6. References

- (38) Safronkina, E.I. et al.: Gig. Truda. i Prof. Zabol. 27(5), 60-61 (1983)
- (39) RTECS, update 8910: Gig. Truda i Prof. Zabol. 27(5), 60 (1983)
- (40) Safronkina, E.I. et al.: Gig. Truda i Prof. Zabol. 27(5), 60-61 (1983)
- (41) BASF AG, Department of Toxicology, unpublished data (XXIII/533) 10/3/1974
- (42) RTECS update 8910: Gig. Truda i Prof. Zabol. 27(5), 60 (1983)
- (43) Salem, H. and Cullumbine, H.: Toxicol. Appl. Pharmacol. 2, 183-187 (1960)
- (44) Steinhagen, W.H. and Barrow, C.S.: Toxicol. Appl. Pharmacol. 72, 495-503 (1984)
- (45) Salem, H. and Cullumbine H.: Toxicol. Appl. Pharmacol. 2, 183-187 (1960)
- (46) Moreno, O.M.: Report to RIFM (1980), quoted in: Ford, R.A. et al.: Fd. Chem. Toxic. 26, 273-416 (1988)
- (47) Fassett, D.W. (S. 1968) in: Industrial Hygiene and Toxicology, Ed. Patty, F.A. New York-London-Sidney (1962)
- (48) Kubow, S. et al.: Clin. Sci. 61, 451 (1981); quoted in: Ford R.A. et al.: Fd. Chem. Toxic. 26, 273-416 (1988)
- (49) Fassett, D.W. (S.1968): Industrial Hygiene and Toxicology, Ed. Patty, F.A. New York-London-Sidney (1962)
- (50) Epstein, W.C.: Report to RIFM (1980), quoted in: Ford, R.A. et al.: Fd. Chem. Toxic. 26, 273-416 (1988)
- (51) Florin, I. et al.: Toxicology 15, 219-232 (1979)
- (52) Kamiya, A. and Ose, Y.: Sci. Total Environ. 78, 131-145 (1989)
- (53) Aeschbacher, H.U. et al.: Fd. Chem. Toxic. 27, 227-232 (1989)
- (54) Matsui, S. et al.: Wat. Sci. Tech. 21, 875-887 (1989)
- (55) Obe, G. and Beck, B.: Drug and Alcohol Dependence 4, 91-94 (1979)
- (56) BASF AG, Department of Toxicology, unpublished data, Report-Project No.: 26M0558/004110, 20/02/2001
- (57) Wilkinson, J., F.; J. Hyg. (London) 40, 555-559, (1940)

## 6. References

- (58) Marshall, A., W., DeSouza, M., Morgan, M., Y.; Clin. Physiol. 5, 53-62, (1985)
- (59) Ford, R., A.; Fd. Chem. Toxic. 26, 379-380, (1988)
- (60) Pettersson, B. et al.: Toxicology 18, 1 (1980), quoted in: Ford, R.A. et al.: Fd Chem. Toxic. 26, 273-416 (1988)
- (61) Thelestam, M. et al.: Toxicology 15, 203 (1980) quoted in Ford, R.A. et al.: Fd. Chem. Toxic. 26, 273-416 (1988)
- (62) Pettersson, B. et al.: Toxicology 23, 41 (1982), quoted in: Ford, R.A. et al.: Fd. Chem. Toxic. 26, 273-416 (1988)
- (63) Hedlund, S.G. and Kiessling, K.H.: Acta Pharmacol. Toxicol. 27(5), 381 (1969), quoted in: DIMDI-HSDB, H590863, 2/22/1991
- (64) Pilotti, A. et al.: Toxicology 5, 49 (1975), quoted in: Ford, R.A. et al.: Fd. Chem. Toxic. 26, 273-416 (1988)
- (65) Ruedell, E. et al.: Beitr. Gerichtl. Med. 41, 211-218 (1983)
- (66) Bagley, D.M. et al.: Toxicology in Vitro 10, 1-6 (1969)
- (67) Bos, B.M.J. et al.: Critical Reviews in Toxicology 21, 423-450 (1992)
- (68) Ford, R.A. et al.: Fd. Chem. Toxic. 26, 273-416 (1988)