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# ACRYLALDEYDE

CAS-No.: 107-02-8

EINECS-No.: 203-453-4

**Summary Risk Assessment Report**

**2001** **Special Publication I.00.126**

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# SUMMARY RISK ASSESSMENT REPORT

*Final report, November 1999*

The Netherlands

Rapporteur for the risk evaluation of acrolein is the Ministry of Housing, Spatial Planning and the Environment (VROM) in consultation with the Ministry of Social Affairs and Employment (SZW) and the Ministry of Public Health, Welfare and Sport (VWS). Responsible for the risk evaluation and subsequently for the contents of this report, is the rapporteur.

The scientific work on this report has been prepared by the Netherlands Organisation for Applied Scientific Research (TNO) and the National Institute of Public Health and the Environment (RIVM), by order of the rapporteur.

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|---|---|
| **Date of Last Literature Search :** | **1994** |
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| **Final report:** | **November, 1999** |

## PREFACE

This report provides a short summary with conclusions of the risk assessment report of the substance acrolein that has been prepared by the Netherlands in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances. For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the original risk assessment report that can be obtained from European Chemicals Bureau[1]. The present summary report should preferably not be used for citation purposes.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.ei.jrc.it

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# 1 GENERAL SUBSTANCE INFORMATION

## 1.1 Identification of the substance

CAS-No.: 107-02-8
EINECS-No.: 203-453-4
IUPAC name: 2-propenal
Molecular formula: $C_3H_4O$
Structural formula: $CH_2 = CH - CHO$
Molecular weight: 56.06
Synonyms: acrolein, acralaldehyd, acrylaldehyd(e), acrylic aldehyde, allylaldehyd(e), propenal

## 1.2 Purity/impurities, additives

Purity: ≥92% w/w
Impurity: ≤3% w/w water (CAS-No. 7732-18-5)
≤0.5% w/w acetaldehyde (CAS-No. 75-07-0)
Additives: ≥0.1% w/w hydroquinone (CAS-No. 123-31-9)
0.1 to 0.25% w/w hydroquinone

## Physico-chemical properties

| Property | Result | Comment |
|---|---|---|
| Physical state | Liquid | |
| Melting point | -87°C | |
| Boiling point | 53°C at 1013 hPa | |
| Relative density | 0.84 g/cm³ at 20°C | |
| Vapour pressure | 293 hPa at 20°C | |
| Water solubility | 206-270 g/l at 20°C | |
| Partition coefficient n-octanol/water (log value) | -0.68 up to +1.02<br>-1.1 up to +0.9 | calculated<br>measured |
| Flash point | -26°C | closed cup |
| Flammability | Flammable<br>flammability limits 2.8-3% by volume | |
| Autoflammability temperature | 234°C | |
| Explosive properties | No data available. Theoretically, explosive properties may be present if handled without care, however, experimental determination is not considered necessary | |
| Oxidising properties | Theoretically not expected | |
| Odour (treshold air) | 0.07 mg/m³<br>0.48 mg/m³ | perception<br>recognition |
| Conversion factors (at 1013 hPa) | 20°C: 1 mg/m³ = 0.43 ppm; 1 ppm = 2.33 mg/m³<br>25°C: 1 mg/m³ = 0.44 ppm; 1 ppm = 2.29 mg/m³ | |

All relevant physicochemical data were provided. The explosive and oxidising properties could be evaluated on basis of structural formula and thermodynamic properties. Although most of the data arise from databases and the underlying reports were lacking, the physico-chemical properties could be interpreted with sufficient certainty to a range that is within an acceptable accuracy. Therefore, further testing of these properties is considered superfluous. It is concluded, that the data submitted are acceptable with respect to the basic requirements as specified in Annex VIIA of Directive 67/548/EC. The values for water solubility and log $K_{ow}$ used as input for EUSES (model calculations for environmental exposure) are 270 g/l and -1.1, respectively.

Classification and labelling: With respect to flammability the criteria for R11 as well as the criteria for R12 are not strictly applicable. R11 is applicable for substances with a flashpoint between 0 and 21$^{o}$C; R12 is applicable for substance with a flashpoint <0$^{o}$C and a boiling point <35$^{o}$C. The flashpoint of acrolein is <0$^{o}$C, but the boiling point is 53$^{o}$C. Because it concerns a borderline case, and because of the use of the substance, labelling with R11 as given in Annex I is agreed.

**Classification**

F; R11
T+; R26
T; R24/25
R43 (**depending on the outcome of discussions at the CMR Working Group**)
C; R34
N; R50

S-phrases: S23-S26-S28-S36/37/39-S45-S61

# 2 GENERAL INFORMATION ON EXPOSURE

The production of isolated acrolein is located at two sites in the European Union. The total EU production volume for 1994 was estimated to be between 20,000 to 100,000 tonnes per annum (HEDSET). There is no detailed information available about the exported and imported volumes of isolated acrolein in the EU.

Besides its production as an isolate, acrolein is also produced as a non-isolated intermediate during the production of acrylic acid. Acrolein further occurs as a by-product during the acrylonitrile production. There are two sites in the EU where acrolein is produced as a non-isolated intermediate during the production of acrylic acid. The BUA report gives a figure of 196,000 t/y for the amount of non-isolated acrolein produced during the production of acrylic acid in Germany. The formation of acrolein as a by-product during acrylonitrile production occurs at seven sites in the EU (EU risk assessment on acrylonitrile IRL).

In the EU acrolein is only used as an intermediate in the chemical industry. The main fraction of the isolated acrolein is reacted via the intermediate product methylmercapto-propionaldehyde (MMP) to the amino acid D,L- methionine, which is used as an animal feed additive. Outside the EU (e.g. Egypt, Argentina, Australia, Canada and USA) acrolein is used as an effective broad-band biocide. It is applied in process water circuits, irrigation canals, cooling water towers and water treatment basins.

# 3 ENVIRONMENT

## 3.1 EXPOSURE

Acrolein may be released into the environment during its production and processing of intermediates. This release, however, is very low compared to emissions from several non-industrial diffuse sources (e.g. formation of acrolein during automobile fuel combustion). Acrolein emissions will occur via water, but predominantly via air.

General characteristics of acrolein that are relevant for the exposure assessment are:

Degradation

*Hydrolysis and hydration.* Acrolein does not contain any hydrolysable groups, but it does react with water in a reversible hydration reaction to 3-hydroxypropanal (HPA). *Photodegradation*. The stability of acrolein in the atmosphere is limited by the rapid gas-phase reactions with the hydroxyl radical and ozone. Other degradation routes, such as the reaction with nitrate radical (nighttime) as well as photolysis (daytime), are considered to be less significant. The reaction with hydroxyl radicals (*OH) is described as the major degradation route of acrolein in the troposphere, whereby acrolein can react both as olefin and an aldehyde. The calculated half-life of acrolein for the reaction with the OH-radical in the troposphere (*OH-concentration $5 \cdot 10^5$ molecules/cm3 and 24 hours) is less than one day.

*Biodegradation*. The current information on several technical aspects is incomplete for nearly all biodegradation tests. Nevertheless, the total set of data is regarded sufficient to draw conclusions upon the degradation potential of acrolein. Based on the entire data set on biodegradation and the QSAR estimates, acrolein will be considered in the current risk assessment as ready biodegradable with a biodegradation rate constant of 1 $h^{-1}$ (STP) .

As a conservative approach the default value of the TGD (30 days) will be used.

Distribution

According to the TGD (1996) a Henry's Law constant of 6.1 $Pa.m^3/mol$ at 20°C can be calculated. A measured Henry's Law constant of 3.1 $Pa.m^3/mol$ at 20°C was found. This indicates that volatilisation of acrolein from surface waters and moisty soil is expected to be high.

Using the measured log $K_{ow}$ of -1.10, a $K_{oc}$ of 2.8 l/kg can be estimated according to the TGD (1996). Experimentally determined $K_{oc}$-values (dimensionless) were in the range of 51-270 for two different soils, but further details of this study are lacking (BUA, 1994). Based on the calculated and experimental $K_{oc}$ values, acrolein is expected to be moderately to highly mobile in soil.

c) Accumulation

On the basis of the high water solubility and chemical reactivity of acrolein and its low experimentally determined log $K_{ow}$ of -1.10, no bioaccumulation would be expected.

### 3.1.1 PECs at production, processing and unintentional

The environmental exposure assessment of acrolein will be based on the expected releases of the substance during the following life cycle stages:

*I. Industrial sources*

Chemical industry

- Production of isolated acrolein
- Production of non-isolated acrolein as intermediate
- Formation of non-isolated acrolein as by-product
- Processing of acrolein as chemical intermediate for seven different products

Other industry

- Formation of acrolein during combustion processes

*II. Non-industrial sources*

- Formation of acrolein by combustion of fuel (traffic)
- Formation of acrolein in tobacco smoking

Both site-specific and generic release data are used for calculating the local predicted environmental concentrations (PECs) in the various compartments. Emissions from unintentional and intentional emissions are summed up to calculate regional PECs.

Local PECs in the sewage treatment plant and surface water are, respectively, 0.006 and 0.012 mg/l, and 0.003 and 0.006 µg/l. Local sediment PECs are 0.03 and 0.05 For air the PECs are between 0.02 and 4.7 µg/$m^3$ and for soil between 0.003 and 0.01µg/kg. Regional PECs are also calculated.

In addition to the calculated PECs, monitoring data are available for air and water both at local and regional scale.

## 3.2 EFFECTS

Aquatic compartment

Both short-term and long-term acrolein toxicity data are available for aquatic organisms. There are also a number of studies with bacteria and protozoans.

The lowest long-term aquatic toxicity test result for acrolein covering four trophic levels is the Scenedesmus NOEC of 10 µg/l. This NOEC would normally be used for the derivation of the PNEC in water using an assessement factor of 10. However, the available long-term tests do not cover the most sensitive species from the short-term tests, i.e. the $LC_{50}$ for Xenopus laevis of 7 µg/l. Therefore the latter result will be used for the derivation of the PNEC. As there are long-term data available for several trophic levels, an assessment factor of 100 (rather than 1000) is considered to be appropriate. It is further known that the acute/chronic toxicity ratio for fish and

daphnids is relatively low (ratio between 1.2 and 5.5). However, the entire aquatic data set for acrolein is considered too small to justify a further lowering of the extrapolation factor. The extrapolation with the factor 100 results in a **$PNEC_{water}$** of 0.1µg/l (rounded off value).

The PNEC for micro-organisms is extrapolated from the $EC_{50}$ for *Proteus vulgaris* (20 µg/l) using an assessment factor of 10. This results in a **$PNEC_{micro\text{-}organisms}$** of 2 µg/l.

There are no data for sediment-dwelling organisms. A **$PNEC_{sediment}$** could be calculated using the equilibrium partitioning method. However, measured data for the concentration of acrolein in sediment are also lacking. Thus a quantitative risk characterisation of acrolein for sediment can not be performed. Furthermore, the low absorption potential suggest that sediment is probably not a relevant compartment for the environmental risk assessment acrolein.

Terrestrial compartment and atmosphere

Some ecotoxicity data with terrestrial micro-organisms and plants are available. Since these data are considered not to be relevant, the $PNEC_{terrestrial}$ is calculated based on equilibrium partitioning. The **$PNEC_{soil}$** is calculated to be 0.01 µg/kg wwt (EUSES).

There is a limited number of studies in which the phytotoxicity of airborne acrolein is investigated. Although it is clear that acrolein is a phytotoxic compound, the set of data for the atmospheric compartment is considered insufficient to derive a meaningful PNEC for this compartment. In addition, the TGD does not give any guidance on the derivation of an atmospheric PNEC. Yet, a prudent attempt is made to estimate an indicative PNEC for acrolein in the atmosphere (plants). This indicative PNEC for plants is derived from the LOEC (9 hours) of 200 µg/$m^3$ for alfalfa in the Haagen-Smit study. Taking into account that it concerns a LOEC and short-term data only, and that very few plant species were tested, an extrapolation factor of 100 is in this case considered to be appropriate. This results in an indicative **$PNEC_{plant\text{-}air}$** of 2 µg/$m^3$.

## 3.3 RISK CHARACTERISATION

Aquatic compartment

Only for two environmental exposure scenarios local PECs in an STP and water could be calculated, i.e. production of isolated acrolein (scenario Ia2, site-specific) and production of 3,4-dihydro-2-methoxy-2H-pyran (scenario IIb, site-specific). At the production of Vertocitral and acroleindiethylacetal 50 kg/a polyacrolein is fed into an STP. At present the fate and toxicity of polyacrolein in an STP and afterwards is unknown. However, an emission of 167 mg/d of polyacrolein is not expected to cause any adverse effects in an STP or the receiving water.

In all other scenarios industry explicitly stated that their waste water was incinerated.

The $PNEC_{micro\text{-}organisms}$ and $PNEC_{aqua}$ for acrolein are 2 µg/l and 0.1 µg/l, respectively. Production scenario Ia2 showed PEC/PNEC ratios <1 for both STP and surface water. **Table 3.1** presents the local PEC/PNEC ratio for micro-organisms and aquatic organisms for the other scenario.

**Table 3.1** Local PEC/PNEC ratios for micro-organisms and aquatic organisms

| | **PEC/PNEC$_{micro-organisms}$** | **PEC/PNEC$_{aqua}$** |
|---|---|---|
| Processing scenario IIb (site-specific) | 2.9 | 0.8 |

For the site specific scenario IIb the $PEC_{STP}$ exceeds the $PNEC_{micro-organisms}$, whereas for the same scenario the PEC/PNEC ratio is lower than 1 for aquatic organisms. With respect to the potential risk in the STP, it has to be noted that the exposure assessment is already based on actual emission data and the actual size of the STP. Yet, the PEC could be refined with e.g. actual monitoring data of the effluent. However, it should be borne in mind that the hydration of acrolein is not taken into account in the current exposure assessment. As this is an important fate process for this compound lower concentrations in the STP are most likely. In addition, according to industry no adverse effects on the biodegradation capacity of this particular treatment plant are noticed. For this last reason, **conclusion ii)** seems to be most appropriate for this scenario.

There are no toxicity data for sediment-dwelling organisms and also measured data for the concentration of acrolein in sediment are lacking. Thus a quantitative risk characterisation of acrolein for sediment can not be performed. Furthermore, the low absorption potential suggests that sediment is probably not a relevant compartment for the environmental risk assessment acrolein.

Terrestrial compartment

Comparing the local PECs in the terrestrial compartment for the various emission scenarios with the PNEC for soil of 0.01 µg/kg shows that for all scenarios the PEC/PNEC ratio is <1 **(conclusion ii)**

Atmosphere

Despite the preliminary character of the $PNEC_{plant,\ air}$ of 2 $\mu g/m^3$, a comparison of the PEC (calculated and measured) and PNEC is conducted. The PEC/PNEC ratios that are larger than 1 are given in **Table 3.2**.

**Table 3.2** Local PEC/PNEC ratios for the atmospheric compartment

| | **PEC/PNEC ratio*** |
|---|---|
| Industrial activities (range of monitoring data) | 50-1250 |
| Streets inner cities (range of monitoring data) | 0.3-18 |

*PEC/PNEC ratio based on annual average values

**Table 3.2** shows that a number of monitoring data from unintentional sources exceeds the indicative PNEC of 2 $\mu g/m^3$. It would be speculative to draw sound conclusions on these results as a) the monitoring data are either outdated or lacking of important background information (e.g. analysis technique, percentiles etc.) and b) the PNEC is only indicative. Nevertheless, it can not be excluded that local atmospheric risks for acrolein may occur. A better insight into the

actual risks of acrolein can only be gained with actual monitoring data (unintentional sources), carried out with up to date analysis techniques, in combination with the performance of an acrolein fumigation experiment with plants **(conclusion i)**.

Non compartment specific exposure relevant to the food chain

Not relevant.

Risk characterisation (regional)

The PECs calculated at a regional scale (air, water and soil) do not exceed the corresponding PNECs **(conclusion ii)**. Most of the available atmospheric monitoring data (ranging from n.d to 2.5 $\mu g/m^3$ ) are also found to be below the indicative PNEC of 2 $\mu g/m^3$.

# 4 HUMAN HEALTH

## 4.1 EXPOSURE

### 4.1.1 Workplace exposure

In the EU acrolein is only used as an intermediate. Outside the EU it is also used as a water treatment biocide. Exposure to workers in the EU is possible due to the production and the use as an intermediate. Furthermore, workers can be exposed due to formation of acrolein by reactions in several processes (not related to the use of acrolein).

Production of acrolein takes place in closed systems. Exposure of workers is possible due to drumming or tanker filling and due to fugitive emissions through valves, flanges, pumps, etc.. Strict procedures and technical control measures are used to minimise the emission of acrolein from the closed system. Based on measured data presented by one producer, potential exposure by inhalation for both short term and reasonable worst case full shift are estimated to be 8 $mg/m^3$ for workers involved in connecting and disconnecting transfer lines to road tankers. Due to well known acute effects of acrolein and based on the available information, it is considered that these workers wear PPE with a protection factor of 40, leading to an actual exposure level of 0.2 $mg/m^3$ (value used in risk characterisation). The potential exposure levels presented by the other producer for the same activity were considerably below the value of the first producer, probably due to better technical control measures (short-term levels of 0.051 and 0.083 $mg/m^3$). Typical exposure levels, based on workers not involved in connecting and disconnecting transfer lines, are estimated to be up to 0.01 $mg/m^3$.

Use of acrolein as an intermediate is also done in strictly closed systems. Only seven measured exposure levels were presented by industry for this scenario. Exposure is also estimated by EASE, assuming closed systems. The estimated exposure level is 0.23 $mg/m^3$. This level is chosen for use in the risk characterisation as the reasonable worst case full shift exposure level, because there is not sufficient information to establish if the measured data are representative. Typical exposure levels, based on the measured data, are estimated to be approximately 0.03 $mg/m^3$.

Exposure due to activities where acrolein is not used, but is formed by reactions, is possible in several situations. Several publications with measured data are available. For most of these situations general exposure levels for periods of an hour or more are estimated to be 0.1 $mg/m^3$, but for smokehouses a reasonable worst case exposure level of 0.25 $mg/m^3$ is estimated. Short-term exposure levels (< 1 hour) of up to 2 $mg/m^3$ are possible in several situations, leading to a calculated reasonable worst case exposure level of 0.33 $mg/m^3$.

Dermal exposure due to the handling of acrolein is normally prevented by technical means. Only accidental dermal exposure is considered to be possible in production and use of acrolein. Dermal exposure in situations where acrolein is not handled, but produced by reactions is considered to be negligible.

**Table 4.1** Workplace exposure

| Scenario | Activity | Frequency (days/year) | Duration (hr) | Reasonable worst case | | Typical concentration | | Dermal | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | (mg/m³) | method | (mg/m³) | method | mg/cm²/ day | dose (mg/day) |
| Production | full shift (filling)* | 50-100 | 6-8 | 0.2 | meas. calc. | 0.01 | meas. | accidental | accidental |
| Processing | general | 100-200 | 6-8 | 0.23 | EASE | 0.03 | lit. | accidental | accidental |
| Exposure not resulting from use of acrolein | general | 100-200 | 6-8 | 0.1 | lit. | 0.01 | lit. | negligible | negligible |
| | exposure activities | | 0-1 | 2 | lit. | | | | |
| | full shift** | 100-200 | 6-8 | 0.33 | calc. | | | | |
| | smoke-houses | | 6-8 | 0.25 | lit. | 0.08 | lit. | | |

*Reasonable worst case levels are based on measurements (full shift) of up to 8 mg/m3 for workers involved in connecting and disconnecting transfer lines, corrected for an assigned protection factor of 40 for full facepiece RPE with particle/gas-filters (BS 4275); typical exposure is for production workers not involved in connecting and disconnecting transfer lines (up to 200 days per year)
**Full shift exposure is calculated with the following equation: (1*2+7*0.1)/8 = 0.33
lit.= literature and measured data from industry
expert = Expert judgement
meas.= Measured
calc.= Calculated

### 4.1.2 Consumer exposure

No use of acrolein in consumer products has been identified.

### 4.1.3 Man exposed indirectly via the environment

Acrolein may be released to the environment via waste water and air effluents at sites where it is produced, processed and formed, and via unintentional emissions (e.g. from traffic, indoor tobacco smoking and cooking). Calculated concentrations (EUSES) in the air near the emission sources for the various site-specific scenarios ranged from 0.02 to 0.1 μg/m$^3$. The calculated total daily human intake via air, drinking water and food for these scenarios were below 3.2E-5 mg/kg bw/day, with the major intake via air. For the regional scale, the concentration in the air and the total human intake are calculated to be 0.03 μg/m$^3$ and 7.3E-6 mg/kg bw/day, respectively. Monitoring data for outdoor air (near industries 100-50000 μg/m$^3$, in streets 0.3-35 μg/m$^3$) and indoor air (11-3030 μg/m$^3$ for side-stream smoke of tobacco products) by far exceed the calculated concentrations. However, the representativity and validity of the monitoring data is questionable, since they are either outdated or lacking of important background information.

An additional source of human exposure can be the presence of acrolein in a variety of foodstuffs and beverages. The dietary intake of acrolein is estimated to be about 1 μg/kg bw/day, which can be considered as background level.

## 4.2 EFFECTS

Humans may be exposed to acrolein at the workplace and indirectly via the environment. Animal and human toxicity data were available.

Toxicokinetic data

Acrolein is very reactive and conjugates easily with glutathione or other thiol-containing molecules, with protein sulfhydryl groups and primary and secondary amine groups. As a consequence of its high reactivity the acrolein molecule will bind primarily at the application site. The retention of acrolein in the respiratory tract of dogs exposed to acrolein vapour (172-258 ppm) amounted to 81-84%. Acrolein mercapturic acid derivatives recovered in the urine upon oral, subcutaneous or intraperitoneal administration to rats amounted to 70-80%, 10-18%, and 29.1±6.5% of the administered dose, respectively. Upon inhalation exposure 11-22% of the estimated absorbed dose was found in the urine. The main metabolic pathway of acrolein *in vivo* presumably includes conjugation with glutathione. The *in vitro* metabolites acrylic acid, glycidaldehyde and glyceraldehyde have not been found *in vivo*.

Toxicokinetic data on absorption, distribution, metabolism and excretion for the dermal route are lacking.

Toxicodynamic data

Assessment of the available acute toxicity data indicates that, according to the EC-classification criteria, acrolein is toxic by the oral and dermal route, and very toxic after exposure by inhalation.

Acrolein is irritating and corrosive to skin and eyes in laboratory animals and humans.

In humans threshold levels for various local effects of acrolein were as follows: slight eye irritation (subjectively reported) was apparent after exposure to 0.14 mg/m$^3$ for 5 minutes; 0.48-0.80 mg/m$^3$ was the odour threshold; continuous exposure to 0.69 mg/m$^3$ resulted in considerable eye and nose irritation after 10 - 20 minutes and a significantly decreased respiratory frequency after 40 minutes of exposure; and exposure to 1.9 mg/m$^3$ for 10 minutes resulted in extreme irritation of all mucosal surfaces.

Despite the fact that the study designs and descriptions do not allow clear conclusions on human (no) effect levels for irritating effects after short-term inhalation exposure to acrolein vapours, risk assessment will be based on the LOAEL of 0.14 mg/m$^3$ from the study of Darley et al. (1960) for subjective symptoms, and the NOAEL of 0.34 mg/m$^3$ from the study of Weber-Tschopp et al. (1977) for measurable effects (increase in eye blinking rate at 0.59 mg/m$^3$).

One - and/or three - day exposures of rats resulted in cell proliferation at the lowest concentration levels examined i.e. 0.2 - 0.25 ppm (0.47-0.58 mg/m$^3$) acrolein and higher, and slight but treatment-related histopathological changes in the respiratory/transitional but not in the olfactory epithelium of the nose of rats exposed to 0.25 ppm (0.58 mg/m$^3$) and higher.

Based on the data available acrolein should be considered as sensitising to the skin.

The results of the repeated-dose inhalation studies do not permit establishment of a NOAEL. Intermittent exposure (6-7 hours per day, 5 days per week for a total period of 62 days - 13 weeks) to 0.9 mg/$m^3$ (0.4 ppm, DCV: 0.16 mg/$m^3$) acrolein vapour (the lowest concentration examined) resulted in slight, but treatment-related changes in rats, but not in hamsters and rabbits. Continuous exposure (24 hours per day, 7 days per week for 90 days) to 0.5 mg/$m^3$ (0.22 ppm) acrolein (the lowest concentration examined) resulted in treatment-related effects in guinea pigs, monkeys, and dogs, but not in rats. The effects found at the lowest-observed adverse effect concentrations, consisted of histopathological changes in the epithelium of the respiratory system and changes in respiratory tract function; they were minimal to slight and were found in one animal or a few animals only. Effects at higher concentrations included signs of chronic inflammatory changes, and epithelial metaplasia and hyperplasia of the respiratory tract, and at even higher concentrations increased mortality.

The overall NOAEL for oral toxicity amounted to 0.05 mg/kg bw/day and was found in a 102-week rat study. The discriminating effects for establishing NOAELs in the oral studies comprised decreased survival in rats (NOAEL 0.05 mg/kg bw), decreased survival and decreased body weight gain in mice (NOAEL 2 mg/kg bw), and an increased incidence of vomiting accompanied by a decrease in total serum protein, calcium and albumin at the highest dose level (1.5-2 mg/kg/bw) in dogs (NOAEL 0.5 mg/kg bw). Effects at higher dose levels included severe gastric lesions and increased mortality.

No data on repeated-dose dermal toxicity were available.

Acrolein is a mutagen for bacteria and may induce gene mutations and sister chromatid exchanges, but no chromosome aberrations in mammalian cells *in vitro*.

The mutagenicity/genotoxicity of acrolein in bacteria and mammalian cells *in vitro* is restricted to a narrow dose range that is near to or overlaps the cytotoxic dose range. Acrolein did not induce DNA damage or mutations in fungi. Acrolein appeared genotoxic in the 'somatic mutation and recombination test' in *Drosophila melanogaster*, but did not exhibit genotoxic activity in the 'sex chromosome loss test', while equivocal results were obtained in the 'sex-linked recessive lethal test' in *Drosophila melanogaster*. Acrolein did not induce dominant lethal mutations in mice or chromosome aberrations in bone marrow cells of rats.

Developmental effects in mammals *in vivo* were only seen at dose levels that also resulted in maternal toxicity. The overall NOAEL in the oral teratogenicity studies amounted to 2 mg/kg bw or higher for developmental and 0.75 mg/kg bw per day for maternal effects.

Except for a slight reduction in *F1* pup weights at 6 mg/kg bw, no effects on reproduction parameters were found in oral 2-generation rat studies. The overall NOAEL amounted to 3 mg/kg bw for developmental and 1 mg/kg bw per day for parental effects.

There is evidence that acrolein is not an oral carcinogen. The available data do not allow a conclusion with regard to possible carcinogenicity upon exposure by inhalation. No dermal carcinogenicity studies were available.

Acrolein has been found to impair pulmonary antibacterial defence mechanisms upon inhalation exposure *in vivo* and *in vitro*.

## 4.3 RISK CHARACTERISATION

### 4.3.1 Workplace

Assuming that oral exposure is prevented by personal hygienic measures, the risk characterisation for workers is limited to the dermal and respiratory routes of exposure. Furthermore, it is assumed that adequate risk reduction measures are taken to prevent accidental exposure. If applicable, quantitative risk characterisation is performed by calculation of the MOS (ratio between NOAEL/LOAEL and exposure levels) and comparison of this value with the minimal MOS. This minimal MOS is established via assessment factors, taking into account inter- and intraspecies differences, differences between experimental conditions and the exposure pattern of the worker, type of critical effects, dose-response relationship, confidence of the database and correction for route-to-route extrapolation. A risk is indicated when the MOS is lower than the minimal MOS.

The MOSs between the $LC_{50}$-values (18-150 mg/m$^3$ in the rat and 58 mg/m$^3$ in hamsters) and the estimated short-term inhalation exposure levels (0.2-2 mg/m$^3$) are small. However, given the concentration levels used in the human studies (exposure up to 1.9 mg/m$^3$) and the effects observed, it is concluded that the risk for adverse effects due to acute exposure to acrolein vapours will be limited to irritation, and therefore additional risk reduction measures are not indicated for acute inhalation toxicity (**conclusion ii**). Since dermal exposure will be limited to accidental exposure in scenario 1 and scenario 2 and to negligible levels in scenario 3, **conclusion ii**) is reached for these scenario's for acute dermal toxicity and for irritation effects on the skin (liquid or vapour). The risk for adverse effects on mucous membranes (eyes, nose and respiratory tract) due to single exposure to vapours of acrolein is estimated by calculation of the MOSs between the LOAEL of 0.14 mg/m$^3$ established for subjective symptoms in a human volunteer study and the NOAEL of 0.34 mg/m$^3$ for measured effects from another volunteer study, and the estimated short-term exposure levels in scenario 1 and 2 (i.e. calculated MOS 0.7-1.7 and 0.6-1.5, respectively). In view of the minimal MOS of 3-6, these MOSs are considered too low, irrespective whether the subjective or objective symptoms are used as starting point and **conclusion iii**) is reached. It is noted that exposure to acrolein not resulting from use (scenario 3) gives also rise to concern for irritation of mucous membranes due to inhalation exposure. **Conclusion ii**) is reached for eye effects due to exposure to liquid acrolein, because eye protection is obligatory for activities where direct handling of acrolein occurs. It has to be noted that there is concern for these effects in scenario 3, but exposure in this scenario is <u>not</u> the result of the intentional production or use of acrolein.

Based on the MOSs (3.9-4.5) between the LOAEL from the repeated dose study by inhalation in rats (0.9 mg/m$^3$) and the anticipated inhalation exposure levels (0.2-0.23 mg/m$^3$) it is concluded that adverse effects due to exposure in scenario 1 and 2 cannot be excluded (minimal MOS 16) (**conclusion iii**). For typical exposure situations in these scenarios the MOSs are approximately 90 and 30, respectively, which indicates that for such situations there is no risk. It has to be noted that there is concern for scenario 3, but in this scenario exposure is <u>not</u> the result of the intentional production or use of acrolein. There are no dermal repeated dose toxicity studies available. Because dermal exposure may occur only accidentally in scenarios 1 and 2, and to negligible levels in scenario 3, it is concluded that health risks due to dermal acrolein exposure are not expected in these scenarios (**conclusion ii**).

From the results of the mutagenicity studies it is concluded that acrolein has intrinsic genotoxic properties. The occurrence of genotoxic effects locally at the site of first contact cannot be completely excluded.

There is evidence that acrolein is not an oral carcinogen. The limited inhalation data available did not indicate carcinogenicity after inhalation. However, none of the available repeated-dose inhalation studies meets the generally accepted requirements for adequate carcinogenicity testing. On the basis of the experimental data it cannot be excluded therefore, that respiratory tumours may be induced at non-cytotoxic concentrations. It can be hypothesised that in analogy with other aldehydes such as formaldehyde and possibly acetaldehyde carcinogenic effects will not occur when irritation, as indicator for cytotoxicity, is avoided, but carcinogenic activity at non-cytotoxic exposure levels cannot be fully excluded. It has been considered to examine the potential genotoxic effects (gene mutations) of acrolein at the first site of contact after exposure by inhalation. However, at this moment, a validated test system or a test system giving sufficiently reliable results for the target cells of concern, i.e. cells of the respiratory tract, does not exist. Therefore, it is concluded that concern remains for carcinogenic and genotoxic effects locally at the exposure site after long-term exposure by inhalation to non-cytotoxic concentrations. This implicates that a quantitative risk characterisation can only be based on the results from a carcinogenicity study by inhalation. However, the request for such a study is not considered justifiable, because exposure to acrolein at the workplace as result of production and use is limited to a few industrial sites and the estimated and/or measured exposure levels are relatively low. Therefore, it is recommended to re-evaluate the current occupational exposure limits with the provisional assumption that the risk for carcinogenic effects after inhalation will be low when irritation is avoided. It is noted an Health-based Occupational Reference Value of 0.06 mg/m$^3$, estimated from the LOAEL from the repeated dose inhalation study in rats, is lower than the current occupational limit values for acrolein (0.2-0.25 mg/m$^3$). Furthermore, it is recommended to include the uncertainties on the carcinogenic profile of acrolein in the Material Safety Data Sheets (**conclusion iii**).

Developmental effects, and effects on reproduction parameters occur only at parental toxic dose levels in oral studies. The oral NOAELs from reproduction studies are higher than the overall oral NOAEL from the repeated dose studies and therefore it is concluded that the risk for reproductive effects after oral exposure will be low when other effects due to repeated exposure are avoided. The data available do not allow a definite conclusion on the risk for reproductive effects after inhalation or dermal exposure, because route-specificity cannot be excluded. However, the risk for reproductive effects after these exposure routes is considered to be low, because (1) acrolein is very reactive and will bind primarily to the application site, (2) the effects observed in the inhalation studies are primarily limited to local effects, and (3) reproductive/developmental effects in the oral reproduction studies occurred only at clear-cut parentally toxic doses. According to the Regulation the reproductive effects should be assessed in a quantitative way. However, given the reasoning as given above it is concluded that there is no need for further studies and **conclusion ii**) is reached for reproductive toxicity for workers under the restriction that measures will be taken to avoid risks for repeated dose toxicity and carcinogenicity.

### 4.3.2 Consumers

As no use of acrolein in consumer products has been identified, consumer exposure is not expected to occur (**conclusion ii**).

### 4.3.3 Man indirectly exposed via the environment

Inhalation exposure

Starting points for the risk characterisation for repeated dose toxicity are the concentration estimates in air for the regional scale and for the site-specific scenarios at local scale, the monitoring data (including indoor data), and the LOAEL of 0.5 mg/m$^3$ from 90-studies in guinea pigs, monkeys and dogs. At local scale, the calculated MOSs (5000-25000) indicate no concern for the site-specific scenarios (**conclusion ii**). In contrast, the MOSs between the inhalatory LOAEL and the monitoring data (0.01-1667) indicate concern for human safety, especially for indoor exposure from cigarette smoke. A better insight into the actual risks of acrolein can only be gained with actual monitoring data, carried out with up to date analysis techniques (**conclusion i)**. At regional scale, the MOS of 16667 indicates no concern for human safety (**conclusion ii**).

With respect to genotoxicity and carcinogenicity, it is concluded that concern remains for carcinogenic and genotoxic effects locally at the exposure site after long-term inhalatory exposure via the environment to non-cytotoxic concentrations. This implicates that a quantitative risk characterisation can only be based on the results from a carcinogenicity study by inhalation. However, the request for such a study is not considered justifiable, because the indirect exposure levels (especially from intentional sources) are relatively low. Therefore, for the risk characterisation for respiratory effects after long-term inhalatory exposure the same LOAEL as above for repeated dose toxicity (0.5 mg/m$^3$) is taken. With the provisional assumption that the risk for carcinogenic effects in humans after indirect exposure by inhalation will be low when irritation is avoided, it is noted that, except for the regional scale and for the site-specific scenarios at local scale (**conclusion ii**), the calculated MOSs are low, indicating concern for human safety. A better insight into the actual risks of acrolein can only be gained with actual monitoring data (**conclusion i**).

For reproductive/developmental toxicity no adequate studies by inhalation are available. In oral studies, reproductive/developmental effects occurred only at parentally toxic doses. Although route-specificity cannot fully be excluded it is concluded that the risk for reproductive effects after inhalation is considered to be low as long as other (local) effects of acrolein exposure are avoided (taking into account that acrolein is very reactive and will bind primarily to the application site and effects observed in the inhalation studies are mainly local effects) **(conclusion ii)**.

Intake via food and beverages and total daily intake

Starting points for the risk characterisation for repeated dose toxicity are the estimated (background) dietary intake, the estimated total daily intakes for the regional scale and for the site-specific scenarios at local scale, and the overall oral NOAEL of 0.05 mg/kg bw/day from a 2-year rat study. The calculated MOSs for the regional scale (6850) and for the site-specific scenarios at local scale (>1600) indicate no concern for human safety (**conclusion ii**). The MOS between the background dietary intake and the oral NOAEL is low (50) and indicates concern for human safety. To calculate more exactly the intake of acrolein via the diet, actual and reliable data on levels of acrolein in foods and beverages are needed (**conclusion i**).

As there is evidence that acrolein is not an oral carcinogen, there is no concern for human safety (**conclusion ii**).

In oral animal studies effects on reproductive parameters, embryo/fetotoxic and teratogenic effects occur only at parental toxic dose levels. The NOAELs from these oral studies are ≥2mg/kg bw/day for developmental effects, and parental effects were seen at doses ≥0.75 mg/kg bw/day. The MOSs for the regional scale (>100000), for the site-specific scenarios at local scale (>23000) and for the estimated dietary background (>750) indicate no concern for human safety (**conclusion ii**).

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# 5 OVERALL RESULTS OF THE RISK ASSESSMENT

Environment (industrial emissions)

( ) **i**) There is need for further information and/or testing.
(X ) **ii**) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
( ) **iii**) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Environment(unintentional emissions)

(X) **i**) There is need for further information and/or testing.
( ) **ii**) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
( ) **iii**) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

**Conclusion** (**i**) is reached because:

- based upon the available monitoring data and the indicative PNEC $_{plants}$, local atmospheric risks can not be excluded. A better insight into the actual risks can only be gained with actual monitoring data, carried out with up-to-date analysis techniques, in combination with the performance of an acrolein fumigation experiment with plants. It is emphasised that these measured critical atmospheric acrolein concentrations are exclusively caused by unintentional sources of acrolein emission (traffic etc.).

Consumers

( ) **i**) There is need for further information and/or testing
(X) **ii**) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
( ) **iii**) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

No use of acrolein in consumer products has been identified.

Man indirectly exposed via the environment(industrial emissions)

( ) **i**) There is need for further information and/or testing.
(X) **ii**) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
( ) **iii**) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Man indirectly exposed via the environment (unintentional emissions)

(X) **i**) There is need for further information and/or testing.
( ) **ii**) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
( ) **iii**) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

**Conclusion** (**i**) is reached because:

- based upon the available monitoring data local risks for humans indirectly exposed by inhalation via the environment cannot be excluded with respect to repeated dose effects and possible genotoxic/carcinogenic effects. A better insight into the actual risks can only be gained with actual monitoring data, carried out with up-to-date analysis techniques. It is emphasised that these measured critical atmospheric acrolein concentrations are exclusively caused by unintentional sources of acrolein emission (traffic etc.).
- based upon the anticipated local risks with respect to repeated dose effects for humans indirectly exposed to "background" concentrations in food, actual and reliable data on levels of acrolein in foods and beverages are needed. It is emphasised that these "background" acrolein concentrations in food are mainly caused by unintentional sources.

Workers

( ) **i**) There is need for further information and/or testing
( ) **ii**) There is at present no need for further information and/or testing or for risk reduction measures beyond those which are being applied
(X) **iii**) There is a need for limiting the risks: risk reduction measures which are already being applied shall be taken into account

**Conclusion (iii)** is reached because:

- classification and labelling according to Annex I and proposed by the manufacture(s) are not correct.
- irritating effects on mucous membranes (eyes, nose, respiratory tract) after single inhalation exposure cannot be excluded for all occupational scenarios.
- adverse health effects due to repeated inhalation exposure cannot be excluded for occupational exposure scenario 1 and 2.
- it is recommended to re-evaluate the current occupational exposure limits with the provisional assumption that the risk for carcinogenic effects after inhalation will be low when irritation is avoided.
- it is recommended to include the uncertainties on the carcinogenic properties of acrolein in target cells at the first site of contact in the Material Safety Data Sheets.

It is possible that in some industrial premises adequate worker protection measures are already being applied.

In relation to all other potential adverse effects and the worker population it is concluded that based on the available information at present no further information or testing of the substance is needed.

# GLOSSARY

| Standard term / Abbreviation | Explanation / Remarks and Alternative Abbreviation(s) |
|---|---|
| *Ann.* | Annex |
| AF | assessment factor |
| BCF | bioconcentration factor |
| bw | body weight / *Bw*, *b.w.* |
| °C | degrees Celsius (centigrade) |
| CAS | Chemical Abstract System |
| CEC | Commission of the European Communities |
| CEN | European Committee for Normalisation |
| CEPE | European Committee for Paints and Inks |
| d | day(s) |
| d.wt. | dry weight / *dw* |
| DG | Directorate General |
| $DT_{50}$ | period required for 50 percent dissipation (define method of estimation) |
| $DT_{50lab}$ | period required for 50 percent dissipation under laboratory conditions (define method of estimation) |
| $DT_{90}$ | period required for 90 percent dissipation (define method of estimation) |
| $DT_{90field}$ | period required for 90 percent dissipation under field conditions (define method of estimation) |
| EC | European Communities |
| EC | European Commission |
| $EC_{50}$ | median effective concentration |
| EEC | European Economic Community |
| EINECS | European Inventory of Existing Commercial Chemical Substances |
| EU | European Union |
| EUSES | European Union System for the Evaluation of Substances |
| $f_{oc}$ | organic carbon factor (compartment depending) |
| g | gram(s) |
| gw | gram weight |
| GLP | good laboratory practice |
| h | hour(s) |
| ha | Hectares / *h* |
| HPLC | high pressure liquid chromatography |
| IARC | International Agency for Research on Cancer |
| $IC_{50}$ | median immobilisation concentration or median inhibitory concentration 1 / *explained by a footnote if necessary* |
| ISO | International Standards Organisation |
| IUPAC | International Union for Pure Applied Chemistry |
| kg | kilogram(s) |
| kPa | kilo Pascals |
| $K_{oc}$ | organic carbon adsorption coefficient |
| $K_{ow}$ | octanol-water partition coefficient |
| Kp | solid-water partitioning coefficient of suspended matter |

| | |
|---|---|
| l | litre(s) / *L* |
| *log* | *logarithm to the basis 10* |
| $L(E)C_{50}$ | lethal concentration, median |
| m | meter |
| µg | microgram(s) |
| mg | milligram(s) |
| MOS | margins of safety |
| NOAEL | no observed adverse effect level |
| NOEC | no observed effect concentration |
| NOEL | no observed effect level |
| OECD | Organisation for Economic Co-operation and Development |
| OJ | Official Journal |
| pH | potential hydrogen -*logarithm* (to the base 10) of he hydrogen ion concentration $\{H^+\}$ |
| pKa | -*logarithm* (to the base 10) of the acid dissociation constant |
| pKb | -*logarithm* (to the base 10) of the base dissociation constant |
| Pa | Pascal unit(s) |
| PEC | predicted environmental concentration |
| PNEC(s) | predicted no effect concentration(s) |
| $PNEC_{water}$ | predicted no effect concentration in water |
| (Q)SAR | quantitative structure activity relation |
| STP | sewage treatment plant |
| TGD | Technical Guidance Document[1] |
| UV | ultraviolet region of spectrum |
| UVCB | Unknown or Variable composition, Complex reaction products or Biological material |
| v/v | volume per volume ratio |
| w/w | weight per weight ratio |

[1] Commission of the European Communities, 1996. Technical Guidance Document in Support of the Commission Directive 93/67/EEC on risk assessment for new substances and the Commission Regulation (EC) No 1488/94 on risk assessment for existing substances. Commission of the European Communities, Brussels, Belgium. ISBN 92-827-801[1234]