Institute for Health and Consumer Protection

European Chemicals Bureau

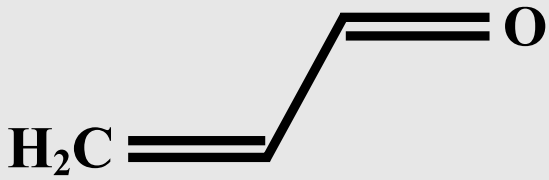
Existing Substances

European Union Risk Assessment Report

CAS No.: 107-02-8

EINECS No.: 203-453-4

acrylaldehyde



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European Union Risk Assessment Report

ACROLEIN

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RISK ASSESSMENT

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RISK ASSESSMENT

Final report, 2001

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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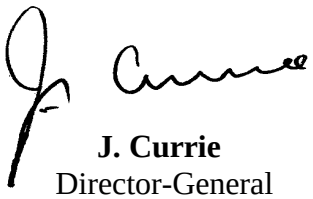
Date of Last Literature Search :	**1994**
Review of report by MS Technical Experts finalised:	**September, 1999**
Final report:	**2001**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.
The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.
The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.
The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.
This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the risks from exposure to chemicals overall.

H.J. Allgeier
Director-General
Joint Research Centre



J. Currie
Director-General
Environment, Nuclear Safety and Civil Protection

[1] O.J. No L 084 , 05/04/199 p.0001 – 0075
[2] O.J. No L 161, 29/06/1994 p. 0003 –0011
[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS-No. 107-02-8
EINECS-No. 203-453-4
IUPAC name 2-propenal

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.

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:

1. of concern for eye, nose and respiratory tract irritation as a consequence of single and repeated inhalation exposure arising from the production and processing of the substance;

and

2. that, in addition to the conclusion given above, the risk assessment shows that there are uncertainties with regard to the possible genotoxic and carcinogenic effects of the substance locally at the exposure site after long-term exposure by inhalation to non-cytotoxic concentrations. However, at this moment no validated genotoxicity test exists to investigate this, and the relatively low exposure levels do not justify there quest for a carcinogenicity study by inhalation.

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.

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.

In addition to the conclusions according to Council Reg. 793/93/EEC given above, the RAR came to the conclusion concerning unintentional emissions as follows:

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 (e.g. traffic, cigarette smoke).

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.

CONTENTS

TABLES

1 GENERAL SUBSTANCE INFORMATION

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

Purity/impurities, additives

Purity:	≥ 95 % w/w
	≥ 92%[4]
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

Physical state:	liquid
Melting point:	-87°C
Boiling point:	53°C at 1013 hPa
Relative density:	0.84 g/cm^3 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)	
	calculated: -0.68 up to +1.02
	measured: -1.1 up to +0.9
Granulometry:	not applicable
Conversion factors 1013 hPa (760 mm Hg)	
	20°C: 1 mg/m^3 = 0.43 ppm; 1 ppm = 2.33 mg/m^3
	25°C: 1 mg/m^3 = 0.44 ppm; 1 ppm = 2.29 mg/m^3
Odour perception threshold:	0.07 mg/m^3
Odour recognition threshold:	0.48 mg/m^3
Flammability:	flammable
Flammability limits:	2.8 - 31% by volume (IPCS 1991)
Explosive properties:	no data available. Theoretically, explosive properties may be present if handled without care, however, experimental determination is not considered necessary
Autoflammability:	234°C
Flash point:	-26°C (closed cup)
Oxidising properties:	not expected theoretically. Data not required, derogation statement

[4]Information provided by KEMI, National Chemicals Inspectorate, Sweden, letter dd 15 December 1997, Reg No 620-70-97

Consulted references: HEDSET (March 1996, Data Sheet Acrolein), IPCS (1991), Hess et al. 1978, Sinkuvene 1970, Leonardos et al. 1969.

Conclusion

All relevant physico-chemical data were reported. The explosive and oxidising properties could be evaluated on basis of structural formula and thermodynamic properties. Although most of the data arise from data-bases 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°C; R12 is applicable for substance with a flashpoint < 0°C and a boiling point < 35°C. The flashpoint of acrolein is < 0°C, but the boiling point is 53°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.

The new classification and labelling was adopted in the 28th ATP[5].

F; R11
T+; R26
T; R24/25
C; R34
N; R50

S-phrases: 23-26-28-36/37/39-45-61

[5] The classification of the substance is established by Commission Directive 2001/59/EC of 6 August 2001 (OJ L 225, 21.8.2001, p.1.) adapting to technical progress for the 28th time Council Directive 67/548 on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

The production of isolated acrolein is located at two sites in the European Union (see **Table 2.1**). The total EU production volume for 1994 was estimated to be between 20,000 to 100,000 tonnes per annum (HEDSET).

Table 2.1 Production sites of isolated acrolein (> 1,000 t/y) in the EU (HEDSET, 1994)

Company	Location
Degussa AG	Wesseling, Germany
Elf Atochem SA	Pierre-Bénite, France

There is no detailed information available about the exported and imported volumes of isolated acrolein in the EU.

Isolated acrolein is produced by heterogeneously catalysed gas-phase oxidation of propene. The production process is a continuous process in closed systems. Propene is mixed with air, steam and inert gas and is preheated. This gas mixture is fed into a multitubular fixed bed reactor. Also fluidized-bed catalysts can be used. As catalysts mostly metal oxides of molybdenum and bismuth are applied. About 90-95% propene reacts with a yield of about 80% acrolein (based on propene). The resulting by-products are mainly acrylic acid and acetaldehyde. Other by-products are small amounts of formaldehyde, acetic acid, oligomers, carbon monoxide and carbon dioxide. The acrolein-containing gas is absorbed in an absorber with cold water and is subsequently separated into about 90% crude acrolein and an aqueous phase. The aqueous phase is recycled as the absorbent. The exhaust gas of the absorber still contains unreacted propene, carbon dioxide, oxygen and nitrogen and is partially recycled as an inert gas that is fed into the reactor. The main exhaust gas stream is disposed off by thermal combustion.

Besides its production as an isolate, acrolein is also produced as a non-isolated intermediate during the production of acrylic acid. Acrylic acid is produced according to a two-step process of propene oxidation. Analogous to the production procedure of acrolein the first procedural step is a catalytic oxidation of propene. In the second step the acrolein is reacted, without prior isolation, on catalysts with a molybdenum and vanadium basis. Both reactions are conducted continuously in a closed system. The transformation rate for acrolein ranges from 98-100%, depending on the catalyst used and the reaction temperatures.

Acrolein further occurs as a by-product during the acrylonitrile production. Acrylonitrile is produced (Sohio process) by the catalytic reaction of propene, atmospheric oxygen and ammonia in a fluidised-bed reactor. Acrolein, formed as a by-product, is removed from this process by polymerisation and reaction with acrylonitrile, acetone and acetonitrile and by quenching of the reaction gas with water.

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 (draft EU risk assessment on acrylonitrile IRL, 1996).

Other sources of acrolein emissions (other industrial sources, diffuse sources) are discussed in paragraph 3.1.1.

2.2 USE PATTERN

In the EU acrolein is only used as an intermediate in the chemical industry (**Table 2.2**). 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. Acrolein is also processed to 3,4-dihydro-2-methoxy-2H-pyran, which is subsequently reacted to glutaric dialdehyde. Glutaric dialdehyde is used as a biocide and as a leather tanning agent (BUA, 1994).

Acrolein is further used for the production of substance X (confidential, letter from industry, 24-8-1995), which is required for the synthesis of a pesticide. Other acrolein products of minor importance are 3-formyl-5,6-dihydro-2H-thiopyran (end product: thiopyran-3-aldehyde) used for the synthesis of a herbicide, tetrahydrobenz-aldehyde, polycarboxylic acid (POC®) and fragrances (Lyral, Myracaldehyde, 5-norbornen-2-carbaldehyde). The content of acrolein in POC® is specified as 10 mg/l (Industry report Acrolein, 1995; BUA, 1994). Residues of acrolein in other endproducts will be discussed in paragraph 3.1.1.2.1.

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 (BUA, 1994).

Table 2.2 Industrial and use category of acrolein in the EU (HEDSET)

Industrial category	EC No.	Use category	EC No.
Chemical industry: used in synthesis	3	Intermediates	33

3 ENVIRONMENT

3.1 EXPOSURE ASSESSMENT

3.1.0 General

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) as will be demonstrated in paragraph 3.1.1.3.1. Acrolein emissions will occur via water, but predominantly via air. General characteristics of acrolein that are relevant for the exposure assessment are discussed in the following subparagraphs.

Degradation

Both the BUA-report (1994) and WHO/IPCS-report (1992) give a comprehensive description of the different environmental degradation routes of acrolein. A summary of the various routes is presented below. Details can be found in the above-mentioned review reports.

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). The half-life for this reaction was found to be 15 hours in sewage water, 45 hours in drinking water and up to 11 days in de-ionised water. Besides this reaction step HPA reacts in a secondary reaction with acrolein to 3,3'-oxydipropoionaldehyde, which further reacts to other secondary products. In field studies (irrigation canals) half-life values for the elimination of acrolein between 3 and 7 hours were calculated. Apparently, processes other than hydration, e.g. volatilisation, also contribute to acrolein dissipation in the aquatic environment.

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 (night-time) as well as photolysis (daytime), are considered to be less significant.

Photo-oxidation in air

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 reaction as an aldehyde is faster than the reaction as an olefin. Degradation products of these reactions are formaldehyde, carbon dioxide, glyoxal, carbon monoxide, glycolaldehyde, ketene and acryloylperoxinitrate (dependent on the formation rate of NO2-molecules).

The calculated half-life of acrolein for the reaction with the OH-radical in the troposphere (*OH-concentration $5*10^5$ molecules/cm3 and 24 hours) is less than one day. The calculated half-life is in correspondence with the half-life values derived from experiments.

Other degradation routes of acrolein in the air are the reactions with ozone, with nitrate radical and O(^{3}P) (atomic oxygen in the electronic ground-state). The reaction with nitrate radicals gains importance primarily at night when the concentration of the OH-radicals decreases and no photolysis occurs. The reaction with ozone is secondary, but nevertheless still plays a substantial role in the degradation of acrolein. Degradation products for the reaction with ozone are formaldehyde, glyoxylic acid, formic acid and glyoxal.

The calculated reaction rate constant for the photo-oxidation of acrolein by OH-radicals in water is $6.52*10^{-9}$ ($M^{-1}*s^{-1}$).

Photolysis

Photolysis competes with photo-oxidation (see above), but plays a lesser role in the degradation of acrolein in the troposphere. Irridiation of acrolein in synthetic air with UV-light results mainly in the formation of carbon monoxide and ethene.

Other organic products, e.g. formaldehyde, carbon dioxide and small amounts of hydrogen and methane, were detected as well. Photolysis is low at normal atmospheric pressure, but increases at lower atmospheric pressure. The half-life of photolysis of acrolein is 10 days in the lower troposphere and less than 5 days in the upper troposphere.

Photolysis in water is low.

Biodegradation

The available aerobic and anaerobic biodegradation test results for acrolein are summarised in **Tables 3.1**, **3.2** and **3.3**. 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.

Table 3.1 Biodegradation test results for acrolein (aerobic)

No.	Type of test	Detection	Result	Day	Method	conc. of TS	R.I.	conc. of inoculum	References
1	BOD5-test	O_2 uptake	no biodegradaton[1]	5	Unknown	unknown	4[a]	Unknown-	WHO,1992
2	BOD5-test	O_2 uptake	no biodegradation[1,4]	5	Unknown	Unknown	4[a]	Unknown-	WHO,1992
3	BOD5-test	O_2 uptake	2%[1];6.7%[2] (BOD/COD)	5	STAS 6560-62	unknown	4[a]	-[f]	WHO,1992
4	BOD5-test	O_2 uptake	30%[2](BOD/ThOD)	5	Unknown	Unknown	4[a]	-	BUA,1994
5	BOD5-test	O_2 uptake	22.5-(BOD/COD)	5	unknown	unknown	4[a]	unknown[b]	BUA,1994
6	Ready test[5]	DOC and TOC[6]	100%[1]	7	Static-culture flask screening[7]	5,10 mg/l	2	10 ml[b]	Tabak, 1981 Bunch and Chambers, 1967
7	Primary biodegradation test	elimination rate of TS	99.9%[2]	2-6	Flow-through reactor system	62 mg/l	4[a]	unknown[c]	BUA,1994

- = no data available
TS = Test substance (=acrolein)
Type of inoculum:
[a]Polyvalent inoculum diluted with natural water
[b]Activated (domestic) sewage
[c]Activated sludge from (industrial) STP
[d]Effluent from STP
[f]River water

Adapted or non-adapted inoculum:
[1]Non-adapted inoculum
[2] Adapted inoculum
[3] No information on adaptation or non-adaptation of inoculum available (pressumably the micro-organisms were acclimated to acrolein)
[4] Lit was reported that the result was due to toxicity to micro-organisms
[5] Expert judgement: test (Tabak, 1981) can be considered as a ready test
[6] Degradation was also shown by gas chromatography
[7]Screening procedure of Bunch and Chambers (1967)
R.I. = Reliability Index (see Annex 1)

Table 3.2 Biodegradation test results for acrolein (anaerobic)

No.	Type of test	Detection	Result	Day	Method	conc. of TS	R.I.	conc. of inoculum	References
1	methane fermentation	Gas production	42%[2]	20	Unknown	10 mg/l	4[a]	Unknown[a]	WHO,1992
2	methane fermentation	Gas production	no biodegradation[1,4]	-	Unknown	500 mg/l	4[a]	-[b]	WHO,1992
3	methane fermentation	Gas production	no biodegradation[3]	8 weeks	Healy & Young, 1978(ASTM)	75 mg/l	4[a]	10%[c]	BUA,1994

- = No data available
[a] Methane fermentation was applied in a mixed reactor with a hydraulic residence time of 20 days and seed with a acetate enriched culture. Micro-organisms were adapted for 90 days to 10 g acrolein/l.
[b]The cultures were acetate-enriched.
[c]activated sludge from industrial STP
[1]Non-adapted inoculum
[2]Adapted inoculum
[3]No information on adaptation status of inoculum available
[4]The authors attributed this result to the toxicity of acrolein to the methanogic micro-organisms.
[5]Methane fermentation (?)

Table 3.3 Other biodegradation test results for acrolein (soil)

No.	Type of test	Detection	Result	Method	conc. of TS	R.I.	conc. of inoculum	References
1	Aerobic soil (C14-labelled)	DT_{50} of TS[1]	DT_{50}= 4.2 hours (free TS) 410 days (bound TS)	EPA-Assessment Pesticide guideline N 162-2/3,1982	10 mg/kg soil sample	2a	unknown[2]	BUA,1994
2	Anaerobic aqueous soil test (C14-labelled)	DT_{50} of TS[1]	DT_{50}=11 days	EPA-Assessment Pesticide guideline N 162-2/3, 1982	4.2 mg/kg watery soil	4a	unknown[2]	BUA,1994

TS = Test substance (=acrolein)
[1]The degradation products (i.e. 3-hydroxypropionic acid etc) are calculated to degraded to 50% to CO2 after 29.2 days in soil and 80-110 days in watery soil by anaerobic micro-organisms.
[2]Micro-organisms were adapted to acrolein

*Ready and inherent biodegradability tests (**Table 3.1**)*

The BOD5-tests 1, 2 and 3 with unadapted inoculum indicate no biodegradation of acrolein (WHO, 1992). This may be due to the toxicity of the substance to micro-organisms (see also paragraph 3.2.1.4). However, the acrolein concentrations in this test are unknown. For BOD5-test (no. 4) with adapted inoculum, 6.7-30% biodegradation was found (WHO, 1992; BUA, 1994). In test no. 6 (from Tabak et al., 1981 cited in WHO, 1992) acrolein was degraded aerobically within 7 days. The unadapted inoculum was taken from a domestic sewage treatment plant. This test, carried out according to the procedures of Bunch and Chambers (1967), can be counted among the ready biodegradability tests. However, it should be emphasised that the biodegradation tests carried out by Tabak have a number of limitations. For example, in mosts cases only primary degradation was assessed and because of the use of yeast as an extra carbon source, co-metabolism may occur.

One inherent biodegradation test was conducted. In this test 100% biodegradation was measured after 2-6 days (WHO, 1992).

In another test the primary degradation of acrolein was measured (BUA, 1994). After 7 days 100% of the substance was eliminated.

*Anaerobic biodegradation tests (**Table 3.2**)*

In test no. 1 anaerobic biodegradation (42%) was measured in an acclimated system (WHO, 1992). No biodegradation was observed in the anaerobic test (no. 2) with unacclimated micro-organisms. This can be explained by the toxicity of the substance to micro-organisms. Test no.3 is difficult to evaluate because no data is available on the adaptation status of the micro-organisms (BUA, 1994).

*Soil biodegradation tests (**Table 3.3**)*

Two tests were conducted according to EPA Pesticide Assessment Guidelines (BUA, 1994). In the first test the biodegradability of acrolein in aerobic soil (sandy loam, pH 7.9) was studied. Half-life values of 4.2 hours and 410 days were found for unbound (73%) and bound acrolein, respectively. The half-life of the degradation products of acrolein, i.e. acrylic acid and 3-hydroxypropionic acid, to CO_2 was found to be 29 days. It should be mentioned that this test deviated in several aspects from current EU- or OECD-guidelines. For instance, the micro-organisms were adapted to acrolein and the storage conditions of soil were inappropriate.

In the second test the biodegradability of acrolein in aqueous soil was examined under anaerobic conditions. The DT_{50} of acrolein was found to be 11 days. The half-life of the degradation products, i.e. 1,3-propandiol and 3-hydroxypropionic acid, to CO_2 was calculated to be 80-110 days.

Conclusion

Despite the lack of a well-performed ready biodegradability test, it is expected that acrolein will be completely mineralised within 3 weeks because of rapid primary degradation of acrolein within 7 days and no stable metabolites are formed. In addition, the outcome of two different QSAR-calculations (BIODEG and OECD-model 75; Rorije et al., 1997) also point to the ready biodegradability of the substance. 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).

A soil DT50 of 4.2 hours could be used in the exposure assessment of acrolein. However, it should be noted that this value is derived from less reliable data (see above). As a conservative approach the default value of the TGD (30 days) will be used. In the risk characterisation for the terrestrial compartment reference will be made to the measured value of 4.2 hours (see paragraph 3.3.2).

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 (BUA, 1994; 33). This indicates that volatilisation of acrolein from surface waters and moisty soil is expected to be high (Lyman, 1982).

Using the measured log K_{ow} of -1.10 (Baker, 1991), 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. However, there are indications that the adsorption of acrolein to soil (bound fraction) is irreversible (BUA, 1994). In a simulation test, assuming the absence of water evaporation, acrolein was found to evaporate for 79% from sandy soil and 47% from loam soil during one year (BUA, 1994). When the water evaporated simultaneously, 85% of acrolein evaporated for both types of soil. In another experimental study acrolein showed a limited (30% of 0.1% solution) sorption to activated carbon (Giusti et al., 1974). These experimental results further support the conclusion that acrolein has a low sorption to soil and therefore that leaching may occur. However, volatilisation and degradation processes are expected to attenuate movement through soil towards groundwater (ATSDR, 1990).

As important details are lacking for the experimentally derived K_{oc}-values, the calculated K_{oc} of 2.8 l/kg will be used throughout the further exposure assessment of acrolein. K_p-values for soil, sediment and suspended matter can subsequently be calculated by multiplying the K_{oc} with the corresponding f_{oc}-values, resulting in K_p's of 0.06 l/kg (soil), 0.14 l/kg (sediment) and 0.28 l/kg (suspended matter). It should be borne in mind, however, that the derivation of a K_p from low log K_{ow}-values is less reliable (estimation outside domain).

Whilst physical removal from the atmosphere by precipitation and dissolution in clouds can occur, the short atmospheric residence time suggests that wet deposition is of limited importance.

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 (Baker, 1991), no bioaccumulation would be expected. Following the exposure of Bluegill sunfish to ^{14}C-labelled acrolein (0.013 mg/l water) for 28 days, the half-time for removal of radiolabel taken up by the fish was more than 7 days (WHO, 1992). The study does not represent bioaccumulation (BCF was 344) of acrolein *per se*, but rather incorporation of the radioactive carbon into tissues following the reaction of acrolein with protein sulfhydryl groups or metabolism of absorbed acrolein and incorporation of label into intermediary metabolites (WHO, 1992).

The calculation of a BCF for fish and worm according to the TGD QSARs and the subsequent risk assessment for secondary poisoning is considered not to be relevant for this compound.

3.1.1 Exposure scenarios

3.1.1.1 General

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

Industrial sources

Chemical industry

Ia. Production of isolated acrolein
Ib. Production of non-isolated acrolein as intermediate
Ic. Formation of non-isolated acrolein as by-product
IIa-g. Processing of acrolein as chemical intermediate for seven different products

Other industry

III. Formation of acrolein during combustion processes

Non-industrial sources

IV. Formation of acrolein by combustion of fuel (traffic)
V. Formation of acrolein in tobacco smoking

For life cycle stages I, II, III and IV both site-specific and generic emission scenarios are used for calculating the local predicted environmental concentrations (PECs) in the various compartments. Stage V is in this context (outdoor air) regarded as a diffuse source of acrolein that will only be used for the regional exposure assessment. Site-specific scenarios are based on actual data from industry on emission patterns etc., whereas generic scenarios are fully based on model calculations for a realistic worst case situation. Generic scenarios are used if no data were obtained from either industry or other bodies.

The exposure assessment is based on the EU Technical Guidance Document (TGD96) applying the European Union System for the Evaluation of Substances, EUSES.

The input data and the results of the various EUSES calculations are presented in Annex 2.

3.1.1.2 Local exposure assessment

3.1.1.2.1 Production (Ia and Ib) and formation of acrolein as by-product (Ic)

Water and air

Production of isolated acrolein (Ia)

In paragraph 2.1 it is mentioned that there are two producers of isolated acrolein within the EU. For one plant (scenario Ia1) site-specific information on releases was submitted. These actual atmospheric data will be used for the OPS-model calculations to derive a PEC for air. According to industry the excess water formed during the reaction process is withdrawn from the bottom residue of the desorption column and subsequently completely incinerated. Therefore it is assumed that there is no emission to water at this plant.

For the second production plant site-specific information on releases to both air and water is available (scenario Ia2).

Production of non-isolated acrolein as intermediate (Ib)

For two plants producing acrolein as an intermediate during acryl acid production, it is known that no environmental releases are expected to occur. This because these two plants incinerate both their waste water and gas.

Formation of acrolein as a by-product

There are seven plants where acrolein is formed as a by-product during acrylonitrile production. A survey among most of these acrylonitrile producers indicated that acrolein emissions during the production process are negligible (Letters from industry, 1998).

Table 3.4 contains the input data and the results for the local exposure assessment in air and water at production (Ia).

Daily releases are obtained by multiplying the production tonnage with the release factor, and then dividing it by the number of production days. The fraction of the main source is set at 1. The daily amounts (kg/d) are the building blocks for the calculations of the various PECs.

It is assumed that the amounts released to water will enter a sewage treatment plant. A further assumption is that there is no polymerisation of acrolein before or in the STP. The latter aspect needs some explanation. In the absence of an inhibitor, acrolein is subject to highly exothermic polymerisation, catalysed by light and air at room temperature, to an insoluble, linked solid. Highly exothermic polymerisation also occurs in the presence of traces of cross-linked solid. Highly exothermic polymerisation also occurs in the presence of traces of acids or strong bases even when an inhibitor is present. The assumption that no polymerisation occurs is made as it is not to be expected that this process will occur under the conditions (temperature, concentration of acrolein in influent/STP/effluent) before or in the STP.

The effluent concentration leaving the STP (PEC_{STP}) is calculated with the formula:

$C_{effluent}$ STP (mg/l) = emission rate (kg/d) · % not-removed STP · 1000/vol. waste water (m^3/d)

For acrolein the assumption is that 13 percent (SimpleTreat model (revised tables; acrolein ready biodegradable) is not removed from an STP and thus will flow into the effluent of the STP. From the effluent concentration in the STP the local concentration in the receiving surface water can be calculated with the equation:

$C_{local} = C_{eff}/(1 + K_{p\ susp} \cdot C_{susp}) \cdot D$,

where $K_{p\ susp}$ = suspended matter - water partition coefficient (= 0.016 l/kg)
C_{susp} = concentration of suspended matter in river (= $1.5 \cdot 10^{-5}$ kg/l)
D = dilution factor

From the daily amounts released to <u>air</u> the EUSES model (OPS module) calculates local atmospheric concentrations.

Table 3.4 gives the PECs for the STP, surface water and air. For the STP the PEC is equal to the $C_{effluent}$. For surface water and air, however, the $PEC_{regional}$ has to be added as a background to the calculated local concentrations. The PECs in **Table 3.4** (and all other PECs in paragraph 3.1.1.2) include already this background (EUSES output). The derivation of regional PECs is presented in paragraph 3.1.1.3.

Table 3.4 Input data for the local exposure assessment for air and water at production. Site specific information is presented in bold

	Production scenario Ia1	**Production scenario Ia2**
	Site-specific	**Site-specific**
Annual production tonnage	-	-
Industrial category **Use category**	3 33	3 33
Main category	cont.closed	cont.closed
Number of days	300 (Table B1.6)[2]	300 (Table B1.6)[2]
Release estimates (%) **air** **water**	 **-** **0**	 **0.0007** **0.0005**
Amount released (kg/d) **air** **water**	 **0.0334** **0**	 0.5 0.35
size of STP (m3/d)	-	**30.000**[1]
dilution	-	**1000**
PEC effluent STP (mg/l)	-	0.012[1]
PEC surface water (mg/l)	-	0.03
PEC air (mg/m3) (100 m. from source)	$3.8 \cdot 10^{-5}$	0.0001

[1] No treatment plant available. Effluent only
[2] Tables refer to Annex I of TGD
[4] Release to air from diffuse sources amounts to 6-10 kg/y. Upper limit is chosen for calculating PEC in air

Sediment

The local concentrations in sediment (mg/kg wet weight) can be estimated from the sediment-water partition coefficient using the equation:

$$C_{local\ (sed)} = K_{susp\text{-}water}/RHO_{susp} \cdot C_{local\ water} \cdot 1000$$
$$= 0.97/1150 \cdot 1000 \cdot C_{local\ water}$$
$$= 0.8 \cdot C_{local\ water}$$

The local PECs (including $PEC_{regional}$) of acrolein in sediment are presented in **Table 3.5**.

Table 3.5 Local PECs in sediment

	Scenario Ia1	Scenario Ia2
	Site-specific	Generic
$PEC_{sediment}$ (mg/kg)	nr	$3.0 \cdot 10^{-5}$

nr = not relevant

Soil

The EUSES model takes into account both the application of STP sludge on agricultural soil and the deposition from air for the calculations of acrolein levels in the terrestrial compartment. For those sites that indicated that their effluent is incinerated, acrolein in soil will be that from deposition. If process gases are also incinerated, deposition will only be from diffuse sources at a plant. The latter is only quantified for one plant (scenario Ia1)

The PECs of acrolein in soil at a local scale are given in **Table 3.6**.

Table 3.6 Local PECs in soil

	Scenario Ia1	Scenario Ia2
	Site-specific	Generic
PEC_{soil} (mg/kg ww)	$3.1 \cdot 10^{-6}$	$1.1 \cdot 10^{-5}$

3.1.1.2.2 Processing intermediates (IIa-g) and end-use

In paragraph 2.2 it is mentioned that acrolein is only used in the EU as an intermediate in the chemical industry. This paragraph focuses on the releases of acrolein during the various processing categories. At the end of the paragraph some attention is paid to environmental releases of acrolein occurring as residue in end-products.

Specific exposure scenarios

Actual information received from industry on environmental releases during specific processing categories is presented below (Industry report Acrolein, 1995; Letters from industry of 7-8-1995 and 24-8-1995; BUA, 1994; Letter from industry 7-4-1998):

According to industry most (exact percentages are treated confidential) of the total amount of acrolein produced in the EU is covered by these processing scenarios.

a) Methylmercaptoproprionaldehyde (MMP) production

Information is available for the major EU sites that are using acrolein for the production of MMP. They indicated that, due to their technical processes, there are no releases of acrolein to either water or air.

b) 3,4-Dihydro-2-methoxy-2H-pyran production

The wastewaters of the production of 3,4-dihydro-2-methoxy-2H-pyran contain about 6 t acrolein per annum. This estimate will be used to calculate the PEC in the local aquatic environment (scenario IIb). Industry indicated that there is no sludge application to soil.

Releases to air from this process are not expected to occur, as the exhaust gases from the process are combusted at high temperatures.

d) 3-Formyl-5,6-dihydro-2H-thiopyran production

No releases to water occur during the production of 3-formyl-5,6-dihydro-2H-thiopyran because no process water is formed (closed system).

Approximately 6 kg acrolein per annum are emitted to the atmosphere during the production of 3-formyl-5,6-dihydro-2H-thiopyran. This estimate will be used to calculate the PEC in the local atmospheric environment (scenario IId).

e) Polyoxycarboxylic acid production

Wastewater and washing liquids are neutralised in a dedicated vessel and fed into the internal sewage system. The neutralised wastewater is free of acrolein, so releases into the hydrosphere are not expected to occur.

Reaction and exhaust gases are extracted by ventilation and are subsequently burned in a dedicated vessel. No releases to atmosphere.

f) Vertocitral and acroleindiethylacetal (fragrances) production

The acrolein released to waste water during the production of Vertocitral and acroleindiethylacetal is polymerised by alkaline treatment. About 50 kg/a polyacrolein is fed into an STP. The fate and toxicity of polyacrolein in an STP and afterwards is unknown.

The exhaust gas is washed twice with an alkaline solution in a cascade column and a gas scrubber and is subsequently incinerated. There are therefore no acrolein releases to the atmosphere.

g) Substance X production

Wastewater, exhaust gases and acrolein containing solid waste from the substance X production process are all incinerated. Therefore no environmental acrolein emissions are expected to occur.
The above mentioned data (both generic and specific) on environmental releases during the processing of acrolein as an intermediate are used for calculating the local PEC in the various environmental compartments. **Table 3.7** contains the input data and the results of this local exposure assessment. Formula details and assumptions are given in the previous paragraph.

Table 3.7 Input data and results of the local exposure assessment for the processing of acrolein. Site specific iinformation is presented in bold

	Processing scenario IIb	**Processing scenario IId**
	site-specific	**site-specific**
annual production tonnage	-	-
industrial category **Use category**	3 33	3 33
main category	-	
number of days	300	300
release estimates (%) **air** **water**	 - -	 - -
amount released (kg/d) air **water**	 - **20**	 **0.02** -
size of STP (m3/d)	**known**	nr
dilution	**known**	nr
$PEC_{effluent\ STP}$ (mg/l)	0.006	nr
$PEC_{surface\ water}$ (mg/l)	$5.7 \cdot 10^{-5}$	-
PEC_{air} (mg/m3) **(100 m. from source)**	-	$3.5 \cdot 10^{-5}$
$PEC_{sediment}$ (mg/kg ww)	$4.8 \cdot 10^{-5}$	-
PEC_{soil} (mg/kg ww)	$1.0 \cdot 10^{-5}$	$2.8 \cdot 10^{-6}$

nr = not relevant
[1]According to emission scenario document of Chemical industry: Chemicals used in synthesis (TGD, 1996)

Acrolein residues in acrylic acid and acrylonitrile

Acrylic acid and acrylonitrile only contain trace amounts of acrolein. Ranges from not detectable for acrylic acid (detection limit < 5 µg/kg) up to 0.4-1.5 µg/kg for acrylonitrile are reported. The amount of acrolein as a residue in acrylonitrile of one producer was calculated to be 160 kg for the total annual production. Acrylic acid and acrylonitrile are exclusively used as intermediates in

chemical synthesis, so it is not expected that residues of acrolein will be present in the final products (polymer matrix). Releases of acrolein to the environment are not expected to occur via this route.

3.1.1.2.3 Formation of acrolein during industrial combustion processes (III) and fuel combustion (IV)

This section will have a closer look on the releases from other industrial and non-industrial sources of acrolein. These are processes involving incomplete combustion or chemical decomposition by the action of heat (pyrolysis) of organic substances (e.g. brown coal, oil fuel, plastics, wood, edible fat and oil).

As an example of local exposure of acrolein formed during industrial combustion processes, the acrolein releases from a metal-processing plant and energy production plant are considered (see also paragraph 3.1.1.3.1). An atmospheric release value of 30 kg acrolein per annum is reported by Slooff et al. (1992) for the metal-processing industry in the Netherlands. An approximately similar estimate is given for the acrolein releases to air from the energy production industry (Emissieregistratie, 1994). The figure of of 30 kg/a is used for the calculation of local PECs around a Dutch metal processing plant or energy production plant (scenario III). The following local PECs were calculated: air: 0.02 $\mu g/m^3$, soil: $3 \cdot 10^{-6}$ mg/kg. Formula details and assumptions are given in paragraph 3.1.1.2.1.

The main source of acrolein in ambient air is automobile exhaust gases. Acrolein is a component of urban smog. Acrolein can be formed during the incomplete combustion of fuels in gasoline and diesel engines. The acrolein emission of cars with spark-ignition engines without a catalytic converter is in general higher than for cars with a 3-way catalyst. Considerably more acrolein is released by diesel engines than by spark-ignition engines. Jet engines are also a source of acrolein emissions.

Recently acrolein concentrations were calculated with the CAR-model for several traffic scenarios in the Netherlands (scenario IV) (Memo 19-7-1996, dr H.Eerens LLO/RIVM). The CAR model (Calculation of Air pollution from Road traffic) is a simple parameterised model for the determination of air quality alongside roads (including street canyons) in cities. More details on the model can be found in Eerens et al. (1993). The 98-percentile daily averages for a busy city street and a busy motorway were found to be 4.8 $\mu g/m^3$ and 1.7 $\mu g/m^3$, respectively. Annual average levels were calculated to be 1.3 and 0.7 $\mu g/m^3$.

3.1.1.2.4 Other non-industrial sources of exposure

Acrolein formed at smoking, during the pyrolysis of tobacco (scenario V) is taken into account at the regional exposure assessment. See remark in paragraph 3.1.1.1. Acrolein is also formed by the photochemical oxidation of various hydrocarbons (e.g. 1,3-butadiene, propene and 1,3-pentadiene) in the atmosphere (WHO, 1992). However, to the knowledge of the rapporteur there is no information on the quantitative contribution of this route to acrolein formation.

3.1.1.2.5 Summary of results for the local exposure assessment

Table 3.8 summarises the local calculated PECs for the various environmental exposure scenarios.

Table 3.8 Summary of the local acrolein PECs for the various environmental exposure scenarios

	production scenario Ia1	production scenario Ia2	processing scenario IIb	processing scenario IId	combustion scenario III	traffic scenario IV
PEC_{STP} (mg/l)	-	0.012	0.006	-	-	-
PEC_{water} (mg/l)	-	$3 \cdot 10^{-5}$	$5.7 \cdot 10^{-5}$	-	-	-
PEC_{air} ($\mu g/m^3$) 100 m. from source (excl.traffic)	0.04	0.1	-	0.04	0.02	4.7 (98P/24h) street 1.3 (annual av.) street 1.7 (98P/24h) motorway 0.7 (annual av.) motorway
$PEC_{sediment}$ (mg/kg)	-	$3 \cdot 10^{-5}$	$4.8 \cdot 10^{-5}$	-	-	-
PEC_{soil} (mg/kg)	$3.1 \cdot 10^{-6}$	$1.1 \cdot 10^{-5}$	$1.0 \cdot 10^{-5}$	$2.8 \cdot 10^{-6}$	$3 \cdot 10^{-6}$	-

3.1.1.3 Regional and continental exposure assessment

Industrial and non-industrial atmospheric emissions of acrolein in The Netherlands and Germany are listed in the **Tables 3.9** and **3.10**, respectively. It is clear from these tables that a) the relative distribution of acrolein sources for Germany and the Netherlands are highly comparable and are assumed to be representative for the EU and b) the non-industrial, diffuse sources of acrolein by far exceed the industrial sources.

Table 3.9 Atmospheric acrolein emissions in The Netherlands (Emissieregistratie, 1994)

Source of emission	Emission (t/a)	Emission (%)
energy production	1.3	0.1
chemical industry (production of acrylonitrile)	0.3	0.04
other industry (founding, casting in metal/metallurgical industry)	2	0.3
Traffic	638	95
consumers	30	4.4
business, services and government	0.4	0.05
Total	672	100

Table 3.10 Atmospheric acrolein emissions in Germany (BUA, 1994)

Source of emission	Emission (t/a)	Emission (%)
production*	0.006-0.01	< 0.01
processing*	0.006	<0.01
Traffic	11,124	98
cigarette smoke	248	2
Total	11,372	100

*Emission data for production and processing are also taken from the BUA-report (1994) and thus not the sum of emissions for these life cycle stages as presented in paragraphs 3.1.1.2.1 and 3.1.1.2.2

The calculations of PECs at a regional and continental scale were done using the EUSES model. Emissions from unintentional and intentional emissions are summed up. The atmospheric emission in the Netherlands, as given in **Table 3.9**, is used as input for the unintentional sources for the regional assessment. This because the BUA data are older (1992) and, more importantly, the figure of 11,124 t/a is in fact the upper limit of a range: 2,806-11,124 t/a for Germany. In addition, new data for the Netherlands have become available that are line with the 1994 data in **Table 3.9**. For the atmospheric compartment the intentional emissions are negligible compared the unintentional ones. The regional atmospheric input for EUSES is thus 1800 kg/d (672.000/365). For the extrapolation from regional to continental emissions a factor of 24 is chosen based on the ratio of driven vehicle kilometres in the Netherlands compared to the EU (OECD Compendium, Environmental data, 1995). The continental input for air is thus 43,200 kg/d.

For the aquatic compartment the sum of the local daily inputs of scenarios Ia2 and IIb (0.35 kg/d + 20 kg/d) are recalculated to a regional emission (factor 300/365). The assumption is further that they are located in the same region. This gives a regional emission input of 17 kg/d. For the continent an extrapolation factor of 10 is chosen, which give a continental aquatic emission of 170 kg/d.

It has to be borne in mind that in EUSES a nested version of the multi-media fate model SimpleBox is implemented and this implies that for calculating continental concentrations both regional and continental release data are taken into account (i.e. continental = continental - regional).

The regional PECs for acrolein are:

PEC_{water}: 0.02 µg/l
PEC_{air}: 0.03 µg/m^3
PEC_{soil}: $2 \cdot 10^{-6}$ mg/kg

3.1.1.4 Measured data in environment

This paragraph contains the monitoring data for acrolein in the various environmental compartments. In case data were obtained from review reports, the original reports were not re-evaluated. **Table 3.11** presents an overview of measured acrolein levels in ambient air. No distinction is made between monitoring data at the local and regional scale.

Table 3.11 Measured acrolein concentrations in the atmosphere

Location	Type of site (no. of measurements)	Levels observed (µg/m³)	Year	Literature
Biscayne Bay, Florida	coastal region (ns)	ca. 2.3[a)]	ns	BUA, 1994
Caribbean	open ocean air (ns)	ca. 0.5[a)]	1988	BUA, 1994
Brasil, Sao Paulo	inner city (3)	n.d.	1986/88	BUA, 1994
	university campus (8)	0.5 - 2.3		
	street (4)	0.5 - 2.6		
Salvador	street with dense traffic (3)	n.d. - 3.3	1988	
Stockholm	busy street inner city (152)	0.35 - 27	1981	BUA, 1994
	quiet street inner city (24)	0.09 - 1.26		
	small island inner city (56)	0.33 - 4.4		
	12 km outside city (56)	0.16 - 1.56		
The Netherlands	residential area The Hague. No industrial centra and major traffic routes nearby. Five measurements at 4 different locations.	< 0.1 (= d.l.)	1993	RIVM, 1994
The Netherlands	average of 1 h measurements in rural area, sub-urban area and industrialised area (n.s)	1.1	1985	IPCS, 1992
Los Angeles, USA	urban	nd - 25	1961	IPCS, 1992
	urban	2 - 32 (avg. 16)	1963	
Sweden	urban, busy road	12	1983	IPCS, 1992
Japan	urban	nd	1983	IPCS, 1992
	urban (max. value road tunnel)	2 - 4	1986	
USSR	urban, highway	nd - 22	1970	IPCS, 1992
	residential 100m from highway	nd - 13		
	industrial 50 m from petr.chem.plant	2500 (max of 25/25)	1957	
	industrial 2 km from petr.chem.plant	640 (max of 21/27)		
	industrial 1 km from oil seed mill	100 - 200	1964	
	industrial 150 m from oil seed mill	320	1966	
Czechoslovakia	near coal coking plant	4-9 (av.7)	1972	IPCS, 1992
	near pitch coking plant	10-370 (av. 223)		
USSR	300 m from 2 enamelled wire plants	280 - 360	1982	IPCS, 1992
	1000 m from 2 enamelled wire plants	140 - 460		
	"control area"	1 - 230		
USA	coffee roasting outlet	590	1970	IPCS, 1992
USSR	beside exhaust of cars: unspecified	460 - 27,710	1961/72/86	IPCS, 1992
USSR	beside exhaust of cars: gasoline	130 - 50,600	1970/83	IPCS, 1992
	beside exhaust of cars: diesel	580 - 720	1970/80	

Table 3.11 continued overleaf

Table 3.11 continued

Location	Type of site (no. of measurements)	Levels observed (µg/m³)	Year	Literature
Unknown	urban	23 - 35	1950	Ware, 1995?
USA	beside exhaust of cars: ethanol	nd	1982	Ware, 1995?
Japan	beside exhaust of cars: unspecified	11,500	1975	Ware, 1995?
Japan	kitchen ventilator outlet	0.21 - 2.90	1991	Ware, 1995?
Unknown	jet engine emission	<0.78 - 5,430	1986/92/95	as quoted in Degussa 1995
Japan	municipal incinerator	500 - 600	1983	as quoted in Degussa 1995
World	clean air regions	0.08 - 2.3	ns	as quoted in Degussa 1995
Mount Everest area	clean air	nd 0.08 - 0.25	1993	as quoted in Degussa 1995
Italy	forest area 25 km west of Rome	0.27	1993	as quoted in Degussa 1995
Germany	forest area 30 km south east of Berlin	0.49	1993	as quoted in Degussa 1995
Japan	urban air: ns	2.3 - 2.8	1986	as quoted in Degussa 1995
USSR	beside exhaust of cars: gasoline	up to 6,100	1976/82	IPCS, 1992
USSR	beside exhaust of cars: diesel	500 - 210	1970	IPCS, 1992
USSR	near jet engine	nd - 120	1986	IPCS, 1992

[a]Sum of acrolein and acetone
nd = not detected
ns = not specified

Measured acrolein concentrations in water are given in **Table 3.12**. The information comprises a wide range of 'types of water', e.g. rainwater, groundwater, industrial effluent, surface water and leachate of landfill.

The Contract Laboratory Statistical Database reports that acrolein was detected in soil at 1 of 357 hazardous waste sites in the U.S., at a mean concentration of 6.5 ppb (ATSDR, 1990). Acrolein was

measured in soil samples of a U.S. fire-fighting training area contaminated with fuels. In 1 of 30 samples a concentration of 58 µg/kg soil could be detected at a depth of ca. 12 meters (BUA, 1994).

The evaluation of a data bank (STORET) of the U.S. EPA showed that acrolein could not be detected in any of 331 sediment samples (BUA, 1994).

Table 3.12 Measured acrolein concentrations in water

Location	Type of site (no. of measurements)	Levels observed (µg/l)	Year	Literature
Japan	rainwater; origin ns (3 / 4) rainwater; origin ns (6 / 9)	5 - 11 1.5 - 11	1986	BUA, 1994 as quoted in Degussa, 1995
USA	ground- and waste water: near plastics manufacturer	nd (detec. limit: 10)	1984	BUA, 1994
USA: EPA data bank	industrial waste water	1265 samples, 19 samples above detec. limit[a)]	ns	BUA, 1994
USA: EPA data bank	surface water	798 samples, 2 samples above detec. limit[a)]	ns	BUA, 1994
USA, Wisconsin	leachate of municipial landfill	detected in 1 of 5 samples: 170	?	ATSDR, 1990
USA	hazardous waste sites[c)]	detected in 3 of 357 sites: 10-51,000	?	ATSDR, 1990
Unknown	ground water (44-55 m below surface), supposed contaminated site	nd (detec. limit: 5)	1990	BUA, 1994
USA	surface water: irrigation canal. Acrolein often used for aquatic plant control	30 - 100	1974	IPCS, 1992
Po Valley, Italy	rain water	nd	1986	IPCS, 1992
USA	groundwater: community well water	nd (detec. limit: 0.1-3)	1986	IPCS, 1992
Japan	rain water (2 samples) rain water (3 samples)	nd (detec limit: 0.04) 1.5 - 3.1	1987	IPCS, 1992
USA	4 urban locations 1 urban location	nd 50 [b)]	1983	IPCS, 1992

[a)]Detection limit unknown
[b)]Including acetone
[c)]No distinction between groundwater and surface water monitoring data
nd = not detected
ns = not specified

3.1.1.5 Comparison of measured and calculated data

The risk characterisation should be based on the most realistic exposure information. It has to be decided therefore whether the available monitoring data can overwrite the calculated concentrations and thus be used in the risk characterisation. For this, a comparison is made between measured concentrations of acrolein in the various compartments and the corresponding calculated PECs.

For acrolein a meaningful comparison of measured and calculated acrolein data is only possible for the atmospheric compartment. The monitoring data set for the other compartments is either too limited (soil and sediment) or too scattered (water).

Although the collection of atmospheric monitoring data in **Table 3.11** is rather diverse (quality of data, year of sampling, location of sampling etc.), it seems to be possible to divide it roughly into four categories. In exhaust gases (1) acrolein concentrations up to 50,000 $\mu g/m^3$ have been measured. Near industrial activities (2) levels range from 100 to 2,500 $\mu g/m^3$. Acrolein levels in streets inner cities (3) were shown to have a minimum of about 0.3 $\mu g/m^3$ and a maximum of 35 $\mu g/m^3$. The regional concentrations (4) were found to be in the range of not detectable to about 2.5 $\mu g/m^3$. Categories 2, 3 and 4 are the most relevant for the underlying acrolein risk assessment and can (to some extent) be compared with calculated local and regional levels.

The type of industrial activities, for which measured acrolein concentrations are available, does not meet those used in paragraph 3.1.1.2. If, despite this imbalance, a comparison is made, it seems as if the calculated acrolein concentrations are generally lower than the measured ones, except for the generic scenarios. The few calculated data of acrolein levels in busy streets (1.3 - 4.7 $\mu g/m^3$) fall within the range of measured data for similar locations. The calculated PEC in air at a regional scale was found to be 0.03 $\mu g/m^3$, which is in line with the most recent (1993) measured concentration of < 0.1 $\mu g/m^3$ for the Netherlands. It is rather low, however, in comparison with several other (older) regional monitoring data.

Summarising, the comparison of measured and calculated atmospheric data is difficult to perform. It seems, however, as if the calculated data tend to be lower than the measured levels. This can be due to several reasons, e.g. a) monitoring data mostly refer to older periods with higher emissions, b) use of inappropriate sampling or analysis techniques c) the OPS model underestimates the acrolein concentrations in air or d) not all sources of acrolein exposure have been taken into account when calculating the PECs. The representativity and validity of the monitoring data set is considered insufficient to replace the calculated concentrations. As a consequence, both calculated and monitoring data will be discussed in the risk characterisation.

3.2 EFFECTS ASSESSMENT

3.2.0 General

The subsequent paragraphs only contain a summary of the ecotoxicity studies with acrolein (HEDSET, 1994). More ecotoxicity data on acrolein can be found in e.g. the BUA report (BUA, 1994) and the IPCS document (IPCS, 1992). These sources were checked in order to ensure that at least all 'key studies' were incorporated in the underlying report and could be used for the risk assessment. In a number of ecotoxicity studies with acrolein the test concentrations were not measured. In these cases, the actual concentrations may have been lower than the nominal ones in view of the volatility of the substance.

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Toxicity to fish (and other vertebrates)

Fresh water

The acrolein short-term toxicity studies with freshwater fish are summarised in **Table 3.13**.

Table 3.13 Short-term toxicity of acrolein to freshwater fish

No.	Species	Exp (h)	LC_{50} (mg/l)	Method	Anal. (yes/no) Closed/open syst.	R.I.	References
1	Catostomus commersoni	96	14	ASTM	yes, open	2	Holcombe, 1987
2	Lepomis macrochirus	96	33	ASTM	yes, open	2	Holcombe, 1987
3	Lepomis macrochirus	96	90	US-EPA	yes, closed	4a	Buccafusco, 1981
4	Oncorhynchus kisutch	96	68	other	no, open	4a	Lorz et al. 1979
5	Oncorhynchus mykiss	96	16	ASTM	yes, open	2	Holcombe, 1987
6	Pimephales promelas	96	14	ASTM	yes, open	2	Holcombe, 1987
7	Rasbora heteromorpha	48	60	other	no, open	4a	Alabaster, 1969
8	Leuciscus idus melanotus	48	250 2500	other	no data	4a	Juhnke, 1978

Table 3.13 shows that the short-term LC_{50}-values for freshwater fish range from 14 to 250 µg/l. For *Leuciscus idus melanotus* two LC_{50}-values (250 and 2500 µg/l; test No.8) were parallelly derived in two different German laboratories according to the same method. In view of the results from the other tests the highest value of 2500 µg/l is considered to be an outlier. The LC_{50}-values from tests no. 1, 2, 3, 5, and 6 are based on measured acrolein concentrations and are thus considered to have the highest reliability.

According to the classification scheme of Verhaar et al. (1992), which is based on chemical structure, acrolein should be classified to class 3 (reactive compounds). The worst-case estimate (QSAR) for a fish LC_{50} amounts to 220 µg/l. This figure fits in quite well with the experimental data.

In addition to the base set information for fish, also a long-term NOEC-value is available (Macek et al., 1976). In a 60-days reproduction study with Pimephales promelas a NOEC-value of 11.4 µg/l is reported (measured value) for effects on mortality of adults, number of spawning, number of eggs per female, number of eggs per spawn, length of offspring and hatchability.

Marine fish

Short-term toxicity data for two marine fish species are available (**Table 3.14**). LC_{50}-values are 56 and 240 µg/l. The data for test no. 1 are obtained from a review. For test No. 2 the complete test report was available and therefore this test is considered to be more reliable. To avoid losses of acrolein from the test solution, normal aeration was dispensed with.

Table 3.14 Short-term toxicity of acrolein to marine fish species

No.	Species	Exp (h)	LC_{50} (mg/l)	Method	Anal. (yes/no) Closed/open syst.	R.I.	References
1	Fundulus similis	48	240	other	no, open	4	Butler, 1965
2	Pleuronectes platessa	96	100<LC_{50} <320	TNO	no, open	1	Degussa, 1983a

Long-term toxicity data for marine fish species are not available.

Other aquatic vertebrates

In addition to the information on the toxicity of acrolein to fish, also a short-term LC_{50}-value for amphibia is available. In a 96-hours multiple species test a LC_{50} of 7 µg/l is reported for the tadpole *Xenopus laevis*, based on measured concentrations (Holcombe, 1987). It is clear that acrolein is also highly toxic to amphibia.

3.2.1.2 Toxicity to aquatic invertebrates

Fresh water invertebrates

A considerable amount of short-term toxicity tests is available for crustaceans, molluscs and insects (**Table 3.15**). The LC_{50}-values range from 22 to 15,200 µg/l. In comparison with molluscs, crustaceans and insects seem to be more sensitive to acrolein. The lowest value is found for the larvae of *Ephemerella walkeri*. However, it has to be noted that this EC_{50}-value is established in an avoidance test, which does not meet important criteria for toxicity testing. Because of this, the *Ephemerella* test is not taken into account for the derivation of the PNEC and will only be used as supportive information. For *Daphnia magna* the 48-hours LC_{50}-values range from 22 to 93 µg/l.

Table 3.15 Short-term toxicity of acrolein to freshwater invertebrates

No.	Species	Exp (h)	EC_{50} (mg/l)	Method	Anal. (yes/no) Closed/open syst.	R.I.	References
1	Daphnia magna	48	51	ASTM	yes, open	2	Holcombe, 1987
2	Daphnia magna	24	90	DIN 38412	no, open	1	Degussa, 1984a
3	Daphnia magna	48	93	other	no, closed	4a	Randall, 1980
4	Daphnia magna	48	57	US-EPA	no, open	4a	Macek et al. ,1976
5	Daphnia magna	48	83	US-EPA	no, closed	4a	LeBlanc, 1980
6	Daphnia magna	48	22		no, open	4	Baker, 1991
7	Biomphalaria glabrata	24	3700	other	no, open	3	Ferguson, 1961
8	Biomphalaria glabrata (eggs)	24	3100	other	no, open	3	Ferguson, 1961
9	Aplexa hypnorum	96	>150	ASTM	yes, open	2	Holcombe, 1987
10	Dreissena polymorpha	120	15,200	TNO	no, open	1	Degussa, 1984b
11	Ephemerella walkeri	1	10	other	no, open	3	Folmar, 1978
12	Tanytarsus dissimilis	48	>150	ASTM	yes, open	2	Holcombe, 1987

In addition to the base set information for aquatic invertebrates, also two long-term NOEC values are available for a crustacean and a mollusc, respectively (**Table 3.16**).

Table 3.16 Long-term toxicity of acrolein to freshwater invertebrates

No.	Species	Exp (d)	NOEC (mg/l)	Method	Anal. (yes/no) Closed/open syst.	R.I.	References
1	Daphnia magna	64	16.9	US-EPA	yes, open	1A	Macek et al. 1976
2	Dreissena polymorpha	14	1800	TNO	no open	1	Degussa, 1984

Mollusc *Dreissena polymorpha* a NOEC (mortality) is derived in a 14 days experiment, which may be considered relatively short for a long-term test with this species (average life time of *D.polymorpha* is about two years).

For *Daphnia magna* a three generation 64-days NOEC-value of 16.9 µg/l is reported. It has to be noted that the long exposure time of 64 days is not according to the recommended exposure time of the OECD guidelines (14 or 28 days).

Marine invertebrates

Short-time marine toxicity data are available for both crustaceans and molluscs and range from 55 to 1740 µg/l (**Table 3.17**). The LC_{50}-values from test no.1 are calculated with the Spearman-Karber method. The lowest value of 55 µg/l is found for *Crassostrea virginica* and is an EC_{50}-value for shell growth. However, this value is reported in a review without further details. For this reason the results of this test will only be used as supportive information. The same is true for the LC_{50}-value of test No. 4. In test No. 2 losses of acrolein from test solutions are reduced by omitting aeration.

Table 3.17 Short-time toxicity of acrolein to marine invertebrates

No.	Species	Exp (h)	EC_{50} (mg/l)	Method	Anal. (yes/no) Closed/open syst.	R.I.	References
1	Balanus eburneus	96	960 1740	other	no, open	3	Dahlberg, 1971
2	Crangon crangon	96	340	TNO	no, open	1	Degussa, 1983b
3	Crassostrea virginica	96	55	other	no data	4	Butler, 1965
4	Penaeus aztecus	48	100	other	no data	4	Butler, 1965

Long-term toxicity data for marine invertebrates are not available.

3.2.1.3 Toxicity to aquatic plants (e.g. algae)

The EC_{50}-values for freshwater algae range from 26 to 1800 µg/l (**Table 3.18**). The lowest EC_{50} is found for *Scenedesmus subspicatus* and is based on the endpoint biomass. Tests No. 1, 2 and 3 are performed in a closed system and are based on the endpoint photosynthesis reduction. It has to be noted that the exposure time of 24 hours in these tests is relatively short and not strictly according to accepted standard guidelines.

Table 3.18 Acrolein EC_{50}-values for freshwater plants

No.	Species	Exp (h)	EC_{50} (mg/l)	Method	Anal.(yes/no) Closed/open syst.	R.I.	References
1	Anabaena sp.	24	690	other	no, closed	1A	Fritz-Sheridan, 1982
2	Cladophora glomerata	24	1000	other	no, closed	1A	Fritz-Sheridan, 1982
3	Enteromorpha intestinalis	24	1800	other	no, closed	1A	Fritz-Sheridan, 1982
4	Scenedesmus subspicatus	72	26[a]	DIN EN 28 692	no, open	1	Degussa, 1994
5	Scenedesmus subspicatus	72	61[b]	DIN EN 28 692	no, open	1	Degussa, 1994

[a]Biomass
[b]Growth rate

NOEC-values are available for freshwater algae and macrophytes and range from 10 to 100 µg/l (**Table 3.19**). The lowest NOEC-value for growth rate of 10 µg/l is reported for *Scenedesmus subspicatus* in a test performed according to an accepted method. In tests nr. 3 and 4 foliar damage of aquatic macrophytes exposed to acrolein is determined. Several other tests with macrophytes have been performed in order to control the efficacy of acrolein as aquatic biocide and are considered not to be directly useful in the context of the current risk assessment. For this reason the results of these tests will only be used as supportive information.

Table 3.19 Acrolein NOEC-values for freshwater plants

No.	Species	Exp (h)	NOEC (mg/l)	Method	Anal. (yes/no) Closed/open syst.	R.I.	References
1	Microcystis aeruginosa	16	40	B & K	no, closed	2	Bringmann, 1976
2	Scenedesmus subspicatus	72	10[a] <10[b]	DIN EN 28 692	no, open		Degussa, 1994
3	Potamogeton nodosus	96	100	other	no, closed	3	Otto, 1966
4	Potamogeton pectinatus	48	10	other	no, closed	3	Otto, 1966

[a]Growth rate
[b]Biomass

Marine plants

Toxicity data for marine plants are not available.

3.2.1.4 Toxicity to microorganisms (e.g. bacteria)

The EC_{50} data for freshwater micro-organisms are shown in **Table 3.20**. For the bacterium *Proteus vulgaris* a 2 hour EC_{50} of 20 µg/l was determined. The 0.5 h EC_{50}- value for activated sludge bacteria from municipal origin was found to be 400 mg/l (respiration inhibition).

Table 3.20 Acrolein EC_{50}-values for freshwater micro-organisms

No.	Species	Exp (h)	EC_{50} (mg/l)	Method	Anal.(yes/no) Closed/open syst.	R.I.	References
1	Proteus vulgaris	2	20	other	no/closed	4	Brown, 1967
2	Activated sludge	0.5	400,000	Pagga (1981)	no data	4	Degussa, 1992

Several NOEC-values are available for both bacteria and protozoa, ranging from 210 to 40,000 µg/l (Table 3.21). Because protozoa are not (directly) involved in the biodegradation of chemical compounds in a sewage treatment plant, the NOEC-values for this taxonomic group (in casu tests no. 1, 2, and 3) are only used as supportive information when deriving a PNEC for micro-organisms.

Table 3.21 Acrolein NOEC-values for freshwater micro-organisms

No.	Species	Exp (h)	NOEC (mg/l)	Method	Anal.(yes/no) Closed/open syst.	R.I.	References
1	Chilomonas paramaecium	48	1700	B & K	no, closed	2	Bringmann, 1980a
2	Entosiphon sulcatum	72	850	B & K	no, closed	2	Bringmann, 1978
3	Uronema parduzci	20	440	B & K	no, closed	2	Bringmann, 1980b
4	Pseudomonas putida	16	210	B & K	no, closed	2	Bringmann, 1977
5	Activated sludge	0.5	40,000	Pagga	no data	4	Degussa, 1992b

3.2.1.5 PNEC for the aquatic compartment (incl. sediment)

The lowest long-term 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 assessment 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 for aquatic organisms of 0.1 µg/l (rounded off value).

$PNEC_{aquatic}$ = 0.1 µg/l

There are no data for sediment-dwelling organisms. A PNEC for 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.

3.2.1.6 PNEC for micro-organisms

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 of 2 µg/l.

$PNEC_{micro\text{-}organisms}$ = 2 µg/l

The rapporteur is aware that this PNEC is very low in comparison with information from the biodegradation tests (see section 3.1.0). Much higher concentrations of acrolein were found not to affect the biodegradation of acrolein.

3.2.2 Terrestrial environment

3.2.2.1 Toxicity to soil dwelling organisms

No data available.

3.2.2.2 Toxicity to terrestrial plants

The effects of acrolein on various crops grown on soil irrigated by acrolein treated water were investigated (Unrau et al., 1965; Ferguson et al., 1965). The concentrations varied between 15 and 50 mg/l of supply water. The effect levels differed among the crops tested. No effects were observed in bean, clover, corn and millet at 50 mg/l. Slight damage to foliage was observed in cucumbers and tomatoes at 40 mg/l, whereas cotton foliage was damaged significantly at 25 mg/l. Vegetable seedlings in contact with treated water were damaged even at the lowest concentrations used.

3.2.2.3 Toxicity to soil micro-organisms

In a study with the yeast *Cryptococcus neoformans*, 30 and 95% mortality was observed after 2 hours of acrolein incubation at 0.56 and 5.6 mg/l, respectively (Levitz et al., 1990; Tzeng et al., 1990).

After exposure of the fungus *Verticillium dahliae* to acrolein concentrations of 5.6 (4 hours) and 28 mg/l (2 hours), no colony forming units could be found as opposite to controls ((Levitz et al., 1990; Tzeng et al., 1990).

3.2.2.4 PNEC for terrestrial compartment

The ecotoxicity data set of acrolein for the terrestrial compartment is considered insufficient for a direct derivation of a PNEC. Therefore the $PNEC_{terrestrial}$ was estimated from the PNEC for aquatic organisms using the equilibrium partitioning approach according to the TGD ($PNEC_{terrestrial} = K_{soil\text{-}water}/RHO_{soil} \cdot PNEC_{water} \cdot 1000$). This results in a $PNEC_{terrestrial}$ (EUSES) of:

$PNEC_{terrestrial}$ = 0.01 µg/kg

3.2.3 Atmosphere

3.2.3.1 Toxicity to plants

There is a limited number of studies in which the phytotoxicity of airborne acrolein is investigated. Masaru et al. (1976) reported on the examination of the effects of several air pollutants, including acrolein, on lily pollen. Pollen germination has previously proved sensitive to various air pollutants, such as ozone. The implication is that the inhibition of pollen germination will be reflected as an adverse effect on reproductive capacity of a plant species. Acrolein proved to be more toxic to pollen than any of the other compounds tested. At a 2 hour exposure of 0.9 mg/m^3, acrolein caused a 60% decrease in pollen tube elongation; at 3 mg/m^3 it completely prevented extension of the pollen tube. The 1 hour EC_{10} (assumed to be equal to a NOEC) was found to be 0.9 mg/m^3. Having previously observed that exposure to acrolein at 1.1 mg/m^3 for 6 hours caused acute foliar injury to lily, the authors concluded that lily pollen was as sensitive as foliage to acrolein treatment.

In an effort to simulate the plant injury observed in California as a result of so-called smog in the mid-1940s, Haagen-Smit et al. (1952) exposed five plant species that appeared to be the most sensitive in the field (spinach, endive, alfalfa, oats and beets), to a variety of organic and inorganic compounds. The experiments were carried out in a fumigation chamber at concentrations generally less than 2 mg/m^3. Several aldehydes, including acrolein, were among the compounds tested. Exposure of acrolein at 0.2 mg/m^3 for 9 hours caused symptoms on alfalfa resembling natural smog damage, but there was no suggestion of damage to the other species. Higher doses of acrolein (1.3 mg/m^3 for 3 hours or 2.6 mg/m^3 for 4.5 hours) produced numerous sunken pits on both surfaces of spinach, endives and beets, but the injury was unlike that observed in the field. Having failed to reproduce typical smog symptoms on four of the five sensitive plant species, the investigators concluded that aldehydes were not responsible for plant damage in the Los Angeles area.

The above-mentioned studies were critically discussed in a National Research Council report 'Formaldehyde and Other Aldehydes' (1981). The report stated that because analytic techniques of varied sensitivity and precision were used for measuring aldehydes, it is futile to compare their results and extrapolate them to occurring concentrations in ambient air. Even assuming the presence of better analytic techniques, one must recognise that aldehydes are present in complex mixtures with other pollutants that may also be phytotoxic and interact with the aldehydes. The NRC report did not contradict that aldehydes may seriously affect vegetation, but it emphasised that many important gaps, e.g. a sound dose-effect relationship or evaluation of chronic effects, can not yet be clarified.

3.2.3.2 PNEC for plants (atmospheric compartment)

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 (see also conclusion of NRC-report). 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 for plants of 2 μg/m^3.

For comparison: the current Dutch atmospheric limit values for acrolein are 20 μg/m^3 (99.99P, hourly av.), 8 μg/m^3 (98P, 24h av.) and 6 μg/m^3 (95P, 24ha av.). These figures are only based on human (mammalian) toxicity data, but, retrospectively, they seem to be more or less protective to vegetation as well.

3.2.4 Non compartment specific effects relevant to the food chain (secondary poisoning)

A 7-days dietary study is performed with the adult starling *Sturnus vulgaris* (Shafer, 1972). The LD50 was found to be >100 mg/kg bw. However, it has to be noted that little information is available on test conditions and test substance. Only two birds per dose were tested. As stated in paragraph 3.1.0, owing to the very low log K_{ow} and the chemical reactivity of acrolein secondary poisoning is considered not to be relevant.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment (local)

Table 3.8 (paragraph 3.1.1.2.5) showed that for only 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 (see paragraphs 3.2.1.5 and 3.2.1.6). Production scenario Ia2 showed PEC/PNEC ratios <1 for both STP and surface water. **Table 3.22** presents the local PEC/PNEC ratio for micro-organisms and aquatic organisms for the other scenario.

Table 3.22 Local PEC/PNEC ratios for micro-organisms and aquatic organisms

	$PEC/PNEC_{micro\text{-}organisms}$	$PEC/PNEC_{aqua}$
processing scenario IIb (site-specific)	2.9	0.8

For the site specific scenario IIb the PEC_{STP} exceeds the $PNEC_{micro\text{-}organisms}$, 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 (see paragraph 3.1.0) lower concentrations in the STP are most likely. In addition, according to industry (company letter 21-2-1997) 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 suggest that sediment is probably not a relevant compartment for the environmental risk assessment acrolein (see paragraph 3.2.1.5).

3.3.2 Terrestrial compartment (local)

The local PECs in the terrestrial compartment for the various emission scenarios are given in Table 3.1.1.6 (paragraph 3.1.1.2.5). The PNEC for soil is 0.01 μg/kg (see paragraph 3.2.2.4). For all scenarios the PEC/PNEC ratio is <1 **(conclusion ii)**.

3.3.3 Atmosphere (local)

Local PECs in air are shown in **Table 3.8** (paragraph 3.1.1.2.5). Monitoring data are discussed in paragraph 3.1.1.3.4. The indicative plant PNEC for acrolein was estimated to be 2 μg/m^3 (paragraph 3.2.3.2). Despite the preliminary character of this PNEC, a comparison of the PEC and PNEC is conducted. The PEC/PNEC ratios that are larger than 1 are given in **Table 3.23**.

Table 3.23 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 3.23 shows that a number of monitoring data from unintentional sources exceed the indicative PNEC of 2 μg/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**).

3.3.4 Non compartment specific exposure relevant to the food chain (local)

Not relevant.

3.3.5 Risk characterisation (regional)

The PECs calculated at a regional scale (air, water and soil: see paragraph 3.1.1.3) do not exceed the corresponding PNECs. The available atmospheric monitoring data (ranging from n.d to 2.5 μg/m^3 are also found to be below the indicative PNEC of 2 μg/m^3).

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.0 General discussion

The human population may be exposed to acrolein at the workplace, from use of consumer products and indirectly via the environment.

In the EU acrolein is only used as an intermediate in the chemical industry, the industrial and use category are given in **Table 2.1**.

Outside the EU acrolein is also directly used. The application of acrolein as an aquatic pesticide is its most common direct use. It is useful for controlling microbial growth in subsurface feed lines, wastewater, hydrocarbon fuels and oil wells (Ghilarducci & Tjeerdema, 1995). Other direct uses of acrolein are as a tissue fixative, warning agent in methyl chloride refrigerants, leather tanning agent, etherification of food starch and the production of perfumes and colloidal metals (WHO, 1992) and recently, in tests, as a fumigant for ground squirrel burrows (O'Connell & Clark, 1992).

Occupational exposure may occur through skin exposure by direct contact or aerosol deposition or exposure by inhalation of vapours and aerosols at workplaces where acrolein is produced or used (see paragraph 4.1.1.1).

Non-occupational exposure can occur through the direct use of acrolein containing products and after indirect exposure through the environment (paragraphs 4.1.1.2 and 4.1.1.3, respectively).

4.1.1.1 Occupational exposure

Acrolein is produced and used in the EU in the chemical industry only. It is used as an intermediate in the production of several substances (see Chapter 2). Outside the EU it is also used as a broad band biocide in several situations. Apart from these uses, some older references mention a number of other possible uses that are not considered to be actually relevant. Residual amounts of acrolein are not expected in the products made from acrolein, such as glutaraldehyde.

There are no published data available on the acrolein quantities which are formed during the acrylic acid and acrylonitrile synthesis as an intermediate or intermediate by-product and which are immediately reacted further in closed units (BUA, 1995).

Emission of acrolein from other areas is possible (US ATSDR, 1990):

- combustion and pyrolysis of materials such as wood and plastics;
- combustion of fuel in spark-ignition and diesel engines;
- tobacco smoking;
- heating of fats;
- acrolein has also been found in foods and food products such as raw cocoa beans, volatiles from cooked mackerel and white bread, and vegetable oils, wine, whisky, and lager beer.

Possible uses, exposure sitiuations and exposed populations within Europe and elsewhere will be discriminated below.

The EU

Acrolein is only used as an intermediate. No uses of products containing acrolein need to be assessed.
Relevant populations potentially exposed are workers in the chemical industry, especially those workers that may have more or less direct contact with the substance, being:

- workers drumming the substance or transferring it to other systems in the chemical industry;
- workers who are exposed to vapours during production of acrolein or the processing of acrolein;
- workers cleaning production facilities and equipment for the production of acrolein or products were acrolein is used as intermediate.

Outside the EU

The use of products outside the EU may include:

- transfer of liquids by means of a transfer line and pumping: biocides;
- manual transfer of liquids: biocides.

Relevant populations potentially exposed outside the EU are the same populations as mentioned for the EU and workers involved in application of the biocide, or coming into contact with water treated with the biocide.

Routes of exposure and data used for exposure assessment

The routes of exposure are exposure by inhalation of vapours and aerosols and skin exposure by direct contact or aerosol deposition.

The following data are used for occupational exposure assessment:

- physico-chemical data of acrolein and products containing the substance; physical appearance, vapour pressure at room temperature, percentage of acrolein in products;
- data regarding methods of use and use pattern of the substance and products potentially containing acrolein and exposure control pattern in relevant industries (from HEDSET or other sources);
- exposure data of acrolein from the HEDSET and other sources (literature, databases);
- exposure data for analogues with similar use patterns from literature and exposure databases;
- results from exposure models (EASE model).

Acrolein is used as an intermediate. In many cases, the processes and activities that may lead to emission of acrolein into the workplace and hence to the exposure of workers are similar. Exposure situations can be clustered in "similar exposure scenarios" based upon the type of process and activity and the possibilities for exposure that relate to that process and activity.

The exposure is assessed using the available information on substance, processes and work tasks. More detailed information on these parameters may lead to a more accurate exposure assessment.

In this part of the assessment, external (potential) exposure is assessed using relevant models and other available methods in accordance with the Technical Guidance Documents and agreements made at official Meetings of Competent Authorities. Internal dose depends on external exposure and the percentage of the substance that is absorbed (either through the skin or through the respiratory system).

The exposure is assessed without taking account of the possible influence of personal protective equipment (PPE). If the assessment as based on potential exposure indicates that risks are to be expected, the use of personal protective equipment may be one of the methods to decrease actual risks, although other methods (technical and organisational) are to be preferred. This is in fact obligatory following harmonised European legislation.

Knowledge of effectivity of PPE in practical situations is very limited. Furthermore, the effectivity is largely dependent on site-specific aspects of management, procedures and training of workers. A reasonably effective use of proper PPE for skin exposure may reduce the external exposure with 85%. For respiratory protection the efficiency depends largely on the type of protection used. Without specific information, a tentative reduction efficiency of 90% may be assumed, equivalent to the assigned protection factors for supplied-air respirators with a half mask in negative pressure mode (NIOSH, 1987). Better protection devices will lead to higher protection. Imperfect use of the respiratory protection will lower the practical protection factor compared to the assigned factor. These estimations of reduction are not generally applicable "reasonable worst case" estimations, but indicative values based on very limited data. They will not be used directly in the exposure and risk assessment. Furthermore, the reduction of external exposure does not necessarily reflect the reduction of absorbed dose. It has to be noted, that the use of PPE can result in a relatively increased absorption through the skin (effect of occlusion), even if the skin exposure is decreased. This effect is very substance-specific. Therefore, in risk assessment it is not possible to use default factors for reduction of exposure as a result of the use of PPE.

In some specific situations the model estimates with normal assumptions for input parameters in the assessed exposure scenarios are expected not to lead to a reasonable assessment of exposure. For situations with high risk of direct acute effects, such as manual handling of corrosive substances and hot materials, or possible inhalation exposure of substances with severe acute effects on the respiratory tract, the total level of containment given by all exposure control measures is assumed to be higher than for similar scenarios with other substances. For estimating a single day exposure an extra protection is assumed, reducing exposure with 90%. The extra protection can be reached by a combination of technical and organisational control measures and personal protective equipment. If the extra protection is reached (mainly) by using personal protective equipment, this is an unwanted situation that should be changed by further technical and organisational control measures.

Repeated exposure to corrosive concentrations will not normally occur. Some exposure to non-corrosive exposure may however still occur, *e.g.* to highly diluted concentrations after decontamination of surfaces. The estimate of repeated dermal exposure depends on the knowledge of a concentration that will probably not cause corrosive effects. If such a concentration can be estimated, this concentration will be used in estimating repeated dermal exposure. Otherwise the estimate for single day exposure will be used.

The following exposure scenarios will be considered:

1- production of acrolein, with emphasis on drumming;
2- processing of acrolein;
3- exposure not resulting from the production or use of acrolein.

Some of the scenarios may have different exposure levels for different subgroups of workers. However, available (exposure) data often do not allow distinguishing between the subgroups and therefore these scenarios will not be subdivided.

Very limited numbers of measured levels of occupational exposure during production or handling of acrolein were found in literature. Measured levels of acrolein in the workplace were mostly from formation of acrolein during combustion and pyrolysis of products. This exposure is not the result of production or use of acrolein or products containing acrolein. Therefore exposure assessment levels are mostly based on exposure assessment models.

In this report for each scenario the general description of exposure will be followed by measured data (if available), followed by the suitable inhalation models. The resulting estimates of inhalation exposure will be compared using expert judgement and a choice for the best applicable estimators will be made. Dermal exposure will be described and assessed by means of EASE.

Scenario 1 Production

Production of acrolein takes place in a closed system.

Inhalation exposure

Inhalation exposure can be caused by drumming; this procedure can cause emission into the air. Details have been provided by one of the producers regarding their techniques and procedures for handling acrolein. Strict procedures are used regarding the opening of transfer lines and other situations in which the closed system is breached. Transfer lines cannot be opened when the local exhaust ventilation is turned off. Filling of large containers and railway cars is done using vapour return systems. The tight connection of all transfer lines is tested before the product flow is started. The actual filling is semi-automatic. The amount of acrolein that can be released during disconnecting is estimated by industry to be no more than 1 g. The use of personal protective equipment, including respiratory protection, chemical protective gloves and eye protection is obligatory in cases of breaching of the closed system (Industry, 1997). Fugitive emissions through valves, flanges and other equipment are also possible.

Some exposure data on acrolein production have been presented by industry (Industry, 1992). Personal sampling during approximately 1 to 2 hours (n=5) resulted in a maximum level of 2.79 mg/m^3 for a worker sealing and unsealing a railway tank car. This level was measured in five measurement intervals over a total duration of 1 hour and 15 minutes. Other results for measurements of similar duration during sampling, analysis and site inspections were substantially below this value, ranging from not detected to 0.01 mg/m^3. Stationary samples for 2 to 3 hours (n=6) resulted in levels between not detected and 0.01 mg/m^3. Short-term samples over 7-16 minutes were taken during activities such as filling railway tank cars (sealing and unsealing), semi-automatic filling of vessels and sampling. The exposure levels ranged from not detected to 10 mg/m^3. The highest value was measured for 16 minutes during sampling. Industry

reports that this was a measurement in an untypical situation and that technical and procedural control measures have been taken to prevent such high peak exposures [Industry, 1997]. Measured values for sealing and unsealing of railway cars are between 1.6 and 8.1 mg/m^3. Company B (1998) provided new limited data on full shift exposure of production workers performing several tasks (including filling of drums and coupling and decoupling of tank cars) and on short-term exposure during sampling and coupling and decoupling of tank cars for the same facility studied in (Industry 1997). These data show a substantial decrease in exposure in that facility. In a POC production plant results of 6 measurements (personal and stationary) for 3 hours were recalculated into 8 hour time weighted averages. These were 0.01-0.06 mg/m^3.

New and additional information was provided in 1998. The results of measurements in one company are distinguished for several activities (work in the filling area, general production and laboratory work).

All measurements were done outside of personal protective equipment. The three measurements of 'production, personal samples' were on workers not involved in sampling or connecting/disconnecting of railway cars. However, they worked throughout the production unit, including the filling area. It is stated, that the manufacturer of the PPE has indicated a nominal protection factor of the PPE in use is 99.95% and that a conservative estimate of real protection factor (taking account of a security factor for fit) is 99.5% (Company A, 1998).

All measurements by industry are reported to have been taken according to a worst case strategy.

The WHO (1992) referred to a publication of Kantemirova (from 1975-1977) in which measurements were taken at a production plant for acrolein. The exposure levels ranged from 0.1 - 8.2 mg/m^3. In the publication it was not stated under which circumstances or during what time measurements were done. These measurements, taken in the USSR, may not be representative for present conditions in Europe.

The exposure data are summarised in **Table 4.1**.

The estimate of exposure levels of a substance of high volatility, used in a closed system by the EASE model is 0 - 0.1 ppm (≈ 0 - 0.23 mg/m^3).

The system will be opened from time to time by specialised workers for cleaning and maintenance.

Table 4.1 Exposure data on the production of acrolein

Substance	Tasks	Duration of sampling (minutes)	n	Exposure level (mg/m³)	References and remarks
Acrolein	sealing, unsealing railway cars	75	1	2.79	(Industry, 1992); measured in 5 intervals; personal samples
	control activities, site inspection	56 - 118	3	nd-0.002	(Industry, 1992); personal samples
	sampling	16	1	10	(Industry, 1992); personal sample
	sealing, unsealing railway cars	7 and 10	2	1.6 and 8.1	(Industry, 1992); personal samples
	not given	8	1	nd	(Industry, 1992); personal sample
	semi automatic filling of vessels with LEV	12	1	0.067	(Industry, 1992); personal sample
	not given	131-180	6	not detected - 0.01	(Industry, 1992); stationary samples
	laboratory analysis	ng	ng	0.012-0.021	(Company A, 1997); personal samples
	filling	full shift	5	2.5-7.8	(Company A, 1998); personal samples; data 1993-1997
	filling	15	9	0.07-8.7	(Company A, 1998); personal samples; data 1993-1997
	production, personal samples	full shift	3	< 0.01	(Company A, 1998); personal samples; data 1998
	laboratory	full shift	10	0.002-0.05	(Company A, 1998); personal samples; data since 1995
	laboratory	15	9	< 0.001-0.17	(Company A, 1998); personal samples; data since 1995
	production	full shift	4	< 0.006-0.008	(Company B, 1998); two workers in late shift and two in night shift
	sampling	15	1	0.043	(Company B, 1998)
	coupling and decoupling	15	2	0.051-0.083	(Company B, 1998)
	not given	ng	ng	0.1-8.2	(WHO, 1992); possibly not relevant for present European situation

n = number of samples;
ng = not given

Dermal exposure

Skin exposure is theoretically possible during drumming. Drumming into rail cars and tank trucks will be performed using transfer lines, while drumming into drums may lead to contact with contaminated drums if drums overflow, or fill spouts are not fitted correctly. It is assumed that drumming of corrosive materials such as acrolein normally does not include direct handling, so dermal exposure in drumming can be considered to be accidental.

Cleaning and maintenance of production equipment (by specialised workers) may also lead to potential skin exposure. Based on the information by one producer regarding the flushing of the system and subsequent assurance of lack of contamination (Industry, 1997) it is assumed that dermal exposure will only occur accidentally, when correct procedures have not been followed. In this assessment it is taken into account that chemical protective gloves are obligatory when a possibility of skin contact is foreseen.

Duration and frequency of exposures

Duration and frequency of inhalation exposure may be up to 8 hours per day (fugitive emissions) on all working days (depending on the amount produced and the organisation of work). Exposure to levels as assessed for drumming will only occur during a limited period (0-2 hours per day).

Conclusion

Specific information on processes and exposure levels in recent years was available from both production facilities. As far as can be established at this moment, the exposure situation for filling is different for the two companies. The measurements in the filling area for Company A, starting from 1993 are taken as representative for the reasonable worst case situation. The potential exposure (not accounting for PPE) is up to 8 mg/m3 for both full shift and short term exposure levels (based on 3 full-shift samples and 9 short term samples). This exposure is taken for workers performing 'filling'. All other activities lead to substantially lower exposure levels. The efficiency of the PPE in practical use has not been shown. The assumptions by the manufacturer of the PPE are presumably based on laboratory testing of the penetration through the mask, and on assumptions related to the fitting factor. The assigned protection factors (APF) for full face-piece masks with gas-filters, according to the British Standards (BSI, 1997) is 20. Assuming this protection factor, the reasonable worst case protected exposure level is 8/20 = 0.4 mg/m3. If particle/gas combined filters are used (APF = 40), the reasonable worst case protected exposure level is 0.2 mg/m3.

No information is available on the frequency of days on which workers are involved in connecting/disconnecting. This is assumed to be less than half of the working days. A frequency of up to 100 days per year is assumed.

Because of the highly toxic characteristics of acrolein, the high flammability and its explosivity with air, acrolein is handled only in closed systems. It must be treated as a serious fire hazard, and ignition sources must be avoided whenever acrolein is handled with an air atmosphere. Also direct exposure may result in severe injury and even dilute solutions can cause residual damage to the eyes and inhalation of the vapours causes, e.g. irritation of nose and throat. Based on the above it is assumed that direct manual or open handling of acrolein does not occur, therefore the estimate of the exposure level should be based on handling acrolein in a closed system. Based on EASE the estimate of the inhalation exposure level of acrolein, used in a closed system, is 0 - 0.1 ppm (0 - 0.23 mg/m^3). The exposure estimate by EASE is more than 10 times the measured data for general activities. EASE therefore appears to overestimate exposure. Based on measured data, the typical exposure level for workers not involved in connecting and disconnecting of tank cars is estimated to be 0.01 mg/m^3.

When high exposures may occur the use of personal protective equipment is obligatory. The proper use of adequate personal protective equipment (PPE) can be an important risk reduction

method for the handling of substances with acute and serious effects at estimated occupational exposure levels. This situation is assumed to be present for the assessed substance in the assessed scenario(s).

Given the known effects of acrolein on skin, workers are expected to be very careful when handling acrolein to avoid contact. Dermal exposure is therefore considered only to occur accidentally.

Scenario 2 Processing

Processing of other substances, where acrolein is an intermediate or by-product, takes place in a closed system.

Inhalation exposure

The industry measured the exposure to acrolein in an acrylic acid unit and during the production of polycarboxylic acid. In the acrylic acid unit the exposure to acrolein was 0.01 mg/m^3. The sampling period was 1.58 hour (Industry, 1992). It is assumed that exposure can occur full shift.
In the polycarboxylic acid plant 6 measurements were taken during 3 hours. The exposure values ranged from 0.01-0.06 mg/m^3. These are 8-hour TWA values (CI, 1995).

Exposure data of the industry are summarised in **Table 4.2**.

Table 4.2 Exposure data during the processing of acrolein

Substance	Tasks	Duration of sampling (minutes)	n	Exposure level (mg/m^3)	Reference and remarks
Acrolein	acrylic acid unit	95	1	0.01	(Industry, 1992); personal sample
	polycarbolic acid production	≈ 180	6	0.01-0.06	(Industry, 1992); personal and stationary samples

n = number of samples

Inhalation exposure was also assessed by EASE. The estimate by EASE of exposure levels of a highly volatile substance, used in a closed system is 0 - 0.1 ppm (≈0-0.23 mg/m^3).

Dermal exposure

According to EASE the dermal exposure is very low. It concerns a liquid substance, where the pattern of use is a closed system and the contact level is incidental.

Duration and frequency of exposure may be up to 8 hours per day on all working days (depending on the amount produced and the organisation of the work).

Conclusion

According to the measurements and the assessments made by EASE, the exposure during the processing is low. The upper end of the estimate by EASE is approximately 4 times the highest measured exposure level. The number of measurements was however very low and the

representativeness of their results cannot be established. Therefore a precautionary approach is used and the more conservative value is used. The value given by EASE will therefore be taken forward to risk characterisation as the estimate of reasonable worst case exposure. Typical values will be about 0.03 mg/m^3 (based on the few measured data). Since it concerns a closed system in which acrolein is an intermediate no high peak levels will occur; the exposure will be below 0.46 mg/m^3 (2 times the reasonable worst case level; expert judgement). The use of PPE is not expected to be a normal procedure, since the substance is contained in closed systems. In non-typical situations involving an unwanted breach of the closed system, exposure levels will be higher, but PPE will be used. Such situations are considered to constitute accidental exposure and will not be further assessed.

Since acrolein is a known corrosive agent, contact with the hands will be avoided by closed systems and proper techniques of handling. Exposure is expected to occur only accidentally.

Scenario 3 Exposure not resulting from the production or use of acrolein

Exposure to acrolein during this scenario is not the result of using acrolein or a product containing acrolein. Although this scenario may not have to be evaluated for the purpose of the existing substances regulation, some data are included for comparison with the other scenarios.

In the work situation acrolein exposure can occur as a result of pyrolysis reactions, for example: fuel exhaust, welding of metals coated with anti corrosion primers and rubber vulcanisation. Acrolein has further been identified as a volatile component of essential oils extracted from the wood of oak trees and it has been found in the smoke resulting from combustion of wood, kerosene and cotton.

The following exposures to acrolein in workplace air have been reported by IARC (1979):

- rubber vulcanisation plant 0.44-1.5 mg/m^3;
- welding of metals coated with anti-corrosion primers 0.11-1.04 mg/m^3;
- pitch cooking plants 0.322 mg/m^3;
- diesel train engine exhaust during repair and servicing <0.1 mg/m^3.

It has to be mentioned that the above mentioned exposure data are from the early 1970s. These data may not be valid for present conditions. Duration and frequency of these processes are not described. More recent exposure levels from the literature were found in a report of the WHO: Rietz, 1985 measured the exposure in an engine workshops during welding, the exposure ranged from 0.031 to 0.605 mg/m^3 (WHO, 1992).

Welding and flame cutting of painted steel in shipyards was reported to lead to levels of 0.04-1.4 mg/m3 (Engstrom et al., 1990). Exposure levels in the metal-industry range from undetectable to 1.66 mg/m3; in this situation probably acrolein formation occurs due to combustion and pyrolysis. No information about frequency and duration of measurements is available (INRS, 1995).

Exposure due to pyrolysis reactions was measured in several industries. The Finnish Environmental Agency (Finish Environmental Agency, 1995) reported exposure concentrations form emptying of steel casting moulds involving thermal breakdown of resins (n = 2), oven treatment of epoxy coated metal articles (n = 4), baking doughnuts (n = 1), heat seaming of polyethylene coated cardboard an processing polyethylene (n = 4) and ABS plastic material (n = 4). Arithmetic mean work place

concentrations were reported to range between 0.009 and 0.023 mg/m3. Duration of the measurements ranged from 57 to 212 minutes. Exposure time was in most cases 8 hours.

Acrolein exposure was also reported during welding and flame cutting of coated steels in Finnish shipyards. Exposure levels were determined in the breathing zone of workers with sample collection inside the welding helmet, sampling duration ranged from 30 to 60 minutes. Median acrolein concentrations during ship building were 0.01 mg/m^3 and 0.021 mg/m^3. The maximum concentration measured was 0.065 mg/m^3. During ship repair a median concentration of 0.016 mg/m^3 was reported (5 measurements; maximum is 0.15 mg/m^3), in ship breakdown operations a median concentration of 0.07 mg/m^3 was given (6 measurements; maximum concentration of 1.4 mg/m^3) (as quoted by Degussa, 1995). It is not clear whether these exposures occur for full shift.

The German "Employers Liability Insurance Association for the Chemical Industry" (BGAA) has provided exposure data on acrolein for a number of processes. The data were gathered between 1991 and 1995. In total 947 measurements were done in 422 companies. Data from the chemical industry were not reported in the available information because of their limited number. Ninety percentiles were from below the limit of detection (approximately 0.01 mg/m^3) up to 0.25 mg/m^3. The latter value was found in smokehouses (BGAA, 1996).

The available exposure data are summarised in **Table 4.3**.

Table 4.3 Exposure data not resulting from the use of acrolein

Industry/task	Duration of sampling (hours)	n	Exposure level (mg/m^3)	References
Rubber vulcanisation plant	ng	ng	0.44-1.5	(IARC, 1979)
Welding materials	ng	ng	0.11-1.04	(IARC, 1979)
Pitch coding plant	ng	ng	0.32	(IARC, 1979)
Diesel train engine exhaust	ng	ng	<0.1	(IARC, 1979)
Welding flame cutting	ng	ng	0.04-1.4	(Engstrom et al., 1990)
Welding in workshop	ng	ng	0.31-0.6	(WHO, 1992)
Metal industry	ng	ng	0-1.66	(INRS, 1995)
Thermal breakdown resins	1-3.5	2	0.01	(Finish Environmental Agency, 1995)
Oven treatment epoxy coated metal	1-3.5	4	0.023	(Finish Environmental Agency, 1995)
Baking doughnuts	1-3.5	1	0.032	(Finish Environmental Agency, 1995)
Heat seaming polyethylene cardboard	1-3.5	4	0.013	(Finish Environmental Agency, 1995)
Working on polyethylene and ABS plastic material	1-3.5	4	0.009	(Finish Environmental Agency, 1995)

Table 4.3 continued overleaf

Table 4.3 continued

Industry/task	Duration of sampling (hours)	n	Exposure level (mg/m^3)	References
Welding, flame cutting in ship building	0.5-1	39	0.01 [AM] 0.043 [max]	as quoted by Industry, 1992
Welding, flame cutting in ship building	0.5-1	32	0.021 [AM] 0.065 [max]	as quoted by I Industry, 1992
Welding, flame cutting in ship repair	0.5-1	5	0.016 [AM] 0.15 [max]	as quoted by Degussa, 1995
Welding, flame cutting in ship breakdown	0.5-1	6	0.07 [AM] 1.4 [max]	as quoted by Degussa, 1995
Hot processing of plastics without LEV	> 1	59	0.015 [90%]	BGAA, 1996
Hot processing of plastics with LEV	> 1	35	< lod [95%]*	BGAA, 1996
Drying, sintering, roasting, melting without LEV	> 1	15	0.015 [90%] 0.03 [95%]	BGAA, 1996
Drying, sintering, roasting, melting with LEV	> 1	19	< lod [90%]* 0.02 [95%]	BGAA, 1996
Smokehouse	> 1	13	0.08 [50%] 0.25 [90%] 0.31 [95%]	BGAA, 1996
Thermal processes	> 1	175	< lod [95%]*	BGAA, 1996
Glueing	> 1	52	< lod [95%]*	BGAA, 1996
Not given	< 1	18	< lod [90%]* 0.2 (95%)	BGAA, 1996

n = number of samples
ng = not given
[AM] = Mean
[max] = maximum
< lod* = below the limit of detection; the limit of detection was for 2 hours of sampling was 0.01 mg/m^3
[x%] = x-percentile

Conclusion

Since the data of IARC (1979) and WHO (1992) are rather old, these data will not be used for the risk assessment. Typical exposure is for most situations assessed to be 0.01 mg/m^3, possibly for a full shift. In smokehouses typical exposures is assessed to be 0.08 mg/m^3. Based on published data, the reasonable worst case levels for periods of an hour or more are generally 0.1 mg/m^3, but are higher for smokehouses: 0.25 mg/m^3 and for short term exposure (< 1 hour) up to 2 mg/m^3.

EASE can not be used for this purpose, because the scenario is not the result of using acrolein or a product containing acrolein.

Skin exposure for this scenario is theoretically possible. However, because the acrolein will be volatile during these processes and skin exposure to vapours is by default assumed to be negligible for uptake, the skin exposure level for this scenario is assumed to be negligible.

The conclusions are summarised in **Table 4.4**.

Table 4.4 Exposure assessment levels of acrolein

Scenario	activity	frequency	duration (hr)	Reasonable worst case		Typical concentration		Dermal	
				(mg/m^3)	method	(mg/m^3)	method	$mg/cm^2/day$	dose (mg/day)
1. production	full shift (filling)*	50-100	6-8	0.2	measured, calculated	0.01	measured	accidental	accidental
2. processing	general	100-200	6-8	0.23	EASE	0.03	lit.	accidental	accidental
3. exposure not resulting from use of acrolein	general exposure activities full shift*** smokehouses	100-200 100-200	6-8 0-1 6-8 6-8	0.1 2 0.33 0.25	lit. lit. calculated lit.	0.01 0.08	lit. lit.	negligible	negligible

*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

4.1.1.2 Consumer exposure

Within the EU acrolein is only used as an intermediate in chemical synthesis by the chemical industry and it is not sold to the public as such or in preparations (Industry report acrolein, 1995).

Moreover, no indications of actual consumer use in the EU have been found in literature and therefore it is concluded that consumer exposure within the EU is not expected to occur.

An exposure assessment for the use of consumer products containing acrolein (e.g. as biocide) outside the EU has not been carried out.

4.1.1.3 Indirect exposure via the environment

4.1.1.3.1 Indirect exposure via the environment resulting from industrial emissions and traffic

Acrolein may be released to the environment via waste water and air effluents at sites where it is produced, processed and formed. The environmental exposure assessment of acrolein is based on the expected releases of the substance during 5 life cycle stages (see paragraph 3.1.1.1).

Acrolein formed during the pyrolysis of tobacco (stage V (outdoor air) is regarded as a diffuse source of acrolein that only will be used for the regional exposure assessment (see paragraph 3.1.1.2.4). Human exposure to acrolein formed at smoking indoor is discussed in paragraph 4.1.1.3.3.

The local (100 m from source) concentration estimates in air for the different scenarios as presented in **Table 4.5** are taken from **Table 3.8**.

Table 4.5 Local (100m from source) concentration estimates in air

Scenario	air concentration (100m from source) (mg/m³)
production scenario Ia1 (site-specific)	0.04
production scenario Ia2 (site-specific)	0.1
processing scenario Iib (site-specific)	-
processing scenario Iid (site-specific)	0.04
combustion scenario III (site-specific)	0.02
traffic scenario IV - busy street - busy motorway	 4.7 (98p/24h) 1.3 (annual av.) 1.7 (98P/24h) 0.7 (annual av.)

The total human intake via air, drinking water and food for the emission scenarios at local scale for stage I-III is estimated by EUSES (see Annex 2) and presented in **Table 4.6**.

Table 4.6 Total daily intake via air, drinking water and food at local scale

Scenario	Total daily intake (mg/kg bw/day)
production scenario Ia1 (site-specific)	$9.1 \cdot 10^{-6}$
production scenario Ia2 (site-specific)	$3.4 \cdot 10^{-5}$
processing scenario IIb (site-specific)	$3.2 \cdot 10^{-5}$
processing scenario IId (site-specific)	$8.4 \cdot 10^{-6}$
combustion scenario III (site-specific)	$5 \cdot 10^{-6}$

The major route for the site-specific scenarios is, as expected, the intake via air.

The regional exposure assessment is discussed in paragraph 3.1.1.3. A regional PEC air of 0.03 $\mu g/m^3$ was calculated using the EUSES model and the subsequently calculated total daily intake was calculated to be 7.3E-6 mg/kg bw/day. The intake via air is the major route and is 92% of the total human intake via indirect regional exposure.

4.1.1.3.2 Measured data in the environment

For the various compartments also monitoring data for acrolein are available (see paragraph 3.1.1.4).

The general population can be exposed to outdoor and indoor air. **Table 3.11** presents an overview of measured acrolein concentrations in ambient air at both the local and regional scale. In paragraph 3.1.1.5 the data were roughly divided in 4 categories which to some extent can be compared with the calculated and regional levels. Indoor air monitoring data are dealt with in paragraph 4.1.1.3.3.

In **Table 4.7** acrolein concentration ranges per category are given.

Table 4.7 Measured acrolein concentrations in the atmosphere per category

Category	Observed acrolein concentration (range) in $\mu g/m^3$
In exhaust gases	up to 50000
Near industrial activities	100 - 2500
In streets (inner city)	0.3 - 35
Regional concentrations	nd - 2.5

nd = not detected

As discussed in paragraph 3.1.1.5 the representativity and validity of the monitoring data set is considered insufficient to replace the calculated concentrations. Therefore as a consequence, both calculated and monitored atmospheric data will be discussed in the risk characterisation paragraph 4.1.3.3. No data on acrolein levels in drinking water are available (see **Table 3.12**).

According to US EPA (1986) acrolein has not been shown to be a contaminant of drinking water or drinking water supplies.

4.1.1.3.3 Indoor exposure through tobacco smoking, cooking activities and the use of fireplaces

Because of cooking activities and smoking, the indoor air acrolein concentrations could reach rather high values. Since acrolein is formed during pyrolysis of tobacco, smokers but also non-smokers belong to the group of exposed individuals by this route.

An extensive data base shows a delivery of 3 - 228 µg of acrolein per cigarette to the smoker via the gas-phase of mainstream smoke, the amount depending on the type of cigarette and smoking conditions (WHO, 1992). More recent data (listed in **Table 4.8**) revealed of up to 264 µg of acrolein per cigarette in mainstream smoke.

Non-smokers are mainly exposed to the side-stream smoke of tobacco products. According to WHO (1992) smoking one cigarette per m^3 was found to lead to acrolein concentrations in the gas-phase off side-stream smoke ranging from 450 to 840 µg/m^3. More recent data (see **Table 4.8**) revealed concentrations up to 3030 µg/m^3.

Dost (1991) observed that sidestream smoke, particularly that generated between puffs, results from lower-temperature pyrolysis and thereby creates more acrolein; it contains about 12-fold more acrolein than does mainstream smoke. Acrolein concentrations in a cooking area, where sunflower oil was heated at 160 - 170°C, reached a value of 1100 µg/m3 (cf. UNEP/IRPTC, 1984).

A relevant selection of acrolein concentrations found in indoor air through tobacco smoking and cooking activities are listed in **Table 4.8**.

Table 4.8 Environmental levels of acrolein in indoor air

Source	Sampling location/ Sample characteristics	Measurement values	Reference
Cigarette smoke, -restaurant -Tavern, indoor	side stream smoke	 11 - 41 µg/m^3 21 - 24 µg/m^3	Ghilarducci & Tjeerdema, 1995
Cigarette smoke	side stream smoke	2100 - 3030 µg/m^3	BUA, 1994
Cigarette smoke (10 brands)	side stream smoke	723 - 1390 µg/cig.	BUA, 1994
Cigarette smoke	main stream smoke	8 - 260 µg/cigarette	BUA, 1994
Cigarette smoke (75 brands)	main stream smoke	<10 - 140 µg/cigarette	BUA, 1994
Cigarette smoke -tobacco -marihuana	main stream smoke	 59 - 139 µg/cigarette 145 µg/joint	BUA, 1994
heated (250°C) pork fat		 1.9 mg/kg pork fat	BUA, 1994
blanching of Brussels sprouts and cauliflower	lab. experiment (90°C)	qualitatively detected	BUA, 1994

4.1.1.3.4 Exposure through food and beverages and natural sources

An additional source of human exposure can be the acrolein content of various food and beverages.

Small amounts of acrolein have been detected in a number of foods, including tomatoes, cooked potatoes, beer, heated and old animal fat, vegetable oils, white bread, wine, rums, whiskey and raw chicken.

Glycerol dehydration is a main source in foods; glycerides are the main constituents of lipids and thus are constituents of all foods with a significant fat content, including lard, butter and vegetable oils. Thus acrolein may be found in every process where animal fats or vegetable fats are exposed to high temperatures (Izard & Libermann, 1978). The distasteful odour of acrolein may account for the rancidity, by oxidation of fats exposed to air in moderate-to-high temperature.

Raw spirits may be contaminated with acrolein as a result of the bacterial action in the mash (Krell et al., 1994).

In **Table 4.9** acrolein concentrations in foodstuffs and food components are listed (WHO, 1992; BUA, 1994).

Table 4.9 Acrolein concentrations in foodstuffs and beverages

Food/beverage	Concentration range	Reference
Beer - freshly brewed - aged	 nd - 2 µg/l 5 µg/l	WHO, 1992
Bone grease - heated and aged	 4.2 mg/kg (average)	WHO, 1992
Bread layer of cod filets fried in used & fresh fat	nd - 1.2 mg/kg	BUA, 1994
Doughnuts (diff.)	0.1 - 0.9 mg/kg	BUA, 1994
Ethyl alcohols - various origins	 0.2 - 0.4 mg/l	BUA, 1994
Wines - spoiled - red	nn - 14 mg/l up to 3.8 mg/l	BUA, 1994
Whiskies	0.67 - 11.1 µg/l	Industry report acrolein,1995
Vegetable oils - heated	 5 - 163 µg/l	Ghilarducci & Tjeerdema, 1995

nd = Not detected
nn = ?

Other sources of acrolein are its occurrence in mammalian tissue as degradation product of polyamines such as spermidine and its suggested formation in skin resulting from UV irridiation of triglycerides of unsaturated fatty acids (Industry report acrolein, 1995).

It is very difficult to estimate the human dietary intake of acrolein from foodstuffs and commodity articles.

4.1.2 Effects assessment: Hazard identification and Dose (concentration) -response (effect) assessment

4.1.2.1 Toxicokinetics, metabolism, and distribution

4.1.2.1.1 Animal studies

Acrolein, an α,β-unsaturated aldehyde, is very reactive and conjugates easily with glutathione or other thiol-containing molecules, with protein sulfhydryl groups and primary and secondary amine groups. Interactions with DNA and proteins have been reported, mainly as the result of reactions with amino groups. As a consequence of its high reactivity the acrolein molecule will bind primarily at the application site (Beauchamp et al., 1985; IPCS, 1991).

Absorption and distribution

Egle (1972) examined the retention of acrolein vapour in the respiratory tract upon inhalation exposure of dogs to atmospheres containing 0.4 to 0.6 mg acrolein per ml (172 - 258 ppm) by subtracting the amount measured in exhaled air from that in inhaled air. The total tract retention was high (between 81 and 84%) and appeared concentration-independent. Separate measurement of the retention in the lower and upper respiratory tract showed a retention of 74 to 82% by the upper tract and 66 to 70% by the lower tract. Systemic absorption after oral, inhalation and subcutaneous administration in rats was evidenced from excretion of acrolein metabolites in urine (Draminski, 1983; Kaye, 1973; Linhart et al., 1996; Parent et al., 1993; Sanduja, 1989). The actual figures are given below in the 'Metabolism and excretion' section.

Parent et al. (1991, abstract only) examined the distribution of ^{14}C-acrolein, labelled in the 2,3 position in male and female rats after single i.v. administration of 2 mg/kg bw, repeated oral administration (gavage) of 2 mg/kg bw per day (14 doses of unlabelled followed by 1 dose of ^{14}C-acrolein), and single oral administration (gavage) of 2 or 15 mg/kg bw. The ^{14}C distribution was assessed in excreta and various tissues (not further indicated). No differences in distributions were found between single and repeated oral dose groups of 2 mg/kg bw. The i.v. dosing resulted in a pattern consistent with acrolein binding to blood elements and the high oral dose (15 mg/kg) demonstrated different excretion patterns relative to lower doses. All orally dosed groups showed the largest ^{14}C concentration in the liver (Parent et al., 1991).

No data on dermal absorption are available. The available acute dermal toxicity data do not allow the assessment of dermal absorption due to the irritant and corrosive properties of acrolein and the limited reporting of these studies.

Metabolism and excretion

Figure 1 gives a scheme of the possible pathway of acrolein metabolism. This scheme has been composed from the schemes published by IPCS and BUA (IPCS, 1991; BUA, 1995).

Animal data, metabolism and excretion in urine, faeces, air

Parent et al. (1993, abstract) studied the metabolism and excretion of ^{14}C-acrolein in rats using the same dosing scheme as described in Parent et al. (1991). For experimental design and concentrations examined see the 'absorption and distribution' section above.

After oral administration of ^{14}C-acrolein to rats the radioactivity was excreted in urine, exhaled air and faeces. The exhaled air contained mainly $^{14}CO_2$ and only traces of organic substances. Urinary metabolites included S-2-carboxyethylmercapturic acid (circa 34%) and S-3-hydroxypropylmercapturic acid (circa 7%). Identification of the faecal metabolites was more complex. About 80% of the radioactivity in faeces was extractable with methanol and 10% with water. None of the expected acrolein metabolites could be identified, except for small amounts of S-2-carboxyethylcysteine and S-3-hydroxypropylcysteine. No other faecal metabolites could be identified (Parent et al., 1993).

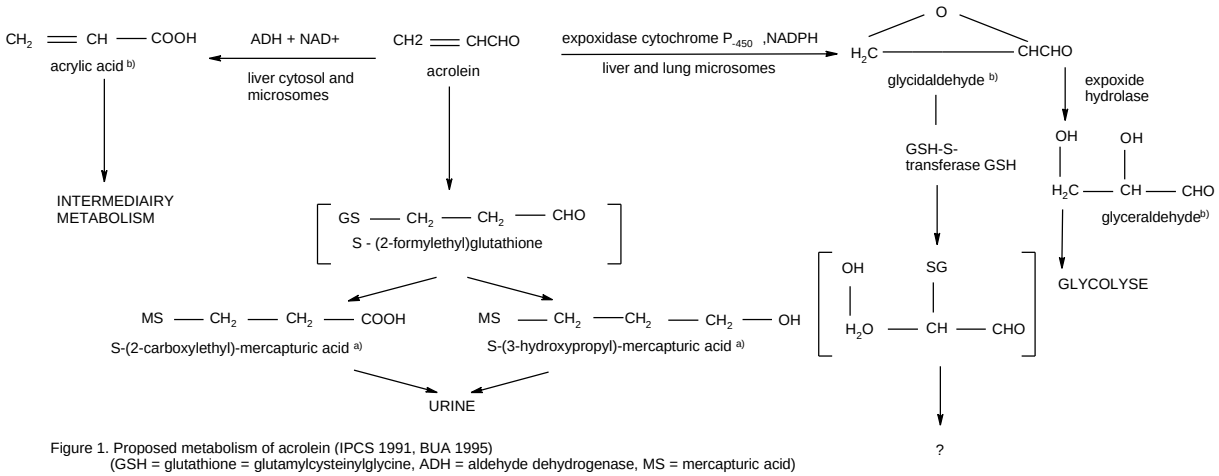


Figure 1. Proposed metabolism of acrolein (IPCS 1991, BUA 1995)
(GSH = glutathione = glutamylcysteinylglycine, ADH = aldehyde dehydrogenase, MS = mercapturic acid)

a) metabolite identified in rat in vivo
b) metabolite identified in in vitro systems
[ ] in brackets: metabolite not yet detected

According to Sanduja et al. (1989) 78% of a single oral dose of acrolein (rats, 13 mg/kg bw, gavage) was excreted in 24-h urine as 3-hydroxypropylmercapturic acid [*S*-(3-hydroxypropyl)-*N*-acetyl-L-cysteine]. The urinary metabolites identified by Draminski et al. (1983) using gas chromatography with mass spectrometric detection in rats orally dosed with 10 mg/kg bw acrolein, were *S*-carboxylethylmercapturic acid and its methylester, the latter possibly being the result of methylation of the urine samples prior to gas chromatography. An unidentified metabolite was found in expired air (Draminski et al., 1983; IPCS 1992). In rats 10-18% of a dose administered subcutaneously (50 to 300 µmol or 2.8 to 16.8 mg acrolein per kg bw) was found in the 24-h urine as 3-hydroxypropyl-mercapturic acid (Alarcon, 1976).

Linhart et al. (1996) identified two mercapturic acids *N*-acetyl-*S*-(3-hydroxypropyl)cysteine (3-hydroxypropylmercapturic acid) and *N*-acetyl-*S*-(2-carboxyethyl)-cysteine in the urine of rats exposed to acrolein either by inhalation or by intraperitoneal injection.

In both cases 3-hydroxypropylmercapturic acid was the major metabolite. In rats exposed for one hour to acrolein concentrations of 23, 48, 77 and 126 mg/m^3, the sum of the mercapturic acids i.e. 3-hydroxypropylmercapturic acid and *N*-acetyl-*S*-(2-carboxyethyl)-cysteine, excreted within 24 hr amounted to 0.87, 1.34, 2.81 and 7.13 µmol/kg bw or 10.9, 13.3, 16.7 and 21.5% of the estimated absorbed dose, respectively. The estimate of the absorbed dose was based on reported values of minute respiratory volume (0.1 l/min for the rat) and respiratory tract retention of acrolein (83%) and was, moreover, corrected for the actual measured acrolein-induced changes in minute respiratory volume. In ip treated rats the portion of mercapturic acids excreted within 24 hr was nearly constant in the relevant dose range (8.9 to 35.7 µmol/kg bw) and amounted 29.1 ± 6.5% of the dose (Linhart et al. 1996).

Animal data, depletion of nonprotein sulfhydryl groups in the nasal respiratory mucosa

Acrolein exposure of rats at 0, 0.1, 0.5, 1.0 or 2.5 ppm in a nose-only inhalation chamber for 3 h resulted in a concentration-dependent depletion of nonprotein sulfhydryl groups in the nasal respiratory mucosa (Lam et al. 1985).

Cassee et al. (1996) found a dose-dependent increase of NPSH-levels in nasal epithelium of rats after a 3-day exposure period to 0.67 or 1.40 ppm acrolein by inhalation in a nose-only inhalation chamber, whereas after a 6-h exposure period NPSH-levels were slightly lower in acrolein treated rats than in controls. The authors concluded that from these findings that nasal epithelium is able to adapt to (a potential) sulphydryl depletion (Cassee et al. 1996, see also section 4.1.2.6 Repeated dose toxicity. Miscellaneous studies, short-term inhalation studies).

In vitro metabolism data

In vitro data show that acrolein can also be a substrate of liver aldehyde dehydrogenase and lung or liver microsomal epoxidase. Two oxidation products of acrolein have been found in experiments *in vitro*: acrylic acid and glycidaldehyde (Patel et al., 1980; Ohno et al., 1985; Rikans, 1987; Mitchell and Petersen, 1989). Acrolein was oxidized to acrylic acid by rat liver fractions, but not by lung fractions in the presence of NAD+ or NADP+, while incubation of acrolein with either rat liver or lung microsomes and NADPH yielded glycidaldehyde and its hydration product glyceraldehyde (Patel et al., 1980). However, none of these metabolites have been demonstrated in mammals *in vivo* and it is unknown whether the metabolic pathways found *in vitro* play also a role in the biotransformation of acrolein *in vivo*.

4.1.2.1.2 Human data

There are no human data available on toxicokinetics

4.1.2.1.3 Conclusions

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 amounted to 81 - 84%. Acrolein mercapturic acid derivatives recovered in the urine amounted to 70 - 80%, 10 - 18%, and 29.1 ± 6.5% of the administered dose after oral, subcutaneous and intraperitoneal administration to rats, respectively. Upon inhalation exposure 11-22% of the estimated absorbed dose is found in the urine. After oral administration of ^{14}C-acrolein to rats, radioactivity is found in urine, exhaled air and faeces. It is noted that the results of the kinetic studies can hardly be used to clarify possible differences in biotransformation of acrolein after oral and inhalation absorption, due to e.g. study design and assumptions made.

The main metabolic pathway of acrolein *in vivo* presumably includes conjugation with glutathione. See also Figure 1. The *in vitro* metabolites acrylic acid, glycidaldehyde and glyceraldehyde have never been demonstrated *in vivo*.

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

4.1.2.2 Acute toxicity

4.1.2.2.1 Animal studies

Table 4.10 summarises the available LD_{50} and LC_{50} tests.

Table 4.10 Summary of acute toxicity studies

Route	Species	LD_{50}/LC_{50}	Unity	Reference
oral	rat	42 - 46	mg/kg bw	Smyth et al, 1951; Albin, 1975
oral	mouse	13.9 - 28	mg/kg bw	Albin, 1975; EPA/OTS 1991*
inhalation	rat	750 (10 min)	mg/m³ (vapour)	Catalina et al, 1966
inhalation	rat	300 (30 min)	mg/m³ (vapour)	Skog, 1950
inhalation	rat	65 (1 hr)	mg/m³ (vapour)	Ballantyne et al 1989
inhalation	rat	18 - 21 (4 hr)	mg/m³ (vapour)	Ballantyne et al 1989; Carpenter et al 1949
inhalation	rat	150 (4 hr)	mg/m³ (vapour)	EPA/OTS, 1992*
inhalation	mouse	ca. 2000 (1 min)	mg/m³ (nature unknown)	Shell, 1957
i.p.	rat	4	mg/kg bw	Murphy et al, 1983
i.p.	mouse	ca. 6 - 7	mg/kg bw	Shell, 1957; Warholm et al, 1984
s.c.	rat	50	mg/kg bw	Skog, 1950
s.c.	mouse	30	mg/kg bw	Skog, 1950
inhalation	mouse	400 (10 min)	mg/m³ (nature unknown)	Shell, 1957
inhalation	mouse	151 (6 hr)	mg/m³ (vapour)	Philippin et al, 1969; Philippin et al, 1970
inhalation	mouse	5225 (13.4 min)	mg/m³ (vapour)	Salem et al, 1960
inhalation	mouse	4624 (13 min)	mg/m³ (aerosol)	Salem et al, 1960
inhalation	rabbit	5225 (26.8 min)	mg/m³ (aerosol)	Salem et al, 1960
inhalation	hamster	58 (4 hr)	mg/m³ (nature unknown)	Kruysse, 1971
inhalation	dog	344 (30 min)	mg/m³ (nature unknown)	Albin, 1975
inhalation	guinea pig	5225 (24.9 min)	mg/m³ (aerosol)	Salem et al, 1960
dermal	rabbit	164 (20% in mineral spirits)	mg/kg bw	Shell, 1957
dermal	rabbit	238 (10% in mineral spirits)	mg/kg bw	Shell, 1957
dermal	rabbit	200**	mg/kg bw	Albin, 1975
dermal	rabbit	562 (undiluted)	mg/kg bw	Shell, 1957
dermal	rabbit	335 (20% in water)	mg/kg bw	Shell, 1957
dermal	rabbit	1022 (10% in water)	mg/kg bw	Shell, 1957

*Report not submitted

**The available data do not indicate whether the test was performed with diluted or undiluted (100%) acrolein

The oral LD_{50} values vary between 13.9-28 mg/kg (mouse) and 42-46 mg/kg bw (rat). When administered dermally the LD_{50}-values in rabbits range from 164 to 1022 mg/kg bw depending on the vehicle and concentration of acrolein applied. The dermal LD_{50} value of undiluted acrolein is reported to amount to 562 mg/kg bw. The 4-h LC_{50} values are 18-150 mg acrolein vapour/m^3 in the rat and 58 mg/m^3 in hamsters (nature of the substance is unknown). In mice the 6-h LC_{50} value is 151 mg acrolein vapour/m^3.

Signs of toxicity after single oral administration included decrease of motor activity, lethargy, loss of reflexes and muscle tone, tremor, respiratory distress, squinted eyes, rough coats, hunching, piloerection, blackening and breaking of tail tips, reduced body weight gain, lung congestion and edema and haemorrhagic stomach and intestines. There are no data on effects (other than mortality) after acute dermal administration. After inhalation exposure, signs of eye and nose irritation, mouth breathing, decreased breathing rate, body weight loss, and discoloration of lungs and liver were reported. Microscopic examination of the lungs revealed congestion, haemorrhages, fibrin deposition and necrosis.

Nephrotoxicity of the 1:1 acrolein-glutathione adduct

Male SD rats, given a single intravenous injection at 0.5 or 1 mmol/kg bw of the 1:1 acrolein-GSH adduct, developed nephrotoxicity characterized by glycosuria, proteinuria, elevation in serum urea nitrogen, and gross and histopathologic changes of the kidneys. The nephrotoxicity was inhibited by acivicin, a γ-glutamyltranspeptidase inhibitor, indicating that the 1:1 acrolein-GSH adduct requires processing through the first step of the renal mercapturic acid synthesis pathway to be activated to a toxic species. Rats given iv 0.1 mmol of the adduct per kg bw once did not show any signs of nephrotoxicity (Horvath et al., 1992).

Remark

It is noted that doses of 0.1, 0.5 and 1 mmol of the 1:1 acrolein-GSH adduct represent 14, 28 and 56 mg acrolein per kg bw, respectively. These dose levels are extremely high in relation to the reported LD_{50}- and LC_{50}-values of acrolein.

4.1.2.2.2 Human data

See the description of human data, accidental exposure, in the chapter irritation.

4.1.2.2.3 Conclusions

The data submitted are acceptable with respect to the basic requirements as specified in Annex VIIA of Directive 67/548/EC, despite the absence of underlying data and/or very limited reporting for many of the reported LD50 and LC50-values. According to the EC-criteria acrolein is toxic by the oral and dermal route and very toxic after inhalation. For classification see Chapter 1.

4.1.2.3 Irritation

4.1.2.3.1 Animal studies

Exposure to acrolein vapour concentrations between 1.9 and 2.6 ppm for 4 hours caused slight irritation of the eyes in rabbits (Mettier, 1960). Exposure of rabbits to 0.6 ppm acrolein vapour (1.4 mg/m3), for 30 days, 4 hours/day, 5 days a week produced no eye irritation (Mettier et al., 1960).

Reduction of the ciliary movement in tracheas was observed in *in vitro* tests with tracheal preparations from rabbits, cattle and sheep (Guillerm et al., 1967; Kensler et al., 1963; Sisson et al., 1991), and in an *in vitro/in vivo* test with hens (Battista et al., 1970).

General appearance and behaviour of the rats exposed to atmospheres containing 0.25, 0.67 or 1.40 ppm acrolein in air (nature of the substance is unknown), 6 h/day for 1 or 3 days in a nose-only inhalation chamber were essentially normal during and after exposure. No clinical signs of eye, nose or respiratory irritation were reported. Microscopic examination revealed, however, slight treatment-related histopathological changes in the respiratory/transitional but not in the olfactory epithelium of the nose of rats exposed to 0.25 or 0.67 ppm acrolein. The 1.40 ppm group was not examined histologically (Cassee et al., 1996, see also section 4.1.2.6 Repeated dose toxicity. Miscellaneous studies, short-term inhalation studies).

Several studies show that acrolein causes sensory irritation of the respiratory tract after inhalation.

The RD50 of acrolein, the concentration causing 50% reduction in respiratory rate, amounted to 2.4 - 6.6 mg/m3 in mice (nature of the substance is unknown) (IPCS, 1992). In rats RD50 values of 9.2 and 13.7 mg/m3 are found (nature of the substance is unknown) (IPCS, 1992, Cassee et al., 1996).

4.1.2.3.2 Human data

Accidental exposure

A few cases of accidental exposure to acrolein and a suicidal attempt with acrolein ingested in orange juice were described. Effects were observed on the primary exposure sites and were characterised by signs of severe irritation, finally resulting in corrosion, of skin and eyes and of the mucosal layer of stomach and respiratory tract.

Volunteer studies

Several studies with volunteers were performed to establish threshold levels for odour perception and recognition, and for effects on eyes, nose and respiratory tract. It is noted that many of these studies are of older date and the analytical methods used are often unspecific or poorly described.

Odour threshold

Leonardos (1969) found an odour threshold, defined as the first concentration at which all persons (n = 4) recognised the odour, of 0.21 ppm (0.48 mg/m^3). Plotnikova reported an odour threshold for acrolein of 0.35 ppm (0.8 mg/m^3) (Plotnikova 1957, abstract, no details)

Irritant effects, inhalation exposure

Several experiments were performed to examine the irritant effects of acrolein vapour on eyes, nose and respiratory tract. In a study of Weber-Tschopp et al. (1977) three experiments were conducted (see also **Table 4.11**):

A. continuous exposure during 35 minutes to a gradually increasing concentrations from 0 to 0.6 ppm, followed by a constant exposure to 0.6 ppm for 5 minutes (n = 54)
B. exposure during 60 minutes to a constant concentration of 0.3 ppm (n = 46)
C. four exposures (1.5 minutes) to increasing concentrations of 0.15, 0.3, 0.45 and 0.6 ppm with 8 minutes recovery time between the exposures (n = 42)

In experiment A subjective irritation of eyes and nose, annoyance and eye blinking rate increased, and the respiratory rate decreased with increasing acrolein vapour concentration. At the following concentration the effects were statistically significant: eye irritation at 0.09 ppm (0.21 mg/m3), nose irritation at 0.15 ppm (0.34 mg/m3), increase of eye blinking rate at 0.26 ppm (0.59 mg/m3) and decrease of respiratory rate at 0.6 ppm (1.3 mg/m3). In experiment B considerable eye and nose irritation was recorded after 10 to 20 minutes, and a significant decrease in the respiratory frequency after 40 minutes exposure to a constant acrolein vapour concentration of 0.3 ppm (0.69 mg/m3). Comparing the effects caused by discontinuous exposure (experiment C) with continuous exposure (experiment A) it is concluded that irritation to the eyes and nose is significantly more severe at continuous exposure, indicating that the effects were dependent on the exposure time.

Table 4.11 Summary of results form the study of Weber-Tschopp et al. (1977)

Exposure regime	Discomfort	Subjective eye irritation [1]	Subjective nose irritation [1]	Subjective throat irritation	Eye blinking rate	Sespiratory rate
A. continuous increase 0-0.6 ppm 40 min. Last 5 min. Constant n = 53	from 0.09 ppm	from 0.09 ppm	from 0.15 ppm	no change	from 0.26 ppm at 0.3 ppm sign doubling; not different from control up to 0.17 ppm	decrease at 0.6 ppm
B. continuous exposure 0.3 ppm, 1hr. n = 46	Effects increased in 20-30 min, thereafter constant	effects starting within 10-20 minutes, constant score[2] after 40 minutes Max. score: 3	effects starting within 10-20 minutes, constant score[2] after 40 minutes Max. score: 2	little increase in effects, constant score[2] after 40 minutes Max. score: 1-2	from ca. 17 blinkings/min to ca. 38 blinkings/min, thereafter constant	slow decrease, significant after 40 min, not much change after longer exposure
C. discontinuous increase 0.15, 0.3, 0.45, 0.6 ppm n = 42	from 0.15 ppm	from 0.3 ppm	from 0.45 ppm	from 0.45 ppm		

[1]Because the results were only presented in graphics from which statistically significance cannot be deviated, the conclusions from the authors were used, which seems to be in correspondence with the results in the graphics
[2]Scale 1-4; 1: no effect, 2: a little bit, 3: medium, 4: high

Volunteers exposed to acrolein vapour for 5 min recorded the eye irritation degree on a scale of 0 to 2 (0 = none, 1 = medium, 2 = severe). The irritation indices amounted to 0.471 at 0.06 ppm (0.14 mg/m^3), 1.2 at 1.3 - 1.6 ppm and 1.5 at 2.0 - 2.3 ppm (Darley et al., 1960).

Sim and Pattle (1957) examined the irritant effects of acrolein in volunteers exposed to atmospheres containing acrolein concentrations of 0.83 ppm for 10 min and 1.2 ppm for 5 min. Acrolein was extremely irritating to all exposed mucosal surfaces. At 0.83 ppm lacrimation occurred within 20 seconds, at 1.2 ppm already after 5 seconds.

Irritant effects, dermal exposure

Patch tests were conducted with acrolein in ethanol at concentration of 0.01, 0.1, 1 and 10% on groups of 8, 10, 48 and 20 volunteers respectively (Lacroix et al., 1976). At 1% positive reactions were recorded in 6 out of 48 persons (12.5%), four cases of serious oedema with bullae and two with erythema. At 10% all subjects (n = 20) showed skin effects with bullae, necrosis, inflammatory cell infiltrate and papillary oedema. No reactions were observed at 0.01 (n = 8) or 0.1% (n = 10). These data cannot be used to establish a no-effect-level for human skin irritation, because the duration of exposure and the onset of symptoms were not reported. In addition at lower concentrations the number of volunteers per group was too small.

Conclusions from human studies

Slight eye irritation (subjectively reported) was apparent after 5 min exposure to 0.06 ppm (0.14 mg acrolein vapour/m^3) (Darley et al., 1960); 0.21 - 0.35 ppm (0.48 - 0.80 mg/m^3; nature of the substance is unknown) was the odour threshold (Leonardos, 1969, Plotnikova, 1957); continuous exposure to 0.3 ppm (0.69 mg acrolein vapour/m^3) resulted in considerable eye and nose irritation after 10 - 20 minutes, and a significantly decreased respiratory frequency after 40 minutes of exposure (Weber-Tshopp et al., 1977), and 10 minutes exposure to 0.83 ppm (1.9 mg/m^3; nature of the substance is unknown) resulted in extreme irritation of all mucosal surfaces (Sim and Pattle, 1957). 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, risk assessment will be based on the LOAEL of 0.14 mg acrolein vapour/m^3 from the study of Darley et al. (1960) for subjective symptoms, and the NOAEL of 0.34 mg acrolein vapour/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).

4.1.2.4 Corrosivity

Acrolein is stated to be corrosive to the skin and eyes of rabbits, and 1 % solutions of acrolein give rise to serious eye and skin damage (Albin, 1975, no reports available).

4.1.2.4.1 Conclusions irritation and corrosivity

The reported animal data do not allow a proper classification according to the EC criteria. However, given the effects observed in humans (see chapter 4.1.2.11) it is concluded that labelling with R34 is indicated and that the data submitted are acceptable with respect to the basic requirements as specified in Annex VIIA of Directive 67/548/EC. For classification see Chapter 1.

4.1.2.5 Sensitisation

4.1.2.5.1 Animal data

Acrolein is reported to be negative in the guinea pig maximisation test (Susten et al., 1990). In this study female guinea pigs were treated with acrolein in water. The concentrations used for the intradermal and topical induction phases and for the topical challenge phase were 0.01%, 2.5% and 0.5%, respectively. DNCB in ethanol 70% was used as positive control. The study was poorly reported , but the raw data of this study were submitted by industry on request. Skin reactions were scored on a scale 0.5, 1, 2 and 3. Challenge treatment induced skin reactions in a maximum of 7 test animals (score 0.5), whereas only one control animal showed the same score. The distinguishment between score 0.5 and 1 is not made in the OECD-guidelines. According to the authors score 0.5 is defined as patches of redness, not confluent, and score 1 as mild redness, confluent. Given this description and the description in the OECD-guidelines (score 1: discrete or patchy erythema) score 0.5 should be interpreted as score 1 according to OECD. Since the incidence of skin reactions was much higher in test animals than in control animals it seems dubious to conclude that the test substance is not a skin sensitiser. However, no definite conclusion with respect to the sensitisation potential can be made on the basis of the present study.

There are no other sensitisation studies available.

4.1.2.5.2 Human data

There are no human data available on sensitising properties of acrolein.

4.1.2.5.3 Conclusion

The sensitisation study available is not performed and reported according to GLP requirements. However, given the results observed acrolein could be considered as a skin sensitiser and labelling with R43 is indicated. The Classification and labelling according to the Council Directive 67/548/EEC came to the conclusion not to classify for sensitisation. For classification see Chapter 1.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Animal studies

Inhalation studies

The study designs of the various repeated dose inhalation studies differ considerably from each other with respect to exposure duration and the parameters studied. The studies suitable for establishment of a NOAEL are summarised in **Table 4.12** and the miscellaneous studies in **Table 4.13**.

In one study designed to evaluate the effects of exposure to 0.17, 1.07 and 2.98 ppm (0.4, 2.5 and 6.9 mg/m^3) of acrolein (nature unknown), 6 h/d, 5 d/w, for three weeks, on immune and host defence functions of male rats the respiratory tract was histologically investigated as well. No effects were seen in the low and mid concentration groups, while in the high concentration group depressed body weights and nasal lesions but no lung lesions were found (Leach et al., 1987).

From this three-week rat study a NOAEL for respiratory tract lesions of 1.07 ppm (2.5 mg/m^3) can be derived.

Lyon et al. (1970) examined the effects of acrolein vapour in rats, guinea pigs, monkeys and dogs exposed to 0.7 and 3.7 ppm (1.6 and 8.5 mg/m^3) 8 h/d, 5 d/w, for six weeks. Nasal passages and trachea were not examined. Treatment did not result in mortality, clinical signs or changes in haematological and biochemical parameters. In all species, lung effects (chronic inflammatory changes, emphysema) were seen. From this six-week study the NOAEL is concluded to be < 0.7 ppm (< 1.6 mg/m^3) for rats, guinea pigs, monkeys and dogs).

In the same series of experiments the effects of continuous exposure for 90 days to 0.22, 1.0 and 1.8 ppm (0.5, 2.3 and 4.1 mg/m^3; nature of the substance is assumed to be vapour, however this was not explicitly stated in the report) were examined in rats, guinea pigs, dogs and monkeys. The nose was not examined microscopically and no organ weights were recorded. Reduced body weight gain occurred in rats only at the two higher concentration levels. Non-specific inflammations in lung, liver, kidneys, brain and heart were seen in all species (rat: high concentration group; guinea pig, monkey: low, high concentration groups; dogs: all groups). In dogs, there were definite treatment-related pathological changes in the lungs of the animals of the low concentration group. Eye irritation was reported for dogs and monkeys of the two higher concentration groups (Lyon et al., 1970). From this study the NOAEL for continuous subchronic exposure is concluded to be < 0.22 ppm (<0.5 mg/m^3) for dogs, guinea pigs and monkeys; for rats the NOAEL is 0.22 ppm (0.5 mg/m^3).

Table 4.12 Survey of repeated dose inhalation toxicity studies. Experiments suitable for derivation of NOAEL

Reference	Experimental	NOAEL	Remarks
Leach et al. 1987	3 wks, 6 h/d, 5 d/wk Conc: 0, 0.4, 2.5, 6.9 mg/m^3 (nature unknown) Examinations restricted to immune function and nasal/lung pathology	2.5 mg/m^3 (rat)	6.9 mg/m^3, depressed body weights, nasal cavity: microscopic changes in mucous, respiratory and olfactory epithelium; lungs not affected.
Lyon et al. 1970	continuous 90 d Conc: 0, 0.5, 2.3, 4.1 mg/m^3 (vapour)	0.5 mg/m^3 (rat); <0.5 mg/m^3 (g.pig, monkey, dog)	0.5 mg/m^3, non-specific inflammatory changes in liver, lungs, kidneys, heart
Lyon et al. 1970	6 wks, 8 h/d, 5 d/wk Conc: 0, 1.6, 8.5 mg/m^3 (vapour)	<1.6 mg/m^3 (rat, g.pig, monkey, dog)	1.6 mg/m^3, chronic inflammatory changes and emphysema in lungs
Feron et al. 1978	13 wks, 6 h/d, 5 d/wk Conc: 0, 0.9, 3.2, 11.2 mg/m^3 (vapour)	< 0.9 mg/m^3 (rat) 0.9 mg/m^3 (hamster, rabbit)	0.9 mg/m^3, rat, treatment-related effects: slightly decreased bw gain, histopathological lesions in epithelium of the nasal cavity in one rat
Kutzman et al. 1982, 1985	62 days, 6 h/d, 5 d/wk Conc: 0, 0.9, 3.2, 9.2 mg/m^3 (vapour), Fischer-344 rats	0.9 mg/m^3 (rat)	3.2 mg/m^3, histopathological changes in the respiratory tract were found in 3/31 animals
Kutzman et al. 1982, 1984, 1986	62 days, 6 h/d, 5 d/wk Conc: 0, 0.9, 3.2, 9.2 mg/m^3 (vapour), Dahl rats, hypertension resistant and sensitive strains	< 0.9 mg/m^3 (rat)	0.9 mg/m^3: histopathological changes in the respiratory tract of both strains
Costa & Kutzman 1982, 1985 Costa et al. 1986	62 days, 6 h/d, 5 d/wk Conc: 0, 0.9, 3.2, 9.2 mg/m^3 (vapour) Fischer-344 rats, probably same experiment as described by Kutzmann et al. 1985 (HEDSET 5.4 20).	< 0.9 mg/m^3 (rat)	0.9 mg/m^3: enhancement of flow volume dynamics and increase in diffusing capacity of the lungs for CO. (Reported examinations were restricted to function and histopathology of the lungs)

Table 4.13 Survey of repeated-dose inhalation toxicity studies. Miscellaneous experiments

Reference	Experimental	Results
Buckley et al. 1984	* Mouse, 5 days, 6 h/d Conc: 0, 4 mg/m^3 (RD50; nature unknown) Examinations restricted to histopathology of respiratory tract	Histopathological changes of respiratory and olfactory epithelium in nasal cavity
Sherwood et al. 1986	* Rat, 3 wks, 6 h/d, 5 d/wk Conc: 0, 0.4, 2.5, 6.9 mg/m^3 (nature unknown) Determination of effects on macrophage functions	No change in pulmonary clearance of inhaled *Klebsiella pneumoniae*. Increased enzyme activities in alveolar macrophages
Bouley et al. 1975, 1976	* Rat, continuous 77 d Conc: 0, 1.3 mg/m^3 (vapour) interim kills, restricted protocol	Lowered body weight and food consumption
Aranyi et al. 1986	* Mouse, 5 d, 3 h/d Conc: 0, 0.23 mg/m^3 (vapour)	Decreased pulmonary bactericidal activity to inhaled *Klebsiella pneumoniae*.
Gusev et al. 1966	Rat, continuous 61 d Conc: 0, 0.15, 0.51, 1.52 mg/m^3 (nature unknown)	Poor reporting
Sinkuvene et al. 1970	Rat, continuous 61 d Conc: 0, 0.03, 0.14, 0.74 mg/m^3 (nature unknown)	Poor reporting
Watanabe & Aviado, 1974	Mouse, 5 wks, 30 min twice daily Conc: 0, 100 mg/m^3 (nature unknown)	Decrease in pulmonary compliance and increase in lung phospholipid content
Feron and Kruysse 1977	Hamster, exposure 52 wks, 7 h/d, 5 d/wk, experimental 52 + 29 wks 0, 9.3 mg/m^3 (vapour) (co)carcinogenicity study	No mortality, decreased body weight gain, increased Hb and PCV in females, treatment-related changes in nasal cavity. See also Section 4.1.2.8
Campbell et al. 1981	* Mouse, 8h/d, 7d/wk Conc: 0, 4.7 mg/m^3 (vapour)	Increased mortality of acrolein treated mice after infection with *Streptococcus pyogenes*
Roussel et al. 1973	* Rat, continuous for 2-6 months Conc: 0, 1.2-1.5 mg/m^3 (nature unknown)	Lowered body weight, lung weight and food and water consumption. Minor respiratory tract lesions indicative of chronic irritation, hepatic tissue injury.

*Studies primarily aimed at evaluation of immune and/or host defence mechanism

Feron et al. (1978) examined rats, hamsters and rabbits of both sexes exposed to 0.4, 1.4 and 4.9 ppm (0.9, 3.2 and 11.2 mg acrolein vapour/m^3), 6 h/d, 5 d/w, for thirteen weeks; the rat was the most sensitive species. The main findings in rats consisted of a significant mortality (50%) in the high concentration group, a concentration-related decrease in body weight gain (not significant in the low concentration group, statistically significant in both other groups) and concentration-related respiratory tract lesions varying from slight squamous cell metaplasia in the nasal cavity of one animal of the low concentration group to severe lesions of several parts of the respiratory tract of the animals of the high concentration group. Rabbits and hamsters did not show treatment-related adverse effects at 0.4 ppm, at 1.4 ppm rabbits showed minimal inflammatory changes in the nasal cavity and in hamster some occasional sneezing and a slightly decreased food consumption and body weight gain were seen, serious respiratory tract lesions in both species occurred at 4.9 ppm (Feron et al., 1978). From these studies it is concluded that the NOAEL for subchronic toxicity in rats is < 0.4 ppm (<0.9 mg/m^3). For rabbits and hamsters the NOAEL is 0.4 ppm (0.9 mg acrolein vapour/m^3).

In a series of separate experiments two strains of rats were exposed to 0.4, 1.4 and 4.0 ppm (0.9, 3.2 and 9.2 mg acrolein vapour/m^3), 6 h/d, 5 d/w, for 62 days. In Fischer rats, no histological changes were seen in the lungs of the animals of the low concentration group, while in Dahl rats - amongst others - hyperplastic/metaplastic terminal bronchiolar epithelial changes were observed. Lung function parameters investigated in the Fischer rats were affected to some extent in the low concentration group (Costa et al., 1986; Kutzman et al., 1984, 1985). From these studies it can be concluded that the NOAEL in both strains of rats was <0.4 ppm (<0.9 mg acrolein vapour/m^3).

Miscellaneous studies, short-term inhalation studies

Male SD rats were exposed by inhalation to 0, 0.2 or 0.6 ppm acrolein in a nose-only inhalation chamber for 6 h per day on one day or on three successive days. The proliferative response was studied in nasal and tracheal epithelial cells and in free lung cells. The proliferative response was expressed as the proportion of DNA synthesising cells determined by the 5-bromodeoxyuridine (BrdU) labelling technique. Single exposure to acrolein resulted in a concentration-dependent increase in the proportion of DNA synthesising cells in the three cell types examined, the increase being statistically significant in lung and trachea cells already at the 0.2 ppm exposure level. After three exposures the increase in the proportion of DNA synthesising cells was distinctly lower possibly due to adaptation (Roemer et al., 1993).

Cassee et al. exposed male, albino Wistar rats to atmospheres containing 0.25, 0.67 or 1.40 ppm acrolein in air (nature unknown), 6 h/day for 1or 3 days in a nose-only inhalation chamber and studied histopathological and biochemical changes in the respiratory and olfactory epithelium of the nose. In addition, cell proliferation was determined. General appearance and behaviour of the rats exposed to the various acrolein concentrations were essentially normal during and after exposure. No clinical signs of eye, nose or respiratory irritation were reported. Microscopic examination revealed, however, slight treatment-related histopathological changes in the respiratory/transitional but not in the olfactory epithelium of the nose of rats exposed to 0.25 or 0.67 ppm acrolein (nature unknown). The 1.40 ppm group was not examined histologically. Cell proliferation in nasal epithelium appeared increased after three exposure days, but not after one exposure day. Measurement of cell proliferation in the latter study was restricted to nasal epithelial cells and was expressed as the number of positive-stained (using PCNA and BrdU labelling) cells per mm basement membrane.

NPSH levels in nasal epithelium were dose-dependently increased after 3 days of exposure to 0.67 or 1.40 ppm acrolein (nature unknown), whereas after a 6-h exposure period the NPSH-levels were slightly lower in acrolein-treated rats than in controls. (Cassee et al. 1996, see also sections 4.1.2.1, 4.1.2.3 and 4.1.2.11).

Conclusion

The results of the inhalation studies do not permit the establishment of a NOAEL. Intermittent exposure (6 - 7 h/d, 5 d/wk for a total period of 62 days - 13 wks) 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 hamster and rabbits.

Continuous exposure (24 h/d, 7 d/wk 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. One- and/or three-day exposure of rats to acrolein resulted in cell proliferation at the lowest concentration levels examined i.e. 0.2 - 0.25 ppm (0.47 - 0.58 mg/m^3) and higher, and slight treatment-related histopathological changes in the respiratory/transitional but not in the olfactory epithelium of the nose of rats exposed to 0.25 or 0.67 ppm (0.58 - 1.56 mg/m^3) acrolein. NPSH-levels in nasal epithelial cells were increased after 3 days of exposure to 0.67 ppm (1.56 mg/m^3) or higher.

Oral studies

Table 4.13 summarises the available oral repeated-dose studies. No short-term oral studies were available.

In a subchronic oral study, acrolein was administered daily in gelatin capsules at dose levels of 0.1, 0.5 and 1.5 (increased to 2.0 after four weeks) mg/kg bw to male and female dogs for 53 weeks. The major treatment-related effect noted was frequent vomiting in the high dose group, mainly during the first four weeks, and in the mid dose group occasional vomiting only. Significantly lower levels of serum total protein, calcium and albumin occurred in animals of the high dose group.

Table 4.14 Survey of repeated-dose studies. Oral experiments

Reference	Experimental	NOAEL	Results
Parent et al. 1992a	Rat, gavage 102 wks, 7 d/wk Dl: 0, 0.05, 0.5, 2.5 mg/kg bw Interim kill at 12 months[6]	0.05 mg/kg bw/d	dose-related decreased survival in males and females at 0.5 mg and higher
Parent et al. 1991	Mouse, gavage, 18 months, 7 d/wk. Dl: 0, 0.5, 2, 4.5 mg/kg bw	2 mg/kg bw/d	decreased body weight gain and survival in males at 4.5 mg
Parent et al. 1992b	Dog, 53 wks, 7 d/wk Dl: 0, 0.1, 0.5, 1.5/2 mg/kg bw 0.1% acrolein solution in gelatin capsules	0.5 mg/kg bw/d	increased vomiting incidence and decreased total serum protein, calcium and albumin in dogs of the high dose group.The incidences of vomiting decreased in time pointing to an adaptive effect

[6] The dosing periods were 12 months for the toxicity and 24 months for the combined oncogenicity-toxicity study

No other treatment-related effects were found (Parent et al, 1992b). From this study a NOAEL for subchronic toxicity in dogs of 0.5 mg/kg bw/day is concluded.

Long-term gavage studies have been performed with rats (102 weeks) and mice (18 months) of both sexes. Mortality in rats and mortality and decreased weight gain in mice were the effects noted (Parent et al, 1991, 1992a). From these studies a NOAEL for chronic toxicity in rats of 0.05 mg/kg bw/day and in mice of 2 mg/kg bw/day are established.

Conclusion

The main effects found in the long-term 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 vomiting incidence accompanied with a decrease in total serum protein, calcium and albumin in dogs (NOAEL 0.5 mg/kg bw). The publications of these studies present only some selected findings, but the study design as described meets the criteria of the relevant OECD and EC guidelines.

4.1.2.6.2 Human data

There are no human data on repeated exposure.

4.1.2.6.3 Conclusions repeated dose toxicity

The data submitted are acceptable with respect to the basic requirements as specified in Annex VIIA of Directive 67/548/EC.

4.1.2.7 Mutagenicity and related end-points

4.1.2.7.1 Gene mutations in bacterial test systems

The genotoxicity of acrolein has been extensively tested in bacteria using a wide variety of experimental designs (e.g. spot test, plate incorporation, preincubation) and different indicator strains and endpoints (e.g. reverse mutation systems, forward mutations, SOS-chromotest, differential killing in DNA repair proficient and deficient bacterial strains). The results of these tests differ among others as a consequence of 1. the physical-chemical properties of acrolein such as its reactivity, volatility and instability; 2. the toxicity of acrolein for the bacteria, resulting in narrow dose ranges suitable for demonstration of mutagenicity; 3. the properties of the bacterial indicator strains used and the set up of the test systems.

Table 4.15 summarises the gene mutation assays with bacteria. Not included in this table are tests for primary DNA damage (umu test, SOS-chromotests, tests for differential killing), and further mutagenicity tests that could not be evaluated due to a too limited set up, poor reporting or lack of essential data.

From the results of the bacterial mutagenicity tests it is concluded that acrolein is a direct-acting bacterial mutagen with the Salmonella typhimurium strains TA 100, TA 104 and TA 98 (Foiles et al., 1989; Khudoley et al., 1986, 1987; Lutz et al., 1980; Marnett et al., 1985; Parent et al., 1996; Waegemaekers et al., 1984). In some of the tests performed with and without S9 mix, the increase in mutants is less with than without metabolic activation or no increase at all is seen

(Khudoley et al., 1986, 1987 Lutz et al., 1980). Addition of gluthatione (GSH) to the test system reduced the toxicity of acrolein for the indicator cells, but did not have any influence on the degree of mutagenicity (Foiles et al., 1989; Marnett et al., 1985).

4.1.2.7.2 Yeast

In yeast acrolein treatment resulted in a slight increase of doubtful biological significance, in petite mutations in S. cerevisiae N123, in the other yeast strains used e.g. S. cerevisiae S211, S138 no increase in number of mutants was apparent (Izard, 1973).

4.1.2.7.3 Mammalian cells in vitro

Table 4.16 summarises the gene mutation assays and **Table 4.17** the cytogenetic assay with mammalian cells *in vitro.*

- *Gene mutations*. Acrolein induced an increase in gene mutations in DNA repair deficient human fibroblasts (Xeroderma pigmentosum cells), but not in normal repair proficient human fibroblasts (Curren et al., 1988). Acrolein was positive in the HPRT test with hamster V79 cells in the absence, but not in the presence of fetal bovine serum (Smith et al., 1990) and negative in a standard HPRT test with CHO cells using serum enriched medium (Parent et al., 1991).

- *Chromosome aberrations*. Au et al. reported that acrolein induced chromosome tangling in a chromosome aberration test at cytotoxic concentrations >= 40 µM, without any indication for induction of obvious chromosome breakage at the lower concentrations tested. The chromosome tangling was considered an indication of potential clastogenicity (Au et al., 1980). In subsequent experiments, Galloway et al. (1987) and Wilmer et al. (1985, 1986) did not find any indications for chromosome breaking activity of acrolein. Based on these data, it is concluded that acrolein does not induce chromosome aberrations in mammalian cells *in vitro*.

- *Sister chromatid exchanges.* Acrolein has been shown to induce SCEs in CHO cells and in human lymphocytes *in vitro* (Au et al., 1980; Galloway et al., 1987; Wilmer et al., 1986). MESNA (2-mercaptoethanesulfonic acid, sodium salt), protected completely against SCE induction and cytotoxicity (Wilmer et al., 1986). In one SCE test with CHO cells, acrolein was reported to be negative (Loveday, Magna Corporation, 1982).

4.1.2.7.4 Drosophila

Sierra et al. (1991) examined the genotoxicity of acrolein in *Drosophila melanogaster* using two different somatic mutation and recombination (SMART) tests, the eye spot and wing spot tests, and two germinal tests, the sex-linked recessive lethal test (SLRLT) and the sex chromosome loss test (SCLT). For the two latter, exposure by feeding as well as injection was used. The results indicated that acrolein was mutagenic in the SLRLT when injected but not when fed and induced genotoxic effects in both types of SMART assays, assays directed at the detection of somatic mutations and recombination.

The results of the SCLT in *D. melanogaster* did not reveal clastogenic effects attributable to acrolein exposure either fed or injected (Sierra et al., 1991).

Acrolein did not induce sex-linked recessive lethals in either *D. melanogaster* adults exposed by feeding or injection or in *D. melanogaster* larvae exposed by feeding (Zimmering et al., 1985, 1989). Rapoport reported a positive result in the SLRLT after larval feeding of acrolein. However, this test could not be evaluated due to poor reporting (Rapoport, 1948).

4.1.2.7.5 Mammals in vivo

Acrolein administered ip to male mice at dose levels representing approximately the LD_{25} (1.5 mg/kg bw, n = 5) and the LD50 (2.2 mg/kg bw, n = 7) did not induce dominant lethals as appeared from the pregnancy rate, the numbers of total and live implants, and early and late deaths in female mice mated with the acrolein treated males (Epstein et al., 1972; Epstein and Shafner, 1968).

Acrolein did not induce chromosome aberrations in bone marrow of male rats treated once ip with 1, 2.1 or 4.1 mg/kg bw (Gorodecki and Seixas, 1982).

4.1.2.7.6 DNA damage, bacteria and mammalian cells in vitro, and in mammals in vivo

Table 4.18 summarises the tests for primary DNA damage with mammalian cells *in vitro*. Acrolein treatment of mammalian cells *in vitro* has been shown to result in an increase of DNA single-strand breaks and, in part of the tests, of DNA protein cross-links. Grafström et al. found indirect evidence of an increase in DNA interstrand cross-links in human tracheobronchial epithelial cells upon exposure to a clearly cytotoxic concentration of acrolein (Grafström et al., 1988).

Treatment with acrolein has been shown to result in several DNA adducts among others the cyclic 1, N^2-hydroxy-propanodeoxyguanosine has been identified in a number of studies. The same adduct was found in lymphocytes of a dog treated with CP (see Table 4.1.2.7-D). In *S. typhimurium* TA100 and TA104, strains that show a clear mutagenic response to acrolein, DNA-acrolein adducts have also been identified (Foiles et al., 1989 in WHO, 1992).

Incubation of homogenates of rat nasal mucosa with acrolein resulted in a concentration-dependent increase in DNA-protein cross-links. However, acrolein did not induce DNA-protein cross-linking in nasal mucosa of rats exposed to acrolein vapour (2 ppm, 6 h). Simultaneous exposure of rats to both acrolein (2 ppm) and formaldehyde (6 ppm) for 6 h resulted in a significantly higher yield of DNA-protein cross-links than with formaldehyde (6 ppm, 6 h) alone (Lam et al., 1985, Heck et al., 1986).

4.1.2.7.7 Miscellaneous

Cell transformation

Acrolein did not show cell transforming potential in two cell transformation assays with C3H/10T½ cells (Loveday et al., Magna Corporation, 1982; Abernethy et al., 1983). Loveday et al. exposed the cells to 0.04 - 0.1 µg/ml, and Abernethy et al. to a concentration of 6.3 µM (0.4 µg/ml). The latter concentration i.e. 6.3 µM, represented the LC50 for the C3H/10T½ cells used. Acrolein appeared to initiate transformation in the presence of a tumour promotor (Abernethy et al., 1983).

Pathobiological effects, Grafström et al., 1988

Grafström et al.,1988 examined the ability of acrolein to affect growth, membrane integrity, differentiation, and thiol status and to cause DNA damage under serum and thiol free conditions using cultured human bronchial epithelial cells.

Acrolein markedly decreased colony survival at 3 μM, whereas about 10 fold higher concentrations were required to increase membrane permeability, measured as uptake of trypan blue dye. Acrolein at micromolar concentrations also caused epithelial cells to undergo squamous differentiation as indicated by decreased clonal growth rate, dose dependent increased formation of cross-linked envelopes, and increased cell planar surface area.

Acrolein caused a marked and dose-dependent cellular depletion of total and specific free low molecular weight thiols as well as protein thiols. Exposure to acrolein did not cause oxidation of glutathione indicating that thiol depletion occurred by direct conjugation of reduced glutathione to acrolein without concomitant generation of active oxygen species. Furthermore, acrolein caused DNA single-strand breaks and DNA protein cross inks in human bronchial epithelial cells (see Table 4.18). The results indicated that acrolein caused several cytopathic effects that relate to multistage carcinogenesis in the human bronchial epithelium (Grafström et al., 1988).

4.1.2.7.7 Conclusion

The data submitted are acceptable with respect to the basic requirements as specified in Annex VIIA of Directive 67/548/EC. Acrolein has been shown to result in several DNA adducts among others the cyclic 1, N^2-hydroxy-propanodeoxyguanosine has been identified in a number of studies.

Acrolein is a mutagen for bacteria and can induce gene mutations and sister chromatid exchanges, but no chromosome aberrations in mammalian cells *in vitro*. The mutagenicity and genotoxicity of acrolein in bacteria and mammalian cells *in vitro* is restricted to a narrow dose range, since acrolein is highly toxic in these test systems and mutagenic/genotoxic doses are near to or overlap cytotoxic doses.

Acrolein did not induce DNA damage or mutations in fungi. Acrolein appeared genotoxic in the SMART test in Drosophila, but did not exhibit genotoxic activity in the SCL test, while equivocal results were reported for the SLRL test in Drosophila. Acrolein did not induce dominant lethal mutations in mice, and did not induce chromosome aberrations in bone marrow cells of rats.

Table 4.15 Gene mutation assays with bacteria

Indicator cells	Experimental	Result	Remarks	References
S. typhimurium TA104 TA102	-liquid preincubation -0 - 1.8 μmoles/plate -with and without glutathione -no S9mix	+ (TA104)	Addition of glutathione reduced toxicity, but not mutagenicity. T: > 0.9 (-GSH); > 1.8 μmol/pl (+GSH)	Marnett et al., 1985
S. typhimurium TA100	-liquid suspension -0, 10, 15 μg/2 ml incubation volume -no S9mix	+ (TA100)	T: no data	Waegemaekers and Bensink, 1984
S. typhimurium TA1535	-microtiter fluctuation test -0 - 62.5 nmoles/25 ml incubate -no S9mix	-	T: ≥ 250 nmoles/25 ml	Pool et al., 1988
S. typhimurium TA1535, 98, 100	-plate incorporation assay -0.005 - 1 μmol/plate -with and without S9mix	-	T: no data	Loquet et al., 1981
S. typhimurium TA98, 100	-plate incorporation assay -with and without S9mix	+ (TA98, TA100, without S9mix)	T: no data	Khudoley et al., 1987 Khudoley et al., 1986
S. typhimurium TA1535, 1537 98, 100	-preincubation assay - 0.03- 100 μg/plate -with and without S9mix	+ (TA100 with S9mix)	Increase in revertants at concentrations of 33, 40, 50 μg/pl. T: 100 μg/pl seen as decline in revertant colonies	Haworth et al., 1983
S. typhimurium TA100	-preincubation assay - 0 - 0.15 μmol/2 ml -with and without S9mix	+ (TA100 without S9mix)	Mutagenic at low concentrations. At higher concentrations bacteriotoxicity interfered with mutagenicity testing	Lutz et al., 1982 Lutz et al., 1980
S. typhimurium hisD3052	-plate incorporation and preincubation assays - with and without S9mix	-	T: no data	Basu and Marnett, 1984
S. typhimurium TA1535, 1537, 1538, 98, 100	-plate incorporation - 0.001 - 0.1 μl/plate -with and without S9mix	+ (TA98 without S9mix)	Dose-related increase in revertants in a very narrow dose range. Due to toxicity decrease in revertants at concentrations ≥ 0.04 μl/pl	Lijinski and Andrews, 1980
S. typhimurium TA100, 104	-preincubation assay with glutathione chase - 0 - 13 mM - without S9mix	+ (TA100 > TA104)	Increase in revertants in the range 1 - 10 mM. Drop in revertants at 13 mM and higher, due to toxicity.	Foiles et al., 1989

Table 4.15 continued overleaf

Table 4.15 comtinued

Indicator cells	Experimental	Result	Remarks	References
S. typhimurium TA102	- plate incorporation assay - 0 - 5000 μg/plate -with and without S9mix	-	T: no data	Jung et al., 1992
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538, TA102, TA104 E.Coli WP2 uvrA	-preincubation assay - dose levels: 0.3-75 μg/plate	+ (TA100 with and without S9 mix) + (TA98 with and without S9 mix) ± (E.Coli with S9 mix)	Cytotoxicity was evident at doses ≥ 33 μg/plate (-S9) and ≥ 67 μg/plate (+S9). Evidence of mutagenicity was obtained at non-toxic dose levels in TA98 (weakly positive), TA100 (clearly positive), and E.Coli (marginally positive)	Parent et al, 1996
E. coli K12/343/113	-preincubation assay - 0 - 1 mM - without S9mix	-	T: at concentrations ≥ 0.5 mM	Ellenberger and Mohn, 1977

+ = Positive
- = Negative
T = Bacteriotoxic

Table 4.16 Gene mutations assays with mammalian cells *in vitro*

Indicator cells	Experimental	Results	Remarks	References
Mc, V79 cells HGPRT test gene mutations	0, 0.02 - 2.0 μM without S9mix +/- FBS	+ (-S9, -FBS)	With FBS acrolein induced mutagenicity declined, but not toxicity. Survival amounted to 91%, 82%, 78% and 66% at 0.1, 0.5, 1.0 and 2.0 μM acrolein, respectively. At 1.0 μM, the lowest mutagenic concentration, the survival was 78% of the controls.	Smith 1990, 1989
Mc, CHO cells HGPRT test gene mutations	0.2 - 8 nl/ml with and without S9mix	-	Medium used was serum enriched Survival seriously affected at high acrolein concentrations.	Parent 1991
Mc, Human cells 1. XP fibroblasts (XPF) 2. Normal fibroblasts (NF) forward gene mutations	1. 02 - 0.6 μM 2. 0.8 - 2.0 μM Without S9mix	1. XPF: + (-S9) 2. NF: -	Medium used was serum free to prevent inactivation of acrolein. NF did not show an increase in mutants over a range of acrolein concentrations which caused a reduction in survival comparable to that seen with XPF. Above 0.6 μM cytotoxicity for XPF interfered with reliable mutagenicity screening.	Curren et al., 1988
Mc, CHO cells gene mutations	0.000002 - 0.0003 % with and without S9mix	*	report not available	EPA 1991
Mc, CHO cells HGPRT test gene mutations	-S9mix: 0.1, 0.2, 0.3, 0.4, 0.5 μg/ml, 16 hrs. +S9mix: 0.04, 0.06, 0.08, 0.1, 0.2, 0.3 μg/ml, 4 hrs	*	+S9mix: highest dose 60% survival. Mutation frequencies in duplicate plates too variable for reliable assessment of potential genotoxicity of acrolein	Loveday and Gorodecki, Magna Corporation 1982

FBS = Fetal bovine serum
+ = Positive
- = Negative
* = Test/report not suitable for assessment of mutagenic/genotoxic activity

Table 4.17 Cytogenetic assays with mammalian cell *in vitro*

Indicator cells	Experimental	Results	Remarks	References
chromosome aberrations				
Mc, CHO cells,	0, 10, 40, 100 μM with and without S9mix	*	MI (-S9): < 1 per 2000 cells MI (+ S9): amounts to 3.57, 0.64, 0.40, and 0% in control, 10, 40, and 100 μM group, respectively	Au et al., 1980
Mc, CHO cells,	0.1 - 1.0 μg/ml with and without S9mix	-		Galloway et al., 1987
Human lymphocytes,	0, 0.001 - 40 μM with and without S9mix	-	T: ≥ 20 μM (decrease in mitotic activity)	Wilmer, 1985, 1986
Mc, CHO cells	0.1 - 2.0 μg/ml (-S9, exposure 6 hrs) 0.4 - 2.0 μg/ml (+S9, exposure 2 hrs)	*	T: ≥ 2 (-S9), ≥ 1.5 ?g/ml (+S9). Duration of exposure rather low. Number of cells analysed too low. Acrolein was reported to be negative.	Gorodecki and Seixas, Magna Corporation 1982
SCE				
Mc, CHOcells	0.000002 - 0.0003 % with and without S9mix	*	Report not available	EPA 1991
Mc, CHO cells	0.1 - 1.0 μg/ml with and without S9mix	+ W (-S9)	Small increase in SCE at 1 μg/ml	Galloway et al., 1987
Mc, CHO cells	0, 5, 10, 20, 40 μM with and without S9mix	+ (-S9)	Acrolein induced a dose-dependent increase of SCE/metaphase at 5, 10, and 20 μM. At 40 μM cytotoxicity interfered with screening of SCEs.	Au et al., 1980
Human lymphocytes	0, 0.001 - 40 μM without S9mix	+ (-S9)	Acrolein induced up to 1.6-fold increase in SCE above baseline but was not clastogenic. MESNA protected against SCE induction and cytotoxicity. T: ≥ 20 μM (decrease in mitotic activity)	Wilmer, 1985, 1986
Mc, CHO cells	without S9mix: 0.3, 0.5, 0.75 μg/ml with S9mix: 0.1, 0.3, 0.5 μg/ml	-	T: ≥ 0.5 μg/ml (with S9mix) T: ≥ 0.75 μg/ml (without S9mix)	Loveday, Magna Corporation, 1982

+ = positive
+ W = weak activity
- = negative
* = report/test not suitable for assessment of mutagenic/genotoxic activity
MI = mitotic index
FBS = fetal bovine serum
MESNA = 2-mercaptoethanesulfonic acid, sodium salt
T = toxic for indicator cells

Table 4.18 Primary DNA-damage in mammalian cells *in vitro*

Indicator cells	Experimental	Results	Remarks	References
Mouse L1210 leukemia cells	20 μM without S9mix	DSS ↑ DPCL = DICL =		Ericson et al., 1980
K 562 human leukemia cells	0 - 20 μM without S9mix	DSS ↑	Cytotoxicity > 5 μM	Crook et al., 1986
CHO cells 1. DNA adducts 2. Gene mutations (HGPRT/CHO)	0.1 - 1 mM 1. DNA adducts 2. Gene mutation	1. cyclic deoxyguanosine adducts ↑ 2. Gene mutations *	Toxicity interfered with measurement of gene mutations	Foiles et al., 1990
Human skin and bronchial fibroblasts DNA alkylation 32P-postlabelling		DNA adducts ↑	Several DNA adducts observed a.o. cyclic 1, N^2-hydroxy-propanodeoxyguanosine. The same adduct was found in lymohocytes of a dog treated with CP	Wei et al., 1992 Wilson et al., 1991
Human tracheobronchial epithelial cells Alkaline elution assay according to Kohn	Cells were exposed to concentrations of 0, 30, 100 or 300 μM acrolein for 1 h in thiol-free growth medium	DSS ↑ DPCL ↑ DICL ↑ (indirect evidence)	Next to DNA damage, growth, membrane integrity, differentiation, and thiol status were studied at serum and thiol-free conditions	Grafström et al., 1988
Human Burkitt's lymphoma cells (EBV-transformed)	Cells were exposed to concentrations of 0, 30, 50 or 750 μM acrolein for 4 h in thiol-free growth medium	DPCL ↑ at exposure concentrations ≥ 0.15 mM	Significant increases in DPLC were only observed at doses that resulted in complete cell death within 4 d following dosing.	Costa et al., 1997
Rat, homogenate of nasal mucosa	Homogenates were exposed to concentrations of 0, 0.3, 3 or 30 mM acrolein for 10 min at 0°C	concentration dependent increase in the percentage of interfacial DNA, pointing to DPCL ↑		Lam et al., 1985

DICL = DNA interstrand cross-links
DPCL = DNA protein cross-links
DSS = DNA single-strand breaks
↑= Increase
= : No increase
* = Report/test not suitable for assessment of mutagenic/genotoxic activity

4.1.2.8 Carcinogenicity

4.1.2.8.1 Animal studies

Inhalation studies

Two long-term experiments using inhalation exposure were available, one with rats and the other with hamsters. However, inhalation experiments of appropriate duration specifically designed to assess the carcinogenicity of acrolein vapour have not been conducted.

No treatment-related tumours or metaplasia were found in the lungs of rats (n = 20 per group) exposed to 18.3 mg/m^3 (8 ppm) acrolein (nature not reported), 1 h/day and 5 days per week, for 10 or 18 months (Le Bouffant et al., 1980).

Remark

Study not suitable for evaluation of carcinogenic potential of acrolein, because of restricted experimental design.

Syrian golden hamsters exposed to 9.3 mg/m^3 (4 ppm) acrolein vapour for 52 weeks (7 h/day, 5 days/week) showed inflammatory changes and metaplasia of the olfactory epithelium of the nose (Feron and Kruysse, 1977, HEDSET section 5.4, 24 and section 5.7, 3). After a withdrawal period of 29 weeks the affected mucosa had partially recovered in most animals. No respiratory tract tumours were found after exposure to acrolein vapour except for a small tracheal papilloma in one female hamster, which was considered an incidental finding, unrelated to acrolein treatment. Nasal tumours or treatment-related tumours at other sites were not encountered. In the same study no conclusive evidence of an enhancing (co-carcinogenic) effect of acrolein on the carcinogenicity of benzo[a]pyrene or *N*-nitroso-diethylamine was found (Feron and Kruysse, 1977). It is noted that the exposure and experimental period, 52 and 81 weeks respectively, were relatively short and did not cover two third of the hamster lifespan.[7]

Conclusion

Since both of the inhalation studies did not meet normal requirements for examination of the carcinogenic potential of a chemical, the study results do not permit a definite conclusion regarding the carcinogenic potential of acrolein upon exposure by inhalation. The conclusion with regard to the absence of co-carcinogenic effects of acrolein in the study of Feron and Kruysse is included in section 4.1.2.11 ‘Effects upon combined exposure’.

Oral studies

Fischer 344 rats were given acrolein in drinking water at concentrations of 100 (5 days/week, 124 weeks), 250 (5 days/week, 124 weeks), or 625 mg/l (5 days/week, 104 weeks). The number of animals amounted to 20/sex/group in the high dose and the untreated control group, and to 20 male rats in low and mid dose groups. Surviving rats were killed at 123 to 132 weeks. Major organs and tissues were examined histologically. A slightly higher incidence of adenomas of the adrenal cortex was found in females of the high dose group, the incidence amounting to 5/20 in high dose females and to 1/20 in untreated control females. No treatment-related increased incidence of other neoplastic lesions was recorded. In the same study no increased incidences of any tumor (including adrenal cortex adenomas) were induced by acroleinoxime, acrolein diethylacetal or allyl alcohol, compounds considered to be converted to acrolein (Lijinsky and Reuber, 1987, Lijinsky, 1988). The results of this study were re-evaluated by a pathology working group especially organised to this end. The working group concluded that the slightly

[7]According to OECD451 “Carcinogencity Studies” it is necessary that the duration of a carcinogencity test comprises the majority of the normal life span of the animal to be used. Generally, the termination of the study should be at 18 - 24 months for hamsters
Remark. In this context “duration of the study” regards duration of exposure of treatment rather than duration of exposure plus an additional observation period

elevated incidence of adrenal cortex adenomas (i.e., pheochromocytomas) found in the treated females was well within the limits for historical controls, and was not of biological significance. Furthermore it was concluded that there was no evidence of any carcinogenic effect of acrolein on the adrenal glands of female rats in the Lijinski/Reuber study (see Parent et al.,1992).

Sprague-Dawley rats were given daily by gavage 0.05 mg/kg, 0.5 mg/kg or 2.5 mg/kg per kg bw acrolein (distilled acrolein, stabilised with 0.25% hydroquinone) for 102 weeks (see **Table 4.14**). The study was conducted according to OECD 453 "Combined chronic toxicity/carcinogenicity studies". The number of animals amounted to 70/sex/group. Interim kills were included at 13 weeks (high dose; n=5/sex) and 1 year (n=10/sex/group). Examinations included daily observations, measurement of various clinical, hematological and urine parameters at 3, 6, 12, 18 and 24 months All animals were subject to necropsy, recording of organ weights, and extensive microscopic examination of tissues. Male rats showed a dose-related reduction in survival during the first year, statistically significant in the high dose group and marginally significant in the mid dose group; this trend did not persist to the end of the study; in female rats a dose-related reduction in survival occurred during the first year persisting to the end of the study; survival was statistically significantly reduced in the high dose group and marginally in the mid dose group. Creatinine phosphokinase levels were decreased in all dose groups at almost all time intervals but only occasionally statistically significant (no data/figures presented!). No other treatment-related effects were seen including neoplastic or non-neoplastic lesions (Parent, R.A. et al., 1992a).

CD-1 mouse were given daily acrolein (distilled acrolein, stabilized with 0.25% hydroquinone) by gavage at dose levels of 0.5 mg/kg, 2.0 mg/kg or 4.5 mg/kg per kg bw for 18 months (see **Table 4.14**). The study was conducted according to OECD 451, "Carcinogenicity studies". The number of animals amounted to 70/sex/group, and in the high dose group to 75/sex. Clinical observations were performed daily for the first 4 weeks and weekly thereafter; blood smears were taken at 12 and 18 months. Mice were subject to necropsy, and extensive microscopic examination of tissues. Observations included a statistically significant reduced survival rate and decreased body weights gain for males at 4.5 mg/kg; decreased body weight gain (not statistically significant) for females at 2.0 mg/kg and 4.5 mg/kg; no other treatment-related effects (including neoplastic and non-neoplastic lesions) were observed.

In summary, oral (gavage, drinking water) administration of acrolein did not induce carcinogenic effects in rats or mice (Lijinski, 1988; Lijinski and Reuber, 1987; Parent et al., 1991, 1992a).

Conclusion

From the results it can be concluded that acrolein is not an oral carcinogen.

Dermal studies

There are no dermal or subcutaneous studies that permit the assessment of the dermal carcinogenic potential of acrolein. The exposure time in the study of Salaman and Roe in which acrolein was applied to the backs of mice once a week for 10 weeks, was too short and the number of animals per group too small to assess the carcinogenic potential of acrolein (Salaman and Roe 1956 cited in US ATSDR, 1990).

4.1.2.8.2 Human data

There are no human data on carcinogenicity.

4.1.2.8.3 Conclusion carcinogenicity

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

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Animal data

In vitro tests

A number of *in vitro* experiments using rat embryo cultures (Hales and Slott, 1987; Mirkes et al., 1981, 1984; Schmid et al., 1981; Slott and Hales, 1987a,b,) murine preimplantation embryos (Spielmann and Jacob-Müller, 1981) or limb bud cultures (Ghaida and Merker, 1992; Hales, 1989; Stahlmann et al., 1985), or hen eggs (Chibber and Gilani, 1986; Kankaanpää et al., 1979; Korhonen, 1983) showed the potency of acrolein to cause growth retardation or embryolethality and malformations.

In vivo tests

Inhalation studies

There is only one inhalation study (Bouley et al., 1975, 1976) available. In this study groups of 3 male and 21 female rats were exposed continuously for 26 days to 0 or 1.26 mg/m^3 (0.55 ppm) acrolein (nature not reported) and allowed to mate on day 4 of the exposure period. No significant differences were observed between control and intoxicated animals with respect to pregnancy rate and number and weight of fetuses. This study is not considered appropriate for evaluation of the reproductive properties of acrolein since the exposure period did not cover the whole spermatogenic cycle, the premating exposure was only 4 days and only a restricted number of parameters was studied. In addition, no details concerning study design and results were presented.

Oral studies

There are two publications of oral studies available: a 2-generation reproduction study and a teratogenicity study, both from Parent et al., (1992c, 1993). Beside these studies, three other unpublished oral reproduction studies are cited in US ATSDR, 1990: an oral 2-generation reproduction study (King, 1984), and two teratogenicity studies, one with rabbits (Hoberman, 1987) and the other with rats (King, 1982).

In an oral 2-generation reproduction study in male and female rats the only effects observed were a decreased body weight gain in the F0 generation at the highest dose of 7.2 mg per kg bw per day and stomach ulcerations at 5.4 mg/kg bw per day and higher (King, 1984 cited in US

ATSDR, 1990). From this study a NOAEL of 7.2 mg/kg bw per day (the highest dose tested) for developmental and of 4 mg/kg bw per day for parental toxicity is established.

In an adequately performed 2-generation oral gavage study, male and female rats were given daily 0, 1, 3, or 6 mg acrolein/kg bw by stomach tube. Reproductive parameters, including male and female fertility, were not affected by acrolein treatment with the exception of reduced pup weights of the *F1*-generation pups at the high dose level (6 mg/kg bw per day). Parental toxicity seen as increased mortality, clinical signs, decreased body weight gain and histopathological stomach changes (erosions of glandular stomach and hyperplasia/hyperkeratosis of the forestomach) occurred in the mid and high dose groups (Parent et al., 1992c). From this study a NOAEL of 3 mg/kg bw per day for developmental and of 1 mg/kg bw per day for parental toxicity is established.

In an oral teratology study in rats (exposure by gavage) increased incidences of skeletal anomalies and delayed ossification and decreased mean fetal weight and total litter weights were observed at a dose level of 10 mg/kg bw per day. The number of implantations or resorptions or the ratio of live/dead fetuses per litter was not affected in the 10 mg group. This dose level, however, was toxic to the dams resulting in the death of 14 out of 40 females in this group. The only effect seen at 6 mg/kg bw per day was a decreased maternal body weight gain, there were no developmental effects (King, 1982 cited in US ATSDR, 1990). From this study a NOAEL of 6 mg/kg bw per day for developmental and of 3.6 mg/kg bw per day for maternal toxicity is established.

Fetal/embryonal mortality was not affected in a teratology study, in which rabbits were exposed to 2 mg/kg bw per day or less during gestation. However, in the preliminary dose-range finding study preceding the final teratology study, exposure to 1 mg/kg bw per day or more resulted in dose-related increased incidences of fetal resorption. No explanation for the discrepancy was provided. No developmental effects were found at 0.5 mg/kg bw per day. In dams a decreased body weight gain was found at 0.5 mg/kg bw per day, and increased mortality and gastric ulcerations were observed at 4 mg (Hoberman, 1987 cited in US ATSDR, 1990). It is concluded that this study is not suitable for the assessment of maternal or developmental NOAEL, in view of the unexplained discrepancy between the results of the range-finding study and those of the main study.

Parent et al., 1993 treated pregnant female rabbits orally by stomach tube with 0.1, 0.75 or 2.0 mg acrolein/kg bw per day on gestational days 7 through 19. In the 2 mg group a transient decrease in maternal body weight gain accompanied by a decreased food intake pointing to maternal toxicity was observed during days 7 through 10. In the subsequent days food intake in this group increased resulting in body weights exceeding those of the other groups. In addition, the high dose group showed an increase in mean fetal body weights, which is not considered to be an adverse effect in this study ($P \leq 0.01$). Acrolein did not induce irreversible developmental effects. From this study a NOAEL of ≥ 2 mg/kg bw per day for developmental effects and a NOAEL of 0.75 mg/kg bw per day for maternal toxicity is established.

Dermal studies

No data available.

Other studies

When pregnant rabbits were intravenously injected with single doses of 3, 4.5 and 6 mg/kg bw per day at day 9 of gestation, maternal toxicity (mortality) was observed in the animals of the mid and high dose group. In the high dose group embryotoxicity (statistically significant increased resorption rate) was found as well (Claussen et al., 1980).

Acrolein induced embryotoxic and teratogenic effects in rats and rabbits by intra-amniotic injection (Claussen et al., 1980; Hales, 1982; Slott and Hales, 1985).

4.1.2.9.2 Human data

There are no human data on reproductive toxicity.

4.1.2.9.3 Conclusion reproduction toxicity

The data submitted are acceptable with respect to the basic requirements as specified in Annex VIIA of Directive 67/548/EC.

A number of *in vitro* experiments showed the potency of acrolein to cause growth retardation or embryolethality and malformations. 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 the oral 2-generation rat studies. The overall NOAEL amounted to 1 and 3 mg/kg bw per day for parental and developmental effects, respectively.

4.1.2.10 Effects on immune system

The effects of acrolein on the immune system were tested in *in vivo* and *in vitro* systems. **Table 4.13** summarises a number of repeated-dose inhalation toxicity studies primarily aimed at an evaluation of immune and/or host defence mechanism. Below a number of acute studies *in vivo* and some *in vitro* data are summarised.

The induction of impairment of the pulmonary antibacterial defense by inhalation exposure to acrolein was observed in studies in mice (Astry and Jakab, 1983; Kawabata and White, 1977) and rats (Carl et al., 1939). Inhalation exposure to 3 or 6 ppm during 8 hours induced a dose-dependent impairment of the pulmonary antibacterial defence against infection with Staphylococcus aureus in mice (Astry and Jakab, 1983). Higher concentrations caused increased sensory irritation, but no additional impairment of antibacterial resistance.

Suppression of bactericidal activity of pulmonary macrophages was observed in several *in vitro* studies. Because acrolein is a metabolite of cyclophosphamide, *in vitro* studies were performed to investigate whether the antitumor activity of cyclophosphamide was mediated by enhanced immune reactivity of acrolein. The results suggest that the immune response is enhanced by acrolein.

4.1.2.11 Effects upon combined exposure

4.1.2.11 Co-exposure to various aldehydes

The effects of exposure to mixtures of aldehydes (formaldehyde, acetaldehyde, acrolein, and/or crotonaldehyde) have been examined in *in vitro* studies and short-term inhalation studies focusing on cytotoxicity, nasal toxicity and sensory irritation.

In vitro studies

The results of the *in vitro* studies, using human and rat nasal epithelial cells show that exposure to mixtures of formaldehyde, acrolein and crotonaldehyde will result in cytotoxic effects that can be predicted by dose addition from single-compound concentration-effect relationships (Cassee, 1995C).

Short-term inhalation studies

Exposure to acrolein (2 ppm, 6 h) did not result in DNA-protein cross-linking in nasal mucosa of rats, while simultaneous exposure of rats to both acrolein (2 ppm) and formaldehyde (6 ppm) for 6 h resulted in a significantly higher yield of DNA-protein cross-links than exposure to formaldehyde alone (6 ppm, 6 h) (Lam et al., 1985, Heck et al., 1986). In addition, there was also some evidence that co-exposure of formaldehyde with acrolein at relatively high concentrations resulted in supra-additive effects due to glutathione depletion in nasal mucosa by acrolein (Lam et al., 1985).

To study the possible additive or interactive effects on nasal epithelium *in vivo* Cassee et al. carried out 1- and 3-day inhalation studies (6 h/day) with formaldehyde (1, 3.2, and 6.4 ppm), acetaldehyde (750 and 1500 ppm), acrolein (0.25, 0.67 and 1.40 ppm) or mixtures of these aldehydes using male Wistar rats and exposure concentrations varying from clearly non-toxic to toxic. Parameters studied included histopathological and biochemical changes in respiratory and olfactory epithelium of the nose. In addition, cell proliferation in nasal epithelium was determined by incorporation of bromodeoxyuridine and proliferating cell nuclear antigen expression. The results indicated that in spite of the similar mode of action of the aldehydes tested, the individual aldehydes exhibited clear regional differences in cytotoxicity. The results obtained with the aldehyde mixtures suggested that, for non-toxic effect levels, combined exposure to these aldehydes with the same target organ (nose) and exerting the same type of adverse effect (nasal irritation/cytotoxicity), but partly with different target sites (different regions of the nasal mucosa), is not associated with a greater hazard than that associated with exposure to the individual chemicals (Cassee et al., 1996a).

Formaldehyde and acrolein have been shown to be competitive agonists for trigeminal nerve receptors in the upper respiratory tract (Kane and Alarie, 1978; Babiuk et al., 1985). The sensory irritation of formaldehyde, acrolein, and acetaldehyde as measured by a decrease in breathing frequency (DBF) was studied in male rats using nose-only exposure. All three aldehydes acted as sensory irritants as defined by Alarie.

The RD_{50} values amounted to 9.2 ppm, 10.0 ppm and 3046 ppm for acrolein, formaldehyde and acetaldehyde, respectively. With formaldehyde and acrolein desensitisation occurred, while with acetaldehyde the breathing frequency gradually decreased with increasing exposure time (up to 30 min.). With the aldehyde mixtures no desensitisation was found; in fact, the breathing

frequency further decreased in the last 15 min. of exposure. From the results it was concluded that sensory irritation in rats exposed to mixtures of irritant aldehydes is more pronounced than that caused by each of the aldehydes separately, and that the combined effect of these aldehydes is basically a result of competition for a common receptor (trigeminal nerve) (Cassee et al., 1996b)

4.1.2.11.2 Co-exposure to acrolein and carbon black

Co-exposure of mice by inhalation to atmospheres containing carbon black (10 $mg.m^{-3}$) and acrolein (5.8 $mg.m^{-3}$; nature not reported) for 4 hours per day, for 4 days resulted in an impairment of the pulmonary defence mechanism as evidenced by a decrease in resistance against a set of infectious agents representative for the functional integrity of the lung defence system. Neither exposure to carbon black alone nor exposure to acrolein alone had any effect on the lung defences against these agents. It was hypothesised that the mechanism for the enhanced biologic effect may be that the carbon black particle acts as a carrier mechanism for acrolein to the deep lung (Jakab, 1993).

4.1.2.11.3 Cocarcinogenicity

Exposure of hamsters to 9.3 mg/m^3 (4 ppm) acrolein vapour for 52 weeks (7 h/day, 5 days/week) had no influence on the carcinogenicity of benzo[a]pyrene or *N*-nitroso-diethylamine (Feron and Kruysse, 1977).

4.1.3 Risk characterisation

4.1.3.0 General aspects

Humans may be exposed to acrolein at the workplace and indirectly via the environment (see 4.1.1.1, 4.1.1.3).

Animal and human 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*.

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 defense mechanisms upon inhalation exposure *in vivo* and *in vitro*.

4.1.3.1 Workers

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.

Acute toxicity

Because it is generally known that acrolein is very toxic and a very strong corrosive agent, workers will attempt to avoid inhalation and dermal exposure. The LC_{50}-values (18-150 mg/m^3 in the rat and 58 mg/m^3 in hamsters) are higher than the estimated short-term inhalation exposure levels (0.2, 0.23 and 2 mg/m^3 in scenario 1, 2 and 3, respectively), but the margin of difference is 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 (see also risk assessment for 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 (conclusion ii) is reached for these scenario's. For comparison, there is also no concern for acute toxicity due to unintentional exposure (scenario 3), because exposure is limited to negligible levels.

Irritation and corrosivity

This paragraph is limited to risk characterisation for irritation/corrosivity after single exposure to acrolein. The risk for irritating effects after repeated exposure is estimated in the concerning paragraph.

Skin

Single exposure, liquid

Acrolein is a strongly corrosive agent. Because dermal exposure may occur in scenario 1 and scenario 2 only accidentally and in scenario 3 to negligible levels, it is concluded that workers are not at risk with respect to skin irritation when adequate worker protection measures (usually used when acrolein is handled) are applied (**conclusion ii**).

Single exposure, vapour

According to the available model for estimating dermal exposure, the dermal exposure to vapours is negligible, and because of the dermal worker protection measures applied, it is concluded that workers are not at risk with respect to irritating effects due to exposure of the skin to vapours (**conclusion ii**).

Inhalation

The risk for adverse effects on mucous membranes (eyes, nose and respiratory tract) due to inhalation exposure is estimated in this paragraph.

Single exposure, vapour

Starting-points for the risk assessment for single occupational exposure by inhalation are (a) the LOAEL of 0.14 mg/m^3 for subjective symptoms from the human volunteer study of Darley et al. (1960), (b) the NOAEL of 0.34 mg/m^3 for measured effects from the human volunteer study of Weber-Tschopp et al. (1977), and (c) the estimated short-term inhalation exposure levels for the different occupational scenarios (see chapter 4.1.1.1 and **Table 4.4**).

The MOSs between the LOAEL and the short-term inhalation exposure levels for scenario 1 and 2 are 0.7 and 0.6, respectively using the subjective symptoms as starting point, and between 1.7 and 1.5, respectively, starting with the NOAEL for objective symptoms (see table 4.1.3.1A). For comparison, the MOS for scenario 3 amounts 0.07 starting with the LOAEL for subjective symptoms, and 0.2 for objective symptoms. In Annex 3, an approach to interpret the MOS are given (**Table A2** in Annex 3).

Based on the risk assessment as given in **Table 4.19**, it is concluded that irritation of the mucous membranes due to short-term inhalation exposure cannot be excluded for all occupational exposure scenarios, irrespective whether the LOAEL/NOAEL for the subjective or the objective symptoms are used as starting point. Risk reduction measures, additional to those already taken, are indicated (**conclusion iii**). It is possible that in (some) industrial premises adequate risk reduction measures are already being applied to avoid irritating effects due to short-term

inhalation exposure. It has to be noted that indicated risks for scenario 3 are not the result of the intentional production or use of acrolein.

Table 4.19 Occupational risk characterisation of acrolein for irritation due to single inhalation exposure

	Risk characterisation for inhalation exposure				
Occupational scenario	**Estimated inhalation exposure (mg/m³) Short-term**	**MOS[a]**	**Conclusion[b]**	**MOS[c]**	**Conclusion[d]**
1. Production of acrolein - filling, sampling	0.2	0.7	iii	1.7	iii
2. Processing of acrolein	0.23	0.61	iii	1.5	iii
3. Exposure not resulting from use	2	0.07	iii	0.2	iii

[a]Based on a LOAEL of 0.14 mg/m³, subjective symptoms
[b]The conclusion is reached by considering the magnitude the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Annex 3
[c]Based on a NOAEL of 0.34 mg/m³, objective symptoms
[d]The conclusion is reached by considering the magnitude the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Annex 3

Eyes

Single exposure, liquid

Theoretically, acrolein is of concern for workers with regard to eye effects, because of its corrosive properties. However, eye protection is obligatory for activities where direct handling of acrolein occurs. If the required protection is strictly adhered to, exposure will occur only accidentally in scenario 1 and 2, so **conclusion ii)** is justifiable. It has to be noted that there is concern for scenario 3, but in this scenario exposure is not the result of the intentional production or use of acrolein.

Sensitisation

Based on the data available acrolein should be considered as sensitising to the skin. For all scenarios dermal exposure is limited to accidental events or to negligible levels and therefore **conclusion ii**) is applicable with respect to skin sensitisation.There are neither data from human experience nor from other sources indicating respiratory sensitisation.

Repeated dose toxicity

Inhalation exposure

The predominant effects observed in repeated inhalation studies at the LOAELs consisted of histopathological changes in the epithelium of the respiratory system and changes in respiratory tract function attributed to irritating effects on sensory cells. Effects at higher concentrations included signs of chronic inflammatory changes, and epithelial metaplasia and hyperplasia of the respiratory tract. The results of the repeated-dose inhalation studies do not permit the establishment of a NOAEL. For the workplace the studies with intermittent exposure (6-7 hr/d, 5 d/w for a total period of 62 days - 13 weeks) are considered the most relevant. Exposure to 0.9

mg/m^3 was a LOAEL for rats, but caused no effects in hamsters and rabbits. There are no human studies with repeated exposure available.

Starting-points for the risk assessment for workers repeatedly exposed by inhalation are (a) the LOAEL of 0.9 mg/m^3 from the above mentioned study, and (b) the estimated inhalation exposure levels for the different occupational scenarios (see chapter 4.1.1.1 and **Table 4.3**). Given the estimated frequency of occupational exposure (100-200 d/year) chronic exposure is assumed for risk characterisation. Risk characterisation is performed by comparing the LOAEL-inh/chronic and the exposure levels, both expressed as concentrations, because irritation is the critical effect. The MOSs between the LOAEL and the inhalation exposure levels vary between 2.7 and 4.5 (see **Table 4.20**). The MOSs can be evaluated by comparison with the minimal MOS. This apporach is presented in Annex 3, where the assessment factors used to establish the minimal MOS are given (**Table A3** in this Annex). Using this apporach, there is concern when the MOS is lower than the minimal MOS.

Given the risk assessment as given in **Table 4.20**, it is concluded that health risks due to repeated inhalation exposure cannot be excluded for the occupational exposure scenario 1, 2 and 3. Risk reduction measures are recommended for exposure scenario's 1 and 2, based on the reasonable worst case estimate of exposure (**conclusion iii**). For typical exposure situations in scenario 1 and 2 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 not the result of the intentional production or use of acrolein.

Dermal exposure

There are no dermal repeated dose toxicity studies available. Because dermal exposure may occur only accidentally in scenarios 1 and 2, it is concluded that health risks due to dermal acrolein exposure are not expected in these scenarios (**conclusion ii**).

Table 4.20 Occupational risk characterisation of acrolein for repeated dose toxicity

	Risk characterisation for inhalation exposure			Risk characterisation for dermal exposure		
Occupational scenario	**Estimated inhalation exposure (mg/m^3) worst case**	**MOS[a]**	**Conclusion[b]**	**Estimated dermal exposure (mg/day)**	**MOS**	**Conclusion[c]**
1. Production of acrolein - full-shift	0.2	4.5	iii	accidentally	not relevant	ii
2. Processing of acrolein	0.23	3.9	iii	accidentally	not relevant	ii
3. Exposure not resulting from use	0.33	2.7	iii	negligible	sufficient	ii

[a]Based on the LOAEL of 0.9 mg/m^3

[b]The conclusion is reached by considering the magnitude the MOS, taking into account a number of additional parameters as described in the TGD. An approach to do so is given in Annex 3

[c]See text

Value of 0.06 mg/m_3 for local effects on the respiratory tract after repeated inhalation exposure

Mutagenicity and carcinogenicity

From the results of the mutagenicity studies it is concluded that acrolein has intrinsic genotoxic properties, being positive in gene mutation tests *in vitro* with bacteria and mammalian cells within a very narrow dose range. Acrolein did not exhibit genotoxic activity in mammals *in vivo* as appeared from the negative results obtained in a dominant lethal test with mice and a bone marrow chromosome aberration test with rats. The occurrence of genotoxic effects locally at the site of first contact can, however, not 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 meet 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 that the HBORV-inh/chronic (0.06 mg/m^3) used in this report for risk characterisation for respiratory effects after repeated exposure 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**).

Reproductive toxicity

Only oral studies on reproductive toxicity are available. Developmental effects, and effects on reproduction parameters occur only at parental toxic dose levels. 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 (MOS/HBORV-approach). 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.

Occupational limit values

In several countries there are occupational limit values for acrolein (see **Table 4.21**).

Table 4.21 Occupational limit values for acrolein

Country /organisation	8-hr TWA		15-min STEL		References
	mg/m³	ppm	mg/m³	ppm	
ACGIH	0.23	0.1	0.69	0.3	[15]
The Netherlands	0.25	0.1	-	-	[16]
UK	0.25	0.1	0.8	0.3	[17]
Germany	0.25	0.1	0.5[1]	0.2[1]	[18]
Sweden	0.2	0.1	0.7	0.3	[19]

15-min STEL

Documentation was only published by the ACGIH (1995) (TLV established in 1976, documentation revised in 1991). It is stated that the TLV-TWA of 0.1 ppm is sufficiently low to minimise, but not entirely prevent, irritation to all exposed individuals. It is not clearly mentioned, but from the studies described it is assumed that this value is based on human data.

Using the approach outlined in Annex 3 HBORV-inh/single (comparable with a STEL-value) for acrolein of 0.02-0.11 mg/m^3 (0.01- 0.05 ppm) and the HBORV-inh/chronic (comparable with a 8-hr TWA-value) of 0.06 mg/m^3 (0.03 ppm) can be derived. These values are lower than current limit values. As for the 8-hr TWA value this may be due to other starting points (animal study in the present evaluation vs. most likely human data in the ACGIH documentation) and to the fact that adverse effects are not completely excluded by exposure to the current values. It is noted that the animal study used in present evaluation was also mentioned by the ACGIH. As for the STEL-value human data are used as starting-point in both evaluations. However, the data mentioned in the ACGIH documentation are of older date, but the effect levels correspond readily with those mentioned in this report. No assessment factor is applied in the derivation of the ACGIH.

4.1.3.2 Consumers

As discussed in the previous paragraphs consumer uses are not identified within the EU and therefore consumer exposure is not expected to occur (**conclusion ii**).

4.1.3.3 Man exposed indirectly via the environment

4.1.3.3.1 Inhalation exposure

Repeated dose toxicity

Acrolein is acutely a very toxic agent and also very strongly corrosive.

Several studies in humans all of short duration are available (see paragraph 4.1.2.12. Despite the fact that the study design and descriptions do not allow clear conclusions on human (no) effect levels for irritating effects after short-term inhalation exposure to acrolein vapours, for risk assessment the LOAEL of 0.14 mg/m^3 from the study of Darley et al. (1960) can be used for subjective symptoms and 0.34 mg/m^3 (Weber-Tschopp et al. 1977) for measured effects.

The results of the repeated dose inhalation studies in animals do not permit the establishment of a NOAEL. Intermittent exposure (6-7 hours/day, 5 days/week for a total period of 62 days - 13 weeks) to 0.9 mg/m^3 acrolein vapour (the lowest concentration examined) resulted in slight, but treatment related changes in the rats (histopathological lesions in the epithelium of the nasal cavity), but not in hamsters and rabbits. Continuous exposure (24 hours/day, 7 days/week for 90 days) to 0.5 mg/m^3 acrolein (the lowest concentration examined) resulted in treatment related effects in guinea pigs, monkeys and dogs, but not in rats. In special inhalation studies exposure to acrolein concentrations of 0.46 and 0.57 mg/m^3 and higher for one or 3 days resulted in cell proliferation in the nasal epithelial cells at both dose levels. From the above-mentioned animal studies it can be concluded that the observed effects (e.g. equal in type) are independent of the exposure duration.

It is assumed that in humans like in animals irritation is the critical effect and from animals studies it is concluded that the severity of this effect is more dependent of the concentration of the exposed acrolein than of the exposure duration. Therefore the LOAELs of 0.14 mg/m^3 and 0.34 mg acrolein/m^3 in studies with human volunteers may be used as starting point for the risk assessment. However, in view of the more elaborate studies performed in animals it is proposed to use the lowest LOAEL of about 0.5 mg/m^3 from the animal studies for risk assessment.
For the scenarios for IV life cycle stages the local concentration estimates in (100 m from source) are presented in **Table 4.5**.

The margins of safety between the local air concentration estimates for the different scenarios and the monitoring data (including indoor data) and the LOAEL of 0.5 mg/m3 are given in **Table 4.22**.

Table 4.22 The margins of safety between the LOAEL (500 μg/m³) for inhalation exposure and the estimated concentrations in air (100 m from source)

Local calculated	Scenario	Margin of safety
	production scenario Ia1 (site specific)	12.500
	production scenario Ia2 (site-specific)	5.000
	processing scenario IIb(site-specific)	-
	processing scenario Iid (site specific)	12.500
	combustion scenario III (site specific)	25.000
	traffic scenario IV - busy street - busy motorway	 385 (annual av.) 714 (annual av.)
Measured		
	industrial activities (range of monitoring data)	0.01 - 5
	in streets (inner city) (range of monitoring data)	14.3 - 1667
	indoor: heated fat (range of monitoring data)	<< 1
	indoor: cigarette smoke - side stream smoke (range of monitoring data)	0.17 - 45

Table 4.22 indicates that, except for the site-specific scenarios (**conclusion ii**), the calculated margins of safety are low (taking into account all data available and the use of the lowest LOAEL in animals), indicating concern for human safety. As mentioned in paragraph 3.3.3 it would be speculative to draw firm conclusions on these results as the monitoring data are either outdated or lacking of important background information (e.g. analysis technique, percentiles etc.). Nevertheless, it can be concluded that some of the unintentional emissions, especially cigarette smoke may cause concerns for humans. 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**), unintentional sources. For the regional scale the margin of safety between the PEC air of 0.03 $\mu g/m^3$ and the LOAEL of 0.5 mg/m^3 was calculated to be 16667 indicating no concern for human safety (**conclusion ii**).

Genotoxicity and carcinogenicity

From the results of the mutagenicity studies is concluded that acrolein has intrinsic genotoxic properties being positive in gene mutation tests *in vitro* within a very narrow dose range. Acrolein did not exhibit genotoxic activity in mammals *in vivo*. The occurrence of genotoxic effects locally at the site of first contact can, however, not completely be excluded.

There is evidence that acrolein is not an oral carcinogen. The limited inhalation data available did not indicate carcinogenicity after inhalation. It can not be excluded however, that respiratory tumours may be induced at non-cytotoxic concentrations. In analogy with other aldehydes as formaldehyde and possibly aceetaldehyde it is most unlikely that carcinogenic effects 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 genotoxicity (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 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. In this report for the risk characterisation for respiratory effects after long-term inhalatory exposure the lowest LOAEL of about 0.5 mg/m^3 was taken (see *Repeated dose toxicity* above). 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 margins 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**), unintentional sources.

Reproductive toxicity

Adequate studies by inhalation are not available. Reproductive/developmental effects in the oral studies occurred only at parentally toxic doses (see 4.1.2.9). 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 (taken 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**).

4.1.3.3.2 Total daily intake

Repeated dose toxicity

The total daily intakes as calculated in paragraph 4.1.1.3.1 (**Table 4.6**) are compared with the oral NOAEL of 0.05 mg/kg bw/day from a 2-year rat study. In this study the main effect was decreased survival. This study is most suitable to use as an overall NOAEL since all other oral studies including those in other species revealed higher NOAEL's.

The values for the total intakes via air, drinking water and food at local scale for the different scenarios as presented in **Table 4.6** are $< 3.2 \cdot 10^{-5}$ mg/kg bw/day for the site-specific scenarios. For the regional scale the value is $7.3 \cdot 10^{-6}$ mg/kg bw/day.

Based on the very limited quantitative information available on acrolein in foodstuffs (see **Table 4.9**) and taking into account that acrolein is present in a variety of foodstuffs (especially in aged products and products that have been heated) it has been estimated that the dietary intake from foodstuffs may be about 1 µg/kg bw/day (Slooff et al., 1994). This value can be considered as a background level and is subsequently used for the risk assessment. The margins of safety between these intakes and the NOAEL of 0.05 mg/kg bw/day are given in **Table 4.23**.

Table 4.23 Margin of safety

Scenario	Margin of safety
site-specific scenarios (range)	>1600
regional scale	6850
"background"	50

Only the margin of safety for the estimated dietary background intake of 50 is considered to be low. Taking into account all data available and the use of a NOAEL in a 2 year rat study, there will be 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**).

Carcinogenicity

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

Reproductive toxicity

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 ≥2 mg/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), the site-specific scenarios at local scale (>23000) and the estimated dietary background (>750) indicate no concern for human safety (**conclusion ii**).

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Pyroforicity was not determined. Structural formula and thermoynamic properties indicate flammable acrolein-air mixtures. The pure substance shoulde be classified as extremely flammable.

Explosive properties were not determined. Theoretically, explosive properties may be present if handled without care. The substance is thermally unstable (dimerisation, polymerisation) and should be stabilised by a radical annihilator such as for instance hydroquinone. A bottom concentration of 0.2% should be applied for uncontrolled cases. During processing the bottom concentration may be reduced while applying appropriate safety measures.

The substance is highly unstable with (strong) acids and bases. Exposure to such chemicals may lead to instantaneous and explosive polymerisation and should be avoided. A general warning to this effects is recommended. Mixtures of acrolein vapours and air are extremely flammable and may even explode depending on concentration levels and confinement. LEL (lower explosive limit) and UEL (upper explosive limit) in air were observed at 2.8 and 31 v-%, respectively.

In conclusion, no classification for explosive properties is required. However, a general warning concerning incompatible chemicals and formation of highly flammable/potentially explodable gases is recommended. Oxidising properties are not considered to form a hazard.

There is no need for further information and/or testing with regard to physico-chemical properties (**conclusion ii**).

5 RESULTS

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.

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:

1. of concern for eye, nose and respiratory tract irritation as a consequence of single and repeated inhalation exposure arising from the production and processing of the substance;

and

2. that, in addition to the conclusion given above, the risk assessment shows that there are uncertainties with regard to the possible genotoxic and carcinogenic effects of the substance locally at the exposure site after long-term exposure by inhalation to non-cytotoxic concentrations. However, at this moment no validated genotoxicity test exists to investigate this, and the relatively low exposure levels do not justify there quest for a carcinogenicity study by inhalation.

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.

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.

In addition to the conclusions according to Council Reg. 793/93/EEC given above, the RAR came to the conclusion concerning unintentional emissions as follows:

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.).

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.

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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 Council of the Paint, Printing Ink and Artists' Colours Industry
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}	Fraction of organic carbon
g	gram(s)

PNEC(s)	Predicted No Effect Concentration(s)
$PNEC_{water}$	Predicted No Effect Concentration in water
(Q)SAR	Quantitative Structure Activity Relationship
STP	Sewage Treatment Plant
TGD	Technical Guidance Document[8]
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
w	gram weight
GLP	Good Laboratory Practice
h	hour(s)
ha	hectares / *h*
HPLC	High Pressure Liquid Chromatography
IARC	International Agency for Research on Cancer (WHO)
C_{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	Solids water partition coefficient
l	litre(s)
log	logarithm to the basis 10
$L(E)C_{50}$	lethal concentration, median
m	meter
µg	microgram(s)

[8] Commission of the European Communities, 1996. Technical Guidance Documents 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]

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 the 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

Annex 1 Reliability Index and usefulness of information in HEDSET

Table A1 Reliability Index and usefulness of information in HEDSET*

Reliability Index	Description reliability	Usefulness	Description usefulness
1 valid without restrictions	the method and description are in accordance with test guidelines[1]	a useful	relevant for RA-report[5]
		b not useful	not relevant for RA-report[5]
2 valid with restrictions	the method **and/or** description are less in accordance with test guidelines[2,5]	a useful	relevant for RA-report[5]
		b not useful	not relevant for RA-report[5]
3 invalid	the method and/or description are **not** in accordance with test guidelines[3,5]	a useful	relevant for RA-report[5]
		b not useful	not relevant for RA-report[5]
4 not assignable	the original data are not available[4,5]	a useful	relevant for RA-report[5]
		b not useful	not relevant for RA-report[5]

* The reliability index and usefulness indication are also applicable for QSAR-data (e.g. log K_{ow}). Usefulness is applicable after evaluating all tests for one endpoint.

[1]for example:
-complete test report available; GLP, Annex V; OECD, EU e.t.c.
See also chapter 2 Risk Assessment for Human Health of TGD (page 28)
-publications are not included

[2]for example:
-validity of data cannot be fully established
-some modifications or omissions in method and description
-acceptable publication (e.g. according to EU- or OECD guidelines)

[3]for example:
-method unknown and/or critical pieces of information are not available (e.g. identity of substance)
-documentation not sufficient for unequivocal assessment
-do not meet important criteria of today standard test methods

[4]for example:
-only abstract available
-secondary literature (reviews, tables etc..)

[5] Motivation/justification should be given:
-when study is useful but as supporting data
-when study is not useful for the RA-report (e.g. Chinese language)

Annex 2 Establishment of the minimal MOSs used for occupational risk characterisation by the Netherlands[9]

In the tables below calculations of the minimal MOS-values via assessment factors are given. The assessment factors are based on the report of Hakkert et al. (1996).

Table A2 Assessment factors applied for the calculation of minimal MOS for local effects observed after single inhalation exposure applicable on results from human studies

Aspect	Assessment factors	
	subjective symptoms	objective symptoms
Interspecies differences	1[1]	1[1]
Intraspecies differences	3	3
Differences between experimental conditions and exposure pattern of the worker	1[2]	1[2]
Type of critical effect	1	1
Dose-response curve	2[3]	1
Confidence of the database	1	1
Overall	6	3

[1]Because a human study is used as starting-point, the factor for interspecies differences is 1
[2]Given the exposure circumstances in the human study, and because the minimal MOS has to be calculated for single exposure, it is justifiable to apply an assessment factor of 1
[3]A factor 2, to compensate for the absence of a NOAEL, is considered to be sufficient in view of the sensitivity of the effect parameter used

Table A3 Assessment factors applied for the calculation of the minimal MOS for chronic inhalation exposure applicable on thechronic inhalation study with rats

Aspect	Assessment factors
Interspecies differences	1[1]
Intraspecies differences	2[2]
Differences between experimental conditions and exposure pattern of the worker	4[3]
Type of critical effect	1
Dose-response curve	2[4]
Confidence of the database	1[5]
Overall	16

[1] The nature of the effects observed in different species is similar. The data available does not give rise to suppose a clear difference in susceptibility between human and rat, and therefore a factor 1 is considered to be justifiable for interspecies differences
[2] The default factor for intraspecies differences is 3 for the occupational population. For local effects the differences in sensitivity between workers are assumed to be smaller. Therefore a factor 2 is considered to be sufficient
[3] Default value for the factor for extrapolation from semichronic to chronic exposure is 10. Because irritation is the critical effect and it is assumed that this effect is more dependent on the concentration than on exposure duration, this factor is considered to be too high. However, a factor of 1 will not suffice given the doubts about the suitability of the results from a semichronic study for the risk assessment of chronic exposure, (a) because of the cell proliferation observed in rats after 3 days exposure to ca. 0.5 mg/m^3, and 1b) because it cannot be excluded that nasal tumours may be induced by cytotoxic concentrations. Considering these points it is justifiable to use a factor 4 for extrapolation to chronic occupational exposure
[4] Because a LOAEL is used as starting point and given the effects observed a factor 2 is considered sufficient to compensate for the absence of a NOAEL
[5] Account is made for the uncertainties on the confidence of the database in the factor for extrapolation to chronic exposure (see footnote 3)

[9] This annex represents the views of the Netherlands. In particular it presents the approach used by the Netherlands to determine, in a transparent way, which conclusion is to be drawn for worker risk characterisation base on the magnitude of the MOS

European Commission

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Acrolein-, Volume 7

Editors: B.G. Hansen, S.J. Munn, S. Pakalin, C.J.A. Heidorn, R. Allanou, S. Scheer, G. Pellegrini, S. Vegro, M. Luotamo, J. De Bruijn, F. Berthault, H. Loonen, K. Vormann, A. Naughton, V. Anfossi, L. Praderio

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The report provides the comprehensive risk assessment of the substance Acrolein. It has been prepared by the Netherlands in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment for Acrolein concludes that there is at present concern for workers. There is at present no concern for consumers and humans exposed via the environment. The environmental risk assessment for Acrolein concludes that there is at present no concern for atmosphere, aquatic ecosystem, terrestrial ecosystem and for micro-organisms in the sewage treatment plant.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commissions committee on risk reduction strategies set up in support of Council Regulation (EEC) No. 793/93.

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