# PROPIONALDEHYDE

# (CAS Reg. No. 123-38-6)

# INTERIM ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

## For
## NAS/COT Subcommittee for AEGLS

## 2009

# PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicological and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels – AEGL-1, AEGL-2 and AEGL-3 – are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or $mg/m^3$]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m$^3$) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects, or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m$^3$) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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# EXECUTIVE SUMMARY

Propionaldehyde is a low-boiling, colorless liquid. It has a good water solubility. The lower explosive limit lies between 2.3-2.9%. The major uses of propionaldehyde is as a reactive intermediate in the manufacture of n-propanol, propionic acid, 2-methyl pentanol, trimethyolethane polyols, polyethylene additives, fragrance chemicals and fungicides.

No human cases are known. Quantitative human data are limited to an old study with human volunteers which showed only mild irritation to the mucosal surface.

Toxicity and mortality data are limited. The main effects in animal studies were irritation of the airways at low concentrations and CNS effects and mortality at higher concentrations. These effects are in general terms similar to the effects of acetaldehyde at comparable concentrations. Propionaldehyde is genotoxic *in vitro* but this could not be clearly confirmed by the only *in vivo* study. No information is available on carcinogenicity. It does not affect the fertility and is not embryotoxic in a limited developmental and reproductive toxicity study.

The AEGL-1 derivation is based on the effects described in the human volunteer study (Sim and Pattle 1957). Mild irritation of the mucosal surface was found at the only tested concentration of 134 ppm after a 30 minutes exposure. This level of severity is considered to be sub-AEGL-1, and a suitable starting point for AEGL-1 derivation. Because the effect is direct irritation, differences between individuals are expected to be small. Therefore an intraspecies factor of 3 is applied to account for differences between humans. Because AEGL-1 is based on irritation, AEGL-1 values of 45 ppm for all time points are proposed. These values are based on the same study and are equal to those proposed for the comparable substance acetaldehyde.

The AEGL-2 derivation is based on the combined repeated dose and reproduction toxicity study (Driscoll 1993). The main effects observed in this study (daily 6-hour exposure to 151, 745, or 1453 ppm for approximately 40 days) were atrophy, vacuolization and metaplasia of the olfactory epithelium of the nose. These effects can be attributed to repeated exposure and are not expected to occur after a single day exposure of 6 hours. Exposure to a higher concentration of 5,230 ppm induced anesthesia after 5 minutes in mice (Axelsson *et al.* 1953). A total uncertainty factor of 10 is applied, consisting of an interspecies factor of 3 and an intraspecies factor of 3. A higher factor would result in AEGL-2 values that are inconsistent with the available human data. Default time-scaling $C^n xt = k$ was performed with default values of n=1 for extrapolation to longer time periods and *n*=3 for extrapolation to shorter time periods. Because the starting point for time extrapolation is 4 hours or longer, the AEGL-2 10-minute value is set equal to the 30-minute value. The AEGL-2 values for propionaldehyde are in the same range as the corresponding values for acetaldehyde.

The AEGL-3 derivation is not based on data from experiments with propionaldehyde because the available data are very limited and/or of doubtful quality. The data on propionaldehyde was considered to be insufficient for AEGL-3 setting. Qualitative much better data were available for the related substance acetaldehyde. The AEGL-3 values for acetaldehyde are based on a well-performed toxicity study that allowed proper dose-response modeling (Appelman *et al*. 1982). The toxicity of both compounds is in quantitative terms similar, it can at least be expected that propionaldehyde will be equal or (more probably) less toxic than acetaldehyde. Because of this similarity in toxicity the AEGL-3 numbers for acetaldehyde are adopted for propionaldehyde.

The AEGL-3 values for acetaldehyde are based on a $BMDL_{05}$ of 5,295 ppm for 4 hours derived from an acute and a subacute inhalation toxicity study in rats (Appelman *et al.*1982). A total uncertainty factor of 10 is applied, consisting of a factor of 3 for interspecies extrapolation and a factor of 3 for sensitive human subpopulations. The value of 5,295 ppm for 4 hours was extrapolated across time periods using $C^n xt = k$ with default values $n$=1 for extrapolation to longer time periods and $n$=3 for extrapolation to shorter time periods. Because the starting point for time extrapolation is 4 hours or longer, the AEGL-3 10-minute value is set equal to the AEGL-3 30-minute value. The resulting AEGL-3 levels are in compliance with the toxicity profile expected for propionaldehyde (including the data from the repeated dose study of Driscoll *et al.* 1993).

The Level of Distinct Odor Awareness (LOA) is calculated to be 0.64 ppm.

**Summary of AEGL Values for Propionaldehyde**

| Classification | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour | Endpoint (Reference) |
|---|---|---|---|---|---|---|
| AEGL-1[a] (Nondisabling) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | Mild irritation to the mucosal surfaces in humans (Sim and Pattle 1957) |
| AEGL-2 (Disabling) | 330 ppm (800 mg/m$^3$) | 330 ppm (800 mg/m$^3$) | 260 ppm (630 mg/m$^3$) | 170 ppm (410 mg/m$^3$) | 110 ppm (270 mg/m$^3$) | Absence of irreversible effects in a repeated inhalation study (Driscoll 1993) |
| AEGL-3 (Lethal) | 1,100 ppm (2,700 mg/m$^3$) | 1,100 ppm (2,700 mg/m$^3$) | 840 ppm (2,000 mg/m$^3$) | 530 ppm (1,300 mg/m$^3$) | 260 ppm (630 mg/m$^3$) | Mortality in an acute and subacute inhalation toxicity study with acetaldehyde in rats (Appelman *et al.*1982) |

[a] The distinct odor of propionaldehyde will be noticeable by most individuals at the AEGL-1.

*References*

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# 1. INTRODUCTION

Propionaldehyde is a low-boiling, colorless liquid. The chemical reactions of propionaldehyde are based on the polarity of the carbonyl group that allows an addition of nucleophiles, an oxidation and a reduction (BUA 1996).

The technically most important way of producing propionaldehyde is the hydroformylation of ethylene (oxosynthesis), whereby the alkene is reacted in the liquid phase with $CO/H_2$ to propionaldehyde. Propionaldehyde can also be synthesized by the dehydrogenation of propanol (BUA 1996).

The worldwide production of propionaldehyde was estimated at 184,000 tons per year (OECD, 1994). The production in the U.S.A. was estimated at 125,000 tons per year (OECD, 1994) and in Germany at 75,000 tons per year (BUA 1996).

The major use of propionaldehyde is as a reactive intermediate in the manufacture of n-propanol, propionic acid, 2-methyl pentanol, trimethyolethane polyols, polyethylene additives, fragrance chemicals and fungicides (OECD 1994).

**Table 1. Chemical and Physical Properties**

| Parameter | Value | Reference |
|---|---|---|
| Synonyms | Methylacetaldehyde, Propanal | Merck 1989 |
| Chemical formula | $C_3H_6O$ | Merck 1989 |
| Molecular weight | 58.08 | Merck 1989 |
| CAS Reg. No. | 123-38-6 | NLM |
| Physical state | liquid | Merck 1989 |
| Color | colorless | NLM |
| Solubility in water | Sol. in 5 vol. water at 20°C | Merck 1989 |
| Vapor pressure | 343 hPa at 20°C | BUA 1996 |
| Vapor density (air = 1) | 1.8 at 100° F | NLM |
| Liquid density (water = 1) | 0.8071 (at 20°C) | Merck 1989 |
| Melting point | -81°C | Merck 1989 |
| Boiling point | 49°C | Merck 1989 |
| Odor | Suffocating odor | Merck 1989 |
| Flammability | Flash point between –18 and –40°C | BUA 1996 |
| Explosive | LEL: 2.3 - 2.9 vol%<br>Upper explosion limits between 16 and 21 vol% | BUA 1996 |
| Conversion factors | 1 $mg/m^3$ = 0.41 ppm<br>1 ppm = 2.41 $mg/m^3$ | BUA 1996 |

# 2. HUMAN TOXICITY DATA

## 2.1. Acute Lethality

No information is available on the acute lethality of propionaldehyde to humans.

## 2.2. Nonlethal Toxicity

Sim and Pattle (1957) exposed (chamber) 12 human male volunteers for 30 minutes to propionaldehyde at a concentration of 134 ppm. The concentration was measured by back titration to pH 4.5 of the HCl liberated by the reaction of the aldehyde with hydroxylamine hydrochloride. It was stated that: "This exposure would have been tolerated for a longer period of time than the actual exposure period. It was only mildly irritating to the mucosal surfaces, and there was only an occasional comment about the odor of the substance.". No further information available.

In Izmerov *et al.* (1982), a human limit of 14 to 16 mg/m$^3$ (5.7 – 6.6 ppm) is stated. This is a listing that does not contain data or additional information.

## 2.3. Summary of human data

Except for limited data on irritation only, data on the toxicity of propionaldehyde to humans are not available. The available study suggests that exposure to 134 ppm for 30 minutes is only mildly irritating to the mucosal surfaces.

# 3. ANIMAL TOXICITY DATA

## 3.1. Acute lethality

### 3.1.1. Rabbits

Five rabbits were exposed to propionaldehyde aerosol at a concentration of 2,868 mg/m$^3$ for up to 10 hours or until death intervened. The concentration was measured but the method was not described. The results of this study are reported very briefly. The animals showed an initial increase in activity described as blinking, closing of the eyes and rubbing their faces with their paws. After the initial phase, the animals settled down and respiration became slow and deep. The animals convulsed just prior to death. All animals (5/5) died during exposure after an average of about 4 hours of exposure. At autopsy, all animals had expanded, edematous, and hemorrhagic lungs. Fluid was observed in the pleural cavity (Salem and Cullumbine 1960).

### 3.1.2. Guinea Pigs

Twenty guinea pigs were exposed to propionaldehyde aerosol at a concentration of 2,868 mg/m$^3$ for up to 10 hours or until death intervened. The concentration was measured but the method was not described. The results of this study are reported very briefly. The animals showed an initial increase in activity described as blinking, closing of the eyes and rubbing their faces with their paws. After the initial phase, the animals settled down and respiration became slow and deep. All guinea pigs survived the exposure period and 3/20 animals died on subsequent days after the exposure period (Salem and Cullumbine 1960).

### 3.1.3. Rats

Mortality of all rats was seen after a 30-minute exposure of 2 male and 2 female rats (Alderley Park) to the saturated vapor of propionaldehyde (Gage 1970). Based on the vapor pressure of propionaldehyde, the saturated vapor concentration can be estimated at 333,000 ppm at 20 ºC. Further information, including details about time of death and observations were not provided.

Groups of 8 rats were exposed for 30 minutes to propionaldehyde at nominal concentrations between 32 and 83 g/m$^3$ (13,120 and 34,030 ppm, respectively). The average concentration level was verified by uptake in absolute alcohol and determined colorimetrically by Schiff's reagent. A close agreement was found between the values read off directly and those obtained by gas analysis. The $LC_{50}$ value was determined at 62 g/m$^3$ (25,420 ppm). Rats died during or shortly after the exposure period or

recovered after about one hour and seemed unaffected on the day after the experiment. Inhalation was stated to "produce a profound anesthetic effect in most rats, at any rate on the larger doses; there was no reaction to pinches or corneal irritation after the end of the experiment". Histology (after three weeks) showed bronchitis and broncho-pneumonias of the lungs and hyperemia of the liver and kidneys (Skog 1950).

Five male and five female Sprague-Dawley rats were exposed for 4 hours to propionaldehyde vapor at a nominal concentration of 2,190 ppm. The chamber concentrations were checked using a Miran infrared spectrophotometer. The mean test material concentration was 1,930 ppm, which represents 88% of the nominal concentration. There was no control group. No rats died during the exposure or subsequent 14-day observation period. Lacrimation was seen in a few animals from 15 minutes after the start of exposure up to 2 days after the exposure. Upon necropsy, no exposure related pathological changes were seen (Eschbach 1981).

In a study by the Union Carbide Corporation (1951) and reported by Smyth *et al* (1951), dynamically generated 'substantially saturated' vapor (800 g/m$^3$ or 333,000 ppm) killed 6 of 6 rats in 10 minutes, 2 of 6 rats in 5 minutes, and 0 of 5 in 2 minutes. Exposure to a measured concentration of 16,000 ppm for 2.5-hours killed 6 of 6 rats, 8,000 ppm killed 5 of 6 rats in 4-hours and 4,000 ppm killed 0 of 6 rats in 4-hours. Gross examination of lungs of animals that died on study revealed edema, congestion, and hemorrhage.

The original data of a study by BASF (1975) were not available. According to a summary (BUA 1996), 1 out of 12 rats died after a 3-minute exposure to an atmosphere enriched or saturated (800 g/m$^3$ or 333,000 ppm) with propionaldehyde at 20°C, and 5 out 6 rats died after a 10-minute exposure. No further details available.

### 3.1.4. Mice

Fifty mice were exposed to propionaldehyde aerosol at a concentration of 2,868 mg/m$^3$ for up to 10 hours. The concentration was measured but the method was not described. The results of this study are reported very briefly. The animals showed an initial increase in activity described as blinking, closing of the eyes and rubbing their faces with their paws. After the initial phase, the animals settled down and respiration became slow and deep. The animals convulsed just prior to death. All mice died (50/50) during exposure after an average of about 5 hours of exposure. At autopsy, all animals had expanded, edematous, and hemorrhagic lungs. Fluid was observed in the pleural cavity (Salem and Cullumbine 1960).

Several summaries (BUA 1996) state an $LC_{50}$ of 21,800 mg/m$^3$ (8,938 ppm) in mice after a 2 hour exposure period based on the list by Izmerov *et al.* (1982) and an $LC_{50}$ of 20,000 mg/m$^3$ (8,200 ppm) in mice after an unknown exposure period apparently based on a study by Wang (1957). The study by Wang could not be retrieved.

**TABLE 2. Summary of Acute Lethal Inhalation Data in Laboratory Animals**

| Species | Concentration | Exposure Time | Effect | Reference |
|---|---|---|---|---|
| Rat | 1,930 ppm (analytical) | 4 hours | No lethality | Eschbach 1981 |
| Rat | 8,000 ppm (unknown) | 4 hours | 5/6 deaths | Smyth *et al.* 1951 |

| TABLE 2. Summary of Acute Lethal Inhalation Data in Laboratory Animals | | | | |
|---|---|---|---|---|
| Rat | 25,420 ppm (analytical) | 30 minutes | $LC_{50}$ | Skog 1950 |
| Rat | Saturated vapor (target) | 30 minutes | 4/4 deaths | Gage 1970 |
| Rat | Saturated vapor (target) | 2 minutes | 'Longest period without lethality' | Smyth *et al.* 1951 |
| mouse | aerosol: 2,868 mg/m$^3$ (analytical) | 5 hours on average | 50/50 deaths | Salem and Cullumbine 1960 |
| rabbit | aerosol: 2,868 mg/m$^3$ (analytical) | 4 hours on average | 5/5 deaths | Salem and Cullumbine 1960 |
| guinea pig | aerosol: 2,868 mg/m$^3$ (analytical) | 10 hours | 3/20 deaths | Salem and Cullumbine 1960 |

## 3.2. Nonlethal toxicity

### 3.2.1. Rats

Four male and four female rats (Alderley Park, 200 g) were exposed 6 hours / day for 6 days to 1,300 ppm (nominal) propionaldehyde, or 6 hours / day for 20 days to 90 ppm propionaldehyde (Gage 1970). The observations included hematology, urine, macroscopic examination and microscopic examination of several organs including the lungs but not the nasal epithelium. There were no concurrent controls but the characteristics of the animal colony was checked every 2 months. Exposure to 1300 ppm resulted in "no weight gain: autopsy (histol.) liver cell vacuolation". Exposure to 90 ppm did not result in toxic signs and organs were normal. The description of the results is very limited.

Babiuk *et al.* (1985) determined the $RD_{50}$ for sensory irritation of propionaldehyde in male Fischer-344 rats. Groups of 4 rats were exposed head-only for 10 minutes to different concentrations and the average reduction in respiratory rate was determined using a plethysmograph. Chamber concentrations were analyzed continuously with an infrared gas spectrophotometer. The $RD_{50}$ value was 6,789 ppm. The regression line equation is available to calculate other levels of respiratory depression. The concentration without an effect on the respiratory rate was 72 ppm.

Propionaldehyde induced a dose-dependent increase of the blood pressure in anesthetized male Wistar rats during a 1-minute inhalation exposure (Egle 1972a). The increase in blood pressure was significant at 4,220, 8,440, 12,660, 21,100, 42,200, 63,300 and 84,400 ppm. Over this range the blood pressure increased between 6 and 47%. The rise in pressure started after 5 seconds of exposure, reached peak effect at 20-25 seconds and persisted at or near maximum response until the end of the exposure period. The pressure rapidly returned to control levels after 5 seconds after end of the exposure. At concentrations above 42,200 ppm, the blood pressure began to fall toward control levels about 5 seconds before vapor exposure ended. A 5 to 6% increase in heart rate was seen at 8,440 and 12,660 ppm and a 26% decrease in heart rate was observed at the highest exposure of 84,400 ppm. The NOEC for cardiovascular effects in this study was 1,266 ppm. There was no information stating whether the concentrations were nominal or analytical.

Melnikova and Tokanova (1983) reported on the effects of propionaldehyde in rats. According to a short translation by the Russian Research Institute of Hygiene, Toxicology and Occupational Pathology in Volgograd, this study used a continuous inhalation of propionaldehyde in a concentration of 10.4 $mg/m^3$ (equivalent to 4.3 ppm) air with whole body exposure for 3 weeks. This exposure did not cause any changes of the behavior, general well-being and body weight gain of male Wistar rats. The autopsy showed changes in the parenchymal organs, desquamative bronchitis and, in 30% of all cases, interstitial pneumonia.

Melnikova and Tokanova (1983) and Tokanova (1982) also reported other studies in male Wistar rats. According to the available summaries of these studies in BUA 1996 and confirmed by a short translation by the Russian Research Institute of Hygiene, Toxicology and Occupational Pathology in Volgograd, male Wistar rats were exposed continuously in a whole-body inhalation chamber to propionaldehyde concentrations of 4 to 1,300 $mg/m^3$ (1.6 to 533 ppm) for up to 75 days. Although several kind of effects were reported (e.g. tachypnea, irritation of the ocular mucosa and of the upper respiratory tract, parenchymal changes in the liver and kidney), no clear conclusions van be drawn due to the limited reporting and the fact that animals were continuously exposed. No changes in body weight, behavior and histopathology were observed in rats continuously exposed to 0.01, 0.1 and 1.0 $mg/m^3$ (0.004, 0.04 and 0.4 ppm) for 3 months.

The results of an OECD 422 study by Driscoll (1993) are reported under 3.3 Developmental / Reproductive toxicity. The highest dose males (1,453 ppm) showed increased hemoglobin levels, hematocrit and monocyte concentration (parental effects). The mean absolute thymic region weight and the relative kidney weight were also increased in males but not females. Microscopic examination indicated an exposure-related effect on the olfactory epithelium in the anterior 2 sections of the nasal cavity. At the low and intermediate doses in males and females (151 and 745 ppm), vacuolization of the nasal epithelium was seen. Some atrophy was seen in the mid dose females and the low dose males. This effect was stronger in incidence and severity at the highest dose and included marked atrophy in 9 out of 15 females and 6 of 15 males. Further, one male in the middose and two in the highest dose showed squamous metaplasia. Rhinitis was seen in high and intermediate dose males and in the intermediate dose females.

### 3.2.2. Mice

An $RD_{50}$ (concentration inducing a 50% reduction in respiratory rate) of 2751 ppm is reported by Alarie (1981).

Steinhagen and Barrow (1984) determined the $RD_{50}$ of propionaldehyde in B6C3F1 and Swiss-Webster mice. Groups of 3 or 4 mice were exposed head-only for 10 minutes to four different concentrations and the respiratory rate was determined in a body plethysmograph during 5-minutes pre-exposure, during the 10-minute exposure, and during 5-minutes post-exposure. The average maximum decrease in respiratory rate for 1 minute was computed from the response of each group of animals and plotted against the log of the exposure concentration. Chamber concentration was analyzed continuously with an infrared analyzer but the results are not provided. The maximum decrease in respiratory rate was observed in the first few minutes of the exposure, followed by some recovery then another decrease in rate near the end of the exposure period. Partial recovery was seen during the recovery period of 5 minutes. The $RD_{50}$ values were 2,078 ppm and 2,052 ppm for B6C3F1 and Swiss-Webster mice, respectively. The regression line equations are available to calculate other levels of respiratory depression. The concentrations without an effect on the respiratory rate were 676 and 471 ppm for B6C3F1 mice and Swiss-Webster mice, respectively.

The sensory irritation ($RD_{50}$) of propionaldehyde was determined in male NIH mice at 3,703 ppm (Luo *et al.* 1993). The method developed by Alarie was used but no further details are available in this abstract.

A group of 10 mice was exposed to a nominal concentration of 5,230 ppm propionaldehyde (Axelsson *et al.* 1953). Some indications of an anesthetic effect were seen after 1 to 2 minutes and full anesthesia after 5 to 6 minutes of exposure. No further information.

According to a summary by Izmerov *et al.* (1982), exposure of mice to 10,000 ppm for 2 hours resulted in narcosis.

**TABLE 3. Summary of Nonlethal Inhalation Data in Laboratory Animals**

| Species | Concentration | Exposure Time | Effect | Reference |
|---|---|---|---|---|
| Rat | 1.6 ppm (unknown) | Prolonged | Hyperemia of the lung, heart, liver and kidney and hemorrhages of the lung<br>Parenchymal cell alterations of the liver and kidney | Melnikova and Tokanova 1983 |
| Rat | 4.3 ppm (unknown) | 3 weeks continuously | Cellular alterations of the parenchymal organs<br>Desquamative bronchitis<br>Interstitial pneumonia (30%) | Melnikova and Tokanova 1983 |
| Rat | 90 ppm (nominal) | 6 hours/day for 20 days | No effect | Gage 1970 |
| Rat | 92 ppm (unknown) | Brief | Increased motility, tachypnea, irritation of the eye mucosa and of the upper respiratory tract, and later atony and decreased motility | Melnikova and Tokanova 1983 |
| Rat | 151 ppm (analytical) | 52 days | Vacuolization and no or minimal atrophy of the olfactory epithelium | Driscoll 1993 |
| Rat | 745 ppm (analytical) | 52 days | No to moderate atrophy and vacuolization of the olfactory epithelium | Driscoll 1993 |
| Rat | 1,266 ppm (unknown) | 1 minute | No effect on blood pressure | Egle 1972a |
| Rat | 1,300 ppm (nominal) | 6 hours/day for 6 days | No body weight gain; liver cell vacuolization | Gage 1970 |
| Rat | 1,453 ppm (analytical) | 52 days | Marked atrophy and squamous metaplasia of the olfactory epithelium | Driscoll 1993 |
| Rat | 1,930 ppm (analytical) | 4 hours | Lacrimation | Eschbach 1981 |
| Rat | 2,592 ppm (analytical) | 52 days | No lethalities or clinical signs, effects on body weight, increase in Hb, Hct and monocytes. | Driscoll 1993 |

| TABLE 3. Summary of Nonlethal Inhalation Data in Laboratory Animals | | | | |
|---|---|---|---|---|
| Rat | 4,220 ppm (unknown) | 1 minute | Increase in blood pressure | Egle 1972a |
| Rat | 6,789 ppm (analytical) | 10 minutes | $RD_{50}$ | Babiuk *et al.* 1985 |
| Mouse Swiss-Webster | 2,052 ppm (analytical) | 10 minutes | $RD_{50}$ | Steinhagen and Barrow 1984 |
| Mouse B6C3F1 | 2,078 ppm (analytical) | 10 minutes | $RD_{50}$ | Steinhagen and Barrow 1984 |
| Mouse NIH | 3703 ppm (unknown) | unknown | $RD_{50}$ | Luo *et al.* 1993 |
| Mouse | 5,230 ppm (nominal) | 5 minutes | anesthesia | Axelsson *et al.* 1953 |

## 3.3. Developmental / Reproductive toxicity

Driscoll (1993) performed an inhalation OECD 422 combined repeated dose toxicity study with propionaldehyde including the reproduction/developmental toxicity screen. The highest dose tested in the range finding of 2,592 ppm (analytical) on pregnant females (day 0-20) did not result in lethality or clinical signs but affected several hematological parameters. Microscopic evaluation of the respiratory system was not performed in the range-finding study. In the main study, groups of 15 animals per sex per dose were exposed to nominal vapor concentrations of 0, 150, 750 and 1,500 ppm for 6 hours per day and 7 days per week. The exposure chamber concentration was measured using a gas chromatograph equipped with a flame ionization detector. The measured concentrations (151, 745 and 1,453 ppm) were in close agreement to the target concentrations Male rats were exposed 2 weeks prior to mating and 38 days afterwards. Females were exposed 2 weeks prior to mating through day 20 of gestation (35 – 48 days). Males were sacrificed on the day after the last exposure and females on day 4 of lactation. Body weight gain and food consumption were reduced in week 1 in the females exposed to 750 and 1,500 ppm. Absolute body weights were sometimes reduced in the highest dose females. Reproductive parameters and the litter size, sex ratio, viability, birth weight and survival of the offspring were not affected. The body weight gain of the pups between day 0 and day 4 was reduced (22%) at the highest dose. The highest dose males showed increased hemoglobin levels, hematocrit and monocyte concentration (parental effects). The mean absolute thymic region weight and the relative kidney weight were also increased in parental males. Microscopic examination indicated an exposure-related effect on the olfactory epithelium in the anterior 2 sections of the nasal cavity. Vacuolization of the olfactory epithelium was observed at the low and intermediate dose levels (150 and 750 ppm), while atrophy was seen in the intermediate and high dose groups (750 and 1500 ppm). Squamous metaplasia was observed in 2 males from the 1500 ppm group and 1 male exposed to 750 ppm. No females displayed squamous metaplasia. Rhinitis was more prevalent in males than females. Slott (1985) determined the teratogenicity and embryolethality of propionaldehyde after intra-amniotic injection in rats. Sprague-Dawley rats (5 or 6 per group) received an intra-amniotic injection with 10, 100 or 1,000 µg/fetus on day 13 of gestation. Fetuses were examined on day 20 of gestation. The number of dead or resorbed fetuses was significantly increased at 1,000 µg/fetus. The incidence of malformations was not affected at any concentration.

## 3.4. Genotoxicity

The genotoxicity was recently summarized by the German Chemical Society (BUA 1996). Most bacterial tests were negative with and without metabolic activation. Only a DNA repair test on *Salmonella typhimurium* TA 1535 (umu-test) was weakly positive with S9-activation (One *et al.* 1991, as cited in BUA 1996). In the recombination test on *Bacillus subtilis*, an increase of the recombination rate was determined (Matsui *et al.* 1989, as cited in BUA 1996) One gene mutation-test (HGPRT assay) in V79 without metabolic activation was negative when tested at a maximum concentration of 2.0 uM (Smith *et al.* 1990 as cited in BUA 1996) but another showed an increase in mutation rate when tested at 10 and 30 uM (Brambilla *et al.* 1989, as cited in BUA 1996).

In an UDS-test in primary rat hepatocytes, a concentration-dependent increase of the repair activity was seen which was significant at 30 mM and above. The same concentrations were negative in an UDS-assay in human hepatocytes. In the alkaline elution test on CHO-K1-cells, propionaldehyde caused a concentration-dependent increase of DNA single-strand breaks and decreased cross-links. In vitro incubation of propionaldehyde with DNA and calf thymus histones induced DNA-protein cross-linking (Martelli *et al.* 1994).

Propionaldehyde caused an increase in chromosome aberration rate and sister-chromatid exchange rate in CHO-cells (NTP 1985, as cited in BUA 1996). In another test on diploid embryonic Chinese hamster cells, a significant increase of the chromosome aberration rate and the number of aneuploid cells were seen at three concentrations without a concentration dependency (Furnus *et al.* 1990, as cited in BUA 1996). In a third test, the sister-chromatid exchange rate in human lymphocytes was within the deviation range of the controls (Obe and Beek 1979, as cited in BUA 1996).

In an in vivo micronucleus test in male and female Swiss-Webster mice with a single intraperitoneal exposure to 240, 480 or 768 mg/kg bw, propionaldehyde induced a significant increase of polychromatic erythrocytes with micronuclei in the male mice at the highest concentration after 24 and 48 hours but not at 12 hours. According to the authors, the increase was not substance related but caused by the low micronuclei level in the control group, which was at the lower end of the normal range. This cannot be confirmed by the evaluator (RIVM staff scientist) because no information on the historical control range is provided in the report (Vergnes and Morabit, 1993).

The available genotoxicity information shows that propionaldehyde is genotoxic in vitro. It is unclear whether this is confirmed by the only in vivo study.

## 3.5. Carcinogenicity

A carcinogenicity study with propionaldehyde is not available.

## 3.6. Summary of animal data

Only limited information is available on the toxicity of propionaldehyde in animals. Inhalation exposure to propionaldehyde induces sensory irritation in mice and rats after exposure during 10 minutes with an $RD_{50}$ in the range of 2,000 to 7,000 ppm (Steinhagen and Barrow 1984, Babiuk *et al.*1985). Airway irritation was found after exposure during approximately 50 days (Driscoll 1993). Minimal effects on the nasal olfactory epithelium were seen at 150 ppm increasing to atrophy and squamous metaplasia at 1,500 ppm. CNS depression was seen within minutes after exposure of mice to 5,230 ppm (Axelsson *et al.*1953), in the rat study by Eschenbach (1981) and in the study by Salem and Cullumbine (1960) on several species. Mortality in mice and rabbits was seen after several hours of exposure to 2868 $mg/m^3$ as aerosol in one very briefly reported study. No mortality was observed in guinea pigs during exposure but 3/20 died on subsequent days after exposure (Salem and Cullumbine 1960). In rats, mortality was found after short exposure to the saturated vapor (approximately 333,000 ppm) (Gage 1970). The 30-min $LC_{50}$

value of 25,420 ppm in rats (Skog 1950) deviates from the results in the other species. Propionaldehyde does not affect the fertility and embryotoxicity in the limited study on developmental and reproductive toxicity (Driscoll 1993). No information is available on carcinogenicity. The available genotoxicity information shows that propionaldehyde is genotoxic in vitro. It is unclear whether this is confirmed by the only in vivo study.

# 4. SPECIAL CONSIDERATIONS

## 4.1. Metabolism and Disposition

*Absorption*

Egle (1972b) determined the retention of propionaldehyde to be approximately 80% in anesthetized mongrel dogs after inhalation exposure to concentrations of approximately 400 to 1200 $mg/m^3$ (164 – 492 ppm) by measuring the inhaled and expelled air. Concentrations were determined using a colorimetric method. No information is provided on toxicological end-points.

*Metabolism*

The aldehyde metabolism takes place mainly via 2 pathways: either the aldehyde is oxidized to the corresponding acid, bound to coenzyme A and incorporated into the fatty acid metabolism and citric acid cycle or it binds to the sulfhydryl group of glutathione, whereby a thiohemiacetal is formed (Brabec 1981).

## 4.2. Mechanism of Toxicity /Physiological effects

*Studies*

Beckner *et al.* (1974) studied the effects of propionaldehyde on contractility, $^{14}$C-norpepinephrine and $^{45}$Calcium binding in isolated smooth muscle. Propionaldehyde induced reversible contraction of the vas deferens at concentrations of 1 mM and above. Contraction was prevented by pretreatment of the rats with reserpine to deplete tissues of endogenous norepinephrine. Pretreatment with propionaldehyde (2 and 3 mM) did not affect the dose-response curve for norepinephrine. Propionaldehyde (1 mM) increased the *release* of norepinephrine from the vas deferens and (at 10 mM) decreased the *uptake* of norepinephrine by the vas deferens. Propionaldehyde did not affect the efflux of calcium from the rabbit aorta in vitro but did reduce the binding of calcium at 10 mM.

Egle *et al.* (1973) studied the effects of iv exposure of anesthetized rats to propionaldehyde on blood pressure and heart rate. At the lowest dose of 5 mg/kg, all animals showed an increase of blood pressure of approximately 10%. At higher concentrations, some animals showed a reduction of blood pressure and some a reduction compared to resting blood pressure. At the highest dose of 40 mg/kg, 13 out of 16 animals showed a strong reduction of 64% (average) in blood pressure and 3 out of 16 animals an increase (average 23%) in blood pressure. Adrenalectomy or adrenalectomy plus reserpine pretreatment reduced the number of animals with increased blood pressure at 20 and 40 mg/kg. Pretreatment with phentolamine reduced the increase of blood pressure and the number of animals with increased blood pressure. Also the level of decrease of blood pressure at the higher concentrations was reduced compared to none pre-treated rats. Pretreatment with propranolol also affected the changes in blood pressure. Pretreatment with atropine strongly reduced the reduction in blood pressure at the higher dose levels as did vagotomy. An inhibitory effect on heart rate was only seen at 40 mg/kg. This effect was enhanced by adrenalectomy and adrenalectomy plus reserpine pretreatment and reduced by pretreatment with phentolamine or atropine. Vagotomy reversed the cardioinhibitory effect of propionaldehyde.

These results indicate that propionaldehyde induces a pressor effect primarily due to vasoconstriction mediated by the release of catecholamines from sympathetic nerve endings in vascular smooth muscle. At higher doses, propionaldehyde induces bradycardia and hypotension as a result of

stimulation from higher centers. These effects may explain the cardiovascular response to propionaldehyde.

*$RD_{50}$ studies*

The suitability of the sensory irritation test as proposed in the past by Alarie for AEGL-setting is questionable. Bos et al. (1992) evaluated this test for the assessment of Occupational Exposure Limits. Among others, the reproducibility, reliability and interpretation were discussed. It was concluded that there was an insufficient basis for the use in standard setting. As to the possible use of the $RD_{50}$ in setting AEGL-values the main point of concern is that no relationship is found between the $RD_{50}$ and other toxic effects like respiratory tract irritation, systemic effects, and mortality. These effects may occur at or below $RD_{50}$ concentrations, e.g. the $RD_{50}$s for epichlorohydrin and chlorine are even lethal concentrations (Bos *et al* 1992, 2002). Therefore, the outcome of the sensory irritation test cannot be placed on a toxicity scale with increasing severity, and can thus for the moment not be directly linked with toxicity endpoints defined for AEGL-1, AEGL-2, or AEGL-3.

## 4.3. Structure Activity Relationships

Guth (1996) provides a detailed comparison of the biochemistry and non-cancer toxicology of propionaldehyde with related low-molecular-weight aldehydes. Several comparisons between propionaldehyde and acetaldehyde were done by the same group of researchers and are summarized in Table 4. The results of other studies, summarized in this report, are added to the table. Further, both substances seem to have a lung irritating and anesthetizing effect. Based on comparisons of biochemical reactivity, cardiovascular and liver effects, kinetics and metabolism and respiratory tract effects from acute exposures between propionaldehyde and acetaldehyde, is was concluded by Guth that ”direct extrapolation of effects of acute exposures from acetaldehyde to propionaldehyde appears justified”. The only data that indicate that the effects of propionaldehyde and acetaldehyde are not comparable are the results on mortality by Smyth *et al.* (1951). However, the results by Smyth *et al.* on acetaldehyde can be doubted because the $LC_{50}$ value for a 4-hour exposure of 13,300 ppm as found in a more recent and well-performed study by Appelman *et al.* (1982) is in contradiction with the absence of mortality after an 8-hour exposure to 8,000 and 16,000 ppm as found by Smyth *et al*. This indicates that the results on propionaldehyde by Smyth *et al.* can be doubted as well. In conclusion, the available data indicate that the acute toxicity of acetaldehyde and propionaldehyde are in general terms similar, which indicates that the AEGL values for propionaldehyde and acetaldehyde should be in the same order of magnitude. In general, chemical reactivity decreases with increasing chain length, it can be expected that propionaldehyde will be less toxic than acetaldehyde and its AEGL-values should therefore not be lower than those for acetaldehyde.

**Table 4. Comparison of effects of propionaldehyde and acetaldehyde**

| Effect | Acetaldehyde | Propionaldehyde | Reference |
|---|---|---|---|
| Rat vas deference smooth muscle contractility tension @10-2M (g) | 0.6 | 0.5 | Beckner *et al.* 1974 |
| Increase in blood pressure in rat | | | Egle *et al.* 1973 |
| 5 mg/kg IV (%) | 10.7 | 10.5 | |
| 10 mg/kg IV (%) | 6.7 | 12.4 | |
| NOEL in ppm for: | | | Egle 1972a |
| Increased heart rate | 5560 | 4220 | |
| Increased blood pressure | 556 | 1266 | |
| Deposition in dog upper respiratory tract (%) | 50-55 | 59-63 | Egle 1972b |
| Aldehyde dehydrogenase, partially purified from mouse liver cytosol | | | Petersen *et al.* 1977 |
| Km (uM) | 0.59 | 0.36 | |

| | | | |
|---|---|---|---|
| Vmax | 4.40 | 3.30 | |
| $RD_{50}$ values (ppm) | | | |
| B6C3F1 mice | 2932 | 2078 | Steinhagen and Barrow 1984 |
| Swiss Webster mice | 2845 | 2052 | Steinhagen and Barrow 1984 |
| Swiss Webster mice | 4900 | 2750 | Alarie 1981 |
| F-344 rat | 2991 | 6900 | Babiuk *et al.* 1985 |
| Mortality | 8000 ppm<br>8 hour: 0/6<br>16000 ppm<br>8 hour: 0/6 | 8000 ppm<br>4 hour: 5/6 | Smyth *et al.* 1951 |
| $LC_{50}$ in 30 minutes (ppm) | 20720 | 25420 | Skog 1950 |
| Mean fatal dose of aerosol (mg * min/m3) | | | Salem and Cullumbine 1960 |
| Mice | $3.3\ 10^5$ | $7.9\ 10^5$ | |
| Guinea pigs | $6.9\ 10^5$ | survival* | |
| Rabbits | $3.9\ 10^5$ | $7.4\ 10^5$ | |

*3 of 20 died in subsequent days after exposure

## 4.4. Other relevant information

### 4.4.1. Species variability

The available data on the acute inhalation toxicity and sensory irritation of propionaldehyde indicate that rats might be less susceptible than mice or rabbits. However, the available information is too limited to indicate quantitative species differences.

### 4.4.2. Irritation and Sensitization

A 75% aqueous propionaldehyde solution caused erythema within 60 minutes after a 5 minutes exposure to the human skin (BUA 1996). Studies summarized by the OECD (1995) indicate moderate to severe skin and eye irritation. Further, propionaldehyde is classified in the EU with R36/37/38: Irritating to eyes, respiratory system and skin. The data on respiratory irritation are discussed in the previous sections.

Skin sensitization testing was performed on guinea pigs at a concentration of 0.1M in an acetone:dioxane:guinea pig fat (1:1:1) vehicle. Phenylhydrazine was employed as a positive control. Propionaldehyde was negative for sensitization under conditions of the test (Gordon, 2000).

# 5. DATA ANALYSIS FOR AEGL-1

## 5.1. Summary of human data relevant to AEGL-1

The only human data available is the study by Sim and Pattle (1957). The only tested concentration of 134 ppm (analytical) was reported to be mildly irritating to the mucosal surfaces. No other human data are available.

## 5.2. Summary of animal data relevant to AEGL-1

The $RD_{50}$ was derived from a series of different exposure concentrations in several species. The regression line equations from these studies are available and were used to determine levels without a reduction in the respiratory rate. The concentrations without an effect on the respiratory rate were 72, 676 and 471 ppm for rats, B6C3F1 mice and Swiss-Webster mice respectively.

According to the report by Melnikova and Tokanova (1983), brief exposure to a concentration of 92 ppm resulted in an increased motility, tachypnea, irritation of the eye mucosa and of the upper respiratory tract, and later caused atony and decreased motility.

## 5.3. Derivation of AEGL-1

The human study by Sim and Pattle (1957) indicates that 134 ppm is a level that induces only mild irritation of the mucosal surface after a 30 minutes exposure (n=12). This level of severity is considered to be sub-AEGL-1, and a valuable starting point for AEGL-1 derivation.

Because the effect is direct irritation, differences between individuals are expected to be small. Therefore an intraspecies factor of 3 is applied to account for differences between humans. Because AEGL-1 is based on irritation, it is proposed to set the AEGL-1 values of 45 ppm for all time points. These values are based on the same study and equal to those proposed for the comparable substance acetaldehyde.

**TABLE 5. AEGL-1 Values for propionaldehyde**

| 10-minute | 30-minute | 1-hour | 4-hour | 8-hour |
|---|---|---|---|---|
| 45 ppm ($110\ mg/m^3$) | 45 ppm ($110\ mg/m^3$) | 45 ppm ($110\ mg/m^3$) | 45 ppm ($110\ mg/m^3$) | 45 ppm ($110\ mg/m^3$) |

# 6. DATA ANALYSIS FOR AEGL-2

## 6.1. Summary of human data relevant to AEGL-2

No adequate human data that address the level of effects defined by the AEGL-2 were retrieved.

## 6.2. Summary of animal data relevant to AEGL-2

No effects were seen in rats after an exposure to 90 ppm for 6 hours/day during 20 days (Gage, 1970). Lacrimation was the only effect reported in some rats exposed for 4 hours to an analytical concentration of 1,930 ppm from 15 minutes after the start of exposure to 2 days after exposure (Eschbach 1981). Anesthesia was seen within minutes in mice exposed to 5,230 ppm (nominal, Axelsson *et al.* 1953). No weight gain and liver cell vacuolization were seen after an exposure to 1,300 ppm for 6 hours/day during 6 days. However, damage to the nasal epithelium, a sensitive endpoint for aldehydes, was not determined in this study (Gage 1970).

In a well-performed study by Driscoll (1993), irritating effects on the olfactory epithelium were seen after 5 to 7 weeks exposure for 6 hours a day to 151, 745 and 1,453 ppm (analytical concentrations). Atrophy and vacuolization of the olfactory epithelium were observed in most animals at the end of the study. In the TSD for acetaldehyde it was shown that such degenerative changes of the epithelium were not observed during a single day exposure but were present first after 3 days exposure and aggravated thereafter. Therefore, it is likely that the histopathologic changes observed in the Driscoll study can be attributed to repeated exposure and would not result from a single exposure.

The studies described by Melnikova and Tokanova (1983) and Tokanova (1982) are not considered because of the limited description of these studies.

### 6.3. Derivation of AEGL-2

The anesthesia after 5 minutes exposure to 5,230 ppm in the mouse might be considered to impair the ability to escape. The higher exposure values without irreversible effects in the study by Eschnach and in the range-finding study by Driscoll are not fully adequate because no microscopic examination of the nasal cavity was performed (one of the most sensitive effects for aldehydes). The value of 1,453 ppm for 6 hours a day from the well-performed study by Driscoll (1993) can be used as a starting point for AEGL-2. The main effects observed in this study on the nasal epithelium can be attributed to repeated exposure and are not expected to occur after a single day exposure of 6 hours (see TSD on acetaldehyde).

A total uncertainty factor of 10 is applied, consisting of an interspecies factor of 3 and a intraspecies factor of 3. A higher factor would reduce the AEGL-2 to levels that were tolerated without any serious effects in the human volunteer study with propionaldehyde. In addition, the resulting AEGL-2 values would than be inconsistent with the values for acetaldehyde. Default time-scaling $C^n xt = k$ was performed with default values of n=1 for extrapolation to longer time periods and *n*=3 for extrapolation to shorter time periods. Because the starting point for time extrapolation is 4 hours or longer, the AEGL-2 10-minute value is the same as the AEGL-2 30-minute value. The AEGL-2 values for propionaldehyde are in the same range as the values for acetaldehyde.

**TABLE 6. AEGL-2 Values for propionaldehyde**

| 10-minute | 30-minute | 1-hour | 4-hour | 8-hour |
|---|---|---|---|---|
| 330 ppm (800 mg/m$^3$) | 330 ppm (800 mg/m$^3$) | 260 ppm (630 mg/m$^3$) | 170 ppm (410 mg/m$^3$) | 110 ppm (270 mg/m$^3$) |

## 7. DATA ANALYSIS FOR AEGL-3

### 7.1. Summary of human data relevant to AEGL-3

No adequate human data that address the level of effects defined by the AEGL-3 were retrieved.

### 7.2. Summary of animal data relevant to AEGL-3

In rats, exposure to saturated vapor concentrations (about 800 g/m$^3$ or 333,000 ppm) induced no lethality within 2 minutes (Smyth *et al.* 1951) and 100% mortality after 30 minutes (Gage 1970). An $LC_{50}$ of 25,420 ppm was determined in rats for 30-minute exposures (Skog 1950). An exposure to 8,000 ppm for 4 hour (analytical concentration) caused 5/6 mortality (Smyth *et al.* 1951). Exposure of 5 male and 5 female rats to an analytical concentration of 1,930 ppm for 4 hours did not result in lethality (Eschbach 1981). Exposure of mice and rabbits to 2868 mg/m$^3$ (nominal) as an aerosol caused mortality after an average exposure period of 5 and 4 hours, respectively (Salem and Cullumbine 1960). Fifteen percent of the guinea pigs died after exposure to the same concentration for 10 hours (Salem and Cullumbine 1960). The data might indicate that mice, guinea pigs and rabbits might be more sensitive to propionaldehyde lethality than are rats. However, the data for acetaldehyde reported in the same study were also rather low compared to other data from well-performed studies and were not used in AEGL-derivation. Furthermore, long term studies indicate that rats survive exposure to 1,300 ppm (nominal, Gage 1970) and 2,500 ppm (analytical, Driscoll 1993).

## 7.3. Derivation of AEGL-3

Limited data are available on the acute inhalation toxicity of propionaldehyde in animals and no data are available in humans. The limited animal data do not allow the determination of a benchmark concentration (BMC) because only one concentration was used or only the $LC_{50}$ value is provided. The results of some dated studies can be clearly doubted. The study description by Salem and Cullumbine (1960) is too limited for an adequate evaluation. Animals were exposed to one concentration of an aerosol until death occurred. The quality of this study is doubted and the results are not used for AEGL-3 setting. The 30-min $LC_{50}$ of 25,420 ppm appears to be rather low; AEGL-3 values for the longer exposure periods derived from this value would be close to or below the corresponding AEGL-2 values. Furthermore, they also report an $LC_{50}$ for acetaldehyde that significantly deviates from an $LC_{50}$ found in a well-performed study. It is concluded that the available acute exposure data are qualitatively insufficient and do not provide an adequate basis for AEGL-3. However, based on the rat data with repeated exposures a level without mortality would be at least 2,500 ppm for 6 hours.

Qualitative much better data are available for the closely-related substance acetaldehyde. The AEGL-3 values for acetaldehyde are based on a well-performed toxicity study that allowed proper dose-response modeling (Appelman *et al*. 1982). The toxicity of both compounds is in quantitative terms similar, it can at least be expected that propionaldehyde will be equal or (more probably) less toxic than acetaldehyde. Because of this similarity in toxicity it is concluded to adapt the AEGL-3 numbers for acetaldehyde also for propionaldehyde.

The AEGL-3 values for acetaldehyde are based on a $BMDL_{05}$ of 5,295 ppm for 4 hours derived from an acute and a subacute inhalation toxicity study in rats (Appelman *et al*.1982). To this level a total uncertainty factor of 10 is applied, consisting of a factor of 3 for interspecies extrapolation and a factor of 3 for sensitive human subpopulations. The value of 5,295 ppm for 4 hours was extrapolated across time periods using $C^n xt = k$ with default values $n$=1 for extrapolation to longer time periods and $n$=3 for extrapolation to shorter time periods. Because the starting point for time extrapolation is 4 hours or longer, the AEGL-3 10-minute value is the same as the AEGL-3 30-minute value. It is proposed to adopt these values for acetaldehyde also for propionaldehyde since the toxicity of both compounds is similar. The scientific basis of the AEGL-3 values for acetaldehyde is better than can be obtained from the limited data of propionaldehyde. Nevertheless, the resulting AEGL-3 levels are in compliance with the toxicity profile expected for propionaldehyde (including the data from the repeated dose study of Driscoll *et al.* 1993). The following AEGL-3 values were derived:

**TABLE 7. AEGL-3 Values for propionaldehyde**

| 10-minute | 30-minute | 1-hour | 4-hour | 8-hour |
|---|---|---|---|---|
| 1,100 ppm (2,700 mg/m$^3$) | 1,100 ppm (2,700 mg/m$^3$) | 840 ppm (2,000 mg/m$^3$) | 530 ppm (1,300 mg/m$^3$) | 260 ppm (630 mg/m$^3$) |

# 8. SUMMARY OF AEGLS

## 8.1 AEGL values and toxicity endpoints

**TABLE 8. Summary of AEGL Values**

| Classification | Exposure Duration | | | | |
|---|---|---|---|---|---|
| | 10-minute | 30-minute | 1-hour | 4-hour | 8-hour |
| AEGL-1 (Nondisabling) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) |
| AEGL-2 (Disabling) | 330 ppm (800 mg/m$^3$) | 330 ppm (800 mg/m$^3$) | 260 ppm (630 mg/m$^3$) | 170 ppm (410 mg/m$^3$) | 110 ppm (270 mg/m$^3$) |
| AEGL-3 (Lethal) | 1,100 ppm (2,700 mg/m$^3$) | 1,100 ppm (2,700 mg/m$^3$) | 840 ppm (2,000 mg/m$^3$) | 530 ppm (1,300 mg/m$^3$) | 260 ppm (630 mg/m$^3$) |

## 8.2 Comparison with other standards and guidelines

There are very view standards derived for propionaldehyde. The AEGL-1 of 45 ppm is about twofold higher than the TLV-TWA of 20 ppm. It is unclear how the TLV-TWA was derived.

**TABLE 9. Extant Standards and Guidelines for Chemical**

| Guideline | Exposure Duration | | | | |
|---|---|---|---|---|---|
| | 10 minute | 30 minute | 1 hour | 4 hour | 8 hour |
| AEGL-1 | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) |
| AEGL-2 | 330 ppm (800 mg/m$^3$) | 330 ppm (800 mg/m$^3$) | 260 ppm (630 mg/m$^3$) | 170 ppm (410 mg/m$^3$) | 110 ppm (270 mg/m$^3$) |
| AEGL-3 | 1,100 ppm (2,700 mg/m$^3$) | 1,100 ppm (2,700 mg/m$^3$) | 840 ppm (2,000 mg/m$^3$) | 530 ppm (1,300 mg/m$^3$) | 260 ppm (630 mg/m$^3$) |
| ERPG-1 (AIHA)[a] | | | -- | | |
| ERPG-2 (AIHA) | | | -- | | |
| ERPG-3 (AIHA) | | | -- | | |
| EEGL (NRC)[b] | | | | | |
| PEL-TWA (OSHA)[c] | | | | | |
| PEL-STEL (OSHA)[d] | | | | | |
| IDLH (NIOSH)[e] | | | --[*] | | |

| | | | | | |
|---|---|---|---|---|---|
| REL-TWA (NIOSH)[f] | | | | | |
| REL-STEL (NIOSH)[g] | | | | | |
| TLV-TWA (ACGIH)[h] | | | | | 20 ppm (48 mg/m$^3$) |
| TLV-STEL (ACGIH)[i] | | | | | |
| MAK (Germany)[j] | | | | | |
| MAK Peak Limit (Germany)[k] | | | | | |
| MAC (The Netherlands)[l] | Not available | | | | |

* In the absence of an established NIOSH IDLH value, NIOSH recommends using 10% of the LEL (LEL= 2.3-2.9%)

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 1994)
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protection action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b]**EEGL (Emergency Exposure Guidance Levels, National Research Council** (NRC 1985)
The EEGL is the concentration of contaminants that can cause discomfort or other evidence of irritation or intoxication in or around the workplace, but avoids death, other severe acute effects and long-term or chronic injury.

[c]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (OSHA 1970) is defined analogous to the ACGIH-TLV-TWA.

[d]**OSHA PEL-STEL (Permissible Exposure Limits - Short Term Exposure Limit)** (OSHA 1970) is defined analogous to the ACGIH-TLV-STEL.

[e]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 1994) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[f]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 1997) is defined analogous to the ACGIH-TLV-TWA , but is for exposures of no more than 10 hours/day, 40 hours/week.

[g]**NIOSH REL-STEL (Recommended Exposure Limits - Short Term Exposure Limit)** (NIOSH 1997) is defined analogous to the ACGIH TLV-STEL.

[h]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 199?) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[i]**ACGIH TLV-STEL (Threshold Limit Value - Short Term Exposure Limit)** (ACGIH 199?) is defined as a 15-minute TWA exposure which should not be exceeded at any time during the workday even if the 8-hour TWA is within the TLV-TWA. Exposures above the TLV-TWA up to the STEL should not be longer than 15 minutes and should not occur more than 4 times per day. There should be at least 60 minutes between successive exposures in this range.

[j]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 2000) is defined analogous to the ACGIH-TLV-TWA.

[k]**MAK Spitzenbegrenzung (Peak Limit [give category])** (German Research Association 2000) constitutes the maximum average concentration to which workers can be exposed for a period up to 30 minutes with no more than 2 exposure periods per work shift; total exposure may not exceed 8-hour MAK.

[l]**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-TLV-TWA.

## 8.3 Data quality and research needs

Only very limited human data are available at one concentration with limited reporting of the effects. However, because this is the only human study it is used as a key study for AEGL-1. There is only a limited number of animal studies with single inhalation exposure for which adequate toxicity information is available on the critical effect expected for propionaldehyde, irritation of the respiratory tract. Other studies are dated and poorly reported. The few studies that are adequately described often used only one concentration.

The proposed AEGL-2 value is based on the absence of effects in a repeated inhalation study. This was a well-reported study with microscopic examination of the effects on the respiratory tract. The available data were concluded to be insufficient for the derivation of AEGL-3 values.

Further research on effects as defined by the AEGL-1 and 3 are needed for propionaldehyde.

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# APPENDIX A: Derivation of AEGL Values

**Derivation of AEGL-1**

| | |
|---|---|
| Key study: | Sim and Pattle 1957 |
| Toxicity Endpoint: | mild irritation to the mucosal surfaces |
| Time scaling: | Flatlining from 10-min to 8-hour |
| Uncertainty factors: | 3 for intraspecies |
| Calculations: | 134 ppm / 3 = 45 ppm |
| 10-minute AEGL-1 | 45 ppm (110 mg/m$^3$) |
| 30-minute AEGL-1 | 45 ppm (110 mg/m$^3$) |
| 1-hour AEGL-1 | 45 ppm (110 mg/m$^3$) |
| 4-hour AEGL-1 | 45 ppm (110 mg/m$^3$) |
| 8-hour AEGL-1 | 45 ppm (110 mg/m$^3$) |

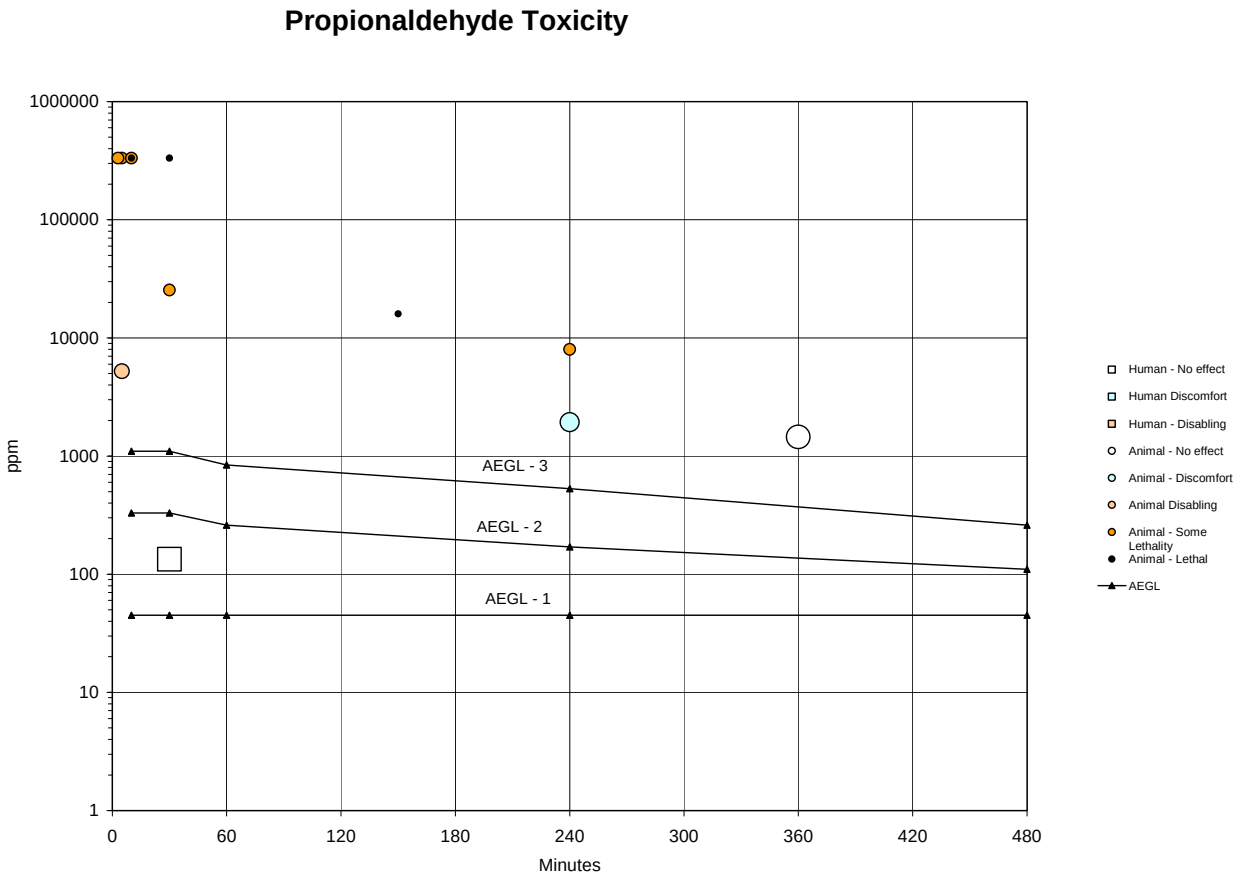
## Derivation of AEGL-2

| | |
|---|---|
| Key study: | Driscoll 1993 |
| Toxicity Endpoint: | Absence of irreversible irritation of the nasal epithelium in rats (sub AEGL-2 effect) at 1,453 ppm (highest concentration tested) for 6 h/d for approximately 50 days. |
| Time scaling: | 6-hour exposure to 1453 ppm. $C^n * t = k$ with default values: n=1 for longer time points and n=3 for shorter time points.<br>$k = (1453 \text{ ppm})^n * 360 \text{ min}$ |
| Uncertainty factors: | 10 (3 for interspecies and 3 for intraspecies) |
| Calculations: | |
| 10-minute AEGL-2 | 10-min AEGL-2 = 330 ppm (800 mg/m$^3$) (set equal to 30-min value) |
| 30-minute AEGL-2 | $C^3 * 30 \text{ min} = (1453)^3 * 360 \text{ ppm}^3 \text{ min}$<br>C = 3327 ppm<br>30-min AEGL-2 = 3327 / 10 ≈ 330 ppm (800 mg/m$^3$) |
| 1-hour AEGL-2 | $C^3 * 60 \text{ min} = (1453)^3 * 360 \text{ ppm}^3 \text{ min}$<br>C = 2640 ppm<br>60-min AEGL-2 = 2640 /10 ≈ 260 ppm (630 mg/m$^3$) |
| 4-hour AEGL-2 | $C^3 * 240 \text{ min} = (1453)^3 * 360 \text{ ppm}^3 \text{ min}$<br>C = 1663 ppm<br>240-min AEGL-2 = 1663 /10 ≈ 170 ppm (410 mg/m$^3$) |
| 8-hour AEGL-2 | $C^1 * 480 \text{ min} = (1453)^1 * 360 \text{ ppm min}$<br>C = 1090 ppm<br>480-min AEGL-2 = 1090 /10 ≈ 110 ppm (270 mg/m$^3$) |

## Derivation of AEGL-3

| | |
|---|---|
| Key study: | Appelman *et al.* 1982 |
| Toxicity Endpoint: | Lethality in rats observed following acute and subacute exposure to the comparable substance acetaldehyde, revealing a 4-h $BMDL_{05}$ of 5,295 ppm. |
| Time scaling: | 4-hour exposure to 5295 ppm. $C^n * t = k$ with default values: n=1 for longer time points and n=3 for shorter time points.<br>$k = (5295 \text{ ppm})^n * 240 \text{ min}$ |
| Uncertainty factors: | 10 (3 for interspecies and 3 for intraspecies) |
| Calculations: | |
| 10-minute AEGL-3 | 10-min AEGL-3 = 1100 ppm (2700 $mg/m^3$) (set equal to 30-min value) |
| 30-minute AEGL-3 | $C^3 * 30 \text{ min} = (5295)^3 * 240 \text{ ppm}^3 \text{ min}$<br>C = 10586 ppm<br>30-min AEGL-3 = 10,586 / 10 ≈ 1100 ppm (2700 $mg/m^3$) |
| 1-hour AEGL-3 | $C^3 * 60 \text{ min} = (5295)^3 * 240 \text{ ppm}^3 \text{ min}$<br>C = 8402 ppm<br>60-min AEGL-3 = 8402 /10 ≈ 840 ppm (2000 $mg/m^3$) |
| 4-hour AEGL-3 | 240-min AEGL-3 = 5295 (point of departure) /10 ≈ 530 ppm (1300 $mg/m^3$) |
| 8-hour AEGL-3 | $C^1 * 480 \text{ min} = (5295)^1 * 240 \text{ ppm min}$<br>C = 2648 ppm<br>480-min AEGL-3 = 2648 /10 ≈ 260 ppm (620 $mg/m^3$) |

# APPENDIX B: Category Plot for Propionaldehyde


Propionaldehyde Toxicity
1000000
100000
10000
1000
100
10
1
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL - 3
AEGL - 2
AEGL - 1
Human - No effect
Human Discomfort
Human - Disabling
Animal - No effect
Animal - Discomfort
Animal Disabling
Animal - Some Lethality
Animal - Lethal
AEGL

1
2

# APPENDIX C: Derivation Summary for Propionaldehyde AEGLs

## ACUTE EXPOSURE GUIDELINE LEVELS FOR PROPIONALDEHYDE (CAS Reg. No. 123-38-6) DERIVATION SUMMARY

| **AEGL-1 VALUES** | | | | |
|---|---|---|---|---|
| **10-minute** | **30-minute** | **1-hour** | **4-hour** | **8-hour** |
| 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) | 45 ppm (110 mg/m$^3$) |
| Key Reference: Sim and Pattle 1957 | | | | |
| Test Species/Strain/Number: 12 human male volunteers | | | | |
| Exposure Route/Concentrations/Durations: The volunteers were exposed to 134 ppm for 30 minutes. | | | | |
| Effects:<br>134 ppm was mildly irritating to the mucosal surfaces. | | | | |
| Endpoint/Concentration/Rationale:<br>The effects seen at 134 ppm are considered to be sub-AEGL-1effects. | | | | |
| Uncertainty Factors/Rationale:<br>Total uncertainty factor: 3<br>Interspecies: 1, subjects were humans<br>Intraspecies: 3, the differences between individuals for direct irritation are expected to be small. | | | | |
| Modifying Factor: NA | | | | |
| Animal to Human Dosimetric Adjustment: NA | | | | |
| Time Scaling:<br>The value of 45 ppm is used for all time points because it is based on local irritation.<br>Data Adequacy:<br>Database is poor | | | | |

| **AEGL-2 VALUES** | | | | |
|---|---|---|---|---|
| **10-minute** | **30-minute** | **1-hour** | **4-hour** | **8-hour** |
| 330 ppm (800 mg/m$^3$) | 330 ppm (800 mg/m$^3$) | 260 ppm (630 mg/m$^3$) | 170 ppm (410 mg/m$^3$) | 110 ppm (270 mg/m$^3$) |

Key Reference: Driscoll 1993

Test Species/Strain/Number: CD rats (15/sex/group)

Exposure Route/Concentrations/Durations:

Inhalation exposure for 6 h/d, 7 d/w for 35 to 52 days to actual concentrations of 0, 151, 745 and 1453 ppm.

Effects:

151 ppm:
Males: Increase in vacuolation of the nasal olfactory epithelium.
Females: Increase in vacuolation of the nasal olfactory epithelium.

745 ppm:
Males: Increase in rhinitis and vacuolation and atrophy of the nasal olfactory epithelium.
Females: Reduced body weight, body weight gain and food consumption. Increase in rhinitis of the nasal cavity. Increase in vacuolation of the nasal olfactory epithelium.

1453 ppm:
Males: Increase in erythrocyte counts, hemoglobin and hematocrit values. Increase in monocytes. Increase in relative kidney weights. Increase in rhinitis and atrophy of the nasal olfactory epithelium.

Females: Reduced body weight, body weight gain and food consumption. Increase in atrophy of the nasal olfactory epithelium.

Endpoint/Concentration/Rationale:

The effects on the nasal cavity at the highest dose can be attributed to repeated exposure and are not expected to occur after a single day exposure of 6 hours.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3

A higher factor would give AEGL-2 values that would be inconsistent with human data.

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: NA

Time Scaling:

Default time-scaling $C^n xt = k$ with default values of n=1 for extrapolation to longer time periods and *n*=3 for extrapolation to shorter time periods. Because the starting point for time extrapolation is 4 hours or longer, the AEGL-2 10-minute value is set equal to the AEGL-2 30-minute value.

Data Adequacy:

Database is poor.

1

| **AEGL-3 VALUES** | | | | |
|---|---|---|---|---|
| **10-minute** | **30-minute** | **1-hour** | **4-hour** | **8-hour** |
| 1,100 ppm (2,700 mg/m$^3$) | 1,100 ppm (2,700 mg/m$^3$) | 840 ppm (2,000 mg/m$^3$) | 530 ppm (1,300 mg/m$^3$) | 260 ppm (630 mg/m$^3$) |

Key Reference: Appelman *et al.* 1982

Test Species/Strain/Number: Rat, Wistar, 5-10 males and 5-10 females per group

Exposure Route/Concentrations/Durations: Repeated inhalation exposure to 0, 401, 941, 2217, or 4975 ppm **acetaldehyde** for 6 h/day, 28 days (n=20/group), and single inhalation exposure to 10,436, 12,673, 15,683, or 16,801 ppm for 4 hours (n=10/group). Acute and subacute data were combined.

Effects:

| | lethality |
|---|---|
| 0 ppm | 0/20 |
| 401 ppm | 0/20 |
| 941 ppm | 0/20 |
| 2217 ppm | 0/20 |
| 4975 ppm | 0/20 |
| 10436 ppm | 2/10 |
| 12637 ppm | 5/10 |
| 15683 ppm | 6/10 |
| 16801 ppm | 8/10 |

Endpoint/Concentration/Rationale: lethality, $BMDL_{05}$=5295 ppm. The limited lethality data on propionaldehyde do not allow the determination of a benchmark concentration. Therefore, the qualitative much better data of acetaldehyde were used. The toxicity of propionaldehyde is in quantitative terms similar to acetaldehyde.

Uncertainty Factors/Rationale:
Total uncertainty factor: 10
Interspecies: 3
Intraspecies: 3

Modifying Factor: NA

Animal to Human Dosimetric Adjustment: NA

Time Scaling: $C^n * t = k$ with n=1 for longer time points and n=3 for shorter time points (10-min value set equal to 30-min value)

Data Adequacy:

Database is poor.

1

# APPENDIX D: Derivation of Level of distinct Odor Awareness

The odor threshold value of propionaldehyde was determined by Tokanova (1982). For reflex effect assessment, their olfactory thresholds have been determined at 30 nearly healthy people at the age of from 17 to 41 under certain environmental conditions (air temperature 20-21 $^{o}$C, relative humidity 50-70 %). The degree of toxicity and hazards of these substances could be established at III according to the classification by olfactory reactions. Olfactory threshold has been determined at 0.048 mg/m$^3$ (0.020 ppm) for propionaldehyde, while no-effect concentration levels at 0.012 mg/m$^3$ (0.005 ppm). No further information available.

Izmerov (1982) reported a value of 1 mg/m3 (0.41 ppm). This report by Izmerov is a summary and does not contain additional information.

The odor threshold in water was determined at 145 ppb in normal humans and at 656 ppb in anosmic humans (Amoore 1976). The odor is described as malty.

According to Hellman (1974), the absolute odor threshold (50% recognition) in air is 0.009 ppm. The odor is described as sweet and ester like.

For propionaldehyde Ruijten (2004) states an odor threshold of 0.0015 ppm using the Japanese triangle olfactometer method. This method has been shown to produce results that agree very well with the standard method CEN13725. The same Japanese source reports an odor threshold of 0.038 ppm for n-butanol. The latter value is very close to the European Reference Odor Mass for n-butanol of 0.040 ppm. Ruijten also states an odor threshold of 0.0017 ppm without reference obtained with methods considered compatible with a precursor of the NVN2820 and EN 13725 methods.

The value reported for the Japanese triangle method and the NVN2820 represent a Level 1 odor threshold. For the purpose of the LOA calculation, the geometric mean of these two values (after n-butanol reference adjustment) is used.

The standardized odor threshold for acetaldehyde ($C_{0,\ stand}$) is equal to:

$$0.0015 * 0.040/0.038 = 0.00158 \text{ ppm}$$

The geometric mean of both acceptable level-1 odor thresholds (0.0158 and 0.0017) is 0.0016 ppm.

For propionaldehyde a Fechner-Weber coefficient for odor intensity ($K_w$) of 1.01 has been established (ONSL0135). I=3. The default adjustment for distraction and peak-to-mean-ratio is 4/3.

The Level of Distinct Odor Awareness (LOA) for propionaldehyde can now be calculated according to Ruijten (2004):

$$LOA = 0.0016 \text{ ppm} \times 10^{((3-05)\ /\ 1.01)} * 4/3 = 0.0016 \text{ ppm} \times 400 = 0.64 \text{ ppm}$$