European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

Existing Substances

European Union Risk Assessment Report

CAS No: 7722-84-1

EINECS No: 231-765-0

hydrogen peroxide

2nd Priority List

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HYDROGEN PEROXIDE

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RISK ASSESSMENT

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HYDROGEN PEROXIDE

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RISK ASSESSMENT

Final Report, 2003

Finland

The rapporteur for the risk assessment report on hydrogen peroxide is the Finnish Environment Institute, in co-operation with the National Product Control Agency for Welfare and Health and in consultation with the Ministry of Social Affairs and Health, Occupational Safety and Health Department.

The scientific work concerning the human health has been prepared by the Finnish Institute of Occupational Health.

Contact point:

Chemicals Division
Finnish Environment Institute
P.O.Box 140
FIN - 00251 Helsinki
Finland
Tel: +358 9 40 3000
Fax: +358940300591

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Final report: **2003**

(The last full literature survey was carried out in 1997 - targeted searches were carried out subsequently).

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.

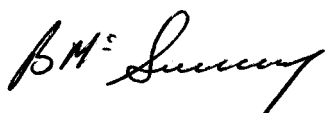
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each 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 overall risks from exposure to chemicals.



Barry Mc Sweeney
Director-General
DG Joint Research Centre

Catherine Day
Director-General
DG Environment

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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: 7722-84-1
EINECS No: 231-765-0
IUPAC name: hydrogen peroxide

Environment

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion is reached because of:

- concerns for effects on the aquatic compartment as a consequence of exposure arising from four production sites and use in manufacture of other chemicals.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to:

- the aquatic compartment for 19 production sites, pulp bleaching, textile bleaching, environmental applications and consumer use.
- microorganisms in the sewage treatment plant, the terrestrial environment and the atmosphere for production, all processing scenarios and consumer use.

Human health

Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion is reached because of:

- concerns for skin, eye and respiratory tract irritation and/or corrosivity, depending on concentration as a consequence of exposure arising from loading operations.
- concerns for skin and eye irritation and/or corrosivity, depending on concentration, as a consequence of exposure arising from bleaching of textiles (batch process), aseptic packaging (old types of immersion bath machines), hydrogen peroxide and peracetic acid use in breweries, etching of circuit boards (old process), metal plating, degrading of proteins.
- concerns for eye irritation and/or corrosivity, depending on concentration, as a consequence of exposure arising from hairdresser's work.
- concerns for repeated inhalation toxicity in loading operations and aseptic packaging (all types of machines), etching of circuit boards (old process) and wastewater treatment.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to:

- acute toxicity, sensitisation, repeated oral toxicity, repeated dermal toxicity, mutagenicity and carcinogenicity for all exposure scenarios.
- skin, eye and respiratory tract irritation and/or corrosivity in production of H_2O_2, synthesis of other chemicals, pulp and paper bleaching, bleaching of textiles (automated process), industrial laundering, aseptic packaging (other than old types of immersion bath processes), peracetic acid use in meat processing, etching of circuit boards (modern process), production of modified starch, drinking water treatment, and wastewater treatment.
- respiratory tract irritation in bleaching of textiles (batch process), aseptic packaging (old types of immersion bath machines), hydrogen peroxide and peracetic acid use in breweries, etching of circuit boards (old process), metal plating, degrading of proteins.
- both skin and respiratory tract irritation in hairdresser's work.
- repeated inhalation toxicity in production of hydrogen peroxide, synthesis of other chemicals, pulp and paper bleaching, bleaching of textiles (batch and automated processes), industrial laundering, hydrogen peroxide and peracetic acid use in breweries, peracetic acid use in meat processing, etching of circuit boards (modern process), production of modified starch, degrading of proteins, drinking water treatment, and hairdresser's work.

Consumers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion is reached because of:

- concerns for eye irritation as a consequence of exposure arising from hair dyeing and bleaching and concerns for eye irritation/corrosivity in use of textiles bleaches and cleaning agents, if the actual concentration of hydrogen peroxide is >5%.
- concerns for specific adverse effects on tooth pulp and teeth as a consequence of exposure arising from tooth bleaching with 35% of hydrogen peroxide by a dentist.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to:

- acute toxicity, sensitisation, repeated oral toxicity, repeated dermal toxicity, mutagenicity and carcinogenicity for all exposure scenarios.
- skin, eye and respiratory tract irritation in the context of contact lens disinfection, tooth bleaching, ingestion in food, and use of mouth care products.
- both skin and respiratory tract irritation in hair dyeing and bleaching, in textile bleaching and use as a cleaning agent.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to:

- all effect endpoints for humans exposed to hydrogen peroxide via the environment.

Combined exposure

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Human health (risks from physicochemical properties)

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies to the workers and to the consumers because of:

- concerns for the risk of fire hazard caused by spills of the more concentrated (≥ 25%) hydrogen peroxide solutions on combustible materials.

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Euses Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS-No:	7722-84-1
EINECS-No:	231-765-0
IUPAC name:	hydrogen peroxide
Synonyms:	dihydrogen dioxide, hydrogen dioxide
Molecular weight:	34.02 g/mol
Molecular formula:	H_2O_2
Structural formula:	H - O - O - H

1.2 PURITY/IMPURITIES, ADDITIVES

Purity: > 99% w/w

Impurities:

Residue on evaporation	<= 0.006% w/w
Total concentration of inorganic impurities	<= 0.001% w/w
Organic impurities (TOC)	0.005-0.1% w/w

Additives:

Stabilisers [4]:

CAS-No	EINECS-No	IUPAC-Name	Value
7664-38-2	231-633-2	phosphoric acid	10-300 mg/l
10049-21-5	--	sodium phosphate	10-300 mg/l
12209-98-2	--	sodium stannate	10-300 mg/l
7783-20-2	231-984-1	ammonium sulphate	10-300 mg/l
1344-09-8	215-687-4	sodium silicate	..
103-84-4	203-150-7	acetanilide	..
1127-45-3	214-430-3	8-hydroxyquinoline	..
		pyridine carboxylic acids	..
147-71-7	205-695-6	tartaric acid	..
65-85-0	200-618-2	benzoic acids	..

Passivators [5]: nitrate salts .. % w/w

(ECETOC, 1993; Schumb et al., 1955)

[4] The stabilisers are of several types: mineral acids to keep the solution acidic, complexing/chelating agents to inhibit metal-catalysed decomposition or colloidal either neutralise small amounts of colloidal catalysts or adsorb/absorb impurities.

[5] Nitrate salts can be added as passivators to improve the chemical resistance of stainless steel and aluminium against H_2O_2.

1.3 PHYSICO-CHEMICAL PROPERTIES

Hydrogen peroxide is a clear colourless liquid which is normally handled as an aqueous solution. Hydrogen peroxide in itself (at NTP) is stable. Also pure aqueous solutions in clean inert containers are relatively stable. Stability is at a maximum at pH 3.5-4.5. Commercial solutions must be stabilised with additives to prevent possibly violent decomposition due to catalytic impurities or elevated temperatures and pressure.

Hydrogen peroxide is not flammable. However there is a dangerous fire hazard by chemical reaction of H_2O_2 with flammable materials. Hydrogen peroxide is a powerful oxidiser, particularly in the concentrated state, and it reacts violently with combustible and reducing material causing fire and explosion hazard.

Hydrogen peroxide can behave both as an oxidising and as a reducing agent.

as an oxidising agent: $H_2O_2 + 2\ H^+ + 2e^- \Longrightarrow 2\ H_2O$ Eo = + 1.763 V at pH 0

$HO_2^- + H_2O + 2e^- \Longrightarrow 3\ OH^-$ Eo = + 0.878 V at pH 14

as a reducing agent: $H_2O_2 \Longrightarrow O_2 + 2\ H^+ + 2e^-$ Eo = - 0.66 V at pH 0

$HO_2^- + OH^- \Longrightarrow O_2 + H_2O + 2e^-$ Eo = + 0.08 V at pH 14

Hydrogen peroxide is used widely as an oxidising and a reducing agent. In these redox reactions hydrogen peroxide is normally degraded. In addition-reactions hydrogen peroxide molecule as a whole is attached to another molecule to form perhydrates (analogous to hydrates e.g. $Na_2CO_3 \cdot 1.5\ H_2O_2$, $(NH_2)_2CO \cdot H_2O_2$). In substitution-reactions the peroxide group is transferred into another molecule and hydrogen atom(s) is substituted (e.g. peroxo compounds). Hydrogen peroxide also forms stable salts with certain cations (e.g. K_2O_2).

Physical and chemical properties are presented in **Table 1.1** and **Table 1.2**.

Table 1.1 Physical and chemical properties of pure hydrogen peroxide (100%) not commercially available in the EU)

Property	Value	Reference
Melting point	-0.40 - 0.43°C	Budavari (1989)
Boiling point	150-152°C decomposition	Budavari (1989)
Density	1.4425 g/cm^3 (25°C)	Schumb et al. (1955)
Vapour pressure	3 hPa (25°C)	Weast and Melvin (1981)
Water solubility	miscible in all proportions	Weast and Melvin (1981)
pK_a	11.62 (25°C)	Weast and Melvin (1981)
Henry's law constant	$7.5 \cdot 10^{-4}$ Pa m^3/mol (20°C) measured	Hwang and Dasgupta (1985)

Table 1.2 Physical and chemical properties of hydrogen peroxide-water solutions

H_2O_2 %	35% w/w	50% w/w	70% w/w	90% w/w	Reference
Melting point	-33°C	-52°C	-40°C	-11°C	ECETOC (1993)
Boiling point	108°C	114°C	125°C	141°C	MCA (1969)
Density (25°C)	1.1282	1.1914	1.2839	1.3867	Goor et al. (1989)
Vapour pressure (partial)	0.48 hPa (30°C)	0.99 hPa (30°C)	2 hPa (30°C)		MCA (1969)
Vapour pressure (total)		24 hPa (30°C)	14.7 hPa (30)°C	6.7 hPa (30°C)	ECETOC (1993)
Saturated vapour concentration at 25 °C (mg/m^3)		787	1,685	3,049	HSDB database
Surface tension mN/m (20 °C)	74.6	75.7	77.3	79.2	Degussa AG (1993)
Viscosity ($1 \cdot 10^{-3}$ kg/ms)	1.11	1.17	1.24	1.26	Degussa AG (1993)

Hydrogen peroxide can decompose explosively. At atmospheric pressure vapours containing 26 mol % or more hydrogen peroxide can be exploded by a spark, by contact with catalytically active materials initially at room temperature, or by "non-catalytic" materials at elevated temperatures. Because of the high relative volatility of water to hydrogen peroxide, the danger of vapour phase explosion on storage of liquid hydrogen peroxide will be encountered only with concentrated solutions above 74% at elevated temperatures (Schumb et al., 1955). At concentrations above 86% wt. the liquid itself can be made to explode (CEFIC, 1998). Hydrogen peroxide (87%) does not however fulfil the criteria for classification as an explosive (Degussa AG, 1977a).

1.4 CLASSIFICATION

1.4.1 Current classification

Classification according to Annex I of Directive 67/548/EEC:

Hydrogen peroxide solution …%

Classification: O; R8
C; R34

Labelling: O; C
R: 8
S: (1/2-)3-28-36/39-45

R8: Contact with combustible material may cause fire
R34: Causes burns
S1/2: Keep locked up and out of the reach of children
S3: Keep in a cool place
S28: After contact with skin, wash immediately with plenty of… (to be specified by the manufacturer)
S36/39: Wear suitable protective clothing and eye/face protection

S45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)

Nota B

Specific concentration limits

C ≥ 20%: C; R34
5% ≤ C < 20%: Xi; R36/38

Footnote

C ≥ 60: O; R8

1.4.2 Proposed classification

The classification and labelling of hydrogen peroxide has been agreed at technical levels (Status 18.11.2002, Rev. 11) to be listed in Annex I to Directive 67/548/EEC following the adoption of the 29th Adaptation to Technical Progress, as follows:

Hydrogen peroxide solution …%

Classification
R5
O; R8
C; R35
Xn; R20/22

Labelling
O; C
R: 5-8-20/22-35
S: (1/2-)17-26-28-36/37/39-45

R5: Heating may cause an explosion
R8: Contact with combustible material may cause fire
R35: Causes severe burns
R20/22: Harmful by inhalation/and if swallowed

S1/2: Keep locked up and out of the reach of children
S17: Keep away from combustible material
S26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
S28: After contact with skin, wash immediately with plenty of… (to be specified by the manufacturer)
S36/37/39: Wear suitable protective clothing, gloves and eye/face protection
S45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible)

Nota B

Specific concentration limits

C ≥ 70%:	C; R20/22-35
50% ≤ C < 70%:	C; R20/22-34
35% ≤ C < 50%:	Xn; R22-37/38-41
8% ≤ C < 35%:	Xn; R22-41
5% ≤ C < 8%:	Xi; R36

Footnote

C ≥ 70%:	R5, O; R8
50% ≤ C < 70%:	O; R8;

R22:	Harmful if swallowed
R34:	Causes burns
R36:	Irritating to eyes
R37/38:	Irritating to respiratory system and skin
R41:	Risk of serious damage to eyes

Environment

No classification.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

There were 22 plants producing hydrogen peroxide in the European Union in 1997 (**Table 2.1**). The total production volume of hydrogen peroxide in Europe has increased rapidly: the production was 600,000 tonnes in 1993, 645,000 tonnes in 1994 (CEFIC, 1996a) and 750,000 tonnes in 1995 calculated as 100% H_2O_2 (CEFIC, 1997c) (percentages referred in Section 2 are weight/weight percentages). One reason for this rapid increase of production has been the replacement of chlorine with hydrogen peroxide in different kinds of application like cellulose pulp bleaching.

Table 2.1 Production sites of H_2O_2 in the EU (CEFIC, 1997c)

Company	Location	
Ausimont	Bussi	Italy
	Bitterfeld (started in 1996)	Germany
Elf Atochem	Jarrie	France
	Leuna (started in 1997)	Germany
Degussa AG	Rheinfelden	Germany
	Antwerp	Belgium
ÖCW Zweigniederlassung der Degussa Austria GmbH	Weissenstein	Austria
EKA Chemicals	Alby	Sweden
	Bohus	Sweden
	Rjukan	Norway
Finnish Peroxides	Kuusankoski	Finland
FMC FORET	La Zaida	Spain
	Delfzijl (started in 1995)	Netherlands
Kemira Chemicals	Oulu	Finland
	Rozenburg	Netherlands
	Helsingborg (started in 1997)	Sweden
Solvay Interox	Bernburg	Germany
	Bad Hönningen (stopped in 1995)	Germany
	Jemeppe	Belgium
	Povoa	Portugal
	Rosignano	Italy
	Torrelavega	Spain
	Warrington	United Kingdom

The production capacity of the 19 plants in 1995 in EU has been presented in **Table 2.2**.

Table 2.2 Production capacity of sites (CEFIC, 1997c)

Production capacity range (tonnes of 100% H_2O_2)	Number of plants
3,000 -15,000	2
15,000 -35,000	4
35,000 -60,000	12
60,000 -85,000	1
85,000 -120,000	2
Total capacity	911,000
Total production	750,000

There are no detailed data on import of hydrogen peroxide to the EU. Five companies have on their HEDSET diskettes informed on import of hydrogen peroxide into the EU, but only two of them have informed on volumes. Volumes range from 1,000 tonnes to 5,000 tonnes per annum. In 1995 about 80,000 tonnes were exported outside Europe (CEFIC, 1997c).

In conclusion, the production volume of hydrogen peroxide which will be used in the exposure assessment in the EU scale is 750,000 tonnes. This is based on the latest information from CEFIC from the year 1995 (19 production plants). After 1995 one production plant has stopped production and four new plants have started. For the overall EU consumption, export will be taken off from the production and since import seems to be negligible compared to export it will not been taken into account. The total consumption volume of hydrogen peroxide in the European market was about 670,000 tonnes in 1995.

The estimated world consumption of hydrogen peroxide in 1989 was 1.023 million t/y (ECETOC, 1993). In 1994 volumes had increased being 1.450 million t/y, distributed between Western Europe 40%, North America 34%, South America 5%, Asia 19% and Africa/Middle East 3% (CEFIC, 1997c). H_2O_2 is produced at approximately 75 production sites worldwide (excluding China), each site having a production capacity in the range of 2,000–90,000 t/y (100% basis) (CEFIC, 1995a). In Western Europe, there are about 30 production sites (CEFIC, 1995a).

The predominant industrial method for manufacturing hydrogen peroxide is by anthraquinone auto-oxidation. Anthraquinone derivate is hydrogenated to corresponding anthrahydroquinone using a palladium or nickel catalyst. H_2O_2 is formed when anthrahydroquinone solution is oxidised back to anthraquinone by bubbling air or oxygen through the solution. Crude H_2O_2 is extracted with water from the organic solution which is returned to the first hydrogenation step producing a cyclic process. The extracted crude aqueous solution contains about 20-40% H_2O_2 and is normally purified in two or three stages by extraction with organic solvent. Finally, the aqueous solution is distilled to give 50-70% H_2O_2 solutions (Goor et al., 1989).

Smaller quantities are produced by older methods using electrolysis of aqueous ammonium sulphate or sulphuric acid solution in water. An organic process based on 2-propanol is in use in the former Soviet Union (Goor et al., 1989).

2.2 USE PATTERN

Hydrogen peroxide is mainly used for pulp bleaching, chemicals manufacture, textile bleaching, environmental applications and miscellaneous (including consumer products) in the European Union.

The largest use (48%) of hydrogen peroxide in Europe in 1995 was bleaching of pulp (mechanical pulps, semi-chemical pulps and chemical pulps) (**Table 2.3**) (CEFIC, 1997c). Hydrogen peroxide has also been used in manufacture of chemicals (38%) like sodium perborate and sodium percarbonate, epoxidised soybean oil, cathecol, hydroquinone, hydrazine, organic peroxides, peracetic acid, caprolactone and fatty amine oxides (for more detailed description, see Section 3.1.1.2). Hydrogen peroxide acts as an oxidiser in these syntheses.

Remaining 15 percent of the total volume consumed in Europe is used for many different applications including textile bleaching, environmental applications (e.g. wastewater, waste gas), metal etching (printed circuit boards*),* sanitisation of chemical instruments and surfaces (surface treatment), metal semiconductor chips manufacturing (cleaning), disinfection of drinking water (food grade), disinfectant in aseptic packaging of juice, milk, etc. (food grade) and bleaching of certain foodstuffs, e.g. tripe and herring (food grade) (CEFIC, 1997c). Applications where consumers may easily be exposed to hydrogen peroxide are hair bleaching, dyeing or fixing of hair perm, household cleaning, tooth bleaching, food processing, disinfection of wounds and mouth and disinfection of eye contact lenses. Also cosmetics, toothpastes and deodorants contain or have contained hydrogen peroxide. Less than 1-4 percent of the production volume is for personal and domestic use (data from producers HEDSETs).

Table 2.3 Usage distribution in EU in 1995 (CEFIC, 1997c)

Use pattern	Volume in 1995 (tonnes as 100% H_2O_2)	Percentage
Pulp bleaching	321,600	48
Chemicals manufacture	254,600	38
Textile bleaching	46,900	7
Miscellaneous	33,500	5
Environment (water treatment)	20,100	3
Total	**670,000**	**101**

Worldwide usage distribution in 1987 was (excluding former USSR and China):

- production of chemicals 39% (of which persalts 22% and others 17%),
- bleaching of pulp and paper 29%,
- bleaching of textiles 19%,
- miscellaneous 13% (including mining metal treatment, environmental and miscellaneous uses) (ECN, 1988).

In the US hydrogen peroxide is also used as a 90% solution in rocket propulsion (MERCK (MRCK online database, available: STN; assessed on Sep. 27, 1996)).

Breakdown/transformation products

The domestic release of H_2O_2 is mainly from the use of sodium perborate (tetrahydrate and monohydrate) and sodium carbonate peroxyhydrate for laundering (ECETOC, 1993). These products as well as peracetic acid, which is used as a disinfectant, will liberate hydrogen peroxide when they are used. In addition the product marketed as "peracetic acid" can contain hydrogen peroxide from less than 5 to 30 percent.

Transport and storage

Hydrogen peroxide is transported in special containers. Large vessels such as road tankers, rail cars and ISO containers, are mostly made from selected grades of stainless steel, although aluminium is also used. The fabrication and surface preparation standards are strictly controlled to prevent hazardous decomposition.

For smaller containers such as drums and Indermediate Bulk Containers (IBCs), specific grades of high-density polyethylene are most commonly used for strengths up to 60% wt. Higher strengths require specific packaging in aluminium or stainless steel.

Handling, packaging, marking and transport conditions are strictly defined by the relevant national and international transport regulations.

The large factory storage tanks of passivated aluminium or stainless steel (volume up to 1,000 m^3) are usually situated outdoors on isolated concrete basin. The tanks are provided with over flow control systems, and tanks meant for high concentrations also with temperature monitoring system. Small leaks are rinsed with water into the drain. The storage tanks are directly connected to processes.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 Environmental releases

Hydrogen peroxide has both natural and anthropogenic sources. Environmental releases from anthropogenic sources may take place during production, formulation, processing and consumer use of products. Natural hydrogen peroxide may be formed by photochemical, chemical or biochemical process.

3.1.1.1 Natural sources

The actual concentration of H_2O_2 in the environment results from a dynamic equilibrium between its production and degradation. Hydrogen peroxide from natural sources is reasonably abundant in the environment. It is produced in photochemical, chemical and biological processes.

In living organisms endogenous H_2O_2 levels can be found in many species. Hydrogen peroxide is normally found in mammalian cells as an endogenous metabolite.

Production of hydrogen peroxide during photosynthesis by photoreduction of oxygen in chloroplasts is natural. For example, H_2O_2 is produced from superoxide in spinach leaf chloroplasts at a rate of 120 μM/s (Xenopoulos and Bird, 1997). Concentrations in plant tissues are relatively high. According to one study, the concentration in tomatoes was 3.1-3.5 ppm, in castor beans 4.7 ppm and potato tubers 7.6 ppm (ECETOC, 1993).

The biological formation of hydrogen peroxide by algae in natural waters has also been studied. Exposure of algae to sunlight results in photogeneration of hydrogen peroxide. This finding indicates that the microbiota contribute to the photoproduction of hydrogen peroxide in natural waters (Zepp et al., 1987).

Atmospheric hydrogen peroxide formation is light dependent and therefore the natural concentrations are latitude dependent if other factors of concern are equal. High solar irradiation leads to high hydrogen peroxide concentrations. Sunlight-induced photochemical reaction rates may fluctuate considerably with respect to time. Natural H_2O_2 in atmosphere is produced through radical reactions. Light, oxygen, hydrocarbons and free radicals in the atmosphere produce hydrogen peroxide.

Superoxide radical $\cdot O_2^-$ is precursor in a H_2O_2 formation reaction:

$$2 \cdot O_2^- + 2\ H^+ \Longrightarrow H_2O_2 + O_2$$

The rate of H_2O_2 formation from O_2^- is of the second order and the rate is also temperature and humidity dependent. Levels of H_2O_2 were raised by 70% when air temperature increased from 10 to 30°C other factors remaining constant (Sakugawa et al., 1990). About twice as much

hydrogen peroxide is formed at 100% relative humidity than at 50% humidity other factors remaining constant (Calvert and Stockwell, 1983).

High concentrations of volatile organic carbon (VOC) compounds increase H_2O_2 concentrations in the air because the degradation processes of VOC compounds, mainly aldehydes, increases the formation of free radicals in the air. Also the photolysis of ozone increases the formation of free radicals (Gunz and Hoffmann, 1990). The H_2O_2 formation may be inhibited by radical scavengers particularly by high levels of SO_2 and NO_x in polluted air (Sakugawa et al., 1990).

In natural waters hydrogen peroxide occurs naturally as a result of dry and wet deposition, photochemical and biological formation or through the oxidation of metals.

Both field and laboratory studies indicate that the major pathway for production of hydrogen peroxide in natural waters is photochemical formation, although it is also introduced to water bodies through rain and biological processes (Cooper et al., 1987; Johnson et al., 1989; Zika et al., 1985; Sturzenegger, 1989).

Rainwater is a remarkable source of hydrogen peroxide in natural waters. Due to high solubility to water atmospheric H_2O_2 will enter the surface water with rainwater. The main input by this wet deposition is normally much higher than dry precipitation by gaseous H_2O_2 (Yoshizumi et al., 1983).

The most essential of the abiotic formation processes of hydrogen peroxide in natural waters are light dependent radical reactions. Photochemical formation of H_2O_2 in natural waters is a process utilising sunlight, light absorbing organic matter and molecular oxygen.

Many of the dissolved organic substances in natural waters absorb sunlight energy in the ultraviolet (UV) region. This results in the formation of exited state (highly energetic) molecules of humic substances (Org*) that transfer their energy to oxygen, resulting in formation of H_2O_2 (Draper and Crosby, 1983; Zika et al., 1985; Sturzenegger, 1989).

$$Org + hv \Longrightarrow Org^*$$

$$Org^* + O_2 \Longrightarrow {}^{\cdot}{}^{\cdot}Org^+ + {}^{\cdot}O_2^-$$

Subsequent disproportionation of ${}^{\cdot}{}^{\cdot}O_2^-$ leads to H_2O_2 formation *via*

$$2\ O_2^- + 2\ H^+ \Longrightarrow H_2O_2 + O_2$$

High-solar radiation intensity enhances peroxide formation, which is consequently higher during the day than at night. The rate at which H_2O_2 accumulates is related to the concentration of light-absorbing (>295 nm) organic substances in these waters. Hydrogen peroxide concentration in natural waters decreases at a nearly exponential rate with depth. In sea water it is usually undetectable below 150 m depth (Johnson et al., 1989; ECETOC, 1993).

In the absence of light, H_2O_2 may by formed in water through the oxidation of iron and copper (Moffett and Zika, 1987). In this mechanism, called Weiss mechanism, reduced metal ions (Fe^{2+}, Cu^+) transfer single electron to molecular oxygen producing superoxide anion intermediate, reacting further to hydrogen peroxide.

3.1.1.2 Anthropogenic sources

3.1.1.2.1 Releases from production

In 1995 hydrogen peroxide was produced in 19 plants, where production volumes ranged from 7,000 to 96,000 tonnes per plant. Total production volume was about 750,000 tonnes. Site-specific data have been provided on production volumes and concentrations in wastewater and is used in the assessment. After 1995 one production plant has been stopped and four new plants have started production (total 22 plants). Site-specific data from these new plants will be used to calculate local exposure. As no site-specific data have been provided on emissions to air or soil, calculations are carried out according to the Technical Guidance Document (TGD) (EC, 1996). The exposure assessment for atmosphere and soil from production (local and regional scales) is based on the highest production volume i.e. 96,000 tonnes H_2O_2 per year.

According to site-specific data from some of the producers, emissions to water during production range from 0.8% to 0.0000003%. ECETOC has estimated that the total loss of H_2O_2 during the production is 0.3% (ECETOC, 1993). This is in good accordance with emission factors from the TGD on new and existing substances (IC 2 Chemical Industry: Basic Chemicals and UC 37: Oxidising Agent), where emissions to water are 0.3%, to air 0.01% and to industrial soil 0.01%. Release estimates to water, air and soil from production are in **Table 3.1**.

3.1.1.2.2 Releases from formulation

Formulation of hydrogen peroxide does occur at each production site, since hydrogen peroxide is a highly reactive substance and stabilisers have to be added. However, since the stabilisers are added in the latest stage in the production process at each and every production plant, there is no need for separate assessment of the exposure from the formulation of the substance by producers. However, dilution is done by importers, distributors or end users. This is because the substance is usually produced as aqueous solutions of 35, 50 or 70 percent, but it is used at concentrations ranging from a few percent to 70 percent. No emissions are expected during dilution.

3.1.1.2.3 Releases from use

<u>Use for bleaching of pulp and deinking of recycled paper</u>

The largest industrial use of hydrogen peroxide in the EU is for bleaching of mechanical and chemical pulp and deinking of recycled paper (48% of the total use). The purpose of bleaching of chemical pulp is to remove remaining lignin and impurities in the pulp and thus obtain certain pulp quality criteria with respect to brightness, brightness stability and cleanness. The bleaching of mechanical pulp aims at changing chromophoric groups in the lignin into a colourless form without causing yield loss. For this reason bleaching processes are somewhat different for mechanical pulp and chemical pulp.

In the bleaching of mechanical pulp either hydrogen peroxide or dithionite (i.e. hydrosulphite) is used. Bleaching is carried out in one or two towers, where the chemical is added. For chemical pulp the most commonly used chemicals are chlorine dioxide, oxygen, ozone and hydrogen peroxide, which are used in several stages (usually four to five) during the bleaching process (Ministry of the Environment, 1997). Bleaching with hydrogen peroxide requires use of metal

chelating agents (EDTA or DTPA) or the removal of metal ions with acid to avoid degradation of hydrogen peroxide during bleaching. The pH is about 11 at the beginning of bleaching and about 10 at the end, the reaction time is about 3 hours and bleaching temperature is usually 70-80°C in both mechanical and chemical pulp (Rasimus, 1998; Interox-a). Bleaching is in general a continuous process.

Usually a 50% solution of hydrogen peroxide is used and the total quantity to be added ranges from 10 to 40 kg H_2O_2 per tonne of pulp (as 100% H_2O_2) (CEFIC, 1997c). According to a customers survey made by CEFIC (1997c) volume used at processing plants ranges from 1,000 to 12,000 t H_2O_2 /a. Concentration of the H_2O_2 in the bleaching tower at the beginning of bleaching ranges from 0.1 g/l to 3 g/l.

There are conflicting data on the consumption rate of the substance during bleaching process. According to Eka Nobel (Eka Nobel, 1990) all of the H_2O_2 is normally consumed during the bleaching of chemical pulp, but with mechanical pulp normally about 75% of the H_2O_2 is consumed. The remaining H_2O_2 (0.1-0.6 g/l or 2-10 kg H_2O_2 per tonne of pulp) is, depending on the process design, partly recycled or diluted into the wastewater system. According to Interox in the bleaching of mechanical pulp under normal circumstances residual is around 10% of the original amount applied. In some plants the H_2O_2 content is not detectable due to reaction with other compounds and decomposition (Eka Nobel, 1990). According to Finnish experts (Rasimus, 1998; Nyman, 1998) almost all of the H_2O_2 is consumed during bleaching of both pulps in Finnish plants, since the water from bleaching is further recycled to previous stages of process. Also SO_2 is added to wastewater from bleaching to eliminate residual H_2O_2.

In the deinking of recycled paper typical dose is 5-25 kg H_2O_2 per tonne of pulp and flotation and/or washing is used (Ministry of the Environment, 1997). Process conditions are alike as with bleaching of mechanical and chemical pulp.

To find out the real emissions and emission factors producers of hydrogen peroxide have conducted a survey on pulp bleaching plants. A total of 29 plants were included in this survey. They represented all types of chemical and mechanical pulping processes as well as deinking. There were 24 plants with activated sludge wastewater treatment and four plants with aerated lagoon. Only one plant has only physical-chemical sewage treatment. Analysis was conducted using the spectrophotometric determination of H_2O_2-titanium complex. Quantification level of the method is 0.1 or 0.2 mg/l depending on the composition of the effluent and on whether ethylacetate extraction was used. Extraction had to be used in the case of highly coloured samples.

The results showed that the majority of hydrogen peroxide is consumed in the bleaching process and as anticipated emission factor according to the TGD highly overestimates the releases. An emission factor of 0.9% could be calculated (90 percentile of results) for bleaching. Concentrations before wastewater treatment varied from < 100 μg/l (quantification limit) up to 8,500 μg/l. Concentrations after activated sludge unit or aerated lagoon were in most cases below quantification limit but there were some plants where H_2O_2 was measured at concentrations 100-200 μg/l. In the one plant where only physical-chemical wastewater treatment exists the concentration in the effluent was significantly higher – ca. 800 μg/l.

Two different estimations are carried out. The first one follows the TGD but takes into account the more realistic degradation rate in the WWTP (99.3%) and the real emission factor (0.9%). The second one is based on the real measured data from the pulp bleaching survey.

Estimation 1 (according to the TGD)

Emissions to wastewater are 0.9% based on the survey. According to the TGD emissions to air are 0.01% and to industrial soil 0.01% of the volume used. Since there are no data on the total number of plants in the EU, 10% of the total continental volume has been used for the regional exposure assessment (32,200 t H_2O_2 /a) and for the local assessment, 10,722 t H_2O_2 /a have been used (calculated according to the TGD). Volume for the local assessment is in accordance with data provided by CEFIC (1997c). In the assessment, wastewater treatment plant (WWTP) of 2,000 m^3/day and degradation of 99.3% in the WWTP are assumed. Local release estimates for use as bleaching agent of pulps are given in **Table 3.1** and the PECs in **Tables 3.11**, **3.13** and **3.16** (Scenario: Processing I). It must be noted that in this scenario the capacity of the WWTP is much lower than in pulp bleaching plants in the reality. Based on the data on 29 plants the average capacity of WWTPs is about 20-times higher than assumed in the TGD. TGD estimation leads to influent concentration to the WWTP which is two orders of magnitude higher than measured concentrations at sites. This scenario is used to assess PECs in air and soil as well as PECregional and PECcontinental in water.

Estimation 2 (based on the measured data)

A maximum concentration of H_2O_2 entering to WWTP is 6,4 mg/l (90 percentile of results). Assuming a removal percentage in the WWTP to be 99.3% in the WWTP effluent concentration would be 0.04 mg/l. A default dilution factor of 10 is used in the PEC estimation and that gives a PEClocal = 0.004 mg/l. When background concentration (PECregional = 0.003 mg/l) is added to this, PEClocal = 0.007 mg/l.

In the following parts of the risk assessment, estimation based on the real measured data (Estimation 2) has been referred to. There are, however, pulp and paper mills where no WWTP exists. In these cases the residual concentrations of hydrogen peroxide in the receiving water might be higher than for the plants without WWTP.

Use for manufacture of other chemicals

The second largest use of hydrogen peroxide in the European Union is in the manufacture of different kinds of chemicals (38% of the total use). Below is a list of chemical syntheses, where H_2O_2 is used (according to Interox-a):

1. Inorganic peroxide derivates: H_2O_2 forms perhydrates and peroxo compounds with alkali metal salts. The best known are sodium perborate and sodium carbonate peroxyhydrate, which are used as detergent raw materials for heavy duty washing powders.

2. Peracid formation: H_2O_2 reacts with many organic acids to form peracids. Best known is peracetic acid, which is used as a bactericide (for example in the food industry) and as a reagent in organic synthesis.

3. Epoxidation: H_2O_2 and peracids react with unsaturated compounds to produce epoxides. Amongst the commercially important products is epoxy soja bean oil, which is used as a stabiliser/plasticiser for PVC. Other products of industrial importance include α-olefin oxides, terpene oxides and talloil.

4. Organic peroxide production: H_2O_2 is used to produce a wide range of organic peroxides, which are used as initiators in the production of polystyrene, PVC, polyethylene and other polymers and curing agents for polyester resins. H_2O_2 is also used in polymer manufacture as a

source of free radicals in emulsion processes for the polymerisation of vinyl chloride, vinyl acetate, methyl methacrylate and many other monomers.

5. Lactone formation: ketones can be oxidised to esters by percarboxylic acids or in some cases by H_2O_2. Cyclic ketones form lactones of which the manufacture of ∈-caprolactone from cyclohexanone is one example.

6. Hydroxylation: by selecting more vigorous reaction conditions than those required for epoxidation, α-olefins and unsaturated oils can be converted to diols with H_2O_2. Hydroxylation of the aromatic nucleus is also possible and is used on an industrial scale to produce hydroquinone and catechol.

7. Organo-sulphur oxidation: reaction of H_2O_2 with organo-sulphur compounds yields disulphides, sulphoxides, sulphones, and sulphenamides. These compounds are important as rubber accelerators, agrochemicals and pharmaceuticals.

8. Organo-nitrogen oxidation: tertiary amines react with H_2O_2 to produce amine oxides, which are used as surfactants in the detergent and the cosmetic industry. Secondary amines give substituted hydroxylamines and primary aromatic amines give nitro compounds.

9. Inorganic chemicals manufacture. H_2O_2 is used mainly in oxidising reactions to produce inorganic chemicals of high purity. These include such diverse products as ferric sulphate, hydrazine, sodium chlorite, potassium hydrogen permonosulphate and arsenic acid.

10. Product purification including bleaching: H_2O_2 is increasingly used to improve the quality of chemical products. Best known is colour improvement (bleaching), but colourless impurities, if oxidisable, can also be removed. Products which may be improved by a H_2O_2 treatment include fatty acids, phthalate esters, sulphonates and sulphuric acids.

11. Other reactions: H_2O_2 has many other applications in organic synthesis including:
- oxidative cleavage of olefins to aldehydes and acids,
- oxidation of aromatic side chains,
- oxidation of polynuclear aromatic hydrocarbons to 1.4-quinone,
- oxidation of aldehydes to various products,
- oxidation of organo-phosphorous compounds,
- bromination to avoid formation of HBr,
- oxidation of iodides to iodoso and iodoxy compounds.

Hydrogen peroxide acts mainly as an oxidising agent in these processes. In different kinds of processes (from open batch applications to closed/automated/continuous indoor plants) concentrations of H_2O_2 are ranging from 21 to 70% and large quantities of H_2O_2 are used (CEFIC, 1997c). In 1995 producers of hydrogen peroxide used almost half of the H_2O_2 volume consumed within this application sector to produce other chemicals. The most important chemicals produced were sodium perborate, sodium percarbonate and peracetic acid. Site-specific data on production volumes of those chemicals have been provided by producers of H_2O_2. Since the size of processing plants is unknown for 52% of the sites, the regional exposure assessment has been carried out with the assumed quantity of 25,500 t H_2O_2/a, which is 10% of the continental volume. For the local assessment 16,500 tonnes H_2O_2/a have been used, since there are several processing plants which use 12,000–16,500 tonnes H_2O_2 to produce other chemicals.

Measured data on emissions from processing plants are available on some production sites. In addition a Swedish producer of organic peroxides reports the H_2O_2 consumption of

300 tonnes/year. 92% of the H_2O_2 used ends up in the product and less than 1% is discharged into the recipient (Eka Nobel, 1990). As no other specific data on emission factors are available, the local worst-case assessment has been carried out according to default emission values of the TGD, i.e. from the volume used 0.7% goes to water, 0.1% to air and 0.01% to industrial soil. In the assessment degradation in the wastewater treatment plant has been assumed but in reality there are plants where no WWTP exists. Local release estimates for use in manufacturing of chemicals are given in **Table 3.1**.

The uses of some chemicals, which are manufactured using hydrogen peroxide, will be covered in some detail in this assessment, as they are a potential source of hydrogen peroxide release through the breakdown of substances. These substances are peracetic acid, sodium perborate (tetrahydrate and monohydrate) and sodium percarbonate, which are used as disinfectants and detergents. In addition products called "peracetic acid" may contain considerable amounts of hydrogen peroxide ranging from less than 5 up to 30%.

Sodium perborate is produced by 7 companies at 12 sites in the EU. According to the risk assessment report by Austria (draft February 2000), production volume in 1997 was 569,600 tonnes.

Sodium perborate degrades to hydrogen peroxide. The total amount of H_2O_2 released from the production and use of sodium perborate is difficult to estimate. ECETOC (1993) has estimated, that the H_2O_2 concentration in the outlet of a washing machine ranges from 0-5 mg/l, assuming 4 kg clothing, 80 l water and 120 g washing powder containing 15% tetrahydrate perborate (with 10% unreacted H_2O_2). In the case of France, with a perborate consumption of 80,000 t/y, the amount of H_2O_2 released would be 1,700 t/y (outlet of a washing machine) (Chemoxal, 1992). After mixing with other domestic wastewater, H_2O_2 concentration is greatly reduced when the wastewater reaches the municipal sewage treatment plant (ECETOC, 1993). However, releases of hydrogen peroxide are possible from the production of sodium perborate.

Peracetic acid is produced/imported by three companies according to IUCLID. The total amount has been 2,000-10,000 tonnes in 1992. There are no data on the amount hydrogen peroxide released through breakdown of peracetic acid. Peracetic acid is used as a biocide and therefore this product will be assessed by Directive 98/8 concerning the placing of biocidal products on the market.

Also sodium percarbonate is produced/imported by three different companies. Total volumes during years 1992 to 1993 have been 12,000 to 60,000 tonnes. The amount of H_2O_2 released from percarbonate has not yet been assessed due to lack of data. Percarbonate is mainly used in detergents. After mixing with other domestic wastewater, the H_2O_2 concentrations greatly reduce when the wastewater reaches the municipal wastewater treatment plant.

Use in textile bleaching

Seven percent of the total volume of the hydrogen peroxide is used for textile bleaching in the textile industry and industrial laundries in the EU. This includes bleaching of vegetable fibres (cotton, linen, hemp, jute), animal fibres (wool, silk), synthetic cellulose fibres (rayon acetate, viscose, Bemberg silk) and mixed fibres (mainly polyacrylic and polyester with animal and vegetable fibres) (Ausimont, 1995). Bleaching of textiles may take place as staple (fibre), yarns or fabrics. According to a customers survey made by CEFIC (1997c), H_2O_2 is used as 35-50% solutions in various types of processes (closed/open, continuous/batch, automated/manual) and the size of the plants vary from 8 to 500 t H_2O_2/a. For the regional exposure assessment 10% of the continental volume has been used (4,690 t/a) and for the local assessment 500 t/a have been

used. A Swedish textile mill, which uses about 40 tonnes H_2O_2 /year reports that 12-15% of the added H_2O_2 is not consumed in the bleaching stage. Most of this quantity is decomposed in the mixed wastewater from the mill, which is alkaline before the final neutralisation (Eka Nobel, 1990). Since specific data on emission factors are missing, the assessment has been carried out according to default values in the TGD but the measured data from bleaching of pulp may be used to estimate the emissions to wastewater. Thus, an emission factor of 0.9% is used for textile bleaching. Emissions according to the TGD are 1% to air and to industrial soil 0.2% of the volume used. Local release estimates for the use in textile bleaching are given in **Table 3.1**.

More recently, new liquid bleaching formulations containing diluted hydrogen peroxide have been developed in Europe, the United States and Japan (data from Ausimont, 1995). These new products are recommended in every day housekeeping as bleaching additives to be used in washing machine, as direct stain removers for fabrics and also as sanitising products for hard surface cleaning (ceramics, bathroom, floor etc.). General concentration of the hydrogen peroxide (100%) in the product is 3-8 percent.

Use for environmental applications

Three percent of the total consumption of the substance is used for environmental applications. This includes for example hydrogen sulphide (H_2S) control. H_2S can be developed in anaerobic conditions when sewage is pumped over long distances. Injection of hydrogen peroxide into the sewer can both eliminate any sulphide already formed and also maintain aerobic conditions, thus preventing further sulphide formation (Interox-b). Sludge and leachate from municipal and industrial refuse tips may also be treated similarly with H_2O_2. Another application of hydrogen peroxide is the purification and detoxification of pollutants such as cyanides, phenols, nitrites and sulphides in the wastewater. Hydrogen peroxide is also used as a source of oxygen in the biological wastewater treatment plant, particularly at times of overload, and for the prevention of denitrification in settling tanks (Interox–b). Two plants with this kind of use of hydrogen peroxide were included in the recent survey on pulp bleaching. The concentrations entering WWTP was as high as 48 mg/l. When a degradation of 99.3% is assumed at the WWTP and a dilution with a default value of 10, the PEC in the local environment could be about 34 µg/l. However, in cases of lack of oxygen available for the microorganisms, H_2O_2 will be used as an oxygen source and will be consumed totally. Hence no emissions are expected.

During recent years, *in situ* bio-reclamation of contaminated soils has been developed. This consists of injection into the ground of microorganisms, nutrients and H_2O_2 which acts as a source of oxygen (Interox-b). Hydrogen peroxide can be used as a cleaning agent of toxic odorous components of waste gases like nitrogen, sulphur and mercaptans. These substances in waste gases can be removed by oxidation with H_2O_2 after their absorption in an aqueous scrubbing liquor.

Detailed information on other processes than the use of H_2O_2 as an oxygen source at WWTP has not been made available by the producers. Concentration of the substance for these other uses has been ≤ 35% and volumes range 10-100(0) t/a (CEFIC, 1997c). For the regional exposure assessment 10% of the continental volume has been used (2,010 t H_2O_2 /a) and for the local assessment 4 t H_2O_2/a has been used (calculated according to the TGD). Since the number of processing plants is unknown and specific data on emission factors are missing, the assessment has been carried out according to default values in the TGD. It is recognised that the emission factors according to the TGD are not quite applicable for this use, but since no data are available on actual emissions, these default values have been used. Local release estimates for use in environmental applications are given in **Table 3.1**.

Miscellaneous uses

Five percent of the total use of hydrogen peroxide (i.e. 33,500 tonnes/a) is used for miscellaneous purposes. This may include use in:

- electric/electronic industry: etching of printed circuit boards and in other cleaning and etching processes,
- metal industry,
- metallurgy: hydrogen peroxide will firstly be converted to Caro's Acid (H_2SO_5) and then used in the separation of cobalt from nickel or from wastewater, the separation of manganese from cobalt and zinc or in the production of drinking water, the reduction of Co and Mn from higher valency states, the oxidation of Mo, V, Cr, Fe, As ions etc.,
- starch modification: to reduce its viscosity in solution can be achieved by oxidation with H_2O_2. This is done especially for the paper industry to produce the desired starch,
- laboratories,
- wood bleaching (one case): about 600 t/y of 35% H_2O_2 diluted down to 4%,
- food (processing) industry: disinfectant in packaging of juice, yoghurt etc. and bleaching of certain foodstuffs. A potential source of H_2O_2 is from drinking water which has been treated with ozone and UV radiation (ECETOC, 1993). The authorised residual concentration of H_2O_2 in potable water is 0.1 mg/l in the USSR and Germany and 0.5 mg/l in France (ECETOC, 1993) (Original reports have not been provided: Antonova, 1974; Bundesminister, 1990; Ministère de la Solidarité, de la Santé et de la Protection Sociale, 1990).

No emission estimation has been carried out for these applications, since no data on quantities are available. Hydrogen peroxide is also used as a biocide (e.g. to prevent bulking of sludge caused by proliferation of filamentous microorganisms) but these uses are beyond the scope of this assessment. Scenarios for consumer use are presented below.

Nuclear power plant cooling water contains traces of H_2O_2 formed by radiochemical processes (ECETOC, 1993) (Original reports have not been provided: Giguire, 1975; IARC, 1985).

Emissions to the environment may occur from the following consumer uses:

- hair bleaching or dyeing or fixing of hair perm,
- household cleaning agents,
- tooth bleaching,
- food processing aids.

Consumption volumes have been calculated as follows:
670,000 t/a · 1% = 6,700 t/a (continental)
6,700 t/a · 10% = 670 t/a (regional)
Local release estimates for the use in consumer products are given in **Table 3.2**.

Emissions from minor uses like disinfection of wounds, mouth and eye contact lenses have not been estimated.

3.1.1.2.4 Calculation of emissions

Some site-specific data are available on all production plants and will be used to calculate PEClocal. Emission volumes to wastewater could be calculated for 18 plants. These plants represent 83% of the total production volume in Europe. For water continental emission can be calculated to be about 4,294 kg/day. However, since many production plants also process

hydrogen peroxide and since effluent from production and processing cannot be separated, the above mentioned emission also includes emissions from processing. Generic exposure assessment has been carried out for nine different scenarios. The emission factors in most cases are default values from the TGD, but specific data are used whenever it has been possible (e.g. emission factors to wastewater for bleaching of pulp and textiles).

Scenarios

Production
Processing I: use in bleaching of pulp and paper
Processing II: use in manufacture of other chemicals i.e. use in synthesis
Processing III: use in textile bleaching (industrial and private)
Processing IV: use in environmental applications (industrial use only)
Consumer use I: hair bleaching or dyeing
Consumer use II: household cleaning agents
Consumer use III: tooth bleaching
Consumer use IV: food processing aids

Table 3.1 Local releases from production and processing

	Production	**Processing I**	**Processing II**	**Processing III**	**Processing IV**
Tonnage per year (regional)	96,000	32,200	25, 500	4,690	2,010
Industrial category	2: Chemical industry: Basic chemicals	12: Pulp, paper and board industry	3: Chemical industry: Chemicals used in synthesis	13: Textile processing industry	IC 6: Public domain
Use category	UC 37: Oxidising agent	UC 8: Bleaching agent	UC 37: Oxidising agent	UC 8: Bleaching agent	UC 39: Biocides, non-agricultural
Main category	Ib contin. production	III Non-dispersive use	III Non-dispersive use	III Non-dispersive use	III Non-dispersive use
Fraction of main local source	(specific data) 1	(Table B 3.10) 0.333	(specific data) 0.647	(specific data) 0.11	(Table B3.3) 0.002
Number of days	(Table B 1.5) 300	(Table B 3.10) 300	(Table B3.3) 300	(Table B 3.12) 300	(Table B 3.3) 15
Release estimates - air - wastewater - industrial soil	(Table A 1.1) 0.0001 0.003 0.0001	(Table A 3.12) specific scen. 0.0001 0.009 0.0001	(Table A3.3) 0.001 0.007 0.0001	(Table A 3.14) 0.01 0.009 0.002	(Table A 3.5) specific comb. 0.1 0.05 0.8
Local emission amount (kg/d) - air - wastewater	 32 960	 3.57 321	 5.49 384	 17.2 15.5	 0 13.4

Table 3.2 Local releases from consumer use

	Consumer use I	Consumer use II	Consumer use III	Consumer use IV
Tonnage (regional)	670	670	670	670
Industrial category Use category	5: Personal/ domestic use UC 8: Bleaching agent	5: Personal/ domestic use UC 9: Cleaning and washing agents	5: Personal/ domestic use UC 41: Pharmaceuticals	15: Others UC 26: Food/ feedstuff additives
Fraction of main local source	0.002	0.002	0.002	$8 \cdot 10^{-7}$
Number of days	365	365	365	300
Release estimates -air -wastewater -soil	Specific scenario 0 0.80 0.001	Specific scenario 0 0.99 0.01	Specific scenario 0 0.05 0	No applicable data found from EUSES
Local emission amount (kg/d) - air - wastewater	 0 2.94	 0 3.63	 0 0.184	 - -

Regional and continental releases have been calculated with EUSES and are given in **Table 3.3**.

Table 3.3 Total regional and continental emissions to environmental compartments

	Regional emissions (kg/d)	Continental emissions (kg/d)
Air	721	6,430
Wastewater	4,090	35,600
Surface water	1,750	15,200
Industrial soil	4,490	40,400
Agricultural soil	0	0

3.1.2 Environmental fate

3.1.2.1 Distribution

Partitioning between air and water: Henry's law constant

The measured values for Henry's law constant at 4 different temperatures at equilibrium gas-phase concentrations of H_2O_2 (0.05-0.15 M) are presented in **Table 3.4** (Hwang and Dasgupta, 1985).

Table 3.4 Henry's law constant (Hwang and Dasgupta, 1985)

Temp. (°C)	H (M/atm)	H (atm · m³/mol)	H (Pa · m³/mol)	log H(Pa · m³/mol)
3	$5.08 \cdot 10^{5}$	$1.97 \cdot 10^{-9}$	$2.0 \cdot 10^{-4}$	- 3.7
10	$2.92 \cdot 10^{5}$	$3.43 \cdot 10^{-9}$	$3.4 \cdot 10^{-4}$	- 3.5
20	$1.35 \cdot 10^{5}$	$7.40 \cdot 10^{-9}$	$7.5 \cdot 10^{-4}$	- 3.1
30	$3.76 \cdot 10^{4}$	$26.6 \cdot 10^{-9}$	$27 \cdot 10^{-4}$	- 2.6

The Henry´s law constant of H_2O_2 was also experimentally determined to be $1.42 \cdot 10^{5}$ M/atm ($7 \cdot 10^{-9}$ atm·m^3/mol = $7.1 \cdot 10^{-4}$ Pa·m^3/mol) at 20°C at ambient concentration levels of H_2O_2 (Yoshizumi, 1983). This method was also applied to the measurement of H_2O_2 concentration in rainwater in Tokyo, Japan, which was in the range of 5-1,065 µg/l (Yoshizumi et al., 1983). Values above are comparable to $1.0 \cdot 10^{5}$ M/atm at 25°C derived from the thermodynamic data on the heat of solution of H_2O_2 (Martin and Damschen, 1981) and $7 \cdot 10^{4}$ M/atm at 25°C derived from the H_2O_2 vapour pressure data (Middleton et al., 1980).

The values of Henry's law constant appear to be reliable and data on the test methods are available. The Henry's law constant of H = 7.5·10-4 Pa·m^3/mol (logH = -3.13) at 20°C measured by Hwang and Dasgupta (1985) will be chosen to be used in the assessment. This value indicates, that volatilisation of hydrogen peroxide from water is very low.

Equilibrium partitioning

An equilibrium partitioning can be calculated according to the Mackay Model I at 20°C, with a vapour pressure of 3 hPa and using measured Henry's law constant H = $7 \cdot 10^{-4}$ Pa·m^3/mol at 20°C (**Table 3.5**).

Table 3.5 Mackay Model I equilibrium partitioning

Compartment	Distribution %
Air	$0.3 \cdot 10^{-3}$
Water	99.98
Soil	0.01
Sediment	0.01

log K_{ow}

Partition coefficient n-octanol/water is a parameter that is not particularly important for highly hydrophilic reactive inorganic chemicals such as the hydrogen peroxide. No experimental results were located concerning log K_{ow} of hydrogen peroxide. Based on fragment structure analyses, the log K_{ow} can be estimated to be about -1.5 (Degussa AG, 1998). Using the LOGKOW program (Meylan and Howard, 1995) results in -1.57.

Adsorption

No experimental results were located concerning adsorption and desorption behaviour of H_2O_2. Being highly soluble in water (in all proportions) and highly polar substance, no remarkable adsorption to soil and sediment is expected (**Table 3.5**) and the mobility in soil is expected to be

high. Mackay Model 1 calculation results support this approximation. Using QSAR K_{oc} may be calculated: $\log K_{oc} = 0.52 \cdot \log K_{ow} + 1.02 = 0.2$ (TGD, QSAR for nonhydrophobics).

3.1.2.2 Degradation

Hydrogen peroxide is a quite reactive substance in the presence of other substances, elements, radiation, materials or cells. Both biotic and abiotic degradation processes are important routes in the removal of hydrogen peroxide in the environment.

Biological degradation of hydrogen peroxide is an enzyme-mediated process. Abiotic degradation of H_2O_2 is due to reaction with itself (disproportionation), reaction with transition metals, organic compounds capable to react with H_2O_2, reaction with free radicals, heat or light.

Hydrogen peroxide is normally a short-lived substance in the environment. Rapid degradation will occur due to many alternative and competitive degradation pathways. However, like most substances, in special circumstances when degradation processes are inactive, hydrogen peroxide can be an extremely persistent substance in the environment.

3.1.2.2.1 Abiotic degradation

Catalytic and reactive decomposition

Hydrogen peroxide decomposes into water and oxygen at rates which depend on contact with catalytic materials (metals, activated carbon, enzymes) and other factors (heat, sunlight) (Degussa AG, 1977a).

$$H_2O_2 \Longrightarrow H_2O + 1/2\ O_2 \qquad H = -98.30\ kJ/mol$$

This reaction is highly exothermic and takes place in the presence of small amounts of catalyst even in aqueous solution. In the absence of catalyst, it occurs only in the gas phase at high temperature (Goor et al., 1989).

Many materials and substances have a catalytic action on degradation of H_2O_2. Most transition metals and heavy metals can induce H_2O_2 decomposition. The range of decomposition rates is large because of the varying catalytic efficiency. With the exception of fluorine, also the halogens catalyse the decomposition of hydrogen peroxide by cyclic oxidation-reduction mechanism (Schumb et al., 1955).

Stability in water

Pure aqueous solutions of hydrogen peroxide are relatively stable. Stability increases with increasing concentration. Stability of pure hydrogen peroxide in pure water is pH dependent. Decomposition is acid and alkali induced. Stability is at a maximum at pH 3.5-4.5 and decomposition rates are highest in alkaline solution.

Degradation in the aquatic environment takes place in the presence of a catalyst. Most transition metals, and especially Fe, Mn and Cu may have significant influence on degradation rates of hydrogen peroxide in natural waters.

Degradation rates in filtered natural waters have been studied. Filtering natural water samples do in some extent allow to differentiate between biodegradation and abiotic elimination processes.

In filtered (0.45 µm) Greifensee water 0.5 µM initial concentration degraded at rate of t½ = 25-100 hours. Greifensee is an eutrophic lake in Switzerland (DOC 4-5 mg/l, nitrate 1.5 mg/l, Fe = 20 µg/l, Mn = 10 µg/l) (Sturzenegger, 1989).

The half-life of H_2O_2 in sea water samples from the Bay of Biscayne (filtered 0.2 µm, initial concentration 3.4 µg/l) was 60 hours (Petasne and Zika, 1987). The half-life of H_2O_2 in sea water samples from the Mediterranean shallow lagoon Etang de Tau (filtered 0.2 µm) was 50-70 hours ($k_{0.2}$= 0.013-0.010 h^{-1}) (Herrmann and Herrmann, 1994).

Reactivity of hydrogen peroxide with organic chemicals

Hydrogen peroxide may react as an oxidant, as a reductant or form addition compounds. Hydrogen peroxide does react easily with various functional groups. Most aromatic and aliphatic amines as well as most aldehydes do react with hydrogen peroxide. Hydrogen peroxide reacts with many organic acids to form peracids (of which peracetic acid is the best known and produced as an industrial chemical). Peracid formation in the aquatic environment is an equilibrium reaction. Peracids react easily with other oxidisable substances.

Typical hydrogen peroxide addition compounds are organic and inorganic peroxo compounds, epoxides. Epoxides are formed when hydrogen peroxide (and peracids) reacts with olefinic double bonds.

On the other hand as an example of non-reactive compounds, saturated alkanes, benzene, toluene and ethanol do not react with H_2O_2 (at NTP) even in concentrated solutions. A catalyst is needed to achieve a reaction between these common substances and hydrogen peroxide.

An important and powerful free radical reaction is the reaction of ferrous iron with hydrogen peroxide to produce Fenton's reagent. Fenton's reagent produces hydroxyl radicals in the aquatic environment with the ability to oxidise a variety of organic compounds. The potential for oxidation/degradation of compounds is much higher with Fenton's reagent than with hydrogen peroxide alone.

An illustrative test of the degradation potential of hydrogen peroxide and Fenton's reagent on tertiary ethers was done by Yeh and Novak (1995). Their test solution system contained distilled water, methyl-tert-buthyl ether (MTBE) and ethyl-tert-buthyl ether (ETBE) (80-90 mg/l each) and H_2O_2 (100 mg/l). No degradation of any of the chemicals was observed during 50 days. This indicates that H_2O_2 is not capable to react with these tertiary ethers at normal room temperatures.

A second set of experiments used solutions containing ferrous iron to produce Fenton's reagent. Oxidation of MTBE and ETBE in the presence of Fe(II) was very fast. The reaction was completed in a few minutes. Although the chemical oxidation was rapid, the oxidation of MTBE and ETBE occurred only after the first dose of H_2O_2 due to oxidation and precipitation of iron (III). Iron (II) was no longer present and capable of catalysing the formation of Fenton's reagent. Tert-butanol (TBA), acetone, and several other unidentified reaction products were observed on gas chromatograms.

Photolysis in air

Hydrogen peroxide absorbs radiation over a wide continuous spectrum 280-380 nm. It has absorption bands also in higher wave lengths (visible and infrared) but is not decomposed by exposure to light of wave length greater than about 380 nm (Schumb et al., 1955).

Direct photolysis reaction: $H_2O_2 \text{----}^{hv}\text{---> } 2\ OH^{\cdot}$

The rate for the direct photolysis of hydrogen peroxide is expected to be relatively slow and the importance of this process in determining the hydrogen peroxide levels is expected to be minor (Sakugawa et al., 1990). Direct photolysis of hydrogen peroxide is however estimated to form 10% of the total $OH^{\cdot}$-radical daytime concentration (Lu and Khalil, 1991). Kleinman estimated direct photolysis half-life of 2.14 days (a lifetime of 3.1 days) (Kleinman, 1986).

Degradation by indirect photolysis is expected to be the degradation mechanism in the air. Besides the direct photolysis, the photodegradation may also follow an indirect photolysis by sensitisation by secondary reactions with OH- and O_2-radicals and organic substances. The most important degradation reaction is the reaction with hydroxyl-radical:

$$H_2O_2 + OH^{\cdot} \Longrightarrow H_2O + HO_2^{\cdot}$$

The formation of organic hydroperoxides (R-OOH) appears to be a pathway for the decomposition of H_2O_2 in the atmosphere (IUCLID data Degussa AG). However, the measured levels of (R-OOH) have been reasonably low compared to ambient air concentrations of hydrogen peroxide.

Gas-phase, cloud and rainwater measurements of hydrogen peroxide at a high-elevation site, Whitetop Mountain (1,689 m), exhibited a slight diurnal variation with daytime values exceeding night time levels by 26% (Olszyna et al., 1988).

In polluted urban air half-lives of few hours have been reported (Sakugawa et al., 1990).

No clear figures of overall photolysis rates have been presented in the literature. A study done by Olzyna in Whitetop Mountain indicates that in unpolluted air at night time (during 8-10 hours) indirect photolytic degradation decreases H_2O_2 levels by about 25% and consequently 50% decrease would take 16-20 hours (it is assumed that the night time production rate of H_2O_2 is low or negligible). In polluted air diurnal variations in concentrations seem to be more or less larger than in unpolluted air.

Conclusion

According to the existing test data from different atmospheric conditions (Olszyna, 1988; Sakugawa et al., 1990; Kleinman 1986) a half-life of 24 hours will be chosen to represent the average degradation half-life in the atmosphere.

Photolysis in water

Direct photolysis is not expected to be an important degradation process in the aquatic environment. Hydrogen peroxide has absorption bands in the infrared, but is not decomposed by the light of these frequencies. The UV absorption spectrum is a continuous spectrum but the measured molar extinction coefficient values are low. Highest value is $\in$ = 4.2 l/mole·cm (at 280 nm) decreasing continuously to 0.22 l/mole·cm (at 320 nm) and 0.00066 l/mole·cm (at 400 nm) (Schumb et al., 1955).

3.1.2.2.2 Biodegradation

Hydrogen peroxide is biologically degradable. Aerobic bacteria produce catalase enzymes that converts H_2O_2 to water and oxygen. Catalase is present in most aerobic bacteria and therefore biological degradation starts readily when H_2O_2 is in contact with microbial material (no remarkable lag-phase). There are no results available from standard test systems. Standard ready biodegradation tests are not directly suitable for hydrogen peroxide because they are designed for organic substances.

It has been shown, that the size of the microbial population in water has a crucial effect on the degradation rate. Therefore the half-life is between minutes and hours in municipal wastewater ($> 10^6$ cells/ml) and only a few seconds in sludge (10^8-10^{10} cells/ml). In natural waters ($\leq 10^3$ cells/ml) the biodegradation haf-life is from hours to a few days. Degradation kinetics is generally assumed to be of first order with respect to H_2O_2 at low concentrations (Barenschee 1990; Spain et al., 1989; Zepp et al.; 1987; Cooper et al., 1990) and not of first order at higher concentrations (hundreds of micrograms or more in surface water) leading to longer half-lives as initial concentrations increase (Cooper et al., 1990).

Screening tests in water

Spain et al. (1989) screened degradation rates of H_2O_2 in water. A decomposition rate of 0.6 /hour with a bacteria number of (CFU/ml) $0.6 \cdot 10^6$ was obtained with non-adapted inoculum. Adapted microbial population degraded H_2O_2 with a rate of 7.0 /hour with bacteria number of (CFU/ml) $3.4 \cdot 10^7$. Hydrogen peroxide concentrations tested were tens to hundreds mg/l. The degradation of hydrogen peroxide in these tests was monitored by short-interval sampling and peroxide analysis.

Sterilisation, either by autoclaving or by $HgCl_2$ addition reduced active bacterial populations and H_2O_2 decomposition rates to undetectable levels. The dramatic reduction in decomposition rates indicates that most of the decomposition was biologically mediated. No attempt was made to identify the bacteria, but on agar plates, virtually all of the bacteria were catalase positive (released gas when the plate was flooded with 1% H_2O_2) (Spain et al., 1989).

In comparison with standard tests, the bacterial density (non-adapted) in standard ready biodegradation tests (OECD Test Guidelines 301A-E) is between $0.01\text{-}1 \cdot 10^6$ colony forming unit per ml (CFU/ml). River water from polluted areas may have a high total cell count of about $5 \cdot 10^6$ CFU/ml (Balk and Block, 1994).

Degradation in STP

The degradation of hydrogen peroxide was studied recently in an activated sludge respiration test (Groeneveld and de Groot, 1999). The test was conducted according to OECD Guideline 209 and according to GLP. Nominal concentrations used were 1, 3, 10, 30, 100, 300 and 1,000 mg/l. In this study the half-life of hydrogen peroxide was less that 2 minutes at all nominal initial concentrations.

The above mentioned result is comparable to the data reported in the risk assessment report on sodium perborate (Austria, draft February 2000) in which half-lives were 0.5-1 min and 0.5-8.2 min in activated sludge and raw wastewater, respectively.

There are data on one industrial STP plant of a H_2O_2 production site. Data showed a 97% reduction of hydrogen peroxide. Measured influent concentration was 62 mg/l and effluent

concentration ≤ 2 mg/l (detection limit). Detailed information on the STP was not available (non published data).

In a laboratory-scale industrial STP study by Larish and Duff (1997), several methods of gauging activated sludge reactor acclimation to hydrogen peroxide were performed. In the test increasing concentrations (5–1,000 mg/l influent) of hydrogen peroxide were continually added to a reactor treating combined TCF (Total Chlorine Free)-bleached kraft mill effluent. Treatment efficiency, as measured by removal of BOD, chemical oxygen demand (COD) and toxicity, was found to be unaffected by hydrogen peroxide concentrations of up to 1,000 mg/l.

The ability of activated sludge to tolerate sudden increases in hydrogen peroxide concentration was determined in determining the viability of the sludge by measuring its oxygen uptake rate (OUR). OUR of unacclimated activated sludge was inhibited by sudden exposure to shock doses of hydrogen peroxide. The effect was reversible, with full recovery of metabolic activity restored within approximately 10 hours of exposure to the initial shock dose of 960 mg/l. OUR was decreased by about 25% with 100 mg/l load, about 50% with 320 mg/l load, and about 70% with 960 mg/l load.

Activated sludge which had been acclimated to hydrogen peroxide in the reactor feed was more resistant to hydrogen peroxide shock loading. Sludge acclimated to 500 mg/l hydrogen peroxide had about 20% OUR decrease with 320 mg/l shock load.

The rate of hydrogen peroxide reduction in effluent appears to be inversely related to the initial concentration of the substance. First order rate constants varied in this study from about 0.05 to 0.15 min^{-1} with 200 mg/l load. Autoclaved sludge yielded negligible rates of peroxide degradation over a 12-hour period, implying that viable microorganisms are required to maintain demonstrable rates of hydrogen peroxide degradation in STP.

Based on this test it can be concluded that activated sludge is able to treat bleached kraft mill effluent which contains high concentrations of hydrogen peroxide (Larish and Duff, 1997).

Simulation tests

The biodegradation rates of hydrogen peroxide have also been investigated in natural waters. Cooper and Lean (1989) studied the summer time degradation rate of hydrogen peroxide in lake water (Jacks Lake, Ontario, oligotrophic lake, pH 7.2, Ca^{2+}/l = 14 mg, phosphorus mean 12 µg/l surface water, DOC 6 mg/l, site location 44° 41′ N, 78° 02′ W). The initial low natural concentration of hydrogen peroxide was 3.4 µg/l. Dark decay of hydrogen peroxide followed apparently first order kinetics. The half-life of H_2O_2 was:

7.8 h	(unfiltered lake water)
8.6 h	(filtered, 5 µm)
31 h	(filtered, 1 µm)
>24 h	(filtered, 0.45 µm)

These results indicate that the fraction containing picoplancton (defined as 0.2-2 µm) contains the major proportion of the biological agent responsible for the degradation of H_2O_2. The fraction < 1 µm contained roughly 90% of the bacterial and < 5% of the phytoplancton biomass (Cooper and Lean, 1988b).

Hydrogen peroxide decay rate was measured in Lake Ontario by Cooper et al. (1989). Half-lives between 14.7 and 21.6 hours were measured (depths 0 and 10 m, and initial concentrations 112 and 44 nM, respectively). When samples were filtered through 0.45 µm membrane filters H_2O_2

concentrations did not change over 7-hour periods. This indicates that bacteria and/or algae are the major agents for the decline in H_2O_2 concentration.

Johnson et al. (1989) measured the dark decay time of hydrogen peroxide in sea water at room temperature. The initial concentrations in surface water samples were 90-150 nmol/l (3-5 µg/l) and with a measured degradation rate of 3.8 nmol/l/h (0.13 µg/l), hydrogen peroxide concentrations reached zero after 23-39 hours.

Laboratory studies on water from the River Saone showed that H_2O_2 degradation kinetics was of a first order and that half-lives were dependent on the initial H_2O_2 concentrations (**Table 3.6**). Filtering out particles over 0.2 µm had little effect. Similar studies with de-ionised water containing 500 mg/l H_2O_2 showed an increase in concentration, probably due to the influence of daylight. The decay of H_2O_2 appeared to be slower at initial concentrations < 500 mg/l (L'Air Liquide, 1991; cited in CEFIC, 1997c).

Table 3.6 Degradation of H_2O_2 in water of the River Saone

Initial concentration (mg/l)	Half-life (days)
10,000	2.5
1,000	8.1
500	8.2 ± 2 (higher values for filtered samples)
250	15.2 ± 2,5 (higher values for filtered samples)
100	20.1

Conclusion

On the basis of the available biodegradation tests it is possible to conclude that the substance is biodegraded under environmental conditions. The observed biodegradation rates of hydrogen peroxide are high and half-lives are short enough to fulfil the criterion “readily biodegradable” (10-day window criterion fulfilled) concerning the degradation rate. Hydrogen peroxide can therefore be considered as readily biodegradable in the aquatic compartment including sewage treatment plant.

The simulation test results show that in most cases biodegradation seems to be the dominant and rate determining degradation pathway of hydrogen peroxide in the aquatic environment. The rate of biodegradation is proportional to the microbial population density and the concentration of hydrogen peroxide. Typical natural concentrations of hydrogen peroxide in freshwater and sea are from a few micrograms to some tens of micrograms per litre. Degradation half-lives observed are typically of the order of some hours. The microorganism/hydrogen peroxide ratio is high and degradation is favoured because there is a substantially large amount of catalase active microbes present compared to the concentration of hydrogen peroxide.

If the concentration of hydrogen peroxide is remarkably higher than natural concentrations, other factors remaining constant, the inhibitive effect of hydrogen peroxide on naturally occurring microbes is beginning to have more influence thus giving longer half-lives. In extreme cases the toxicity of hydrogen peroxide will slower the degradation process remarkably (test by L'Air Liquide, 1991).

Shortest half-lives << 1d can be found in surface waters of eutrophic lakes. These tests are carried out in summer time in warm surface waters and do not represent very well average degradation rates in natural waters of more unfavourable conditions and seasons. Half-lives of 1-3 days may represent quite well annual average degradation rate in mesotrophic/oligotrophic surface waters with low microbial density. Longest half-lives can be found in oligotrophic cold waters with low microbial density and low transition metal concentrations (Fe/Mn). A half-life of 5 days in surface water has been estimated to represent realistic (worst case) half-life in surface water.

As a conclusion half-lives of 2 minutes and 5 days in STP and in surface water, respectively, will be used in the risk assessment (**Table 3.7**).

Table 3.7 Estimated degradation rates of H_2O_2 in aquatic compartment

Test result	Rate constant k	Half-life
Wastewater treatment plant (STP)	21 (h^{-1})	2 minutes
Surface water	0.139 (d^{-1})	5 days

Elimination in sewage treatment plants (STPs)

Based on the physical chemical properties log H = -3; log P_{ow} < 0, and the biodegradation rate of 21 h^{-1} (half-life 2 min) in a STP, the elimination through biodegradation and distribution can be estimated with the model Simpletreat (**Table 3.8**).

Table 3.8 Estimation of removal of H_2O_2 in STPs according to Simpletreat

Removal of H_2O_2	
% to air	0
% to water	0.7
% to sludge	0
% degraded	99.3
% total removal in STP	99.3

Treatment systems other than Sewage Treatment Plants will be considered case by case in site-specific estimations. Degradation efficiency of catalytic or chemical treatment may be as good or even better than in STP.

Degradation in soil

In soil H_2O_2 is normally a short-lived substance. Rapid degradation will occur due to high concentration of catalytic material like transition metals, enzymes, easily oxidised/reduced organic substances and living microbes (Spain et al., 1989).

Hydrogen peroxide is used as a source of oxygen (for aerobic microbes) in polluted groundwater sites (enhanced bioremediation). Therefore specific information on degradability in soil is available. The problem in these applications where hydrogen peroxide is introduced directly into

the ground is linked to a too rapid degradation. Observed half-lives of H_2O_2 in soil vary from 15 hours (soil without microbiological activity and few minerals) to several minutes (soils with 10^8-10^9 cells/g total solids, and in the presence of iron and manganese (Aggarwal et al., 1991; ECETOC 1993; Hinchee and Downey 1988; Pardieck et al., 1992).

In the assessment it is estimated that the degradation half-life in soil is 12 hours.

Degradation in sediment

For sediment, there are no results from standardised biodegradation systems available. No remarkable adsorption of hydrogen peroxide to sediment is expected and it may also be assumed that the adsorbed portion of hydrogen peroxide may still be effectively degraded because normally sediments contain a lot of catalytical abiotic and biotic material capable to degrade hydrogen peroxide. Rapid degradation is expected.

3.1.2.2.3 Conclusion on degradability

As a conclusion half-lives presented in **Table 3.9** will be used in the assessment. Degradation rates in STP and surface water are taken from specific studies and the rate constant values are higher than presented in the TGD leading to shorter degradation half-lives.

Table 3.9 Degradation half-lives in different compartments

Compartment / medium	Degradation half-lives
Air	24 hours
STP	2 minutes
Surface water	5 days
Soil	12 hours

Rapid degradation - as well as poor adsorption - in the sediment is expected and therefore a risk assessment for sediment compartment is not conducted.

3.1.2.3 Accumulation

There are no experimental results on bioaccumulation available. Hydrogen peroxide is reactive and short-lived polar substance and no bioaccumulation is expected. Also the estimated log K_{ow} of about -1.5 indicates negligible potential of bioconcentration in aquatic organisms. BCFs calculated according to the TGD for fish and earthworm are low, 1.4 and 3.3, respectively.

3.1.3 Aquatic compartment

Since there is no guidance on how to deal with substances that occur naturally in the environment such as hydrogen peroxide, the added risk approach has been used. This means that PECs have been calculated on the basis of the amount of H_2O_2 that originates from anthropogenic sources and natural background concentrations are excluded.

3.1.3.1 Local predicted environmental concentration

The concentration of the substance in the WWTP effluent is calculated as follows:

$$Clocal_{eff} = \frac{Elocal_{water} \cdot 10^6}{EFFLUENT_{stp}} \cdot Fstp_{water}$$

where $Elocal_{water}$ = local emission rate to (waste) water during episode (kg/d) (**Tables 3.1, 3.2 and 3.3**)
$EFFLUENT_{stp}$ = effluent discharge rate of STP (l/d) (default 2,000 m^3/d)
$Fstp_{water}$ = fraction of emission directed to water by STP (0.007 i.e. 0.7%)
$Clocal_{eff}$ = concentration of the chemical in the STP-effluent (mg/l)

According to the TGD the local concentration of the substance in surface water is calculated as follows:

$$Clocal_{water} = \frac{Clocal_{eff}}{(1 + Kp_{susp} \cdot SUSP_{water} \cdot 10^{-6}) \cdot DILUTION}$$

where $Clocal_{eff}$ = concentration of the chemical in the STP-effluent (mg/l)
Kp_{susp} = solids-water partition coefficient of suspended matter (0.0195 l/kg)
$SUSP_{water}$ = concentration of suspended matter in the river (15 mg/l)
DILUTION = dilution factor (default 10)
$Clocal_{water}$ = local concentration in the surface water during emission episode (mg/l)

From the concentration of the substance in the surface water, the PEC $local_{water}$ will be calculated by adding the regional concentration of the substance:

$$PEClocal_{water} = Clocal_{water} + PECregional_{water}$$

For all H_2O_2 production plants and some of the processing plants (within Scenario Processing II) site-specific effluent concentrations data are available and are used for calculating aquatic PECs (**Table 3.10**). If there is both production and processing at the same site, the sum of concentrations will be used as PEC for that site. PECs for other scenarios are presented in **Table 3.11**. As there are data only on a limited number of processing plants for Scenario Processing II (in **Table 3.10**), PEC is calculated according to the generic scenario.

Table 3.10 Local concentrations of H_2O_2 in surface water from production (and processing II)

Plant code	Concentration in effluent from H_2O_2 production plant (mg/l) (in some cases also from processing plant)	WWTP	Flow of receiving water (m^3/s)	Dilution factor	PEClocal (mg/l) (incl. PECregional = 0.003 mg/l)
A	2	yes	230	332	0.003
B	70 (mean)	yes	130	11,233	0.009
C	< 0.1 (from influent and effluent of WWTP, and from receiving water)	yes	20	> 150	<0.1 (measured)
D	0.03	no	0	10	0.006
E	effl. 1: 3.5 (mean) effl. 2: 0.1	no	6.8	302 (effl. 1) 72 (effl. 2)	0.014
F	< 2 < 0.05 (from receiving water)	no	22	14 – 31	<0.05 (measured)
G	80	yes	1.5	811	0.004
H	0.6 (mean) (some measurements without WWTP, some after WWTP)	capacity on 2% of effluent -> no	17.5	102	0.009
I	effluent 1 before STP: 63 (mean) after STP: not detected; effluent 2: 12 (mean)	prod. & pross: yes prod. & cooling water: no	40.3 dilutes to $36.62 \cdot 10^9$ l	808	effl 1: 0.0035 effl. 2: 0.0086 (calculated from total emissions)
J	< 0.15	yes	2	241	0.003
K	2.5 (mean)	yes	366.7	4,593	0.003
L	0.02	no, but has active carbon treatment	82	282,264	0.003
M	Production: < 25 (mean) Processing 1: not measured, 1 mg/l used; Processing 2: no effluent; Processing 3: not measured, 1 mg/l used	no, but dilutes to total effluent flow	40.1	140	0.005
N	< 10 (min, max, average) (combined effluent, after WWTP)	yes	Diluted firstly to 500,000 m^3 then 1:12,000		0.003
O	9.9	no	Diluted to total effluent flow 11,000 m^3		0.004
P	Production: not detected Processing 1: 2.7 (mean), Processing 2: 1.5 (mean) Use: 120 (mean)	Production: yes Processing 1 & 2: no, effluents merged with cooling water Use: no	Production, Processing 1 & 2 and use: 518	Production: 7,460 Processing 1& 2: 1,032 Use: 481,184	0.003
Q	0.6	no	1.7	20	0.033
R	< 0.2 (after WWTP)	yes	95	1,070	0.003
S	86,8 (calculated)	yes	16.7	175	0.006
T	< 3	yes	60	1,441	0.003
U	0.5	no	200	380	0.004
V	0.05	no	no data	10	0.008
X	< 0.2 mg/l (mean) (after WWTP)	Yes	28.2	407	0.003

Table 3.11 Local concentrations in waste and surface waters from processing and consumer use calculated by EUSES

	Concentration in untreated wastewater (mg/l)	Concentration in treated wastewater of WWTP ($Clocal_{eff}$) (mg/l)	Local concentration in surface water ($Clocal_{water}$) (mg/l)	Local PEC in surface water (mg/l) (reg.= 0.003 mg/l)
Processing I	161	1.1	0.11	0.113
Processing II	192	1.32	0.132	0.135
Processing III	7.74	0.053	0.0053	0.0083
Processing IV	6.7	0.0459	0.00459	0.00759
Consumer use I	1.47	0.0101	0.00101	0.00401
Consumer use II	1.82	0.0125	0.00125	0.00425
Consumer use III	0.0918	0.0006	0.00006	0.00306

The concentration of the substance in wastewater ($Clocal_{eff}$) is the concentration for which microorganisms are exposed and which is regarded as PEC for microorganisms.

The PEC for sediment is not calculated. Hydrogen peroxide does not adsorb to the sediment and is rapidly degraded in the sediment. Thus, $PEC_{sediment}$ does not exceed PEC in surface water.

3.1.3.2 Regional and continental predicted environmental concentrations

$PECregional_{surface\ water}$ = 0.003 mg/l.

$PECcontinental_{surface\ water}$ = 0.0004 mg/l.

Regional and continental PECs are taken from a separate EUSES calculation where continental emissions from production are estimated from site-pecific data. More realistic emission figures are used also for processing II (use in manufacture of other chemicals). Almost 50% of the amount H_2O_2 used for this purpose is used at the hydrogen peroxide production plants and thus is included in the site-pecific emission data. The above-mentioned PECs are added to PEClocal values.

3.1.3.3 Measured environmental data

Background concentrations of hydrogen peroxide in sea water and freshwater are typically from some micrograms to some tens of micrograms per litre. Freshwater and estuarine concentrations of H_2O_2 have been measured only in a few locations. There are much more existing data on sea water concentrations.

The photochemical formation of H_2O_2 in surface waters is the most important formation process in natural waters. It is a process using sunlight, light absorbing organic matter and molecular oxygen. Normally a high concentration of dissolved organic matter in the water correlates with a high hydrogen peroxide concentration in the uppermost surface water.

The occurrence of hydrogen peroxide in sea water was studied by Van Baalen et al. as early as in 1966. They used sensitive scopoletin-peroxidase fluorescence technique and measured in Port Aransas Area surface water concentrations 0.5-6.7 µg/l.

The vertical distribution in sea water has been studied and normally at depths of 150 m or more, H_2O_2 cannot be found. In the western Mediterranean Sea water hydrogen peroxide

concentrations were 2.6 µg/l and 1.1 µg/l at depths of 20-29 m and 80-89 m, respectively (Johnson et al., 1989).

The groundwater occurrence of hydrogen peroxide has been studied. However, the existing data on groundwater concentrations are very limited. Mean concentration of 111 groundwater samples was 20.2 nM (0.7 µg/l), variation was from < 0.03 to 2.25 µg/l. Samples were taken from 11-32-meter deep wells. There was a relationship between molecular oxygen and hydrogen peroxide concentrations but no relationship with depth (Holm et al., 1987).

Measurements of hydrogen peroxide in polar ice samples older than 20,000 years have been done by Neftel et al. (1984; 1986). Measured hydrogen peroxide concentrations ranged up to 150 µg per kg ice.

In Appendix B, existing data on measured concentrations of hydrogen peroxide in different environmental compartments are presented (CEFIC, 1997c).

A summary of measured hydrogen peroxide concentrations in the environment is given in **Table 3.12**.

When comparing the PEC calculated it must be noted that the monitoring data comprise both the natural background and the anthropogenic part.

Table 3.12 Measured hydrogen peroxide concentrations in the environment

Compartment	Typical mean values	Highest values	Comments
Air	0.14-1.4 µg/m^3 (0.1-1 ppb)	10 µg/m^3 (7 ppb)	
Cloud water	50-1,000 µg/l	> 8,000 µg/l	
Rainwater Summer time Winter time	100-500 µg/l < 100 µg/l	> 8,000 µg/l	
Sea water	0.5-5 µg/l	14	
Lake water	1-30 µg/l	> 100	highest values: reliability poor, but probable realistic
Groundwater	0.7 µg/l	2.25 µg/l	only one study referred

3.1.4 Atmosphere

3.1.4.1 Local predicted environmental concentration

The concentration of the substance in air is estimated according to the TGD at a distance of 100 meters from a point source. In the calculation of PEClocal for air, both emissions from a point source and emissions from a STP are taken into account. However the maximum from the two concentrations (direct) is used as the PEClocal.

$$Clocal_{air} = \max (Elocal_{air}, Estp_{air}) \cdot Cstd_{air}$$

where $Elocal_{lair}$ = local direct emission rate to air during episode (kg/d) (**Tables 3.1, 3.2**)
$Estp_{air}$ = local indirect emissions to air from STP during episode (kg/d)
$Cstd_{air}$ = concentration in air at source strength of 1 kg/d ($2.78 \cdot 10^{-4}$)

Annual average concentration (**Table 3.13**) in air is calculated as:

$$Clocal_{air,ann} = Clocal_{air} \cdot T_{emission}/365$$

where $T_{emission}$ = number of days per year that the emission takes place (**Tables 3.1, 3.2**)

Table 3.13 PECs in air from production, processing and consumer use

	Concentration in air during emission episode (mg/m³)	Annual average conc. in air, 100 m from point source (mg/m³)	Annual PEClocal in air (mg/m³) (local + regional)
Production	0.0089	0.00731	0.00731
Processing I	0.000992	0.000816	0.000818
Processing II	0.00153	0.00125	0.00126
Processing III	0.00478	0.00393	0.00393
Processing IV	$6.17 \cdot 10^{-9}$	$2.54 \cdot 10^{-10}$	$2.23 \cdot 10^{-6}$
Consumer use I	$1.35 \cdot 10^{-9}$	$1.35 \cdot 10^{-9}$	$2.23 \cdot 10^{-6}$
Consumer use II	$1.67 \cdot 10^{-9}$	$1.67 \cdot 10^{-9}$	$2.23 \cdot 10^{-6}$
Consumer use III	$8.45 \cdot 10^{-11}$	$8.45 \cdot 10^{-11}$	$2.23 \cdot 10^{-6}$

In calculating the deposition flux (**Table 3.14**) the emissions from the two sources (direct and STP) are summed:

$$DEPtotal = (Elocal_{air} + Estp_{air}) \cdot (Fass_{aer} \cdot DEPstd_{aer} + (1 - Fass_{aer}) \cdot DEPstd_{gas})$$

where DEPtotal = total deposition flux during emission episode ($mg/m^2 \cdot d$)
$Fass_{aer}$ = fraction of chemical bound to aerosol ($3.33 \cdot 10^{-7}$)
$DEPstd_{aer}$ = standard deposition flux of aerosol-bound compounds at a source strength of 1 kg/d ($mg/m^2 \cdot d$) ($1 \cdot 10^{-2}$)
$DEPstd_{gas}$ = deposition flux of gaseous compound as a function of Henry's law coefficient, at a source strength of 1 kg/d ($5 \cdot 10^{-4}$ $mg/m^2 \cdot d$, when $^{10}\log$ Henry $\leq$ -2)

Table 3.14 Deposition fluxes from air for production, processing and consumer use

	DEPtotal (mg/m² · d)	$DEPtotal_{annual}$ (mg/m² · d)
Production	0.016	0.0132
Processing I	$1.79 \cdot 10^{-3}$	$1.47 \cdot 10^{-3}$
Processing II	$2.75 \cdot 10^{-3}$	$2.26 \cdot 10^{-3}$
Processing III	$8.6 \cdot 10^{-3}$	$7.07 \cdot 10^{-3}$
Processing IV	$1.11 \cdot 10^{-8}$	$4.56 \cdot 10^{-10}$
Consumer use I	$2.43 \cdot 10^{-9}$	$2.43 \cdot 10^{-9}$
Consumer use II	$3.01 \cdot 10^{-9}$	$3.01 \cdot 10^{-9}$
Consumer use III	$1.52 \cdot 10^{-10}$	$1.52 \cdot 10^{-10}$

3.1.4.2 Regional and continental predicted environmental concentrations

PECregional in air = $2.23 \cdot 10^{-6}$ mg/m^3
PECcontinental in air = $2.69 \cdot 10^{-7}$ mg/m^3

3.1.4.3 Measured environmental data

Atmospheric background daytime concentrations of hydrogen peroxide are typically 0.14-1.4 μg/m^3 (0.1-1 ppb). In rural air, concentrations are normally highest during day time, late afternoon, and lowest at night, often below detection limit.

Concentrations increase toward the south at about 0.046 ppbv per degree of latitude during Winter over the south-central United States (Van Valin et al., 1987).

Vertical profiles of H_2O_2 levels have been developed from aircraft-based observations. In general, H_2O_2 levels appear to be at a minimum near the surface and to increase with altitude; a maximum content occurs near the top of the atmospheric boundary layer (1-3 km) or just above cloud tops (Sakugawa et al., 1990).

Airborne H_2O_2 shows a strong tendency to dissolve in the aqueous phase and high concentrations, more than 5 mg/l, can be found in rainwater.

In Appendix B, existing data on measured concentrations of hydrogen peroxide in different environmental compartments are presented (CEFIC, 1997c).

A summary of measured hydrogen peroxide concentrations in the environment is given in **Table 3.12**.

3.1.5 Terrestrial compartment

3.1.5.1 Local predicted environmental concentration

A substance can reach agricultural soil through two exposure routes: dry and wet deposition from the atmosphere and application of sewage sludge in agriculture.

The total deposition flux ($DEPtotal_{annual}$) as calculated above (**Table 3.14**) will be converted to a concentration of mg substance per kg soil per day (D_{air}) (**Table 3.15**) as follows:

$$D_{air} = \frac{DEPtotal_{annual}}{DEPTH_{soil} \cdot RHO_{soil}}$$

where $DEPTH_{soil}$ = mixing depth of soil (m) (for ass. of terrestrial ecosystem 0.20 m)
RHO_{soil} = bulk density of (wet) soil (1,700 kg/m^3)

The concentration in dry sewage sludge, C_{sludge}, is estimated to be 0 since hydrogen peroxide is rapidly degraded in the sludge.

Table 3.15 Concentration of the substance in deposition from production, processing and consumer use

	D_{air} (mg/kg/d)
Production	$3.88 \cdot 10^{-5}$
Processing I	$4.32 \cdot 10^{-6}$
Processing II	$6.65 \cdot 10^{-6}$
Processing III	$2.08 \cdot 10^{-5}$
Processing IV	1.34 · 10-12
Consumer use I	7.15 · 10-12
Consumer use II	8.85 · 10-12
Consumer use III	4.47 · 10-13

Using local atmospheric deposition rates as estimated above, the resulting concentrations in agricultural soil from production and processing can be estimated with EUSES [6]. **Table 3.16** gives the terrestrial PECs at local scale for the various generic scenarios.

[6] Euses Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

Table 3.16 PECs in soil for production, processing and consumer use

	Local PEC_{soil} (mg/kg) (wet weight)
Production	$1.36 \cdot 10^{-4}$
Processing I	$1.11 \cdot 10^{-4}$
Processing II	$1.13 \cdot 10^{-4}$
Processing III	$1.23 \cdot 10^{-4}$
Processing IV	$1.08 \cdot 10^{-4}$
Consumer use I	$1.08 \cdot 10^{-4}$
Consumer use II	$1.08 \cdot 10^{-4}$
Consumer use III	$1.08 \cdot 10^{-4}$

3.1.5.2 Regional and continental predicted environmental concentrations

Regional PEC in agricultural soil = $2.85 \cdot 10^{-5}$ mg/kg (wet weight)
Regional PEC in natural soil = $1.08 \cdot 10^{-4}$ mg/kg (wet weight)
Regional PEC in industrial soil = $9.01 \cdot 10^{-3}$ mg/kg (wet weight)

Continental PEC in agricultural soil = $3.44 \cdot 10^{-6}$ mg/kg (wet weight)
Continental PEC in natural soil = $1.31 \cdot 10^{-5}$mg/kg (wet weight)
Continental PEC in industrial soil = $9.23 \cdot 10^{-4}$ mg/kg (wet weight)

3.1.5.3 Measured environmental data

There are no measured data available on the terrestrial environment.

3.1.6 Secondary poisoning

Exposure assessment through secondary has not been carried out for hydrogen peroxide since it has only low potential to accumulate to living organisms, and it is not considered acutely toxic according to the mammalian toxicity data.

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT) ASSESSMENT

Hydrogen peroxide is a special substance since all cells with the exemption of anaerobic bacteria produce hydrogen peroxide in their metabolism. H_2O_2 is also formed abiotically in the environment. To prevent oxidative cell damage cells have developed ability to decompose H_2O_2.

Reactive oxygen species (ROS), also called oxyradicals, are produced in biological systems as unwanted toxic by-products of normal metabolism. ROS are detoxified by the action of antioxidant protection systems, e.g. antioxidant enzymes or low molecular weight scavengers. The antioxidant enzyme system consists of several enzymes. The most important of them are SOD (superoxide dismutase), CAT (catalase) and GPX (glutathione peroxidase). SOD converts O_2^- to H_2O_2. CAT and GPX converts H_2O_2 to water. Examples of low molecular weight scavengers are vitamins C and E, carotenoids and glutathione.

Antioxidant enzymes are known to be widespread in aquatic organisms and generally present at highest levels in the liver of fish or similar tissues concerned with the processing of food in invertebrates e.g. digestive gland of mollusks. Antioxidant enzymes have been detected in many fish. Hepatic antioxidant activities have been detected in 14 fish families representing 7 orders and non-hepatic antioxidant enzyme activity in 14 families representing 8 orders. Invertebrates have been observed to have similar activities of catalase as vertebrates but lower activities of SOD and much lower activities of GPX.

It can be concluded that organisms are able to deal some amount of excess H_2O_2. The antioxidant enzyme activity varies, however, between cells, tissues and species and also seasonally within same species and in relation to such factors as age.

The use of added risk approach implies that PNEC is derived from toxicity data that are based on the added H_2O_2 concentrations. No measurements of background concentrations of hydrogen peroxide in the test water of the laboratory studies have been conducted. However, it can be assumed that the background concentration of hydrogen peroxide is negligible in the laboratory tests because reconstituted water is normally used for testing. The amount of hydrogen peroxide produced by the test organisms, especially algae, cannot be distinguished in the tests which have been used in the risk assessment.

3.2.1 Aquatic compartment

There are a large number of toxicity tests with hydrogen peroxide to aquatic organisms. However, only few of them are both relevant for risk assessment purposes and adequately done. In those tests where the concentration of the solution of the test substance is reported (i.e. 30% or 50% H_2O_2,), the results are calculated as 100% hydrogen peroxide.

3.2.1.1 Toxicity test results

3.2.1.1.1 Fish

Toxicity data of hydrogen peroxide to fish are summarised in **Table 3.17**. Acute LC_{50} values for fish range from 16.4 to 37.4 mg/l. The test with the lowest LC_{50} is done according to US EPA guidelines, the test solution is renewed and the concentration of the test substance is measured

every 24 hours. The other two LC_{50}s for fish are somewhat higher but the results are based on nominal concentrations. Taking into account the instability of the test substance these two results cannot be considered as reliable enough. The LC_{50} value of 16.4 mg/l for *Pimephales promelas* will be taken into consideration with the test results of other taxonomic groups for the derivation of PNEC for the aquatic environment.

Table 3.17 Short-term toxicity of hydrogen peroxide to freshwater fish

Species	Duration	Method	Type	Analytical monitoring	LC_{50} (mg/l)	Reference
Pimephales promelas	96 h	US EPA	semi-static	measured	16.4	Shurtleff (1989a)
Leuciscus idus	72 h	DEV DIN 38	static	measured, but results as nominal	35	Degussa (1977b)
Ictalurus puctatus	96 h	other; fish from commercial farm; tap water	semi-static	nominal	37.4	Kay et al. (1982)

There is only one test available on long-term effects on fish. It is an 8-month dietary carcinogenicity test that shows the ability of H_2O_2 to enhance liver tumours on rainbow trout in a dose-dependent manner. In this test, however, unrealistically high concentrations of H_2O_2 were used. Fish were also treated with a tumour initialising agent and an antioxidant simultaneously. Therefore this test is not regarded valid.

3.2.1.1.2 Aquatic invertebrates

Acute toxicity data for H_2O_2 to aquatic invertebrates are available. Hydrogen peroxide seems to be most toxic to daphnids with EC_{50} values of about 2 mg/l (**Table 3.18**). H_2O_2 is only slightly less toxic to *Gammarus sp.* Snail *Physa sp* is more tolerant to hydrogen peroxide with an EC_{50} of 17.7 mg/l. An EC_{50} value for zebra mussel is 6 mg/l.

There is one chronic test on invertebrates (Klerks and Fraleigh, 1991). In a 56-day test (flow-through, 11°C, pH 8.25, concentrations 1,0–5,0 mg/l) NOEC for zebra mussels was 2 mg/l which will be taken into consideration with the test results of other taxonomic groups for the derivation of the PNEC for the aquatic environment.

Table 3.18 Short-term toxicity of hydrogen peroxide to freshwater invertebrates

Species	Duration	Method	Type	Analytical monitoring	EC_{50} (mg/l)	Reference
Daphnia pulex	48 h	US EPA; 50% distill. water and 50% lake water	semi-static	measured	2.4	Shurtleff (1989b)
Daphnia magna	24 h	modification of Bringmann and Kühn	static	nominal (test conc. not given)	2.3 (2.0-2.6)	Bringmann and Kuhn (1982)
Gammarus sp.	96 h	other; aerated tap water; no data on controls	semi-static	nominal (test conc. not given)	4.4	Kay et al. (1982)
Physa sp.	96 h	other; aerated tap water; no data on controls	semi-static	nominal (test conc. not given)	17.7	Kay et al. (1982)

3.2.1.1.3 Algae

There are several studies carried out to assess the toxicity of hydrogen peroxide to algae. However, in most algae tests, no EC_{50} value has been calculated. In **Table 3.19** results of relevant and valid studies are presented.

EC_{50} values for freshwater algae range from 1.6 to 5 mg/l except 17 mg/l for *Chlorella emersonii* and 27.5-43 mg/l for *Scenedesmus quadricauda* (both green algae). Also the effective concentration to sea water algae is approximately at the same level (0.85 mg/l) as the lowest effective concentration to freshwater algae. The lowest EC_{50} value for freshwater algae is about 1.6 mg/l for blue-green algae *Anabaena A4*. The test method used in this test is not a standard method, but has been considered valid. The test was carried out in microtitre plates which contain 96 wells (each of 300 µl) and plates were incubated under lidded dish. The duration of the test was 140 hours and the effect on growth was measured by optical density. The EC_{50} value was graphically derived. In a standard OECD 201 test with *Chlorella vulgaris* a slightly higher EC_{50} value is reached. EC_{50} value fort marine diatom (*Skeletonema costatum)* is 1.38 mg/l and NOEC 0.68 mg/l.

Table 3.19 Short-term and long-term toxicity of hydrogen peroxide to algae

Species	Duration	Method	NOEC (mg/l)	EC_{50} (mg/l)	LOEC (mg/l)	Reference
Chlorella vulgaris	72 h	Modified OECD 201	0.1 mg/l	2.5 (growth curve 0-72 h) 4.3 (growth rate 24-72 h)	-	Degussa (1991)
Anabaena flos-aquae	32 d	Other	-	-	0.1	Kavanagh (1992)
Oscillatoria agardhii	32 d	Other	-	-	1	Kavanagh (1992)
Oscillatoria rubescens	29 h	Other	-	-	0.35	Barroin and Feuillade (1986)
Anabaena A4	140 h	Other	-	About 1.6 (growth rate)	-	Clarke (1991)
Anabaena variabilis	140 h	Other	-	About 5 (growth rate)	-	Clarke (1991)
Chlorella emersonii	240 h	Other	-	About 17 (growth rate)	≤ 10	Clarke (1991)
Scenedesmus quadricauda	240 h	Other	-	27.5 - 43 (growth rate)	≤ 20	Clarke (1991)
Synechoccus leopoliensis	140 h	Other	-	-	≤ 10	Clarke (1991)
Chlamydomonas eugametos	200 h	Other	-	-	≤ 10	Clarke (1991)
Nitzschia closterium (sea water)	72 h	Other		0.85 (growth rate)		Florence and Stauber (1986)
Sceletonema costatum (marine diatom)	72 h	OECD 201	0.63 mg/l	1.38 mg/l	-	Knight et al. (1995)

There are some studies where LOEC values, but no EC_{50} or NOEC values, can be derived (**Table 3.19**). These LOECs are lower than the lowest EC_{50} (1.6 mg/l):

1. LOEC 0.1mg/l, *Anabaena flos-aquae* (blue-green algae): at 0.1 mg/l some growth inhibition was observed. After treatment with 0.25 mg/l H_2O_2 growth inhibition of algae was obvious over the test period. Concentration 0.75 mg/l totally prevented the growth (Kavanagh, 1992).
2. LOEC 1 mg/l, *Oscillatoria agardhii* (blue-green algae): 1 mg/l H_2O_2 was sufficient to prevent the growth of algae and algae did not recover within 1 week after the treatment (Kavanagh, 1992).
3. LOEC 0.35 mg/l, *Oscillatoria rubescens* (blue-green algae): lowest effects on pigments, biliproteins destruction started at the lowest level tested, i.e. 0.35 ppm, whereas carotenoids begun to be destroyed only at 1.4 ppm and chlorophyll a at 1.75 ppm. At H_2O_2 concentration around 1.5 ppm growth potential of *O. rubescens* was destroyed. H_2O_2 efficiency is threshold shaped (around 1.75 ppm) and the threshold value is inversely related to culture density (Barroin and Feuillade, 1986).

According to the TGD when LOEC is > 10 and < 20% effect, the NOEC can be calculated as LOEC/2. When the effect percentage of the LOEC is unknown no NOEC can be derived.

In addition there are some studies (Kay et al., 1982), where the threshold toxicity has been determined (endpoint: optical density of chlorophyll):

1. *Microcystis* sp. (blue-green algae), threshold toxicity < 1.7 mg/l (algae collected in the field from a commercial catfish pond),
2. *Raphidiopsis* sp., threshold toxicity < 3.4 mg/l (algae from a aquarium containing goldfish),
3. *Ankistrodesmus* sp., threshold toxicity 6.8-10.2 mg/l (algae from Carolina Biological Supply).

Hydrogen peroxide concentrations of 1.7 mg/l, 6.8 mg/l and 17 mg/l reduced the optical densities of chlorophyll extracts to 5% of the controls for *Microcystis*, *Raphidiopsis* and *Ankistrodesmus*, respectively.

Most of the toxicity tests in **Table 3.19** can be regarded as long-term tests. However, according to the TGD only NOECs of long-term tests can be considered as long-term toxicity values. Then a NOEC value of 0.1 mg/l with *Chlorella vulgaris* (Degussa, 1991) can be regarded as the only long-term result on algae in freshwater.

3.2.1.1.4 Microorganisms

The toxicity of hydrogen peroxide to microorganisms has been studied frequently, but nearly all tests have been performed in milk and so they cannot be used in the risk assessment.

Recently an activated sludge respiration test has been conducted according to OECD guideline 209 and in compliance with GLP (Groeneveld and de Groot, 1999). In the test nominal concentrations of 1, 3, 10, 30, 100, 300 and 1,000 mg/l and non-adapted sludge were used. EC_{50} was 466 mg/l.

In addition, there is one study on the effects of hydrogen peroxide on individual bacterial population. It is an 18-hour cell multiplication inhibition test with *Pseudomonas putida*. In this

study an EC_{10} of 11 mg/l was derived and the study was done according to Bringmann and Kühn (Knie et al., 1983) (there were no analytical monitoring or data on the test substance in the study).

There is also a study made by Baldry (1983) in which hydrogen peroxide was bacteriostatic above 0.15 mmol/l (5.1 mg/l) for *Pseudomonas aeruginosa* (pH 5) and *Staphylococcus aureus* (pH 6.5 and 8). However, H_2O_2 was found to be a weak bactericide, as a solution containing 0.88 mol/l (29.9 g/l) did not give a total kill within 3.5 hours. The very same concentration was lethal to spores, so according to this study hydrogen peroxide is more effective as a sporicide than as a bactericide. This study, however, cannot be used in the risk assessment since data are missing on dose-response.

3.2.1.2 Field Tests

Single species laboratory tests have been the basis in deriving the PNEC value for the aquatic compartment in this risk assessment. However there are also existing field test data that quite well support the magnitude of the $PNEC_{aquatic}$ value derived (Xenopoulos and Bird, 1997). The tests carried out by Xenopoulos and Bird had sensitive, ecosystem-specific endpoints and *in situ* test method.

Xenopoulos and Bird (1997) examined the acute influence of hydrogen peroxide exposure on production of phytoplancton and bacterioplancton in Lac Cromwell, a small humic lake in Canada. A range of hydrogen peroxide concentrations were added to natural samples that were incubated *in situ*, comparing photosynthetic uptake of $^{14}CO_2$ as the measure of algal response and the incorporation of ^{3}H-leucine (nutrient protein of bacteria) as the bacterial response, in the presence or absence of different concentrations of hydrogen peroxide. A high variance of hydrogen peroxide concentrations (100 nM to 0.1 M) was used.

The initial H_2O_2 concentration of the lake water was not measured before the experiments. However, it was presumed that concentrations were always < 1,000 nM (< 34 µg/l) and 100-200 nM (3.4-6.8 µg/l) at 10 a.m. Most experiments were conducted under clear skies and no experiments were conducted following rain to avoid the additional load of H_2O_2 found in rainwater.

The natural levels of hydrogen peroxide in Lac Cromwell have been examined in a Canadian survey. Lac Cromwell is a humic lake (DOM 7-10 mg/l, chl-a 7.5 µg/l, tot-P 9µg/l, pH 6.2, 1% UVA radiation depth 0.56 m, 1% UVB radiation depth 0.21m, max depth 9 m). In a study in a series of 20 temperate and Arctic lakes carried out by Scully et al. (1996), Lac Cromwell had the highest H_2O_2 formation rate at 2.120 $\mu M \cdot L^{-1} \cdot h^{-1}$.

At concentrations higher than 0.1 mM (3.4 mg/l) H_2O_2 always had strong negative effects on both phytoplancton and bacteria. Because levels as high as used in the test are rarely or never seen in natural aquatic systems, they were not considered further.

Results indicate that even small amounts of added hydrogen peroxide, < 50 nM (1.7 µg/l), inhibited bacterial production in this lake. A 100 nM (3.4 µg/l) addition inhibited bacteria by as much as 40% and inhibition in bacterial production was observed even at 3.4 nM (0.12 µg/l), the lowest concentration examined.

Photosynthetic activity of phytoplancton increased or was not affected by additions of 100 nM (3.4 µg/l) and 1,000 nM (34 µg/l) H_2O_2 but bacterial production always decreased severely. In all experiments, addition of catalase stimulated bacterial activity, which indicated that natural levels of hydrogen peroxide were suppressing bacterial production.

There seemed to be differences in susceptibility of phytoplancton to hydrogen peroxide following daily solar (and H_2O_2 concentration) cycle. At sunrise, i.e. during the lowest period of natural H_2O_2 concentration, no effect of H_2O_2 addition *in situ* on photosynthesis was observed, even at 5,000 nM (170 µg/l). On the same day but a couple of hours before sunset a decrease in primary production, at only 50 nM (1.7 µg/l) was observed. It was suggested that the detoxification capacity of the cells was not exceeded at sunrise and temporarily exceeded at late afternoon.

Low concentrations of added hydrogen peroxide usually stimulated photosynthesis; 0.1 µM (3.4 µg/l) of added H_2O_2 increased CO_2 fixation by 15-20%.

The results of this study indicate very different sensitivities of phytoplancton and bacteria to oxidative stress. Phytoplancton may have an advantage over the bacteria during oxidative stress.

The composition of the bacterial population used in the test is not known and thus it is difficult to determine the relevance of results in the STP. The results of this study have not been used in $PNEC_{microorganisms}$ determination due to above-mentioned uncertainties in the test. There are also indications that activated sludge is quite resistant to hydrogen peroxide (see Section 3.1.2.2).

3.2.1.3 Effects of reaction products

Degradation of hydrogen peroxide in the aquatic environment leads to different kinds of reaction products depending on the reacting substances. Hydrogen peroxide may also affect the oxidation state and speciation of metal-ions. The assessment of composition and effects of those reaction products is extremely complicated and out of the scope of this risk assessment.

3.2.1.4 PNEC for the aquatic compartment

PNEC is calculated based on added concentrations i.e. background concentrations have been excluded.

Freshwater

Hydrogen peroxide is a naturally occurring substance. According to the available studies natural background concentrations are typically < 1–30 µg/l. Concentrations near 30 µg/l are rare – occurring during summer afternoons in surface waters with a high DOC level. On the basis of field studies it is evident that even natural levels may be harmful to some organisms causing "natural risks".

There is a complete "base-set" of acute toxicity data for hydrogen peroxide. From the three base-set species tested, algae seems to be the most sensitive species for the aquatic compartment with an EC_{50} of 1.6 mg/l. The lowest EC_{50} for daphnia (2.3 mg/l) is of the same order.

There is one freshwater algae study (72-hour), where a NOEC value can be regarded as long-term toxicity value. A long-term study on zebra mussel which represents the same trophic level as daphnids is available and can be taken into account when determining the assessment factor.

However, as there are no long-term data available on fish, an assessment factor of 50 should be used. Using the result from the algae test (NOEC = 0.1 mg/l) and the assessment factor of 50 the $PNEC_{aquatic}$ would be 2 µg/l.

Based on the available data on natural background concentrations it seems obvious that the calculated PNEC of 2 μg/l overestimates the toxicity. Furthermore, it is not probable that a further long-term NOEC from fish would be lower than the NOEC available from the most sensitive taxonomic group - algae. Therefore a lower assessment factor of 10 is used and PNEC is 0.1 mg/l / 10 = 10 μg/l.

$PNEC_{aquatic}$ = 10 μg/l.

Microorganisms

The EC_{50} value of the activated sludge respiration test has been used in the calculation of PNEC. According to the TGD the EC_{50} value from the OECD 209 guideline (466 mg/l) is divided by an assessment factor of 100.

$PNEC_{microorganisms}$ = 4.66 mg/l.

However, it is well known that wastewater treatment plants, especially adapted industrial WWTPs, are able to tolerate much higher concentrations without adverse effects on the functioning of the WWTPs.

Sediment dwelling organisms

Hydrogen peroxide does not absorb to sediment and is rapidly degraded there. Sediment dwelling organisms are adequately covered by the PNEC for water phase.

3.2.2 Atmosphere

3.2.2.1 Toxicity to plants

Some experiments are available on fumigation of plants (wheat, spruce and red beech) with H_2O_2. Effects on assimilation rate and photosynthesis of wheat were observed, but they were reversible in a test with concentrations of 1.4 to 2.0 mg/m^3 for some hours. With trees (Norway spruce and red beech) more severe effects were discovered than with wheat. There were changes in the internal structure of needles and leaves e.g. decrease in tissue area and dry weight and increased number of stomata and accumulation of tannin. No NOEC or EC_{50} levels were determined in tests. For trees, exposure periods changed from 6 to 8 weeks and H_2O_2 concentrations in fog water varied from 0.2 to 5 mg/l. As there are no studies for which dose-response has been measured, no quantitative assessment for atmosphere can be performed.

3.2.2.2 Abiotic effects

Direct anthropogenic emissions of H_2O_2 do not play an important role in determining its atmospheric concentration. Photochemical activity and precursors concentrations are the main factors controlling the formation and concentration of this molecule.

Hydrogen peroxide has indirect effects on acidification due to its oxidative property. As one of the powerful oxidants in the air, hydrogen peroxide oxidise SO_2 in atmospheric water droplets, converting SO_2 to SO^{2-}_4 especially at low pH conditions (pH <5.0). Nitrogen oxide N(III)

compounds are also effectively oxidised by hydrogen peroxide. In this way hydrogen peroxide has an important role in the acidification of rain-, cloud- and fog-water.

Global warming effect of a substance depends on IR absorption characteristics and atmospheric concentration. Hydrogen peroxide has not been considered as a significant contributor to the greenhouse effect. Its very small atmospheric concentration (0.02 to 6 ppbv) and poor IR-adsorption suggests that this contribution is very small if not negligible.

As the substance has a short atmospheric lifetime and it does not contain chlorine or bromine substituents it is very unlikely that tropospheric hydrogen peroxide could have any effect on the stratospheric ozone depletion.

3.2.3 Terrestrial compartment

No studies are available on effects of hydrogen peroxide on soil dwelling organisms. Some studies on plants (rice, soybean, corn, tomato, pigweed and barnyard grass) are available but these data cannot be used in the risk assessment since in one test there is no information on the actual concentration of the substance in soil, but only data on concentration of water used for watering the plant and in another test seeds were exposed to H_2O_2 in water instead of using soil.

When there are no relevant test results available with terrestrial organisms, the risk assessment will be performed on the basis of equilibrium partition method.

$$PNEC_{soil} = \frac{K_{soil\text{-}water}}{RHO_{soil}} \cdot PNEC_{water} \cdot 1{,}000 = 1.19 \cdot 10^{-3} \text{ mg/kg (wet weight)}$$

$K_{soil\text{-}water}$ = soil - water partition coefficient (0.206 m^3/m^3)
RHO_{soil} = bulk density of (wet) soil (1,700 kg/m^3)

3.2.4 Secondary poisoning

BCFs calculated according to the TGD for fish and earthworm are low, 1.4 and 3.3, respectively. Therefore secondary poisoning is not likely.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic compartment (incl. sediment)

Site-specific PEC/PNEC ratios for aquatic organisms from production (and processing II) plants are presented in **Table 3.20**. There are 19 sites with no risk: **conclusion (ii)**. For four production sites there is a risk in the local aquatic environment: **conclusion (iii)**.

Table 3.20 Site-specific aquatic PEC/PNEC ratios from production (and processing II)

Plant code	PEC/PNEC
A	0.3
B	0.9
C	<10
D	0.6
E	1.4
F	<5
G	0.4
H	0.9
I	effl. 1: 0.35 effl. 2: 0.86
J	0.3
K	0.3
L	0.3
M	0.5
N	0.3
O	0.4
P	0.3
Q	3.3
R	0.3
S	0.6
T	0.3
U	0.4
V	0.8
X	0.3

The generic scenario for the use in manufacture of other chemicals (processing II) indicates that there would be a risk at local scale for aquatic organisms. Hence, **conclusion (iii)** would apply. There is no risk for the aquatic environment from pulp bleaching, textile bleaching, environmental applications or consumer use: **conclusion (ii)** (see **Table 3.21**).

Table 3.21 PEC/PNEC ratios at local scale from production, processing and consumer use

	Aquatic organisms	Microorganisms
Production	See Table 3.20	0.706
Processing I (Pulp bleaching)	0.7 *	0.236
Processing II (Manufacture of other chemicals)	13.5	0.283
Processing III (Textile bleaching)	0.83	0.0114
Processing IV (Environmental applications)	0.759	0.00985
Consumer use I (Hair bleaching and dyeing)	0.401	0.00216
Consumer use II (Household cleaning agents)	0.425	0.00267
Consumer use III (Tooth bleaching)	0.306	0.000135

* Estimation 2 presented in Section 3.1.1.2 has been used.

H_2O_2 does not adsorb to the sediment and is rapidly degraded there. Therefore a separate risk characterisation for sediment has not been performed. The risk assessment for surface water adequately covers the sediment.

There is no risk for microorganisms from any of the use scenarios: **conclusion (ii)**.

Also the PEC/PNEC ratios at regional scale based on generic emission estimation from production, processing and consumer use are all below 1: **conclusion (ii)**.

3.3.2 Atmosphere

No quantitative risk assessment has been carried out for the atmospheric compartment due to a lack of EC_{50} values for terrestrial plants.

In a test carried out with trees some effects on needles and leaves have been observed when the hydrogen peroxide concentrations in fog water varied from 0.2 to 5 mg/l. These values are comparable to typical concentrations in rainwater during Summer. Thus, effects of hydrogen peroxide on plants cannot be totally excluded but it must be born in mind that also plants have an enzymatic capacity of decomposing H_2O_2 to some extent.

Conclusion (ii).

3.3.3 Terrestrial compartment

The PEC/PNEC ratios at local scale based on the generic emission estimation (i.e. according to the TGD) from production, processing and consumer use are all below 1 (see **Table 3.22**): **conclusion (ii)**.

Table 3.22 PEC/PNEC-ratios for local production, processing and consumer use

	Terrestrial organisms
Production	0.114
Processing I (Pulp bleaching)	0.0934
Processing II (Manufacture of other chemicals)	0.0948
Processing III (Textile bleaching)	0.103
Processing IV (Environmental applications)	0.0908
Consumer use I (Hair bleaching and dyeing)	0.0908
Consumer use II (Household cleaning agents)	0.0908
Consumer use III (Tooth bleaching)	0.0908

Also the PEC/PNEC ratios at regional scale based on the generic emission estimation from production, processing and consumer use are all below 1: **conclusion (ii)**.

3.3.4 Secondary poisoning

As there is no indication of bioaccumulation potential for hydrogen peroxide, no assessment for the secondary poisoning needs to be carried out: **conclusion (ii**).

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 Occupational exposure

4.1.1.1.1 General discussion

Humans can be exposed to hydrogen peroxide directly by inhalation of airborne concentrations, by dermal contact and via ingestion. Exposure to hydrogen peroxide may arise from working processes, consumer products and indirectly via food and the environment.

Hydrogen peroxide (H_2O_2) is a reactive compound, an oxidiser and a reductant. Its diluted water solutions are well known bleaching agents and disinfectants. Concentrated solutions are used for many chemical reactions in the synthetic chemistry. H_2O_2 functions as an active component in industrial formulations, such as an initiator for polymerising reactions or a hardener (curing agents) for polymers. Especially in industry, H_2O_2 increasingly substitutes chlorine and its compounds mainly for environmental reasons.

It is also an active ingredient in several hygienic, cosmetic, hairdressing and stain removal products for consumers.

Data available for the occupational exposure assessment

The present data concerning occupational exposure available for the exposure assessment of H_2O_2 were found to be very scarce. Some data could be collected from the CEFIC report and its Appendices C and D (CEFIC, 1997c;d;e) concerning manufacture of H_2O_2 and its loading for transportation. The exposure database of the Finnish Institute of Occupational Health (FIOH), had two reports concerning exposure in creameries, two reports on site visits in small electronic factories and one report on a survey in a chemi-mechanical pulp mill. In the open literature, there were three short papers on creameries, one from Germany (Dietschmann, 1996a; Dietschmann et al., 1996b), one from Japan (Suenaka et al., 1984) and one from Switzerland (Kaelin et al., 1988).

Because the available data concerning H_2O_2 exposures in the process industry were scanty and originated mainly from the 1980s, the domestic industries known to use H_2O_2 were visited. The visits were performed by an experienced industrial hygienist thoroughly familiar with the EU methodology of assessing occupational exposure. Apart from collecting data in the processes, working habits etc., described in the main text, the hygienist took also 5-10 grab samples per workplace with the Dräger instrument (indicator tubes, H_2O_2 0.1/a), close to the breathing zone or as area samples at locations judged to be important for the workers' exposure.

Additionally, production managers, factory physicians, industrial hygiene officers and the other safety staff in factories were interviewed about the processes and the peroxide use, about working habits and industrial hygienic circumstances. The inspectors of the Finnish Labour Inspectorate and representatives of H_2O_2 producers and importers were contacted. Exposure

(inhalation and dermal) was also evaluated with the EASE (Estimation and Assessment of Substance Exposure) model.

Quality of the existing data important for the exposure assessment

Exposure information submitted by industry (CEFIC, 1997c) for H_2O_2 production and loading for transport was limited and poorly described. The methods used for H_2O_2 measurements were often not reported. Sampling times were seldom reported and the number of collected samples was unknown. It was not clear whether the given result involved a single sample, if it was a mean of several samples, or if the measurements were done only once or repeatedly in some companies. In addition some short-term measurements were apparently converted to 8-hour averages resulting in very low concentrations.

In the hygienic survey reports from the Finnish Institute of Occupational Health (FIOH) Database, the method of sampling and analysis was liquid sampling (1 to 2 hours) and $TiCl_4$ spectrometry with a detection limit of 0.02 mg/m^3. At least four samples per workday were usually collected i.e. two during the morning shift and two during the afternoon shift. Details concerning processes, working habits and protective equipment were recorded. An agreement between the employer and the worker that the work practice was performed in a normal way was also recorded. Personal samples were collected with stationary sampling equipment at the worker's breathing zone as close to the worker as possible. Stationary area samples were collected in the factory halls further away from the emitting machines. Defects in the Finnish data are that the number of samples was small, repeated measurements in the factories were not performed, and that the measurements concerned only one or two companies per process type.

The three papers published in the open literature provide little information. Dietschmann (1996) measured hydrogen peroxide in creameries in order to compare the performance of the Polytron Sensor (Dräger) with the performance of the conventional titanium salt method. Apart from the method comparison, the results could, however, give some information about the peroxide concentrations at aseptic packaging machines at two creameries and one wine factory. The two other publications, Suenaka et al. (1984) and Kaelin et al. (1988), informed about exposure concentrations found in connection with clinical studies. In these reports, all the necessary details for the exposure assessment were lacking. For this report the figures are, however, handled as personal measurements.

Supposing that the Dräger-method and the method using liquid absorption with spectrometric determination were correctly applied, the results of these two methods of analyses were interpreted valid (Puskar and Plese, 1996; Dietschmann, 1996) and have been used for exposure estimations. In fact these methods are not strictly suitable for long-term H_2O_2 measurements, because the sampling times are only from a few minutes with Dräger tubes to the maximum of 1 to 2 hours with bubblers. Therefore, these short-term results represent at their best the true concentration in a workplace air during their respective sampling times. If the number of consecutive samples is large enough covering the whole work shift in a continuous process, reliable conclusions could also be drawn about 8-hour exposures.

All the results found published or recorded were single figures with no statistical analysis and lacking details necessary for later statistical handling. The number of observations was also insufficient. For this report some statistical calculations were done by calculating the overall mean levels ± standard errors of the means (x ± sem) per production job or a process. The figures given in the CEFIC report were understood as company means per one sampling occasion. These calculated figures may include errors and inaccuracy originating both from

sampling and analysis and errors from variations in the measurements in various companies. Further statistical analysis is impossible.

In spite of the inadequacy of the data concerning H_2O_2 exposure at work, the material shows that in continuous processes the mean 8-hour exposures seldom exceed the 8 hour-OELs, but higher short-term exposures are quite common and they may also exceed the STEL value. This was also confirmed during the site visits in Finnish factories using H_2O_2.

Use of hydrogen peroxide and sources of exposure

The major use of hydrogen peroxide (brochures of the producers; CEFIC, 1997c;d;e) is in bleaching processes of pulp and textiles. H_2O_2 is also widely used in the production of inorganic and organic chemicals. It forms perhydrates and peroxo compounds with alkali metal salts, which are further used for washing powders. It reacts also with organic acids to form peracids among which peracetic acid is the best known. Hydrogen peroxide and peracids react with unsaturated compounds to produce epoxides of which e.g. the modified natural oils are used as plasticisers and stabilisers for plastics and as ingredients in alkyd paint resins. Hydrogen peroxide and peracetic acid are further used as disinfectants. H_2O_2 is also used for etching of circuit boards and in metal plating baths. The amount of H_2O_2 (as 100%) used in various processes varies greatly, i.e. from a few litres per year in small metal factories to thousands of tonnes per year in pulp and paper mills.

For various purposes, H_2O_2 is available as aqueous solutions at various concentrations from 30 to 70%, the most common concentrations being 45-50% used for pulp bleaching and chemical syntheses. The concentrations of 35-50% are used for textile bleaching and industrial laundering, and the concentrations in range of 25-35% for disinfection purposes. The commercial concentrate of peracetic acid used for disinfection contains 15-30% of hydrogen peroxide.

In Finland, the number of plants using hydrogen peroxide at various concentrations is about 250 and the number of exposed workers is about 3,000. For the whole of Europe, the estimation of corresponding numbers is difficult because of the great variety of industries using the compound. If the small Finnish figures are multiplied by the ratio of the populations in the European Union countries and that of Finland (73.4), the number of factories using hydrogen peroxide in the European Union countries may amount to 18,500 factories and that of exposed workers to 225,000.

Worker exposure occurs generally via inhalation caused by peroxide vapour or water-peroxide mist escaping from open or half-open processes. There is also the possibility of receiving dermal exposure from splashes in the feeding phase of the peroxide to the processes and during the transfer operations of the compound. Workers' skin may also be exposed when wearing unsuitable or damaged protective gloves and clothing. In normal continuous work processes, the use of protective equipment is unusual but the equipment is generally available. In all the processes, the maintenance and transportation workers may be exposed accidentally to the peroxide.

According to the use of hydrogen peroxide, the processes and applications can be divided into three groups: major users, minor users, and processes and applications in which the products which contain hydrogen peroxide are used (mainly peracetic acid).

Major users

The major processes (pulp bleaching, chemical syntheses) use ca. 86% (CEFIC, 1997c) of the hydrogen peroxide produced. Also big textile factories (7%) and industrial laundries use H_2O_2 for bleaching of cotton material (and linen). These processes are practically closed, continuous

and automated systems. At the peroxide feeding phase, the concentrate (35-60%) is diluted for the process flow according to the process requirements. These major processes are mostly well ventilated, and the concentration of airborne hydrogen peroxide usually remains well below the occupational exposure limit (OEL; 1 ppm =1.4 mg/m^3) – often even lower than the detection limit of 0.01 ppm (0.02 mg/m^3). In these big plants, the only possibility of workers' exposure to higher concentrations concerns short-term maintenance operations, and via accidental splashes or leaks from the H_2O_2 feeding pipework, or during loading and unloading. The maintenance and transportation workers have the necessary protective equipment available, and they are trained to handle the peroxide safely.

Minor users

Industries using H_2O_2 (35%) in smaller amounts, such as creameries and the refreshment industry, use the compound for disinfection of the packaging material and the machines, electronic industry uses the compound for etching of circuit boards, and small dyeing shops for textile (cotton) bleaching. In these factories, the handling of the compound occurs either in automated, semi-automated or manual systems and the processes are half-open or open. The ventilation arrangement or its efficiency may be inadequate. The process workers are exposed continuously (4-8 hours) to low airborne H_2O_2 concentrations and occasionally (daily) to higher short-term (5-10 min) peak concentrations. The peroxide is moved into the process from small containers (30 l) with pumps, siphons or manually. Splashes and leaks are common. The workers may wear face protection and protective gloves, but not regularly. Protective aprons, overalls or shoes of relevant material are rarely used. In the smallest enterprises, there is often also a lack of knowledge about the hazards involved in handling hydrogen peroxide.

The manufacturing of and working with consumer products may also expose workers to hydrogen peroxide at various concentrations, e.g. during formulation of the products or in the optician's and hairdresser's work. In hairdresser's shops, the maximum airborne concentration of 0.20 mg/m^3 H_2O_2 was measured during hair bleaching. For medical purposes, H_2O_2 nowadays finds limited uses. Hydrogen peroxide is also used for bleaching and disinfection of dishes (in dishwashers) in the army, hospitals and restaurant kitchens.

Exposure from products containing hydrogen peroxide (peracetic acid)

Diluted peracetic acid solutions are used in industry as an effective disinfection agent (Flemming, 1984; Finnish Peroxides, 1998). The foodstuff industry uses peracetic acid for cleaning and disinfecting machines, equipment, pipework and surfaces. Laundries also use it for disinfection. The acid is also used in dilute solutions for disinfection on cattle farms. For disinfection purposes, the concentrate is usually diluted on site to concentrations ranging 0.02-1% just before use.

Occupational exposure limits (OELs)

In the European countries and the USA, the OEL of H_2O_2 for an 8-hour TWA exposure is 1.4 mg/m^3, and the short-term exposure limit (STEL) for a 5 to 15-min exposure is 3 mg/m^3 (CEFIC, 1997e).

In the USA (ACGIH, 2001), TLV-STEL was withdrawn in 1986. The TLV-STEL is marked with the notation A3, (confirmed animal carcinogen with unknown relevance to humans). There is also a warning for irritation in the German list (DGF, 1994).

Methods for measuring exposure

Airborne concentration

The airborne concentrations are usually measured with sample collection in bubblers followed by spectrophotometric (Pilz and Quapach, 1972; Pilz and Johan, 1974), fluorometric (Lazrus et al., 1985) or differential pulse polarometric (Chemetrics Inc., 1997) determinations in water solutions. Methods using peroxidase-catalyzed oxidation of H_2O_2 are also used in many studies: Le Lacheur et al. (1996) and Benitez et al. (1996) used a spectrophotometric method employing N,N-diethyl-p-phenylenediamine and Schick et al. (1997) a fluorometric method employing p-hydroxyphenyl acetic acid.

In an acidic water solution, titanium (Ti) salts give a coloured complex with hydrogen peroxide (Cohen and Purcell, 1967; Pilz and Quapach, 1972; Pilz and Johan, 1974; Schutz, 1987; Sellers, 1980) the concentration of which can be determined by spectrophotometry at λ=415 nm. With the Ti-methods the lowest detected concentration was found to be at 0.03-0.07 mg/m^3 (0.02-0.05 ppm) level with an air sample of 15 to 100 l. Chemetrics Inc. (1997) has developed a colorimetric method which is based on thiocyanate reagent. In this method, H_2O_2 oxidises ferrous ion to ferric ion resulting in the formation of a red thiocyanate complex which can be determined by spectrophotometry. In an acidic potassium iodide solution (OSHA VI-6 method; OSHA, 1978), the peroxide oxidation gives yellowish colour of iodine. The determination of iodine is performed by thiosulphate titration. The addition of ammonium molybdate accelerates the reaction. These methods may suffer from interference caused by other oxidising agents such as ozone and nitrogen oxides. All the bubbler methods are difficult to use for personal samplings.

Drägerwerk AG (1991) has developed a direct reading detector tube (Waserstoffperoxid 0,1/a) for H_2O_2. Its working range for determination is 0.14-4.2 mg/m^3 (0.1-3 ppm). The determination is based on a colour reaction between potassium iodide and H_2O_2. Chlorine, chlorine dioxide and nitrogen oxides may interfere.

Airborne hydrogen peroxide can also continuously be measured in real time at OEL concentration with analysers, such as an ion mobility spectrometer (IMS) of ETG (Environmental Technologies Group, Inc., Baltimore, MD, USA) or a "Polytron instrument", Polytron H_2O_2 measuring head of Dräger (Pittsburgh, PA, USA) or with a single point monitor (SPM equipped with the hydrogen peroxide Chemcassette) of MDA Scientific, Lincolnshire, IL, USA.

Puskar and Plese (1996) evaluated the Dräger-tube method, the OSHA VI-6 method and the three direct reading instruments. They found that the Dräger tube and SPM instrument did not function at low air humidity (<20 RH %), which is an important observation especially for the cold climate conditions. IMS and Polytron instruments as well as OSHA VI-6 method approximated well the NIOSH ± 25% method accuracy requirement for H_2O_2 concentration ranging from 0.7 to 7 mg/m^3 (0.5 to 5.0 ppm) in the air. The methods had estimated CVs (coefficient of variation) averaging from 5 to 6%. Digital read out of IMS was capable of recording 0.07 mg/m^3 (0.05 ppm), while with the Polytron the lowest read out was 0.14 mg/m^3 (0.1 ppm). Both these instruments gave false readings when exposed to nominal concentrations of methanol, chlorine, and sulphur dioxide. Also acetone interfered with the Polytron instrument. The performance of the Polytron instrument was also validated by Dietschmann (1996a;b). For the other methods mentioned before, except the Ti-salt method from Schutz (1987), no validation data were found.

Dietschmann (1996a;b) validated the performance of the Polytron Sensor instrument at two creameries and one wine factory. He compared the performance of the sensor, which reads the

concentration directly and continuously, with the performance of the titan oxalate dihydrate-method (Schutz, 1987) (**Table 4.1**). The Polytron Sensor method is based on an electrolyte solution and its electric conductivity, while the titan oxalate method functions by liquid absorption and spectrophotometry. The methods gave very similar results (the regression equation being y = 0.9374x + 0.0958; y = photometric conc. x = Polytron Sensor conc.). The photometric method showed a slightly higher result (only 3% higher at the concentration level of the OEL). The high standard deviations in the measurements are likely more due to the air concentration variations at the workplaces than to the method variations. As a result of this work, both methods seem to be suitable for the determination of airborne H_2O_2 concentrations.

Table 4.1 Method comparison by measuring parallelly with Polytron sensor and titanium oxalate method (Dietschmann, 1996)

Factory	Concentration, mg/m³	Titanium oxalate -method	Polytron sensor
Creamery A	Arithmetic mean ± sd, RSD, (n), range	1.19 ± 1.07; 90.0% , (6), 0.23 - 3.08	1.19 ± 1.05; 88.6%, (6), 0.84 - 2.80
Creamery B	Arithmetic mean ± sd, RSD, (n), range	0.93 ± 0.61; 65.6%, (9), 0.16 - 1.97	0.75 ± 0.68; 90.7%, (9), 0.18 - 2.80
Wine factory	Arithmetic mean ± sd, RSD, (n), range	0.29 ± 0.01; 21.4%, (4), 0.21 - 0.35	0.29 ± 0.11; 38.0%, (4), 0.16 - 0.41

Sd = standard deviation, RSD= relative standard deviation, n= number of samples. Sampling time 15 min for both methods.

Articles and reviews concerning the analytical methods of H_2O_2 at atmospheric concentrations have been written by Gunz and Hoffman (1990), Hartkamp and Bachhausen (1987), Kleindienst et al. (1988), Kok et al. (1978b; 1989), Sakugava et al. (1990) and Sakugawa and Kaplan (1992). Most methods aimed at atmospheric hydrogen peroxide determinations use enzymatic catalyzed principles (Thus and Fenstra, 1996).

Hydrogen proxide and organic peroxy acids have been determined in a mixture by Ledaal and Bernatek (1963) and Frew et al. (1983). Hydrogen peroxide and peroxyacetic acid were also simultaneously determined in brewery disinfection solutions by Pinkernell et al. (1997) with triphenyl phosphine and p-tolyl sulfide, respectively. The low detection limit for both compounds shows promise for the development of an analytical method for airborne samples as well.

Sampling at workplaces

For field measurements of airborne H_2O_2 Dräger indicator tubes or bubbler samplings and spectrophotometry are mainly used (see the previous section). The Dräger-Instrument (indicator tube) determinations are short-term (spot) determinations (5 to 10 minutes). The ambient conditions should be as follows: temperature from 10 to 25ºC and air humidity from 3 to 10 mg/l. The direct readable results show an exposure level in the air between 0.1 to 3 ppm (0.14 to 4.2 mg/m^3). The lowest approximation of the concentrations with the detector tubes is 0.07 mg/m^3.

For bubbler samples, titanium compounds are favoured as the colour-producing reagent for spectrophotometry. The liquid sampling restricts the average volume of sampled air to 100 l and the average sampling time to a maximum of 1.5-2 hours depending on the sampling rate (l/min). The lowest detection limit for the bubbler sampling with $TiCl_4$-determination is 0.02 mg/m^3.

The measurements with these two methods have the character of a short-term measurement. Therefore, for the estimation of an 8-hour TWA exposure, several consecutive samplings during work shifts ought to be collected. Neither of the methods is directly convenient for personal

samplings. "Personal samplings" are, therefore, mainly performed as static point measurements, but as close to the workers breathing zone as possible.

Today it is also possible to use instruments which measure exposures continuously in real time as mentioned above. The detection limit for the Dräger Polytron Sensor (Dietschmann, 1996) is 0.14 mg/m^3. However, published exposure data measured with these instruments were not yet available.

Scenarios of occupational exposure to hydrogen peroxide

The following scenarios of industrial use of H_2O_2 were chosen on the basis of industry data (CEFIC, 1997e) and after interviewing various industrial and commercial experts. The overview of the industrial use categories and exposure scenarios is given in **Table 4.2**. The figures in the parentheses are the Numbers of Standard Industrial Classification (SIC).

Table 4.2 Scenarios for industrial categories and use of hydrogen peroxide

Industrial category	Use
Manufacture of chemicals: - Production of hydrogen peroxide (H_2O_2) (241): synthesis, distillation, stabilisation, dilution, laboratory, general works and storage	- Bleaching agent, disinfectant, oxidiser/reductant in further syntheses
- Synthesis of other chemicals: epoxidation, hydroxylation, and manufacture of inorganic and organic peroxides and peracids (24-245)	- Use for product formulations, e.g. for detergents, plastic plasticisers and stabilisers, chemicals for environmental and water treatment, pharmaceutical and hygienic products
Loading, unloading and transportation (60-61)	Drum, tank, road/rail tanker: loading, unloading, transportation. Small container filling and transportation
Bleaching: - Pulp and paper industry (21) - Textile industry and industrial laundering (171-2, 93)	Bleaching of pulp and recycled paper Bleaching of raw cotton and textiles in dyeing shops Bleaching in industrial laundries
Disinfection: - Food processing industry (15)	- In creameries and other food processing factories: disinfection of machines, equipment, packaging material and premises,
- Use of peracetic acid for disinfection	- In breweries, meat processing factories, cheese and sugar factories: disinfection of machines, equipment, packaging material and premises
Other processes: Electronic industry (31-32) Metal plating (27-35)	- Etching of electronic circuit boards - Cleaning of metal plating baths
Other industrial uses: - Production of modified starch - Degrading proteins	- For paper coatings - Peptide production

Table 4.2 continued overleaf

Table 4.2 continued Scenarios for industrial categories and use of hydrogen peroxide

Industrial category	Use
Water treatment and environmental applications (41, 90)	Purifying of: - Drinking water - Wastewater (industrial and domestic) - Environment
Hairdresser's work (93021)	- Hair dyeing - Hair bleaching - Setting a perm

4.1.1.1.2 Manufacture of chemicals

Production of hydrogen peroxide

The predominant industrial method for the production of hydrogen peroxide (Goor et al., 1989) is the anthraquinone autoxidation process. The crude aqueous hydrogen peroxide from the extraction stage (H_2O_2 15-40%, w/w) is concentrated by distillation, diluted further to commercial products of 30-70% (w/w) and collected in storage tanks. The product is stabilised.

Hydrogen peroxide production is an automated, closed and continuous process. Some exposure to the compound may incidentally occur during distillation, stabilisation, dilution and sampling/laboratory works. Small leaks may also occur.

CEFIC (1997e, Appendix D) reports on occupational exposure measurements during 1985-1995 (**Table 4.3**). When summarising the exposure at different assignments, the personal 8-hour TWA exposures ranged from 0.24 to 0.79 mg/m^3, the overall mean being 0.37 ± 0.05 (sem) concerning four different jobs. Area concentrations (8-hour TWA) were measured only at stabilisation with a mean concentration of 0.24 ± 0.14 (sd), n=2. The short-term exposures (15 min) ranged from <0.01 to 1.85 mg/m^3 with the overall mean of 0.55 ± 0.26 (sem) concerning two different assignments, laboratory work and diverse tasks. The highest short-term mean, 0.92±0.66 mg/m^3 (sd), n=6, was measured in the laboratory where the highest measured peak value was 3.6 mg/m^3. At stabilisation and dilution, peak concentrations of 5.66 and 6.34 mg/m^3, respectively, were found indicating probably occasional incidents, and one measurement gave 10.2 mg/m^3 which was caused by a leaking valve. The results show that the measured 8-hour TWA airborne mean concentrations were well below the OEL (1.4 mg/m^3 8-hour TWA), but incidental short-term exposures at stabilisation, dilution and laboratory jobs could sometimes be higher than the 15-min STEL (3 mg/m^3).

The highest personal exposure in production (reasonable worst case), 0.8 mg/m^3, was at stabilisation.

Table 4.3 Occupational exposure at production of H_2O_2 (according to data from CEFIC, 1997e, Appendix D)

Chemical manufacture/job	Personal exposure	Area concentration	Short-term exposure	Highest value measured	Method
Production of hydrogen peroxide	**Mean ± sd, (n), range, mg/m³**	**Mean ± sd, (n), range, mg/m³**	**Mean ± sd, (n), range, mg/m³**	**mg/m³**	**(m)**
- Synthesis	0.24 ± - (1)	-	-		Dr (2)
- Distillation	0.4 ± - (1)	-	-		Dr (2)
- Stabilisation	0.52 ± 0.22 (3) 0.26-0.79	0.24 ± 0.14 (2) 0.10-0.37		a) 5.66	Dr (4), ns (2), lq (1)
- Dilution	-	-	-	b) 6.34 (area)	lq (1)
- Laboratory	0.32 ± 0.22 (3) 0.02-0.5	-	0.92 ± 0.66 (6) 0.11-1.85	3.6	Dr (6), ns (2)
- Other jobs - Storage, packaging	-	-	0.18 ± 0.26 (8)<0.01-0.85	c) 10.2 (leak)	ns (4), lq (2), Dr (1), pm (1)

x= arithmetic mean, n= number of measured events, M= number of various jobs, sd= standard deviation, sem= standard error of the mean, ns= not stated, lq= liquid absorption, Dr= Dräger instrument, pm = portable monitor , m= use frequency for the method
a) over opened vessel, b) not stated what happened, c) unmanned pump house, leakage

The EASE model for hydrogen peroxide (outdoor) production predicts that inhalation exposure to the vapour (under conditions presented below) is 4.2-14 mg/m^3 (3-10 ppm). The volatility of the substance is low. This EASE prediction corresponds best with the measured short-term (worst-case) incidents. If the pattern of control is LEV, the prediction corresponds better with the measured data. EASE predicts that incidental dermal exposure to hydrogen peroxide ranges 0-0.1 mg/cm^2/day.

Input parameters for inhalation exposure, incidental

Physical state: liquid
Weight fraction: 70%
Temperature: 30 °C
Vapour pressure: 0.19 kPa
Aerosol forms: no
Pattern of use: non-dispersive
Pattern of control: segregation
Exposure: 4.2-14 mg/m³ (3-10 ppm)

Input parameters for dermal exposure, incidental

Physical state: liquid
Weight fraction: 70%
Temperature: 30 °C
Pattern of use: non-dispersive
Pattern of control: direct handling
Contact: incidental
Dermal exposure: 0-0.1 mg/cm²/d

Synthesis of other chemicals

Chemical reactions in which hydrogen peroxide is a reaction partner are substitution or redox-reactions. Inorganic persalts and organic peroxides are the largest applications. The chemical industry uses 246 kt/a (as 100% substance, 38% of the total consumed) of H_2O_2 (CEFIC, 1997d) at various concentrations.

Other peroxides

Ca. 57 kt/a (CEFIC, 1997d) of peroxide produced is used for the production of other peroxides.

Hydrogen peroxide forms perhydrates and peroxo compounds with alkali metal salts. The best known compounds are sodium perborate and sodium carbonate peroxo hydrate which are the major ingredients of washing powders.

Hydrogen peroxide reacts easily with aldehydes, ketones and organic acids yielding organic peroxides and peracids (Tobolsky and Mesrobian, 1954; Swern, 1971). H_2O_2-derived oxygen can readily be converted to a peroxy acid by the reaction with an organic acid or an anhydride. Peracetic acid is an equilibrium product prepared from hydrogen peroxide, acetic acid or acetic anhydride and water. Diluted peracetic acid solutions are used as disinfectants (Kirchner, 1979; Flemming, 1984).

Hydrogen peroxide is also used for producing organic peroxides, which are further used as initiators in polymer syntheses and as curing agents in polymer chemistry (e.g. methylethyl ketone peroxide, benzoyl peroxide, dicumyl peroxide). Methyl ethyl ketone peroxide is prepared commercially by the reaction of methylethyl ketone with hydrogen peroxide (Chan et al., 1991). The product is used as a hardener for curing unsaturated polyester resins in the production of fiberglass reinforced plastics.

Epoxidation with hydrogen peroxide

The epoxidation of unsaturated compounds with hydrogen peroxide is an important commercial reaction (Swern, 1970) in which ethylenic unsaturation is converted directly to oxirane (1,2-epoxide, α-epoxide) by reaction with a peroxy acid, either preformed or generated *in situ.* Compounds with multiple saturation can also be epoxidised, either partially or completely, depending on the quantity of H_2O_2 used.

The active oxygen in H_2O_2 (Tobolsky and Mesrobian, 1954) is not readily available for most organic oxidation reactions, but the oxygen can be used by conversion of H_2O_2 to peroxy acid. It is sufficient to dissolve or disperse the substance to be oxidised in an organic acid or anhydride and add H_2O_2. Temperatures above room temperature and a strong acid catalyst may be required. As the peroxy acid is formed, it is immediately consumed and, since its formation is an equilibrium reaction, the peroxy acid, which is an intermittent compound, will continue to be formed and consumed until no oxidisable substance remains, provided the amount of H_2O_2 is enough.

Industry using epoxidised products
- examples of terminal applications of epoxidised compounds (Swern, 1971):

- epoxidised tallates and oleates can be used both as primary plasticisers and stabilisers for polyvinyl chloride (PVC) formulations, epoxidised soybean oil is a stabiliser for PVC plastics and PVC paint plastisols,
- use as an inexpensive modifying agent in alkyd resins, polyesters, epoxy resins, all of which are used in surface coatings and adhesives,
- emulsions of the epoxidised oils are valuable additives for paper, fabrics and leather production to improve the shrink, crease and abrasion resistance as well as wet strength,
- epoxidation of the latexes of butadiene/styrene co-polymer used as paper chemicals,
- non-ionic detergents are prepared from polyethylene glycol and epoxidised soybean oil,
- lubricant additives are produced from epoxidised fatty materials,
- epoxidisation is also needed in the syntheses of herbicides.

The large processes such as the production of sodium perborate and sodium percarborate take place in closed systems (Degussa-Hülls, 1999), which are fully automated sequels (units) of the H_2O_2 production, i.e. H_2O_2 is directly fed into the process in pipes from H_2O_2 storage tanks

which are parts of the H_2O_2 production systems. The reaction vessels themselves are kept under reduced pressure. The exhaust gases from the vessels are fed into wet exhaust cleaning devices. Therefore there is essentially no possibility for exposure to H_2O_2 or at least the exposure is very low in the perborate and percarbonate production. In a plant producing persalts, a measurement performed close to an aerated buffer tank gave as a result < 0.07 mg/m^3 (0.05 ppm). According to an EASE WIN 2.0 calculation, the 8-hour exposure via inhalation in closed systems is low 0-0.14 mg/m^3 (0-0.1 ppm). The dermal exposure is also very low. Incidental exposures, however, are possible and may occur via leakage in pipe connections and also later via spills during loading operations (see loading operations). The workers may use personal protective equipment during maintenance operations and during accidental occasions.

The type of exposure is inhalation (8-hour)

The temperature of the process is 100 ºC
The physical-state is gas or vapour
The exposure-type is gas/vapour
The ability-airborne-vapour of the substance is high
The use-pattern is automated, continuous and closed
Significant-breaching is false
The pattern-of-control is full containment
The predicted gas/vapour exposure to hydrogen peroxide is 0-0.14 mg/m^3 (0-0.1 ppm)

The type of exposure is dermal

The predicted dermal exposure to hydrogen peroxide is very low

In larger units, the synthetic processes are automated and closed, whereas in smaller plants, they are mainly batch processes. The exposure may take place at the starting phase of the synthesis i.e. during weighing and mixing operations before closing the reactor. This charging task lasts usually about 30-45 minutes at a time and occurs normally once per shift. Thereafter the process is practically closed. Mechanical general ventilation and local exhausts are common. During these weighing and mixing operations the airborne concentrations of H_2O_2 were measured to vary between 0.14 and 0.7 mg/m^3 (0.1-0.5 ppm; mean 0.3 mg/m^3; n= 6; CEFICc, 1997). According to the EASE WINDOW Version 2.0, the predicted exposure to H_2O_2 during this charging operation is 0.7-1.4 mg/m^3 (0.5-1.0 ppm)**.** This corresponds with the short-term exposure i.e. charging. The reasonable worst-case exposure during this "short" operation may be the highest EASE WIN 2.0-prediction of 1.4 mg/m^3 or a little higher of 2.0 mg/m^3. After that, when the reactor is closed, the exposure is reduced fairly fast even with natural ventilation. Incidental exposures from splashes may occur during charging, of course, and these may increase the vapour concentration of the compound. The worker may use protective equipment during this exposing phase of the process.

The reasonable worst case (8-hour) for closed systems is 0.2 mg/m^3 and for batching process 0.5 mg/m^3. For short-term exposure during batching, the RWC is 2.0 mg/m^3.

The type of exposure is inhalation

The temperature of the process is 25ºC
The physical-state is liquid
The exposure-type is gas/vapour
Aerosol-formed is false
The use-pattern is non-dispersive use
The pattern-of-control is LEV
The status-vp-value 0.046 kPa at 22 ºC
The vp-value of the substance 0.0553kPa (calcul.)
The volatility of the substance is low
The ability-airborne-vapour of the substance is low
The predicted gas/vapour exposure to hydrogen peroxide is 0.7 - 1.4 mg/m^3 (0.5-1.0 ppm)

The type of exposure is dermal

The use-pattern is non-dispersive use
The pattern-of-control is not direct handling
The predicted dermal exposure to hydrogen peroxide is very low

4.1.1.1.3 Loading operations

Hydrogen peroxide is transported to the users in special containers (Kirchner, 1979; CEFIC Peroxygen Sector Group; Ausimont Spa; Degussa AG; Solvay Interox S.A.). Large vessels such as road tankers, rail cars and ISO containers are mostly made of carefully selected grades of stainless steel, although aluminium is also used. The production and surface preparation standards are very strictly followed to prevent hazardous decomposition. Tank cars and trucks are used to ship grades containing up to 60 wt % of H_2O_2. Grades with higher concentrations are shipped in special double-headed drums, or aluminium tank trucks or cars. The volume of a large transportation vessel is up to 40 m^3. The containers designed for H_2O_2 transportation are not used for other transportation.

The valves of the truck tanks to be connected to the storage tanks are of special size in order to avoid a misunderstanding. The large factory storage tanks of passivated aluminium or stainless steel (volume up to 1,000 m^3) are situated outdoors. The tanks are well protected against leaks while standing on concrete and having overflow control systems. Accidentally occurring leaks are rinsed with water into the drain. The storage tanks are directly connected to processes.

The peroxide is also supplied in smaller containers such as drums and Intermediate Bulk Containers (IBCs). Specific grades of high-density polyethylene are the most commonly used materials for the vessels for strengths up to 60 wt % of H_2O_2. More concentrated substance requires specific packaging in aluminium or stainless steel. The drivers are equipped with protective equipment and are trained for the possibility of accidents.

A summary of the exposure data concerning loading provided by industry (CEFIC, 1997e, Appendix D) is given in **Table 4.4**. During filling of drums/small containers and when loading road/rail tankers the personal 8-hour exposures ranged from 0.18 to 1.05 mg/m^3 of hydrogen peroxide in air, the overall mean being 0.47 ± 0.02 (sem). The full-shift airborne area concentrations ranged 0.03-1.75 mg/m^3; the overall mean was 0.79 ± 0.30 (sem). Short-term concentrations varied from <0.2 to 3.5mg/m^3, the overall mean was 1.08 ±0.36 (sem). A high short-term incidental value of 15 mg/m^3 was measured in tanker loading, but the worker had worn respiratory protection.

The highest exposures are likely to occur at drum filling. The 8-hour measured area concentrations had a mean of 1.21 mg/m^3 (n= 9) and the short-term area measurements gave the mean of 1.58 mg/m^3 (n= 15). The highest single short-term area value measured was 3.5 mg/m^3. The personal 8-hour exposures had a mean of 0.44 mg/m^3 (n= 3), whereas the personal

short-term exposure had a mean of 1.80 mg/m^3 (n= 3), and the highest personal short-term value measured was 2.83 mg/m^3. All the personal exposures were measured in different occasions or workplaces. Thus, the given personal mean 8-hour exposure value for drum filling appears be too low when compared both with the area and short-term measurements. The worst-case personal 8-hour exposure during drum filling was judged to be 2.0 mg/m^3; the exposure may be composed of repeated variably high-peak concentrations.

No exposure data were found for transportation or unloading, but it can be anticipated that the 8-hour exposure would be lower than that for loading. Higher exposures could occur in accidental events.

Table 4.4 Occupational exposure at loading of H_2O_2 (according to data from CEFIC, 1997e, Appendix D)

Work	Personal exposure	Area concentration	Short-term exposure	Highest value measured	Method
Job	**Mean ± sd, (n), range, mg/m^3**	**Mean ± sd, (n), range, mg/m^3**	**Mean ± sd, (n), range, mg/m^3**	**mg/m^3**	**(m)**
Drum small cont. filling	0.44 ± 0.13 (3) 0.25-0.56	1.21 ± 0.44 (9) 0.5-1.75	1.58 ± 0.91 (15 areas) 0.5-3.5, 1.80±1.18 (3 persons)	3.50 (area) 2.83 (pers.)	ns (15), Dr (1), lq (4)
Tank filling	0.50 ± 0.32 (5) 0.18-1.05	0.37 ± 0.48 (3) 0.03-1.05	0.57 ± 0.50 (7)<0.2-1.3	[d] 15 (area)	Ns (9), Dr (8), lq (1)

x= arithmetic mean, n= number of measured events or samples, sd= standard deviation, sem= standard error of the mean, ns= method not stated, Dr= Dräger instrument, lq= liquid absorption sampling, (m) = use frequency for the method, d) respiratory protection worn

During loading operations (outdoors) the EASE model predicts that inhalation exposure to the vapour of substance, which is not directly handled, results by the patterns of use and control (segregation) presented below in a high exposure range of 4.2-14 mg/m^3 (3-10 ppm). If the pattern of control was LEV, the EASE prediction (0.7-4.2 mg/m^3)) corresponds better with the measured values. The volatility/ability of the substance to become airborne is low. According to the EASE model an incidental dermal exposure to hydrogen peroxide is 0-0.1 mg/cm^2/day.

Input parameters for inhalation exposure *

Physical state: liquid
Weight fraction: 50%
Temperature: 30 °C
Vapour pressure: 0.14 kPa
Aerosol forms: no
Pattern of use: non-dispersive
Pattern of control: segregation
Exposure: 4.2-14 mg/m^3 (3-10 ppm)

Input parameters for dermal exposure *

Physical state: liquid
Weight fraction: 50%
Temperature: 30 °C
Vapour pressure: 0.14 kPa
Pattern of use: non-dispersive
Pattern of control: direct handling,
Contact level: incidental
Dermal exposure: 0-0.1 mg/cm^2/d

* The input parameters represent the worst-case thinking

4.1.1.1.4 Use for bleaching

Pulp and paper bleaching

Pulp and paper industry (chemi-mechanical, chemical and recycled fibre pulp) is the biggest user of peroxides: 322 kt/a (100%), which is 48% of the total amount consumed (CEFIC, 1997c;d;

Ausimont Spa; Degussa AG; Solvay Interox S.A.). The peroxide supplied is a distillate from hydrogen peroxide production, the concentration ranging from 35 to 60%. In the pulp mills, the peroxide consumption ranges between 1,000 and 12,000 t/a (100%) depending on the size and the type of the process. The production capacity in major plants is up to 700-1,000 kt/a of pulp. The peroxide is transported to the mills in road/rail tankers (volume: 10-40 t/tanker) and stored in bulk tanks of 50 to 1,000 m^3.

The processes are continuous (24 h/d, 360 d/a), automated, often underpressured and practically closed systems. The peroxide concentrations in the mass flow (fibre concentration 5-20%) are some 0.5 to 4% (as 100% substance) depending on the whiteness of the final pulp required. The normally applied process temperatures range between 40 and 75°C.

The only measurement results of airborne H_2O_2 during bleaching in the pulp and paper industry were located in the FIOH database (1997) (**Table 4.5**). In a chemi-mechanical pulp process, the airborne H_2O_2 exposure ranged between <0.07 and 0.3 mg/m^3 (mean 0.18 ± 0.13 (sd) mg/m^3, n = 5). The method of the measurement was liquid absorption with spectrophotometry.

During a site visit at a chemical bleaching process, airborne H_2O_2 concentrations in factory halls were found with Dräger tubes to be undetectable (<0.07 mg/m^3, n = 10). During the same visit a leak of 50% hydrogen peroxide was found in an unmanned pump room. Dräger tubes indicated an airborne concentration of approximately 9 mg/m^3 in the room.

There were no data available of airborne H_2O_2 levels during bleaching of recycled paper. The concentrations may, however, be at the same low level as those in other continuous pulp processes, because the mills use H_2O_2 for bleaching in an analogous way.

In the laboratory of a chemical pulp mill, the measurements showed minimal exposure to H_2O_2 (< 0.02 mg/m^3, n = 5; liquid absorption and spectrophotometry; FIOH database). The work was performed in a fume cupboard.

Because of the limited measurement data industrial hygienists performed a site visit to one of the biggest pulp and paper mills in Finland as mentioned above. Additionally, production managers and foremen, factory physicians, industrial hygiene officers and other safety staff from other mills were interviewed by telephone.

Pulp and paper mills are today highly automated continuous processes. Process workers' exposure conditions are well under control and they spend most of the time in well-ventilated control rooms. In the flowing mass, H_2O_2 concentration is relatively low (4 down to 0.5%). Therefore even during maintenance operations at the process lines the airborne exposure is unlikely to be very high. Some exposure may occur in the very beginning of the process when H_2O_2 is diluted and fed into the process lines. Such occurrences would however be incidental because the facilites are unmanned. If incidental situations caused by leaks are not accounted for, the worst-case airborne exposure (for 8 hours) is not higher than 0.7 mg/m^3.

Workers are equipped with protective equipment in relevant material, and they are also trained to act in case of accidents.

Table 4.5 Occupational exposure to H_2O_2 in pulp and paper mills (FIOH database and a site visit)

Industry	Area concentration, mg/m³	Short-term exposure, mg/m³	Highest value measured	Method
Pulp and paper, continuous processes	**Mean ± sd (n) range, [M]**	**Mean ± sd (n) range**	**mg/m³**	
Chemi/mechanical process	0.18±0.13 (5) <0.07-0.3 [1]	-	0.3	Iq
Chemical process	<0.07 (10) [1]	-	c) ~ 9	Dr
Laboratory	>0.02 (5) [1]	-	-	Iq

n = number of measured samples, M= number of mills, sd= standard deviation, Dr= Dräger instrument, Iq= liquid absorption sapling,
c) leakage in an unmanned pump room

For the pulp bleaching processes, the EASE model predicts that inhalation exposure to vapour, which is not directly handled, results, with the patterns of use and control as presented below, in a very low exposure range of 0-0.14 mg/m³ (0-0.1 ppm) corresponding to the measured values. The volatility and the ability of the substance to become airborne are also low. The EASE model predicts that incidental dermal exposure (e.g. from splashes) to hydrogen peroxide is also very low.

Input parameters for inhalation exposure in pulp bleaching

Physical state: liquid
Weight fraction: 4%
Temperature: 75 °C
Vapour pressure: 0.13 kPa
Aerosol forms: no
Pattern of use: non-dispersive
Pattern of control: full-contaiment
Exposure: 0-0.14 mg/m³ (0-0.1 ppm)

Input parameters for dermal exposure in pulp bleaching, incidental splashes

Physical state: liquid
Weight fraction: 50%
Temperature: 25 °C
Pattern of use: non-dispersive
Pattern of control: not direct handling,
Contact level: incidental
Dermal exposure: very low

Bleaching of textiles and industrial laundering

Dyeing houses

A large single use of hydrogen peroxide is the bleaching of textiles, mainly of cotton (47 kt/a; CEFIC, 1997d; Ausimont Spa; Degussa AG; Solvay Interox S.A.). A minor amount is used to bleach, cotton-synthetic blends, wool, silk, and some other vegetable or animal fibres. In dyeing houses, 95% of the peroxide is used for the bleaching and the rest amount for oxidising of textile colours.

Cotton fabrics are bleached with hydrogen peroxide in stabilised alkaline H_2O_2 solutions at 80-95°C. The H_2O_2 concentration in the bleaching solution varies from 7 to 25 g/l (100%) in the hot bleaching and from 30 to 40 g/l in cold bleaching, i.e. 0.7-2.5% and 3-4%, respectively. In a bigger textile factory the H_2O_2 consumption of 35-50% H_2O_2 ranges from 100 to 200 t/a.

In big plants, bleaching is a continuous automated process in practically closed systems with local exhausts and mechanical general ventilation in the hall. The peroxide is supplied and transported in tankers, stored in 10 m³ tanks outdoors, and pumped via dilution to the automated bleaching process. In smaller factories, the process conditions may vary greatly being continuous, automated or semi-automated, but open. Numerous dye houses are, however, small enterprises doing bleaching as batch processes in smaller machines, such as normal washing

machines. The peroxide (35%) is purchased in tanks (800 l), barrels (80 l) or in polyethylene containers (30 l), and the substance is often dosed manually into the machines.

In textile bleaching, exposure to hydrogen peroxide arises from incidental leaks from pipework connections in automated processes and from splashes when handling the product manually. Protective equipment may be used, but not always in smaller enterprises.

Industrial laundries

Big industrial laundries washing 2-6 million kg/a of clothing and linen use peroxide bleaching in the similar way as the textile factories do. The washing machines are automated and practically closed washing lines ("tube" machines). A big automated laundry may consume 20 t/a (100%) of hydrogen peroxide as 3-35% solutions. Small amounts of peracetic acid used for disinfection with 15-30% of H_2O_2 are included. The H_2O_2 concentration in wash water during the bleaching is about 0.1 g/l (0.01% of 100% substance).

During the site visit by a FIOH industrial hygienist the measured airborne H_2O_2 concentrations in an industrial laundry between and around the machines (two parallel lines) remained less than the detection limit of the method (< 0.07 mg/m^3). The factory hall was large and generally well ventilated and the machines had local exhausts. Exposure to H_2O_2 may only arise from small leaks in the storage room (unmanned pump room) of the washing chemicals, where the peroxide barrels (200 l) were connected to the machinery pumps.

Exposure

Concerning the use of hydrogen peroxide in dyeing and laundering there were no measurement data on exposure. When the processes are closed, automated and continuous the workers airborne exposure to H_2O_2 normally remains low. In small factories, manual charging of the machine is usual and may cause short-term peak exposures. When the machine is closed and started exposure is stopped. If the dyeing is made (nearly) manually in open systems e.g. when dyeing very sensitive natural fibres such as wool, the batches are small and thus the chemical consumption is also small.

For textile bleaching (and laundering), EASE WIN 2.0 modelling predicts that inhalation exposure to vapour, which is not directly handled, results with the patterns of use and control as presented below in a very low exposure range of 0-0.14 mg/m^3. The volatility and the ability of the substance to become airborne are also low. Exposure is higher at the batch machines, but corresponds to short-term exposure, i.e when the batch is charged. The EASE model predicts that intermittent dermal exposure (e.g. from splashes) to hydrogen peroxide is 0.1-1 mg/cm^2/day.

The type of exposure is inhalation (closed system)

The temperature of the process is 95
The physical-state is liquid
The exposure-type is gas/vapour/liquid aerosol
Aerosol-formed is false
The use-pattern is closed system
Significant-breaching is false
The pattern-of-control is full containment
The status-vp-value is: measured at process temperature
The vp-value of the substance is 0.33
The volatility of the substance is low
The ability-airborne-vapour of the substance is low
Conclusion: The predicted gas/vapour/liquid aerosol exposure to hydrogen peroxide is 0-0.1 ppm

The type of exposure is dermal (closed system)

The use-pattern is non-dispersive use
The pattern-of-control is not direct handling
Conclusion: The predicted dermal exposure to hydrogen peroxide is very low

The type of exposure is inhalation (short-term batching)

The temperature of the process is 95° C
The physical-state is liquid
The exposure-type is gas/vapour/liquid aerosol
Aerosol-formed is false
The use-pattern is non-dispersive use
The pattern-of-control is direct handling
The direct-handling is direct handling with dilution ventilation
The status-vp-value is measured at process temperature
The vp-value of the substance is 0.33 kPa
The volatility of the substance is low
The ability-airborne-vapour of the substance is low
Conclusion: The predicted vapour exposure to hydrogen peroxide is 14.1-28.2 mg/m^3 (10-20 ppm) during 30 min per shift

The type of exposure is dermal (short-term batching)

The use-pattern is non-dispersive use
The pattern-of-control is Direct handling
The contact-level is Intermittent
Conclusion: The predicted dermal exposure to hydrogen peroxide is 0.1-1 mg/square cm/30 min per shift

In the automated process, inhalation exposure (reasonable worst case) for 8 hours is 0.2 mg/m^3. For the batch process the mean exposure calculated over 8 hours is 1.0-1.8 mg/m^3 [assuming the short-term exposure for 30 min/shift (3 charges/shift) and the level of 0.1 mg/m^3 for the remaining worktime]. The calculated level of exposure for the batch process is probably overestimated, and it is proposed to use the lower end (1 mg/m^3) as the reasonable worst case.

4.1.1.1.5 Use for disinfection

Aseptic packaging

Hydrogen peroxide has an important use in the production of dairy products in creameries which pack various aseptic milk products and juice, and in the refreshment drink industry (Ausimont Spa; Degussa AG; Solvay Interox S.A.). The packaging materials are disinfected with concentrated (35%) hydrogen peroxide solutions of specially purified grade before the material is used for food packages. The disinfection is performed either by an immersion bath or a spray process. One type of spray machines use prediluted solutions of 2% H_2O_2. The machines packaging foodstuffs aseptically in dishes, cartons, jars, tubs, bottles are automated, but not totally closed and so the peroxide can escape into the workplace atmosphere. During every work shift, the total packaged amounts of the products are tens of thousand litres in dishes of 0.2 to 1 litre by volume.

In the immersion bath process, the packaging material (sheets of laminated paper, plastic or laminated aluminium) passes through a bath of 35% hydrogen peroxide in order to disinfect it. After immersion in the bath, rollers remove extra peroxide from the packaging material and the remaining film of the solution is then evaporated with sterile hot air at ca. 100°C. Thereafter the casing is formed and filled. The exhaust peroxide vapour coming out of the machine is from the top caught by local exhausts. During the work shift, the hydrogen peroxide strength in the immersion bath is gradually used up, therefore, the solution has to be boosted or totally changed every day at the end of the shift.

The spray method is used for packaging materials of preformed or partly preformed packs and tubes. Depending on the size of the receptacle, an amount of up to 1 ml of (2 or 35%) hydrogen peroxide is sprayed or nebulised stepwise via a nozle to disinfect the receptacle. After that, the excess of peroxide is evaporated with hot sterile air at ca. 130 °C and at one type of machine the receptacles are additionally sterilised with UV-radiation. The receptacle is then filled and sealed. The hot exhaust air is caught from these overpressured, semi-closed machines with local exhausts also in these methods and conducted out. Temperatures of about 180-200°C are usual for the evaporation unit.

Hydrogen peroxide consumption in a medium creamery is around 20 to 100 t/a of 35% H_2O_2. The peroxide is supplied either in small polyethylene containers (30-60 l), 200 kg barrels or in smaller tanks (ca. 800 l). In the beginning of the work shift (immersion bath method), the amount of the peroxide needed (3-10 l) is either pumped to the reservoir of the machine or moved there manually with a can (in the older type of machines). In the end of the shift, the remaining peroxide is conducted from the reservoir to the drain and washed down with water. In the spray type machines, the amount of consumed H_2O_2 may go up to 15 l of the peroxide during a shift depending on the capacity of the machines and the degree of its use.

Depending on the number of machine lines in operation two to seven operators are working at the machines. In addition to supervising the functioning of the machine at the filling points, one operator has occasionally to check the peroxide reservoirs and the movement of the packaging material at the disinfecting point.

Three reports concerning occupational exposure measurements were found in the open literature (Dietschmann, 1996a;b; Kaelin et al., 1988; Suenaka, 1984). The reports of two creamery surveys were also stored in the FIOH database (1985; 1986). The published papers were lacking any detailed information. These results are, however, handled as personal measurements, because it seemed that there was no idea to measure the concentrations in the surrounding area. Additionally, two industrial hygienists made site visits in two Finnish creameries and checked peroxide concentrations in the air with Dräger tubes. Although the sampling times were short and restricted by the sampling method, the measured values can be argued to represent the exposure levels because several samples were collected consecutively for most of these continuous processes.

According to the results (**Table 4.6**) the "semi-closed" packaging machines of immersion-type released hydrogen peroxide into the hall (general air) resulting in concentrations which ranged from 0.20 to 0.70 (overall mean 0.50±0.14 sem; 3 creameries) mg/m^3. The personal average exposure of the machine operator was 0.34-1.5 (mean 0.81±0.21 sem; 4 creameries) mg/m^3 when working at the floor level next to the machine, but on the average higher (calculated mean 1.13 mg/m^3) when intermittently visiting once per hour for 10 min at the maintenance level. At the maintenance level (short-term exposure), the airborne concentrations were measured and varied between 1.06 and 4.5 (mean 2.74±0.58 sem; 5 creameries) mg/m^3. Occasional peak concentrations

up to 4.5 mg/m^3 were measured in the normal processes. One short-term exposure approximation of 6-7 mg/m^3 was made as a Dräger-tube measurement during the site visit. Higher concentrations of 12 mg/m^3, and 41 mg/m^3 transiently, were measured by Kaelin et al. (1988), when no mechanical ventilation was available at the packaging line. But afterwards when mechanical ventilation was in function the exposures were lowered to 1.5 and 4.5 mg/m^3, respectively.

At the spray-type machines**,** the concentration in general air ranged <0.14-0.57 (mean 0.20±0.12 sd, n=9 samples, 1 creamery) mg/m^3. The operator's personal exposure ranged from 0.1 to 1.19 (mean 0.73±0.20 sem; 5 creameries) mg/m^3, but may be higher in view of the worker's visits about once per hour at the sterilisation station. At the sterilisation station, where the working was periodical, the average concentration varied from 0.96 to 1.83 (mean 1.40±0.31 sem; 2 creameries) mg/m^3. Occasional peak exposures found were measured up to 3.08 mg/m^3 at the station.

Summarising the exposure for both types of machines the overall mean personal 8-hour exposure was 0.76 mg/m^3 and thus less than the OEL level. However, the measurements show that some workers have encountered exposures at or even above the OEL. For short periods of working time (at the maintenance level) the exposure was on average 2.35 mg/m^3 which is 78% of the STEL value for 15 min. The creamery processes are continuous with little variation in the process during working shifts. Generally, the machines are situated in large halls which are equipped with mechanical ventilation, and the semi-open packing machines are equipped with local exhausts. The exposure in the vicinity of the machines is quite stable.

The reasonable worst-case personal exposure to hydrogen peroxide over a work shift (8 hours) for a desinfection machine operator was considered to be 1.5 mg/m^3.

Table 4.6 Hydrogen peroxide exposure in creameries (mg/m^3)

Disinfecting method	**Personal exposure**	**Area concentration**	**Short-term exposure**	**Highest value measured**	**Method**	**References**
Method	**Mean ± sem [M] range, mg/m^3**	**Mean ± sem [M] range, mg/m^3**	**Mean ± sem [M] range, mg/m^3**	**mg/m^3**		
Immersion method x ± sem, [M], range	0.81 ± 0.21 [4] 0.34-1.5	0.50 ± 0.14 [3] 0.20-0.70	2.74 ± 0.58 [5] 1.06 - 4.5	4.5 (e) 41, 12) 6-7 (Dr)	lq, Dr, sv	FIOH (1986-97); Kaelin et al. (1988)
Spray-method x ± sem, (M), range	0.73 ± 0.20 [5] 0.1-1.19	0.20±0.12 <0.14-0.57 [1] (sd, n= 9)	1.40 ± 0.31 [2] 0.96 - 1.83	3.08	lq, Polytron real time meter	FIOH (1985); Dietschmann (1996); Suenaka et al. (1984)

x= arithmetic mean, M= number of creameries, sem = standard error of the mean, e) no mechanical ventilation, lq= liquid absorption sampling, Dr= Dräger, sv= site visit

For aseptic packing of foodstuffs in creameries and refreshment factories, the EASE model predicts that inhalation exposure to vapour at immersion type machine results by the patterns of use and control presented below in an exposure range of 0.7-4.2 mg/m^3 (0.5-3 ppm) and at spray type machine in the range of 14-70 mg/m^3. The volatility/ability of the substance to become airborne is low or moderate. The EASE prediction corresponds to the exposure which was measured at immersion type systems, but was clearly too high for the spray type machine. Naturally, the ventilation arrangements, which the EASE-programme does not take in account, decrease the airborne concentrations. However, the airborne concentrations could be slightly higher at spray type machines than at immersion machines because the consumption of the peroxide was also higher. The EASE model predicts with the patterns of use and control presented that intermittent dermal exposure to hydrogen peroxide is 0.1-1 mg/cm^2/day.

Input parameters for inhalation exposure during aseptic packing of foodstuff (in parentheses the parameters for spray machine

Physical state: liquid
Weight fraction: 35%
Temperature: 80 (100) °C
Vapour pressure: 1.1 (3) kPa
Aerosol forms: no
Pattern of use: non-dispersive
Pattern of control: LEV
Exposure: immersion machine 0.7-4.2 mg/m^3 (0.5-3 ppm) spray machine 14-70 mg/m^3 (10-50 ppm)

Input parameters for dermal exposure, incidental splashes

Physical state: liquid
Weight fraction: 35%
Temperature: 25 °C
Pattern of use: non-dispersive
Pattern of control: direct handling,
Contact level: intermittent
Dermal exposure: 0.1-1 mg/cm^2/d

Use of peracetic acid for disinfection

Peracetic acid is an equilibrium product prepared from hydrogen peroxide, acetic acid or acetic anhydride and water (Finnish Peroxides, 1998). The composition of the product is: 15-30% of hydrogen peroxide, 5-15% of peracetic acid, 5-15% of acetic acid, and water. Additionally, some products may also contain mineral acids, such as phosphoric and sulphuric acids. Peracetic acid is mainly supplied in tanks (800 l), barrels (200 l) or polyethylene containers (30 l). Disinfection with peracetic acid is recommended with water solutions containing 0.2 to 3% of the concentrate in cold water.

Peracetic acid is used for disinfection in food and soft drink production (creameries, breweries, meat processing, cheese and sugar factories) which use peracetic acid as dilute solutions for disinfection of the pipework (for circulating water), equipment, surfaces and conveyor belts. In dishwashers of industrial size (army, hospitals, restaurants), hydrogen peroxide is also used for bleaching and disinfection. It is also used (by spraying) for disinfection of animal gages, coops and stalls on cattle farms. For agricultural purposes, the concentration of peracetic acid delivered is 5%; the concentrate is diluted for use at the site in ratios of 1:50. Peracetic acid is used also as a slimicide in circulation waters of paper mills (Rantakokko et al., 1994).

Brewery and refreshment drink factory

In an industrial size brewery and refreshment drink factory, peracetic acid and in minor amounts hydrogen peroxide are used for disinfection of brewing, mixing and storage tanks and also process pipework. The consumption of peracetic acid is about 10-20 t/a.

In the brewery departments, automated machines dilute first the concentrate to the concentration of 0.5 to 2%, and then pump the solution while further mixing with water to the kettles, brewing

and storing tanks (50 to 150 m^3) for final disinfection of the dishes. This operation occurs after the normal washing procedure. The final peracetic acid concentration in the tanks is 0.1 to 0.2%. After the suitable time of disinfection, the tanks are emptied into the drain and the dishes are blown dry with compressed carbon dioxide or air.

The disinfection of juice mixing and packing machines occur in a similar way except that the concentrated product is first manually dosed to the dilution containers. Depending on the process, the volume of the first dilution container is from 10 to 200 l and the amounts of concentrated peracetic acid used from 0.2 to 2 l. This amount is manually moved with plastic cans from dark polyethylene containers (30 l) to the dilution tank.

No published or register data on exposure during disinfection with peracetic acid in breweries were found. During site visits in a Finnish brewery (**Table 4.7**) airborne concentrations of H_2O_2 were measured with Dräger tubes. Although it is not known whether acetic and peracetic acids affect the H_2O_2 results in the vapour mixture, the experts are of the opinion that the exposure could not be much higher than the response recorded with Dräger tubes.

Airborne exposure in the storage room of the peracetic acid tanks at the feeding point of the chemicals to the big brewery tanks was found to be traces (<0.07 mg/m^3). The aerosol atmosphere generated during drying the tanks with compressed gas after disinfection gave the result of 0.07 to 0.14 mg/m^3. Normally, the workers' exposure to aerosol is even lower, because they are mainly working in the control room of the automated process.

Possibilities to be exposed by splashes are during the maintenance operations with the valves, feeding pumps and barrels. The workers had experienced white spots on the skin of the hands, if they had not used protective gloves when handling the concentrate.

In departments of juice mixing and packaging, aerosol concentrations in the air at breathing zone were also traces (<0.07 mg/m^3) while emptying the disinfection solution from a juice mixing tank (600 l) to the drain. The manual transfer of the concentrated peracetic acid (1.5 l) to the dilution tank (once or twice a day) caused an airborne concentration of 1.4 mg/m^3 during 10 minutes. The operation may cause an accidental exposure from splashes if protective equipment is not used. Also these workers had experienced white spots on the hands and forearms, but no hair bleaching.

In the brewery cellar, there are other incidental operations, such as cleaning of brewing kettles which need greater amounts of disinfection agent (diluted solutions of 35% H_2O_2 and peracetic acid). The concentrations in working solutions vary from 2 to 14% of H_2O_2. These work procedures are performed manually a few times per year. The work period lasts 0.5-2 hours per day, over one to two weeks at a time. Inhalation exposure measured at the worker's breathing zone (during active handling) varied from 0.14 to 2.8 mg/m^3. There is also a possibility to be accidentally exposed to bad splashes. The worker knew well the white flecks on the skin which lasted several hours. Between the kettle washing periods, the worker's exposure was low (<0.07 mg/m^3).

The worst-case exposure situations in the brewery involved short-term exposures when peracetic acid and H_2O_2 were handled in greater amounts as concentrated products, especially in the brewing cellar and during dilution operations in the juice departments. The short-term exposure concentration in the cellar had a mean value of 0.47 mg/m^3, with peak exposures at 2.8 mg/m^3 (OEL_{stel} 3 mg/m^3). In the juice departments, the manual transfer of concentrated peracetic acid caused daily short-term exposures at 1.4 mg/m^3.

Table 4.7 Hydrogen peroxide exposure in breweries

Brewery departments [1]	Personal exposure	Area concentrations	Short-term exposure	Highest value measured
Job	**Mean (n) mg/m³**	**Mean (n), range, mg/m³**	**Mean ± sd, (n), range, mg/m³**	**mg/m³**
Automated beer process, - store for chemicals, - tank wash	<0.07 (6)	<0.07 (6) 0.07-0.1 (6)	-	0.1
Automated juice departments	<0.07 (6)	<0.07 (6)	1.4 (3)	1.4
Brewery cellar	<0.07 (6)	<0.07 (6)	0.47 ± 0.69 (6) 0.14-2.8 [2]	2.8

1) Dräger instrument measurements during site visits in a Finnish brewery (FIOH, 1998)
n = number of measurements, sd= standard deviation,
2) The procedure is occasionally done during 0.5 to 2 hours per day, about 15 d/a

The workers in the factory are equipped with appropriate protective clothing, but it is not usual to wear it. In the factory halls, there is good general ventilation but no local exhausts.

For the disinfection process with peracetic acid in a brewery, the EASE model predicts that inhalation exposure to vapour, which is not directly handled, results with the patterns of use and control as presented below in an exposure range of 0.7-4.2 mg/m^3 (0.5-3 ppm). The volatility/ ability of the substance to become airborne is low. The EASE model predicts that intermittent dermal exposure to hydrogen peroxide is 0-0.1 to 1 mg/cm^2/day. EASE gives the same values to the "cellar man" by inhalation, but a higher exposure of 0.1-1 mg/cm^2/day on his skin.

Input parameters for inhalation exposure during disinfection with peracetic acid in brewery (diluted solutions)

Physical state: liquid
Weight fraction: 1%
Temperature: 25 °C
Vapour pressure: 0.01 kPa
Aerosol forms: no
Pattern of use: non-dispersive
Pattern of control: LEV
Exposure: 0.7-4.2mg/m³ (0.5-3 ppm)

Input parameters for inhalation exposure during disinfection with peracetic acid in brewery industry (concentrate)

Physical state: liquid
Weight fraction: 25%
Temperature: 25 °C
Vapour pressure: 0.03 kPa
Aerosol forms: no
Pattern of use: non-dispersive
Pattern of control: LEV
Exposure: 0.7-4.2mg/m³ (0.5-3 ppm)

Input parameters for dermal exposure, incidental splashes of the concentrate or in parentheses intermittend use of diluted solutions

Physical state: liquid
Weight fraction: 25% (0.5%)
Temperature: 25 °C
Pattern of use: non-dispersive
Pattern of control: direct handling,
Contact level: incidental (intermittent)
Dermal exposure: 0-0.1 mg/cm²/d

Meat processing factories

In the meat processing factory, cleaning operations with diluted peracetic acid (0.5% of peracetic acid, 0.15% H_2O_2) also concern, in addition to machines and pipework, large open surfaces (floors, tables, conveyors). The cleaning process is partly automated and partly manual when the solution is sprayed. After handling the disinfectant, the pipes, equipment and surfaces are still rinsed out with sterile water. The whole factory is cleaned and disinfected every night.

When the dilution of the disinfectant is done on site by automatic instruments the exposure to splashes is minimal. As spraying of the diluted product occurs at low pressure without any atomiser, aerosol generation is minimal. The disinfection per operation area lasts about 30 min; the exposure period per work shift has the maximum of 2 hours. During a site visit in a Finnish

meat product factory, the exposure measured with Dräger tubes amounted to 0.07-0.14 mg/m^3 (n = 15) of H_2O_2. The highest concentration of 0.14 mg/m^3 (n = 5) was measured during the spraying operation. No published or registered data were found for disinfection with peracetic acid in meat processing factories. A Dutch survey on a similar work using a different disinfection chemical found somewhat higher concentrations. In view of the possibility that other methods of application could generate more aerosol of hydrogen peroxide, the reasonable worst-case exposure over the full work shift is judged to be 0.5 mg/m^3.

Because the utility solutions are very diluted and the spreading occurs with low pressure without atomising during short periods of time, the EASE WINDOW Version 2.0 -model overestimates the inhalation exposure 4.2-7.0 mg/m^3 (3-5 ppm) in the disinfecting process of meat processing factories. EASE predicts that dermal exposure to hydrogen peroxide with direct contact is 0-0.1 mg/cm^2/day.

The type of exposure is inhalation

The temperature of the process is 15º C
The physical-state is liquid
The exposure-type is gas/vapour
Aerosol-formed is false
The use-pattern is non-dispersive use
The pattern-of-control is segregation
The status-vp-value is calculated at process temp.
The vp-value of the substance is 0.007 kPa
The volatility of the substance is low
The ability-airborne-vapour of the substance is low
The predicted gas/vapour exposure to hydrogen peroxide is 4.2-7.0 mg/m^3 (3-5 ppm)

The type of exposure is dermal

The use-pattern is non-dispersive use
The pattern-of-control is direct handling
The contact-level is intermittent
The predicted dermal exposure to hydrogen peroxide is 0.1-1.0 mg/cm^2/d

4.1.1.1.6 Etching of circuit boards

Hydrogen peroxide (30-60%) is used in the electronics industry for removing unwanted copper from the printed circuit boards in mineral acidic (micro)etching baths (expert interviews and LeaRonal, Technical Bulletin No. 306215, 1990). A modern process is fully automated and practically closed with exhaust ventilation. Older processes may still be of the batch type, where the plates to be etched are immersed in cages into the bath. Also in these baths, the cages are moved up and down with robots and let to settle (drop) upon the bath before moving further. The open baths are often equipped with local exhausts, but not always. The number and the size of the baths in factories may vary (60 - >1,000 l) depending on the size and type of the process. The peroxide concentration in the oxidising etching bath may vary from 1 to 20%. Additionally, persulphates are used in the baths. The temperature in the bath is usually in the range of 40-45^{o}C. The reaction is exothermic and if necessary the baths are either warmed or cooled to the proper temperature. In the batch type of processes, the dosing of the peroxide into into the baths is mainly done manually.

According to Finnish experts the exposure to airborne hydrogen peroxide remains low in modern automatic continuous closed etching systems. At older batch baths (FIOH database, 1989, **Table 4.9**) the measured 8-hour mean concentration of hydrogen peroxide in air was 0.83 ± 0.33 (sem) mg/m^3 [3 factories] and the highest measured value was 1.51 mg/m^3. The concentrations were measured at points of emission which means that the concentration was lower further away in the hall. During the etching process the workers moved around in the hall visiting the batches occasionally. The personal exposure may therefore have been slightly lower. Neither personal

nor short-term exposure data were available. In factories A and B, the ventilation was insufficient but factory C was well ventilated.

Working in factory A represents the highest exposure to hydrogen peroxide (the 8-hour area mean concentration was 1.48 mg/m^3 and the highest value was 1.51 mg/m^3). Thus, the reasonable worst-case full-shift exposure concentration at etching (old process) was chosen as 1.5 mg/m^3. For a modern process, inhalation exposure (0.2 mg/m^3 is derived from an EASE calculation (see below).

Table 4.8 Hydrogen peroxide exposure at etching baths in electronic industry

Production of circuit boards	Personal exposure	Area concentrations	Short-term exposure	Highest value measured
Etching	**Mean ± sd, (n), range, mg/m^3**	**Mean ± sd, (n), range, mg/m^3**	**Mean ± sd, (n) range, mg/m^3**	**mg/m^3**
Factory A	-	1.48 ± 0.04 (sd) (2) 1.44-1.51	-	1.51
Factory B	-	0.92± 0.14 (sd) (2) 0.78-1.05	-	1.05
Factory C	-	< 0.15 (2)		< 0.15

Method of measurements was liquid absorption ($TiCl_4$) and spectrophotometry, sd= standard deviation, sem= standard error of the mean, x= mean, n= number of samples collected

At the batch type of bath (old process), the EASE model gives an inhalation exposure of 0.7-4.2 mg/m^3 (0.5-3 ppm) with the use and control patterns shown below. The volatility of the substance is low and the ability to develop airborne concentrations is low. At the batch bath, the predicted concentration is close to the normal working situation. For factories with automated closed systems and good ventilation (modern process), the model predicts a low E level of exposure, 0-0.14 mg/m^3 (0-0.1 ppm). The dermal exposure predicted by EASE for handling the concentrate is 0-0.1 mg/cm^2/day.

Input parameters for inhalation exposure at etching bath (closed, automated)

Physical state: liquid
Weight fraction: 20-35%
Temperature: 45 °C
Vapour pressure: 0.1 kPa
Aerosol forms: no
Pattern of use: non-dispersive
Pattern of control: full containment
Exposure: 0-0.14 mg/m^3 (0-01 ppm)

Input parameters for inhalation exposure at etching bath (batch system)

Physical state: liquid
Weight fraction: 20-35%
Temperature: 45 °C
Vapour pressure: 0.1 kPa
Aerosol forms: no
Pattern of use: non-dispersive
Pattern of control: LEV
Exposure: 0.7-4.2 mg/m^3 (0.5-3 ppm)

Input parameters for dermal exposure

Physical state: liquid
Weight fraction: 35%
Temperature: 20 °C
Pattern of use: non-dispersive
Pattern of control: direct handling,
Contact level: intermittent
Dermal exposure: 0-01 mg/cm^2/d

4.1.1.1.7 Metal plating

The amounts of hydrogen peroxide used in the metal industry are relative small. It is mainly used once a month or a few times per year for the cleaning of metal (Cr, Zn) plating basins. In those occasions, hydrogen peroxide (50%) is diluted 1:3 and handled either with small pumps or manually with pails. If the substance is pumped, it is connected with a flexible tube under the liquid surface in order to avoid aerosol formation. The amounts used per factory varies from 10 to 300 l of 50% H_2O_2 per year depending on the volume of the process.

There are no measured data available, but according to the EASE WINDOW Version 2.0 model, inhalation exposure varies from 14.1 to 28.2 mg/m^3 (10-20 ppm) and dermal exposure from 0 to 0.1 mg/ cm^2/day. The work is, however, occasional and occurs outdoors. The exposure predicted by EASE concerns the 0.5-hour phase of adding 50% hydrogen peroxide to the metal plating baths and is probably a significant overestimation. Actual measurements during a similar type of manual transfer of 35% H_2O_2 in a dairy and in a brewery gave only about 2 mg/m^3 in air. Therefore it was considered that the value of 2 mg/m^3 was the short-term exposure concentration and that for the remaining 7.5 hours, the ambient concentration was at the detection limit (0.07 mg/m^3). The calculation of the RWC for the full shift gives 0.14 mg/m^3.

The type of exposure is inhalation / short-term (30 min)

The temperature of the process is 30 ºC
The physical-state is liquid
The exposure-type is vapour
Aerosol-formed is false
The use-pattern is non-dispersive use
The pattern-of-control is direct handling
The direct-handling is direct handling with dilution ventilation
The status-vp-value is measured at process temperature
The vp-value of the substance is 0.1
The volatility of the substance is low
The ability-airborne-vapour of the substance is low
Exposure: The predicted gas/vapourexposure to hydrogen peroxide is 14.1-28.2 mg/m^3 (10-20 ppm) during 30 minutes per shift

The type of exposure is dermal during 30 min

The use-pattern is Non-dispersive use
The pattern-of-control is Direct handling
The contact-level is incidental
Exposure: The predicted dermal exposure to hydrogen peroxide is 0
-0.1 mg/ cm^2/d

For environmental reasons the metal industry may in the future start using hydrogen peroxide for pickling in stainless steel production (NJ Sanders; Solvay Interox, Research and Development, UK, 1996; and expert interviews). The method is, however, still under development and not in practice.

4.1.1.1.8 Other uses of hydrogen peroxide

Production of chemically modified starch

Hydroxylated starch is treated further with H_2O_2 to achieve extensive fragmentation of carbon hydrate molecules (Swern, 1971). Because of its adhesive properties, the oxidised, degraded starch is used in the paper production as a surface sizing and coating binder mainly for pigmented paper to achieve good printing quality; it also provides strength, stiffness and ink holdout for the paper. The modified starch can also be used for textiles as warp sizing agents.

The H_2O_2 concentration in the reaction mass varies up to 3% depending on the product quality desired. The process temperature is 40^{o}C and pH is about 10. The automated, outdoor reactors

are closed systems and are operating continuously. The only occasions when the workers may be exposed to H_2O_2 is from splashes or leaks while transfering the peroxide to the storage tank. The sampling process for product control occurs via small tubes via faucets.

EASE WIN 2.0 modelling predicts that in closed, continuous starch process the inhalation exposure to vapour results, with the patterns of use and control presented below, in a low exposure range of 0-0.14 mg/m^3 (0-0.1 ppm), although the volatility/ability of the substance to become airborne is moderate. The EASE model predicts that dermal exposure to hydrogen peroxide is very low.

The reasonable worst case for 8 hours is 0.2 mg/m^3.

The type of exposure is inhalation

The temperature of the process is 40° C
The physical-state is liquid
The exposure-type is vapour/liquid
Aerosol-formed is false
The use-pattern is closed system
Significant-breaching is false
The pattern-of-control is full containment
The status-vp-value is measured at process temperature
The vp-value of the substance is 0.016 kPa
The volatility of the substance is low
The ability-airborne-vapour of the substance is low
Exposure: The predicted vapour exposure to hydrogen peroxide is 0-0.1 ppm

The type of exposure is dermal

The use-pattern is closed system
Significant-breaching is false
The pattern-of-control is not direct handling
Exposure: the predicted dermal exposure to hydrogen peroxide is very low

Degrading of proteins

Hydrogen peroxide may be used in processes in which leather proteins are degraded to soluble peptides in a basic solution and with an enzyme. The role of the peroxide in the process is to operate as a disinfectant and to oxidise and remove the malodorous sulphur compounds. The process is a batch process.

In a factory visited by a FIOH hygienist, 24 t/a of 50% hydrogen peroxide were used in the production of 420 t/a of dry, but soluble peptide. Every day 38 to 42 l of H_2O_2 was manually transferred in pails from the storage tank (800 l) to the reactors. The cooking of the batch lasted 16 hours. Two batches were cooked in parallel.

Workers' exposure occurred mainly during feeding of the peroxide to the reactor. That occurs 4-6 times/day. Each addition operation lasts about 15 min. The type of exposure was a peak exposure caused simultaneously by vapour and incidentally by splashes. The workers did not use any protective equipment. The workers had experienced white flecks on the skin. Ventilation in the process building was only "natural".

FIOH experts measured with Dräger tubes the airborne H_2O_2 in the vicinity of the reactors operating in parallel. The concentrations were low (ca. 0.14 mg/m^3, n = 5), but the measurement was made five hours after the batches were charged, i.e. after starting the basic hydrolysis and enzyme addition, i.e. representing exposure conditions between the peroxide additions. The exposure was therefore a high short-term (peak) exposure which occurred 4 to 6 times per work shift, each time lasting 15 min. The workers may also encounter skin contact to the concentrate.

No other measured exposure data of hydrogen peroxide were found for this type of uncommon process, and no appropriate hygienic measurements were performed in the factory visited.

The EASE WIN 2.0 model would predict that the reasonable worst case for a 8-hour inhalation exposure to vapours is 1.9 mg/m^3, if the 8-hour TWA is calculated using the lower limit of the EASE prediction (14.1 mg/m^3) as the short-term exposure (1 hour) and the actual measured concentration (0.14 mg/m^3) for the remaining 7-hour exposure. Ventilation in the process building was "natural". The values for short-term and full-shift exposure are however considered overestimations because actual measurements of airborne hydrogen peroxide during manual transfer of 35% solutions were about 2 mg/m^3, because the containers were situated outdoors, and ventilation in the process facility took place through wide, open doors.

The value of 0.27 mg/m^3 was chosen as the reasonable worst-case inhalation exposure for the whole shift (8 hours) and 2 mg/m^3 for the short-term (60 min) exposure. EASE predicts that the intermittent dermal exposure during these short-term operations is 0-0.1 mg/cm^2/day.

The type of exposure is short-term inhalation exposure during 60 min/shift

The temperature of the process is 25º C
The physical-state is liquid
The exposure-type is vapour
Aerosol-formed is false
The use-pattern is non-dispersive use
The pattern-of-control is direct handling
The direct-handling is direct handling with dilution ventilation
The status-vp-value is measured at process temperature
The vp-value of the substance is 0.08 kPa
The volatility of the substance is low
The ability-airborne-vapour of the substance is low
Exposure: The predicted vapour exposure to hydrogen peroxide is 14.1-28.2 mg/m^3 (10-20 ppm).

The type of exposure is dermal during 60 min/shift

The use-pattern is non-dispersive use
The pattern-of-control is direct handling
The contact-level is incidental
Exposure: the predicted dermal exposure to hydrogen peroxide is 0-0.1 mg/ cm^2/1h (during 6 times 10 min per shift).

4.1.1.1.9 Water treatment and environmental applications

Drinking water

Drinking waters and, especially, raw waters may be treated with hydrogen peroxide (European Standard draft PrEN 902).

Only one recorded measurement was found in the FIOH database concerning a case of preliminary testing which involved H_2O_2 exposure (emission) (<0.02 mg/m^3) during treatment of raw water. Bubbler sampling and $TiCl_4$ spectrometry were used for the assay.

The EASE model also predicts very low inhalation exposure (0-0.14 mg/m^3; 0-0.1 ppm) with the use and control patterns shown below. The volatility of the substance is very low as is the ability to develop airborne concentrations. Also dermal exposure is predicted to be very low.

The reasonable worst-case exposure for an 8-hour work shift is estimated to be 0.14 mg/m^3.

Input parameters for inhalation exposure

Physical state: liquid
Weight fraction: 4%
Temperature: 10 °C
Vapour pressure: 0.001 kPa
Aerosol forms: no
Pattern of use: non-dispersive
Pattern of control: LEV
Exposure: 0-0.14 mg/m³ (0-0.1 ppm)

Input parameters for dermal exposure

Physical state: liquid
Weight fraction: 4%
Temperature: 10 °C
Pattern of use: non-dispersive
Pattern of control: not direct handling
Contact level: incidental
Dermal exposure: very low

Wastewater

Because hydrogen peroxide has been regarded as an ecologically desirable agent (yielding only oxygen and water), it is used in increasing quantities (20 kt; 3% of total consumed) to treat industrial (CEFIC, 1997e; Ausimont Spa; Degussa AG; Solvay Interox S.A.; Gilbert, 1984; Wagner et al., 1984) and domestic effluents. The compound (Kirchner, 1979) can be used to treat wastewater and sewage effluents and to control hydrogen sulphide generation in the anaerobic processes of raw sewage in sewer lines or collection points. Iron salts may be used as catalysts.

In industrial scale, hydrogen peroxide and peracids have also been reported to be suitable for the detoxification (Kirchner, 1979) of cyanide-containing effluents, removal of nitrite ion from waters and treating of arsenic containing wastewaters. The compounds are also used for detoxifying organic pollutants in wastewaters, such as formaldehyde, phenol (Eisenhauer, 1964), lignin sugars, surfactants, sulphur derivatives, etc.

No measured data were available on airborne hydrogen peroxide exposure for wastewater treatment.

The EASE WINDOW Version 2.0 prediction for wastewater treatment is 4.2-7 mg/m^3 (3-5 ppm) which could apply to a short-term exposure for the worker visiting the treatment area for short periods several times a day. The reasonable worst case for 8-hour exposure is 1 mg/m^3, if the highest value from EASE, 7 mg/m^3, is used for about 60 min (short-term RWC) and for the remaining 7 hours the low level of 0.14 mg/m^3 is used.

The type of exposure is inhalation (for short-term 60 min)

The temperature of the process is 6 ºC
The physical-state is liquid
The exposure-type is gas/vapour
Aerosol-formed is false
The use-pattern is non-dispersive use
The pattern-of-control is segregation
The vp-value of the substance at 22 ºC is 0.046 kPa
The vp-value of the substance is 0.0161 kPa
The volatility of the substance is low
The ability-airborne-vapour of the substance is low
The predicted gas/vapour/exposure to hydrogen peroxide is 4.2-7 mg/m³ (3-5 ppm)

The type of exposure is dermal

The physical-state is liquid
The use-pattern is non-dispersive use
The pattern-of-control is not direct handling
The predicted dermal exposure to hydrogen peroxide is very low

Other environmental applications

Toxic or malodorous pollutants (NO_x, SO_2, reduced sulphur compounds, amines, phenols) can be removed from industrial gas streams and liquid manure by reaction with hydrogen peroxide or peracetic acid (Finnish Peroxides, 1998; Kirchner, 1979). No exposure data were available.

4.1.1.1.10 Hairdresser's work

Hairdressers' exposure to H_2O_2 is caused by chemicals used for hair bleaching and dyeing. The same chemicals are also used for dyeing of eyelashes and eyebrows. The colour mixture consists of a dye paste and a developer (oxidiser). The developer may contain from 3 to 12% H_2O_2 being either a stabilised water solution or a stabilised crème containing dispersing and "nourishing" agents. Different concentrations are needed for various purposes. A thick hair tress needs more chemicals and more concentrated oxidation solutions than a thin hair. A dark hair and coloured hair need more chemicals if totally bleached than a blond hair. Thus, the degree of bleaching or dyeing required determines the concentration of the developer. The most often used concentration of H_2O_2 is 6%. This developer is always mixed with a dye paste just before use. The usual mixing ratio is 1:1, but also the ratio of 1:2 (developer:dye) is used for lighter colours. For strong bleaching, concentrations of 9 to 12% mixed (1:1) with dye paste containing ammonium persulphate are used.

One hair treatment needs between 50 and 120 ml of the mixture. Sometimes, if only striped hair is required, the scalp is covered with plastic or laminated aluminium foil with holes. Hair curls are pulled through the holes and dyed. The peroxide concentration used for eyelashes is 2 to 3% and for eyebrows either 3% or 6% which concentrations are again diluted (1:1) with dye paste

The dyeing process is as follows: the hairdresser mixes the chemicals (during 2 to 3 min), spreads the mixture onto the customer's hair (10 min), lets the colour develop (20 to 30 min), and washes the rest of the dye away. Sometimes the colour development is speeded up with heating (during 10 min at about 38ºC) and thereafter cooled with a fan (1-2 min). Striping of long hair may need a little longer handling time.

The number of treatments (customers) per day varies with the size of the hair salon. In a big salon there may be several treatments every day, and even concurrently (3 to 5/day/hairdresser; 5 to 7 hairdressers may be working full time). Sometimes the bigger salons are mechanically ventilated, but most of the smaller and medium ones have only "natural" ventilation. Therefore, the 8-hour exposure to H_2O_2 may also vary.

The mean exposure in ambient air of six hair salons (various sizes, 5 to 6 measurements with Dräger-tubes in each) varied from 0.07 to 0.14 mg/m^3 (n = 2). The short-term exposure at a customer's during colour development reached its maximum at 0.2 mg/m^3 (n = 8). This exposure concerns the customer during 30 to 45 min, but the hairdresser, who works in the meantime with other customers, and only checks that everything in dyeing is going well, is concerned during shorter periods. The hairdresser's exposure is between these two concentrations. The results were similar to the measurements in two German hair salons (Wella, 1992), which however showed that 5-min peak concentrations may reach 0.6 mg/m^3.

According to the EASE WINDOW Version 2.0 modelling, the hairdressers' exposure is from 4.2 to 7.1 mg/m^3 (3-5 ppm). Actual observations, however, indicate that this is an overestimation, because the H_2O_2 concentration in the dye mixture is fairly low and the amount of the substance used per customer is small. The maximum amount of H_2O_2 used at a time is ($0.12 \cdot 120/2$) 7.2 ml.

About half of that volume, 3.6 ml, is still left on the hair after the colour development when the hair is washed (Henkel KkaA, 1998). If it is assumed that half of the consumed peroxide was used for oxidation, the remaining 1.8 ml may have been vapourised.

It is concluded that a conservative, reasonable worst case is 0.5 mg/m^3. Without any ventilation, 1.8 ml of 100% H_2O_2 could generate a concentration of 0.5 mg/m^3 in a space of 3.6 m^3. If seven hairdressers performed a maximum of five dyeings (= 35) per day concurrently in a salon, they would need a space of 126 m^3 (42 m$^2 \cdot$ 3 m) to generate the suggested reasonable worst-case concentration. Usually, they have better working conditions to enhance customer comfort. Hairdressers use normally protective gloves (of latex) when handling dyes, but not always in both hands. According to EASE, the direct dermal exposure is low.

The reasonable worst case is 0.5 mg/m^3.

The type of exposure is inhalation during mixing H_2O_2 and dye (5 min)

The temperature of the process is 25 ºC
The physical-state is liquid
The exposure-type is gas/vapour
Aerosol-formed is false
The use-pattern is non-dispersive use
The pattern-of-control is Segregation
The status-vp-value is measured at a different temp.
The vp-value of the substance is 0.12 kPa at 60 ºC
The vp-value of the substance is 0.0157 kPa at 25 ºC
The volatility of the substance is low
The ability-airborne-vapour of the substance is low
The predicted gas/vapour/liquid aerosol exposure to hydrogen peroxide is 4.2-7.0 mg/m^3 (3-5 ppm)

The type of exposure is dermal during mixing H_2O_2 and dye

The use-pattern is non-dispersive use
The pattern-of-control is direct handling
The contact-level is intermittent
The predicted dermal exposure to hydrogen peroxide is 0.1-1 mg/cm^2/day

The type of exposure is inhalation during spreading the dye mixture on the customer's hair (15 min)

The temperature of the process is 25 ºC
The physical-state is liquid
The exposure-type is gas/vapour
Aerosol-formed is false
The use-pattern is inclusion onto matrix
The pattern-of-control is direct handling
The direct-handling is direct handling with dilution ventilation
The vp-value of the substance is 0.12 kPa at 60 ºC
The vp-value of the substance is 0.0157 kPa at 25 ºC
The volatility of the substance is low
The ability-airborne-vapour of the substance is low
The predicted gas/vapour exposure to hydrogen peroxide is 4.2-7.0 mg/m^3 (3-5 ppm)

The type of exposure is dermal during spreading the dye mixture on the customer's hair (15 min)

The use-pattern is inclusion onto matrix
The pattern-of-control is direct handling
The contact-level is intermittent
The predicted dermal exposure to hydrogen peroxide is 0.1-1 mg/cm^2/day

The type of exposure is inhalation in ambient air

The temperature of the process is 25 ºC
The physical-state is liquid
The exposure-type is gas/vapour
Aerosol-formed is false
The use-pattern is inclusion onto matrix
The pattern-of-control is segregation
The status-vp-value is measured at process temperature
The vp-value of the substance is 0.07 kPa
The volatility of the substance is low
The ability-airborne-vapour of the substance is low
The predicted gas/vapour exposure to hydrogen peroxide is 4.2 to 7.1 mg/m^3 (3-5 ppm)

The type of exposure is dermal

The use-pattern is inclusion onto matrix
The pattern-of-control is not-direct-handling
The predicted dermal exposure to hydrogen peroxide is very low

4.1.1.1.11 Summary of occupational exposure

The available data, published or otherwise recorded, for a valid H_2O_2 exposure assessment were very scanty and represented mainly poorly recorded industrial hygiene. No industrial area was sufficiently documented concerning occupational H_2O_2 exposure. The three papers published in the open literature were not strictly meant for exposure evaluation, and the data recorded/measured by industry (CEFIC, 1997c) were not amenable for later data analysis. There were also important industries or exposure areas using plenty of H_2O_2 without any measurements, such as synthesis of chemicals, textile dyeing, metal industry, or water treatment and environmental applications. Even for the high H_2O_2 consumer, pulp and paper industry, the available exposure data were minimal. As a whole, there were not enough reliable data on H_2O_2 exposures to give a good scientific basis for any reliable occupational exposure assessment. The exposure evaluation in this report is performed on the basis of scarce published data, Finnish industrial hygienists' site visits and Dräger tube measurements during the visits, and expert interviews in industry, authorities, and among Finnish H_2O_2 producers and importers.

However, there were some measured data and together with general knowledge about the use of hydrogen peroxide, the reasonable worst-case exposure levels were estimated for most industrial categories chosen from the industry report (the categories are presented in **Table 4.2)**. In spite of the inadequacy of data, the material showed that in continuous processes 8-hour exposures rarely greatly exceed the OELs in the workplace. High short-term exposures were nevertheless common and could occur in every process especially when H_2O_2 was dosed or diluted manually.

Predicted exposures were also calculated with the EASE model. Often the EASE calculation gave values close to the level which was also measured or otherwise evaluated. Sometimes EASE gave higher results corresponding better to the worst-case exposures. Reasons for the high exposure levels obtained with EASE could be that the effect of exhaust ventilation, size of the space, and amount of the substance used/emitted in a process (e.g. spray disinfection in a creamery) were not accounted for. The best results with the EASE model were obtained when the evaluator had a good knowledge of the process in question.

Table 4.9 is a summary table of the scenarios identified for the occupational exposure to hydrogen peroxide. The duration and frequency of exposure, numerical values for the proposed reasonable worst-case exposures, data sources and the results of the EASE estimations are given.

Table 4.9 Summary of occupational exposure estimates for hydrogen peroxide

Industrial category	Conditions of exposure		RWC/TWA/8h *(unless indicated RWC/STE)*	Reference	EASE model exposure estimation	
	Working time (h/d)	Frequency (d/a)	mg/m³		Inhalation (mg/m³)	Dermal (mg/cm²/d)
Production of H_2O_2 (synthesis, distillation, stabilisation, dilution, diverse tasks)	7-8	200	0.8	CEFIC (1997e)	4.2-14	0-0.1
Synthesis of other chemicals	7-8	200	0.2 closed process 0.5 batch process 2.0 batch, RWC/STE	CEFIC (1997e); Degussa-H (1999)	0-0.14 closed 0.7-1.4 batch -	very low very low -
Loading operations	~ 4	200	2	CEFIC (1997e); Degussa-H (1999)	4.2-14	0-0.1
Pulp and paper bleaching	8	200	0.7	FIOH (1997, 1998)	0-0.14	very low
Bleaching of textiles and laundering: automated batch bleaching	 8 ½	 200 100	 0.2 1	FIOH (1998)	 0-0.14 14.1-28.2	 very low 0.1-1
Aseptic packaging: immersion bath (im), spray method (sp)	8	200	1.5	FIOH (1985, 1998); Dietschmann (1996) Kaelin (1988); Suenaka (1984)	0.7-4.2 (im) 14-70 (sp)	0.1-1
Hydrogen peroxide and peracetic acid use: brewery	1-2	200	0.5	FIOH (1998)	0.7-4.2	0-0.1
Peracetic acid use: meat processing	1-2	200	0.5	FIOH (1998)	4.2-7.0	0.1-1
Etching of circuit boards: modern process (closed) old process (batch)	8 8	200 100	0.2 1.5	FIOH (1989, 1996)	0-0.14 0.7-4.2	- 0-0.1
Metal plating	½	20	0.14 2 RWC/STE/30 min	Expert	14.1-28.2	0-0.1
Production of modified starch	8	200	0.2	FIOH (1998)	0-0.14	very low
Degrading of proteins	1	200	0.27 2 RWC/STE	FIOH (1998)	14.1-28.2	0-0.1
Water treatment: Drinking water, Wastewater			Drinking 0.14 Waste 1.0 Waste 7.0 RWC/STE		Drink. 0.014 Waste 4.2-7	very low very low
Hairdresser's work	8	200	0.5	FIOH (1999); Wella AG LAN (1992)	4.2-7.1	0.1-1

RWC/TWA (8 h): reasonable worst case; RWC/STE: reasonable worst case for short-term exposure

4.1.1.2 Consumer exposure

In Sweden, based on the product register, hydrogen peroxide is found in 77 products whereof 7 products used for cleaning and bleaching are available to consumers (see Appendix H). The Danish product register also includes several products that contain hydrogen peroxide. The product types are cleaning and bleaching agents, paints, lacquers and varnishes, and cosmetics.

It became clear that the product registers were not an exhaustive data source in case of hydrogen peroxide, since it is used in cosmetics, medical products and as a processing aid in the food industry, for which use categories are usually not covered by product registers. Therefore, more information was acquired from experts in the branch, from companies involved, and from regulatory bodies.

Bleaching, disinfection and cleaning are the main uses of hydrogen peroxide in consumer products. Also in the specific uses, such as contact lens disinfection, hair bleaching and dyeing, and tooth bleaching, these basic properties of hydrogen peroxide are used.

The exposures were estimated with EUSES (for dermal exposure), and SCIES by the US EPA (for inhalation). The EUSES model for inhalation exposure of consumers was not used, since the model is static (the amount of compound used is divided by the room volume) and resulted in a vast overestimation.

The following data were used for the assessment:

- physical and chemical data of hydrogen peroxide,
- contact parameters,
- concentration parameters (e.g. percentage of hydrogen peroxide in the product),
- results from consumer exposure models,
- measured concentrations.

Concentration limits set by the European Union or by Member States for hydrogen peroxide in various consumer products and in drinking water are shown in Appendix J.

Hair dyeing and bleaching

In the Finnish product register, there are about 40 products containing hydrogen peroxide, which are used for hair dyeing and bleaching and for fixing the hair perm. Typical concentration is 6%. Occasionally, oxidiser with a higher concentration i.e. 9-12% is used for dyeing dark or thick hair or for bleaching. For dyeing, the agent containing hydrogen peroxide (oxidiser) is mixed with a dye solution in 1:1 proportions and thus, the concentration of hydrogen peroxide in mixture applied to hair is usually 3%, and 6% in a realistic worst-case (RWC) scenario (see Appendix I). The mixture is applied to hair, which is sometimes covered with membranes (e.g. aluminium), whereby the scalp is protected. Higher temperatures are used in some cases to shorten the time of treatment.

Same kinds of products are used in the hair salon and at home. There is some indication that the concentration of hydrogen peroxide in dye products used at home is lower, e.g. maximum concentrations of hydrogen peroxide in oxidisers used at home are estimated to be 9% (oral information, Raija Kara, 10.8.1999). When hair dyeing is made at home, adverse effects might occur more easily due to inexperienced use of a relatively strong and irritating oxidant.

The maximum concentration of hydrogen peroxide in hairdressing chemicals according to a status given by the Ministry of Trade and Industry in Finland is 12% (KTMp 1415/1993), which

is in accordance with the respective EU directive. In spite of the regulation that limits hydrogen peroxide concentration in hairdressing chemicals to 12%, information obtained from hairdressers indicated that 18% solutions are used in some rare cases to produce completely blond hair. However, these solutions are not applied as such, but are mixed with an equal volume of dye to make the preparation used for the bleaching of and fixing to the hair. Although this practice is infrequent because of low demand, it is known to cause symptoms of irritation.

Regarding inhalation exposure, measurements of air concentration of hydrogen peroxide were made with Dräger detection tubes in three hair salons, 2-3 measurements per salon. Measurements were made for this risk assessment. During the measurement, the client's hair was dyed using 40-80 ml of mixture, which contained 3-6% of hydrogen peroxide. Temperature of the salon was 23-24°C, relative humidity 12-16% and the room volume was 50-60 m^3. The measured concentrations varied between <0.07 and 0.2 mg/m^3 (n = 8).

Colipa studied hydrogen peroxide concentrations in two hair salons, the larger had a total room volume of 222 m^3 and two air condition units, which supplied 1,900 m^3 per hour and the smaller had a room volume of about 142 m^3 and no air-conditioning. In general, the concentrations measured were 0.05-0.1 ppm, with a maximum peak concentration of 0.4 ppm (0.6 mg/m^3) over 5 minutes in the smaller hair salon (unpublished study results submitted by Wella AG, dated 18.12.1992). These results are in agreement with other measurements and modelling results.

The SCIES model (Screening Consumer Inhalation Exposure Software) provided by the US EPA was used to estimate the concentration of hydrogen peroxide in the breathing zone. The mixtures of interest contain 3-6% of H_2O_2. For this estimation it was assumed that the amount of the product used for one treatment was 40-120 ml and the temperature in the hair salon is 30ºC. Parameters used and results of modelling are presented in Appendix I. In some cases, bleaching is fastened using higher temperatures (about 40ºC). This has not been taken into account in the reasonable worst-case (RWS) scenario to avoid accumulation of extreme assumptions. However, other assumptions of the RWC scenario are extreme and thus it gives a reasonable basis for assessment. The "worst-case" concentration in the air of the salon according to SCIES gives 0.24 mg/m^3 which is about the same as the measured concentration 0.2 mg/m^3 (maximum peak value 0.6 mg/m^3) for a duration of 30-45 minutes. According to the SCIES model, the peak concentrations after use could reach a level of 1.1 mg/ m^3.

The EUSES model was used in a similar way for the assessment of consumer exposure in the hair salons. The input data were the same as for the SCIES. The concentration in the air of the salon given by EUSES is 5 mg/m^3 for "normal scenario" and 100 mg/m^3 for the "worst-case scenario". These estimates are about 500-fold higher than those from the SCIES model. They are obvious overestimates since they are derived by dividing the amount of hydrogen peroxide in the hair dye product by the room volume ($0.05 \cdot 20g/200\ m^3 = 5mg/m^3$). In the EUSES model, room ventilation is not considered. Furthermore, a large part of the hydrogen peroxide is likely to decompose forming oxygen and water before it evaporates.

Using the estimate presented by CEFIC (1998), namely that 10% of the hair preparation is in contact with the scalp and the rest in the hair, the following worst-case estimation can be made: 120 g of a hair bleaching/dye product is used per treatment, it may contain up to 6% of hydrogen peroxide. Thus, 720 mg (i.e. 12 mg/kg of body weight) is the total deposition on the scalp skin.

Mixtures (of oxidisers and dyes) used for dyeing of eyelashes and eyebrows contain 1-3% of hydrogen peroxide (oral information from hairdressers, 1999).

Textile bleaching

Textile bleaching agents are more concentrated than household cleaning products. Although the commonly used household bleaches contain less than 8% of hydrogen peroxide, one textile bleaching product containing 35% of hydrogen peroxide available for consumers was identified in Sweden. For textile bleaching, usually 1 dl of the product is added to the washing machine. The EUSES skin deposition modelling resulted in an estimate of 0.6 mg/kg bw on the skin, assuming that gloves are not used.

To estimate the air concentration of hydrogen peroxide, two scenarios were used for SCIES modelling. First, it was assumed that according to instructions of an identified textile bleaching solution, 1 dl of the product containing 7% is diluted with 10 litre of water in a washbasin. Room volume is 20 m^3, and air exchange rate is 1/hour. Normally, the cloth is immediately washed with the washing machine. For a reasonable worst-case scenario, it is assumed that the user manually washes/bleaches the cloth for 10 minutes or leaves the solution in the washbasin and works is the same room. In that worst-case scenario the average concentration during the period of use in the zone of release is 0.02 mg/m^3, which is relatively low. Secondly, it was assumed that, again following the instructions, 0.5 dl of 7% solution is applied directly to the textile/cloth. The room volume is 20 m^3, and the air exchange rate is 1/hour. Normally, the cloth is immediately washed, but for a reasonable worst case, it is assumed that the cloth is handled for 5 minutes. The resulting average concentration during period of use in zone of release is 0.13 mg/m^3. If the bleaching agent is directly added to the washing machine the air concentrations are lower than in the first scenario mentioned above, since the washing machine is a semi-closed system. Because the user is normally in another room, the exposure is very low.

Although the available data are incomplete, it seems that strong hydrogen peroxide solutions (up to 7%, and exceptionally 35%) are used for textile bleaching, disinfection and cleaning of air locks in sewers. The skin deposition and air concentrations are rather low, but the risk caused by splashes of strong solutions of hydrogen peroxide to the eye is obvious. It is assessed that the conditions of use of these products in households are such that the risk of splashes cannot be excluded.

Cleaning agents

Information on the number of products in the market and the percentage of hydrogen peroxide in the products was collected from the maintainers of the product registers in Denmark, Sweden and Norway. The two products and several alternate products in the Finnish market were examined for composition, product formulation and use instructions.

In the Finnish market two products were identified, one “all purpose cleaner” and one toilet cleaner containing <5% and 5-20% of hydrogen peroxide, respectively. Both are relatively new products in Finland and their market share in these product categories is presumably low. There are several alternate products offered to consumers, most of them are based on various detergents, sodium hydroxide, carbonates or chlorine (hypochlorite).

According to the information received from industry, in the Spanish market, there are several products containing hydrogen peroxide in both product categories. The products commonly contain about 8% of H_2O_2.

In the Swedish product register, one toilet cleaner, which contains 35% of hydrogen peroxide, was identified. In addition, three “all purpose cleaners” containing 0,2%, 4,5% and 7% were found.

In the Norwegian product register 5 products belonging to these categories were found; they contain between 1% and 20% H_2O_2. The total use of H_2O_2 based on the data in the product register is 10,566 tonnes, distributed in 77 products (38 companies) in 2000.

Floors, sink, clinkers, furniture in bathroom and kitchen, etc. are cleaned with undiluted or diluted products. According to the instructions, undiluted products are washed and removed from the surfaces after cleaning, but tdiluted products can be left to dry. It is considered that room temperature and ventilation rate are normal and thus, the evaporation of hydrogen peroxide is slow.

Considering the use pattern of these products, the exposure of skin is possible at some stages of the application. According to the instruction of the "all purpose cleaners", they are used either undiluted (for difficult stains) or diluted (e.g. 60 ml for 7 l of water). In case of gels, the risk of splashes is reduced. When the bottle is opened, and the product dosed to be mixed with water, or when the product is spread and the bottle closed, the hands may be contaminated with the solution. The hands could introduce the solution to the eye area, causing the risk of mild or severe eye irritation depending on the concentration applied.

Inhalation

To estimate the concentration of H_2O_2 in the air during cleaning, measurements made on hair dyeing/bleaching are utilised, because the conditions are rather similar. During the measurement, hair of the client was dyed using 40-80 ml of mixture, which contained 3-6% of hydrogen peroxide. Temperature of the salon was 23-24°C, relative humidity 12-16% and the room volume was 50-60 m^3. The measured concentrations varied between <0.07 and 0.2 mg/m^3 (n = 8). Modelling of the worst-case scenario of exposure caused by textile bleaching (50 ml of 7% solution was applied directly to the textile) gave similar results (maximum 0.13 mg/m^3).

These concentrations are well below the OEL value (1.4 mg/m^3) and below the level, which was found harmful in recent worker health surveillance (3-4 mg/m^3). The concentration of hydrogen peroxide in diluted solution of cleaning agents is lower than that in hair bleaching mixtures. The amount of product used and the temperature are rather similar in both scenarios. Therefore, when cleaning agents are used, the concentration of H_2O_2 measured in the air is below that measured in the hair salon. Furthermore, in hair bleaching, application is done nearer to the consumer's breathing zone and the exposure could be higher. This comparison with hair bleaching agents can be regarded as a worst-case scenario.

When undiluted cleaning agents are used to remove stains, the amount of product is small and therefore, the air concentration of hydrogen peroxide remains low.

Skin

To approximate the skin exposure, the estimates made for textile bleaching agents are used. The estimate was made for products containing 35% of H_2O_2, which is higher than the dilution normally used in cleaning agents. For textile bleaching, usually 1 dl of the product is added to the washing machine. The EUSES skin deposition modelling resulted in an estimate of 0.6 mg/kg bw on the skin, assuming that gloves are not used.

Taking into account the amount of product used and the percentage of hydrogen peroxide, it is assessed that the skin exposure level is not exceeded, when all purpose cleaners and toilet cleaners are used.

Ingestion

Exposure via ingestion in normal use is assessed to be negligible, since ingestion of the product (by an adult) is unlikely and residues of H_2O_2 in surfaces (e.g. sinks and tables), which may be in contact with food items, are minor.

However, there may be accidental ingestion of the solution by small children. A small child may accidentally swallow these products like other household chemical, which is not equipped with child resistant fastening, if the bottle of the product is left non-attended.

Eyes

The exposure scenario of highest concern, similarly to other uses of H_2O_2, is that splashes of the undiluted product get to the users'eyes. It is unlikely that a consumer would use eye protection/goggles, because the package of the product does not contain them and because most consumers would regard wearing goggles as unpractical/uncomfortable.

Table 4.10 Factors affecting the consumer exposure to hydrogen peroxide caused by cleaning agents

Factor	Approximate value/state of the factor in these scenarios	Remarks
Percentage of H_2O_2 in the product	1-20%	More data on the products are needed
Amount of the product used per treatment	20-100 ml diluted or undiluted	
Formulation of the product	All purpose cleaners are gels	Gel formulation reduces the splashes and risk of eye irritation
Temperature	About +25 °C	In these uses, higher temperatures are unlikely
Dilution	Depending on the stain and the item to be cleaned, the products can be used diluted or undiluted	Diluted product could not cause eye irritation
Use of gloves	Not always indicated in the instructions of all purpose cleaners	
Warning for eye irritation in the instructions/label of the product		Risk communication by this means could be an efficient tool of risk reduction

Contact lens disinfectants

Hydrogen peroxide solutions (1-3%) are used for disinfecting contact lenses. After the lens disinfection, the remaining hydrogen peroxide is broken down using catalase or platinum. The instructions give 20 min - 6 hours as the neutralisation time. Time for neutralisation is sufficient when lenses are left in the solution overnight. This may not always be the case and adequate neutralisation times are not always recommended or applied (experts of Finnish importers and the opticians association, 1996). The experts regarded 10-50 mg/l of residual hydrogen peroxide level in soft lenses as a realistic/normal range. A similar range of concentrations is given by McNally (1990). According to McNally (1990) residual concentration in lenses is normally 60 ppm or less. More recent measurements, however, have shown that the content of hydrogen peroxide in lenses is 15 mg/l at the maximum and that with the currently applied neutralisation, usually no hydrogen peroxide residues can be measured (oral information, Juha Päällysaho, Finnish Institute of Occupational Health). The concentration of residual hydrogen peroxide in

contact lenses varies depending e.g. on the neutralisation time and the quality of the catalase. In soft lenses with a high water content, the residual concentration can be higher since catalase does not penetrate into the matrix and thus some of the hydrogen peroxide remains in lenses.

Tooth bleaching

Gels containing hydrogen peroxide are used for tooth bleaching. According to US data products, which are designed for bleaching at home, contain 2-10% of hydrogen peroxide (Hanks et al., 1993). In home bleaching, the treatment of teeth with the gel takes 4-10 hours and is repeated for several days (over one or two weeks). The technique uses a soft, plastic, night guard-styled prosthesis/tray filled with 10% carbamide peroxide gel (Haywood, 1992). After injection of the gel into the tray, extra gel can be removed with a tooth brush. This carbamide peroxide dissociates into 3-4% of hydrogen peroxide and 6-7% of urea. About 0.6 g of the gel is used per application. Some gels become firmer in contact with saliva which prevents release of hydrogen peroxide and irritation of soft tissues. Some patients may suffer moderate pain after wearing the tray overnight or a mild sensitivity to temperature changes (technical product data), (Haywood and Heymann, 1991). Since the gel is between the teeth and the plastic tray, contact with gingivae as well as inhalation exposure are limited. Usually, the dentist gives special instructions to the user and controls the possible disorders or irritation.

Bleaching gels applied by dentists are an alternative to home bleaching agents. Products used at the dentist's ("office bleaching") often contain 35% of hydrogen peroxide. In that application, the exposure to the bleaching agent is limited to the teeth only. To protect the soft tissues before treatment with hydrogen peroxide solutions, e.g. a metacrylate resin is spread over gingivae, and hardened with UV-light. Thereafter the hydrogen peroxide gel is applied to the teeth surface (product information/Opalescence). When several teeth are bleached and a 1 mm layer of solution is applied on the teeth surface, approximately 1 g of the solution is used at the most. The exposure time is about 30 min. Due to decomposition and efficient removal of the gel made by the dentist only minor amount of hydrogen peroxide (less than 1 mg) comes in to contact with gingival surfaces and/or is ingested. The partial vapour pressure of hydrogen peroxide in the gel is low and thus also the inhalation exposure remains low.

Table 4.11 Consumer exposure to hydrogen peroxide

Scenario	Exposure time		Inhalation (mg/ m³)		Ingestion (mg/kg of bw/d)	Skin / Eye deposition	
	Duration of treatment	Frequency of treatments per year	Measured	Estimated	Estimated	Concentration of H_2O_2 in the product	Estimated dose
Hair dyeing and bleaching	30 min	4	<0.07-0.20	0.01-0.24 a)	na	1-6%	12 mg/kg bw, on the skin b)
Textile bleaching	5-10 min	25		0.02-0.13	na	<8 (35) %	0.6 mg/kg bw, on the skin c)
Cleaning agents	10-20 min	25		<0.13	na	usually about 8% (0.2-35%)	<0.6 mg/kg bw, on the skin c)
Contact lens disinfectants	1-5 min	365	na	na	na	15mg/l residual concentration in lenses	
Tooth bleaching	30 min -10 h, over up to 2 weeks	5-10		negligible d)	negligible	2-35%	<1 mg per application on gingival surfaces
Food items (natural and residual H_2O_2)		365	na	na	0.033-0.13	na	na
Mouth care products	5 min	5 · 365	na	na	0.088	0.1%	

a) 0.2 mg/m³ represents a realistic worst-case scenario, where the original solution contains 12% of hydrogen and the mixture, which is actually applied, contains 6% of hydrogen peroxide (SCIES modelling system was used)
b) 12 mg/kg of body weight per day is the potential dermal deposition. Systemically distributed amount of hydrogen peroxide is considered insignificant
c) 0.6 mg/kg of body weight per day is the potential dermal deposition (estimated by the EUSES)
d) Evaporation from the gels used for tooth bleaching is assumed to be minimal
na na=not applicable

Ingestion in food

Low concentrations of hydrogen peroxide occur in many food items. In potatoes, tomatoes (Warm and Laties, 1982), soybean, rice, groundnuts, olives and margarine, concentration vary between 0.1 and 11.5 mg/kg (Coxon et al., 1987). Instant coffee contains about 4 mg of hydrogen peroxide/l (Nagao et al., 1986). It is estimated that dietary intake of naturally occurring hydrogen peroxide is usually below 1 mg.

Residues of hydrogen peroxide can be found in some dairy products, e.g. 10-60 mg/kg were measured in pasteurised cream (Black and Cunnington, 1985). Hydrogen peroxide is not an approved food additive according to the EU directives. Hydrogen peroxide is, however, used as a processing aid or antimicrobial agent in cheesemaking, whey, dried eggs, baked products, fats and oils, meat products etc. in the EU and in the USA. In the EU, processing aids are not regulated like the food additives, but their use can be controlled on a case by case basis when adverse health effects are anticipated (Liisa Rajakangas, KTM, personal information, 1998).

In the USA, hydrogen peroxide is generally regarded as safe (GRAS) in the following uses: bleaching of lecithin, bleaching of herring, washing and bleaching of beef feet. It is also used to remove glucose from dried eggs, for controlling microbial growth in stored milk before cheesemaking (US FDA, 1983).

The residual hydrogen peroxide can be removed by catalase or water rinse. In a national survey made in the USA, zero residues were reported in most foods after treatment with hydrogen peroxide (US FDA, 1983). Consumer exposure data (from food manufacturers) indicated a potential intake of 8 mg per day but most of it is destroyed during processing.

In the food industry, hydrogen peroxide is also used for sterilisation of packaging materials for milk products and juices. This use is allowed in the USA if residual quantities are removed by appropriate physical or chemical means or if the residual levels in food directly after aseptic packaging are max. 0.5 ppm (US FDA, 1990).

Sterilisation of drinking water by treatment with ozone and UV radiation is a potential source of hydrogen peroxide. The allowable residual concentration of hydrogen peroxide in drinking water is 0.1 mg/l in Germany and 0.5 mg/l in France (Solvay Interox, 1996).

It is estimated that dietary intake caused by natural hydrogen peroxide in food is 1 mg at the most. Since most to the added hydrogen peroxide will decompose during processing and storage, it is estimated that intake caused by residual hydrogen peroxide is normally below 1 mg. For an adult (60 kg), dose of 2 mg causes an exposure of 0.033 mg/kg/day, whereas for a child (15 kg) the exposure is 0.13 mg/kg/day (see **Table 4.11**).

Mouth care products

In Finland, no mouthwash products containing hydrogen peroxide were identified. According to the EU cosmetics directive mouth care preparations for consumer use may not contain more that 0.1% hydrogen peroxide. According to the TGD, the typical amount of mouthwash used per application is 10 g (EC, 1996*)*. Colipa has estimated that 1 g of mouthwash is ingested per application, and that frequency of application is 5 per day. Thus, assuming that mouthwash products contain no more than 0.1% of hydrogen peroxide, the daily exposure is 5 mg/day, i.e. about 0.08 mg/kg of bw per day for an adult (CEFIC, 1997c).

Toothpastes may contain hydrogen peroxide (ECETOC, 1996; Helsinki University Pharmacy, personal communication, 1996; Letter of Bundesanstalt für Arbeitsschutz und Arbeitsmedizin,

dated 29 January 1997). Toothpastes contain a maximum of 0.1% of hydrogen peroxide according to a Finnish regulation (Status of the Ministry of Trade and Industry, KTMp 1415/93). According to the TGD, a typical amount per application is 1.4 g. For toothpastes, a reasonable value of the amount ingested is 17%, which is 0.48 g/day assuming that frequency of application is twice per day (SCCNFP/0119/99*).* Thus, the intake of hydrogen peroxide by an adult (60 kg) is (0.48·0.001/60) 0.008 mg/kg of bw. It is likely that most of the hydrogen peroxide is decomposed after using the toothpaste and is not ingested.

Other uses

In households, products containing 3% of hydrogen peroxide have been used for disinfecting small wounds (Sainio, personal communication/letter). The amounts used as a wound disinfectant (at home) are low and the frequency is incidental. In terms of exposure via inhalation the concentrations are less that 1/10 as compared to those generated in hair bleaching/dyeing.

Hydrogen peroxide may be a component in deodorants (ECETOC, 1996). A typical amount of deodorant spray used is 3 g (EC, 1996). No data on concentrations of H_2O_2 in deodorants were available. However, concentrations are presumed to be low. Thus, it seems likely that the exposure caused by deodorants is negligible.

Cosmetic products used for hardening of the nails and for the skin care may include 2% and 4% of hydrogen peroxide, respectively, according to a Finnish regulation (KTMp 190/1996). Information on typical amounts used is not available.

Combined exposure

The oral exposure from food, mouthwash products and toothpastes are 0.033-0.13, 0.08 and 0.008 mg/kg of body weight, respectively. Based on the current knowledge, the use of toothpaste and mouth rinses containing hydrogen peroxide is not a common practice. However, consumers may have daily exposure to hydrogen peroxide from these three sources. This exposure scenario would resemble that of drinking water studies in mice, from which an oral repeated dose NOAEL has been derived. In such a case, the total oral exposure would be 0.12-0.22 mg/kg bw per day. Parts of hydrogen peroxide in the toothpaste and mouthwash are likely to decompose before the residual amount in the mouth is swallowed. The oral exposure from tooth bleaching agents is occasional and therefore it is not added to the daily oral exposures.

Combining exposures via the gastrointestinal tract, via inhalation and through the skin is not appropriate, because the expected effects are local and not systemic.

4.1.1.3 Humans exposed via the environment

After hydrogen peroxide has been released into the environment, it rapidly decomposes when organic material is present. In animals and vegetables used as human food, or in drinking water, no accumulation of exogenous hydrogen peroxide has been observed (see also the section on intake in food).

According to modelling done with EUSES, the average concentration of hydrogen peroxide in air and the concentration during emission episodes near point sources (production plants) remain low (about 0.005 mg/m^3). It was found that the concentration of hydrogen peroxide in human exhaled air was of the order $0.5 \cdot 10^{-8}$ M (CEFIC, 1996b) and thus much higher than the

concentration in the ambient air. Therefore, ambient air does not represent a source for human exposure to hydrogen peroxide.

Drinking water may contain low concentrations of hydrogen peroxide originating from industrial point sources, natural sources and possibly from water treatment processes. EUSES modelling gave a hydrogen peroxide concentration of about 0.2 mg/l near the production plant (maximum of different release scenarios). Further decomposition probably decreases this concentration level in water before it is used as drinking water. The maximum concentration of residual hydrogen peroxide in potable water allowed in France is 0.5 mg/l (CEFIC, 1997c). It can be estimated that the intake from drinking water would thus be 1 mg/day (i.e. 0.017 mg/kg bw per day), which is low compared with other sources of oral exposure to hydrogen peroxide. Overall contribution from drinking water is not significant.

EUSES predicted high estimates of hydrogen peroxide concentrations in leaf crops (16.1 mg/kg) at a local scale, caused by releases from a local point source. These concentrations cause an intake of 0.28 mg/kg of bw per day, which is relatively high compared with other sources of oral exposure. The route of hydrogen peroxide from the point of release to the leaf plants is unclear. Amounts of dietary intake from other food items e.g. from fish, milk and meat predicted by EUSES are negligible.

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 Endogenous occurrence

Hydrogen peroxide is a normal metabolite in aerobic cells. It has been stated that the cellular concentration is regulated at 10^{-9}-10^{-7} M depending on the balance between formation and degradation (Chance et al., 1979). In normoxia, the rate of H_2O_2 production in the liver of normal anesthetised rats was measured as 380 nmol H_2O_2/min per g of liver. The total estimated production of 1,450 nmol/min per 100 g rat would indicate that about 75% of all H_2O_2 generated may be attributed to the liver (Chance et al., 1979). The effective rate of H_2O_2 formation depends on the substrate and oxygen supply. Production is markedly enhanced in the hyperbaric environment. Studies with isolated fractions of rat liver suggest that mitochondria (through a variety of enzymic reactions leading to univalent or divalent reduction of oxygen), microsomes (through normal electron transport reactions, glycolate oxidase, D-aminoacid oxidase, urate oxidase), peroxisomes (through β-oxidation of fatty acids), and soluble enzymes provide 14%, 47%, 34% and 5%, respectively, of the cytosolic H_2O_2 when fully supplemented with their substrates (Boveris, 1977).

Apart from intermediary metabolism, hydrogen peroxide together with other reactive oxygen species plays a role in cellular defences against invading organisms. H_2O_2 generated by phagocytes can destroy normal or malignant cells and alter erythrocyte, platelet, neutrophil or lymphocyte function. As an oxidant hydrogen peroxide is unusual because (1) it reacts slowly with organic substrates and thus can diffuse at a certain distance in biological systems, (2) its small size and lack of charge facilitate its movement across plasma membranes, and (3) its intracellular concentration is controlled by several enzymes. As the plasma membrane of the polymorphonuclear neutrophil encircles an opsonised particle, superoxide anion and hydrogen peroxide are released directly into the extracellular medium until the particle is completely engulfed. Inside this environment hydrogen peroxide may remain in the vacuole or diffuse either into the cytoplasm or outside the cell. H_2O_2 equilibrium will be regulated by the relative amounts of substance generated or consumed in each of these sites, transiently the concentrations may reach 10 μM (Test and Weiss, 1984).

There is uncertainty about the true levels of hydrogen peroxide in biological media due to analytical difficulties. Investigation of published spectrophotometric and HPLC techniques for analysing hydrogen peroxide in human and dog plasma showed that the measured substance probably was not H_2O_2 but most likely peroxides because (1) catalase treatment did not abolish the peaks (in contrast to H_2O_2 control), and (2) added exogenous hydrogen peroxide did not markedly increase the peak area (Nahum et al., 1989). Blood and plasma of humans and rats were analysed for hydrogen peroxide with a radioisotopic method. Among six male laboratory workers, aged 30-35 years, H_2O_2 concentrations in the whole blood ranged from 114 to 577 μM (reflecting the high levels in phagocytic cells) and in the plasma from 13 to 57 μM. The corresponding H_2O_2 concentrations in rat blood samples were similar (Varma and Devamanoharan, 1991). Data on hydrogen peroxide concentrations in human exhaled air have given values ranging from non-detectable or maximally $0.5 \cdot 10^{-8}$M (CEFIC, 1996b) to 0.5 μM (Madden et al., 1997); the methods of sampling and analysis have varied. Williams et al. (1982)

found that a normal human subject breathing normally had $1–3 \cdot 10^{-8}$ M H_2O_2 in breath (measured as chemiluminescence intensity). The breath luminescence increased greatly after breathing pure oxygen and 5 minutes after smoking a cigarette in the morning. It was presumed that smoking activated macrophages in the lung, releasing H_2O_2. The human aqueous humour is reported to contain normally 19-31 μM of H_2O_2, and similar concentrations have been measured in the corresponding primate and bovine samples (Spector and Garner, 1981; Chalmers, 1989). Among 17 cataract patients hydrogen peroxide levels in aqueous humour ranged from 10 to 660 μM (Spector and Garner, 1981).

Obviously the biological functions for hydrogen peroxide and other reactive oxygen species require strict regulation of concentration in various intracellular and body compartments (see below).

4.1.2.1.2 Absorption and distribution

Biological membranes are highly permeable to H_2O_2; the permeability constants of 0.2 cm/min for peroxisomal membranes and 0.04 cm/min for erythrocyte plasma membranes may be compared with those for water in a variety of membranes, ranging from 0.02 to 0.42 cm/min (Chance et al., 1979). Thus, hydrogen peroxide is expected to be readily taken up by the cells constituting the absorption surfaces, but at the same time it is effectively metabolised, and it is uncertain to what extent the unchanged substance may enter the blood circulation. Moreover, in the blood the red blood cells have an immense metabolic capacity to degrade hydrogen peroxide.

Absorption from mucous membranes

Administration of hydrogen peroxide solutions to body cavities lined by mucous membranes, such as sublingually (Ludewig, 1959), intraperitoneally and rectally (Urschel, 1967) resulted in increased oxygen content of the draining venous blood and, if the amounts of hydrogen peroxide were sufficiently high, formation of oxygen bubbles. Mongrel dogs were treated with colonic lavage, or the lavage of small and large bowel was performed through an enterotomy with dilute saline solutions of hydrogen peroxide. Small amounts of the more concentrated solution (1.5% or higher) produced immediate whitening of the mucosa, with prompt appearance of bubbles in the circulation. More dilute (0.75-1.25%) solutions had the same effect when left in contact with the bowel for a longer time or when introduced under greater pressure or in greater volume for a given length of bowel. Venous bubbling was never observed at concentrations less than 0.75% H_2O_2. In none of the animals did mesenteric thrombosis or intestinal gangrene develop (Shaw et al., 1967). Application of 1% hydrogen peroxide to the serosal membrane caused whitening due to gas filled small vessels; higher concentrations (up to 30%) on the skin and mucous membranes (of various species) caused lasting damage when subcutaneous emphysema and disturbances of local blood circulation impaired tissue nutrition (Hauschild et al., 1958). In two cats, sublingual application of 1.5 ml of 9% ^{18}O-labeled hydrogen peroxide or 0.1 ml 19% ^{18}O-labeled hydrogen peroxide was followed up with mass spectrometric analyses in arterial (femoral artery) blood and exhaled air. Within about one hour in the former case, and within half an hour in the latter case, 1/3 of the labeled oxygen administered was exhaled. There was a rapid initial rise of the arterial blood ^{18}O-concentration, but the arterial blood oxygen saturation gradually declined, probably because of impaired gas exchange in the lung due to oxygen embolism (Ludewig, 1965).

Absorption from skin

After the application of 5-30% solutions of hydrogen peroxide on rat skin *in vivo*, some H_2O_2 could be localised in the excised epidermis within a few minutes. By contrast, with human cadaver skin *in vitro*, only after the application of high H_2O_2 concentrations for several hours, or after pretreatment with hydroxylamine (inhibitor of catalase), was H_2O_2 detectable in the dermis. Based on histochemical analysis, H_2O_2 was not metabolised in the epidermis, and the passage was transepidermal, avoiding the "preformed pathways" of skin appendages. The localisation of dermal emphysema, caused by liberation of oxygen, correlated for the most part with the distribution of catalase activity within the tissue (Ludewig, 1964). In acute dermal toxicity studies with 90% hydrogen peroxide in rabbits, cats, pigs and rats, Hrubetz et al. (1951) found that the rabbit appeared to be the most sensitive animal species. The high susceptibility of the rabbit to embolism, and interspecies differences in the levels of tissue and blood catalases were noted. The authors also proposed that there may be more hydrogen peroxide available subcutaneously in the rabbit to enter the blood stream and release the oxygen which gives rise to lethal embolic effects.

Absorption from the lungs

Anesthetised rabbits were administered 1-6% hydrogen peroxide aerosol by inhalation. The left atrial blood was found to be supersaturated with oxygen up to levels that corresponded to oxygen administration at 3 atm. When this level was increased, small bubbles began to appear in the samples. The 1% aerosol, which was least irritating, provided as high arterial oxygen levels as the higher hydrogen peroxide concentrations (Urschel, 1967). Concerning acute inhalation toxicity studies, it is not clear whether the mechanisms of lethal effect are local or systemic. However, Kondrashov (1977) stated in a poorly documented study that the LC_{50} level for rats derived from 4-hour exposure to hydrogen peroxide vapours was 2,000 mg/m3 (inhalation and whole-body shaved skin exposure), and that the primary cause of death was gas (oxygen) embolism.

Conclusions from experimental studies

Animal studies show that administration of high concentrations of hydrogen peroxide by various routes, resulting in high rates of absorption, leads to oxygen bubble formation in blood vessels. This indicates indirectly that hydrogen peroxide has been absorbed systemically but then rapidly degraded by metabolising enzymes in the circulating blood. Under some conditions systemic embolisation of oxygen (micro)bubbles has been found to occur. This was demonstrated in a study of a new technique for oxygenating blood in which 3% H_2O_2 in normal saline was infused at a controlled rate into the right ventricle of 12 pigs whose blood catalase activity was only slightly less than in humans. The rate of infusion was limited by bubble formation leading to pulmonary and systemic embolisation (Fuson et al., 1967). Hrubetz et al. (1951) demonstrated that the intravenous acute toxicity of hydrogen peroxide in rabbits was inversely related to the substance concentration (the studied range of dilutions was 3.6-90%). With successive dilutions the blocking effects at the injection site were less, allowing hydrogen peroxide-derived oxygen bubbles to be distributed in the blood circulation and to cause more toxicity, as evidenced by convulsions, and more deaths.

Observations from human incidents related to absorption and distribution

There are two reported cases of accidental ingestion of 35% hydrogen peroxide which resulted in brain injury presumed to be due to cerebral oxygen embolism (Giberson et al., 1989; Sherman et al., 1994). The latter of these cases was more convincing as it concerned a specific pattern of

multiple cerebral infarctions (detected with MRI) occurring immediately after the ingestion. The authors speculated on the pathophysiologic mechanism: a patent foramen ovale of the heart (not said to the be involved in the case), some unmetabolised hydrogen peroxide crossing the pulmonary capillary bed into the arterial circulation, or aspiration and absorption of hydrogen peroxide from the pulmonary capillaries. In a third case a child ingested about 230 g of 3% hydrogen peroxide solution. He was found dead 10 hours later and gas emboli were found in the intestinal lymphatics and the pulmonary vasculature. Moreover, there were clear vacuoles in the spleen, kidney and myocardium (Cina et al., 1994).

Hydrogen peroxide has often been used for irrigation of surgical wounds. A 54-year-old male received irrigation under pressure of an infected and fistulous herniorrhaphy wound with $5 \cdot 20$ ml volume of 3% hydrogen peroxide. Not all irrigating volume seemed to have drained from the wound. On the fifth irrigation the patient suddenly lost consciousness, showed cardiac shock and fell to coma which lasted 15 minutes. There was no indication of red cell damage. ECG showed signs of transient myocardial ischaemia. The patient made a full recovery within 3 days. The authors proposed that the most likely mechanism of this occurrence was widespread embolisation of oxygen microbubbles, especially to the cerebral and coronary arteries (Bassan et al., 1982). Two patients had their right thoracic cavity irrigated with 300 ml of 3% hydrogen peroxide during lung surgery (Konrad et al., 1997). After one of the patients had showed clinical signs of pulmonary embolism, the other patient was monitored with transoesophageal echocardiography. Within some seconds after the irrigation bubbles were detected in the right atrium and ventricle lasting for about 3 minutes. The patient did not show any haemodynamic or respiratory complications, however. The authors cited four further case reports of gas embolism (involving five patients) in the context of surgical irrigation of body cavities with hydrogen peroxide (Shah et al., 1984; Tsai et al., 1985; Ferrari et al.; 1994, Saissy et al., 1994; Morikawa et al., 1995), and two further case reports were subsequently located (Sleigh and Linter, 1985; Timperley and Bracey, 1989). Thus, hydrogen peroxide may be particularly dangerous in surgical operations when used in closed spaces or under pressure, where liberated oxygen cannot escape.

4.1.2.1.3 Metabolism

Detoxification (scavenging) reactions

There are two main hydrogen peroxide metabolising enzymes, catalase and glutathione peroxidase, which control H_2O_2 concentration at different levels and in different parts of the cell. Catalase deals with large amounts of H_2O_2 that may be generated in peroxisomes. Glutathione peroxidase (GSH peroxidase) metabolises H_2O_2 in both the cytosolic and mitochondrial compartments (Chance et al., 1979). A variety of small molecule, nonenzymatic antioxidants complete an efficient intra- and extracellular network of defences such as vitamin E, ubiquinols, carotenoids, ascorbic acid and glutathione (Kelly et al., 1998). α-Keto acids such as pyruvate nonenzymatically reduce hydrogen peroxide to water while undergoing decarboxylation at the 1-carbon position and may thus function as efficient scavengers of H_2O_2 (Salahudeen et al., 1991). The kinetics of removal for extracellular H_2O_2 was examined in cultured fibroblasts. The process involved two kinetically different reactions, the first one being characterised by a relatively low K_m value (about 40 μM), the second one showed a linear dependence of the rate up to 500 μM. By using specific inhibitors, it could be concluded that the first reaction involved GSH peroxidase and the second catalase. It was inferred that 80-90% of H_2O_2 is decomposed by GSH peroxidase at hydrogen peroxide levels lower than 10 μM. The contribution of catalase increases with the increase of H_2O_2 concentration (Makino et al., 1994).

The activities of catalase and GSH peroxidase are unevenly distributed in various tissues and across different species. The brain, lung and heart have low catalase activities while the muscle tissue is lacking effective concentration of GSH peroxidase (Chance et al., 1979). Measurement of antioxidant enzyme activities in the rat gastrointestinal tract showed that the specific activity of glutathione peroxidase was maximal in the stomach while catalase activity was uniform in all regions of the g-i tract. There was no change in activity by age. The maximum activities were located in the cell cytosol (Manohar and Balasubramanian, 1986). Various antioxidant enzyme activities were measured in lung homogenates from rats, hamsters, baboons and humans. Glutathione peroxidase was higher in rat lung than in baboon or hamster lung. Catalase activity was variable, being 10 times higher in baboons than in rats. Rat lung antioxidant enzyme activities were different from the other species. Hamster seemed to mimic most closely humans (Bryan and Jenkinson, 1987).

Studies in freshly isolated human bronchial epithelial cells indicated significant antioxidative capacity. Inactivation of both catalase and glutathione reductase (resulting in impaired glutathione redox cycle) made the cells more susceptible to hydrogen peroxide-mediated injury (Kinnula et al., 1994). However, in another study, most human volunteers who were exposed for about 15 hours to 100% oxygen developed tracheobronchitis due to oxidant toxicity but the genes for the major antioxidant enzymes (superoxide dismutases and catalase) were expressed at very low levels and were not upregulated by exposure. Catalase activity in the human bronchial epithelium at baseline was 0.008±0.002 $U/10^6$ cells and did not change significantly after exposure to 100% oxygen (Erzurum et al., 1993).

Selective inhibition of catalase and glutathione reductase activities in freshly isolated and cultured human alveolar macrophages demonstrated that catalase was the bulk hydrogen peroxide scavenger; however the glutathione redox cycle was more important in maintaining cell membrane integrity. The primary localisation of catalase was in peroxisomes, and there were low levels in the cytoplasmic and nuclear matrices. Even a highly efficient catalase activity in the cell membrane was speculated but not proven (Pietarinen et al., 1995).

Freshly isolated rabbit lung alveolar type II pneumocytes (ATII) were coincubated with either hydrogen peroxide generating xanthine-xanthine oxidase system yielding about 300 μM H_2O_2 at steady-state, or with 300 μM H_2O_2 for up to one hour. Cellular metabolic defences were modified either by inhibition of catalase with aminotriazole or by conjugation of reduced glutathione with chlorodinitrobenzene. ATII cells cleared H_2O_2 at a higher rate than an equivalent amount of free catalase. Aminotriazole decreased ATII cell catalase activity by 89% and prolonged the clearance half-life of H_2O_2 from 1.3 min to 18.1 min; the treated cells were more susceptible to oxidant injury, as shown by their decreased ability to exclude trypan blue after 60 min of H_2O_2 exposure. Glutathione-depleted cells scavenged H_2O_2 at the same rate as controls. Hence ATII cells reduce the extracellular hydrogen peroxide (at high physiological concentrations) mainly by a catalase-dependent pathway. ATII cells secrete surfactant and actively transport sodium across the alveolar space. They are a minor component of the alveolar epithelial surface that is mainly (>95%) made up of alveolar type I cells. While ATII cells are resistant to exogenous oxidants, ATI cells are more sensitive. In conclusion, ATII cells play an important role in protecting the alveolar epithelium from injury by high H_2O_2 concentrations via a predominantly catalase-dependent process (Engstrom et al., 1990).

In the blood red blood cells efficiently remove intracellular and extracellular hydrogen peroxide. Under physiologic conditions the ability of the red blood cells to protect haemoglobin from oxidation depends largely on the presence or absence of glucose and its utilisation for the production of NAD(P)H and maintenance of sufficient levels of reduced glutathione. Glutathione

peroxidase is of major importance in this scheme. If additional (exogenous) sources of peroxide formation are present, catalase concentration in the red cell becomes important. Under these conditions formation of methaemoglobin by peroxide depends on catalase concentration: the higher the catalase activity, the more resistant the cell (Aebi and Suter, 1972). Another study demonstrated that human red blood cells efficiently removed extracellular hydrogen peroxide and protected the surrounding tissue against damage mediated by peroxide and its secondary products hydroxyl radical and hypochlorous acid. The scavanger capacity depended on catalase wheras haemoglobin, GSH and glucose metabolism contributed only minimally. The red cells were approximately one quarter as efficient at removing H_2O_2 as an equivalent concentration of free catalase, i.e. the potential of red cells to remove hydrogen peroxide from blood is immense (Winterbourn and Stern, 1987). Catalase activity in human erythrocytes is 3,600-fold higher than in serum. Serum catalase was somewhat lowered (0.62) in patients of nonhaemolytic anaemia and increased in patients of haemolytic anaemias (8.3-fold) and in pernicious anaemia (6.6-fold) (Góth et al., 1983).

The brain has low concentrations of catalase and glutathione peroxidase (Olanow, 1993). Dopaminergic neurons of the striatum are exposed to relatively high concentrations of reactive oxygen species, including hydrogen peroxide, during the metabolism of dopamine. The vulnerability of neurons to hydrogen peroxide was found to be attenuated by the presence of glial cells (Langeveld et al., 1995). Exposure of striatal neurons (from mouse embryos) for 30 min to hydrogen peroxide led to a concentration-dependent (10-1,000 µM) decrease of cell viability. Toxic effect of 100 µM was totally prevented by added catalase or glutathione peroxidase in the presence of reduced glutathione. The capacity of striatal neurons to remove external H_2O_2 (100 µM) was 46±6 nmol/mg protein/min. Differential inhibition of catalase or glutathione peroxidase (decreased content of reduced glutathione) indicated that the neuronal defence was mediated primarily by glutathione peroxidase. The viability of striatal astrocytes was not affected by exposure to hydrogen peroxide (up to 1 mM for 60 min), and the neurotoxic effect on the neuronal population was markedly decreased in astrocytoneuronal cocultures. A significant neuroprotection was detectable for 1 astrocyte to about 20 neurons. The capacity of striatal astrocytes to remove external H_2O_2 (100 µM) was 317±27 nmol/mg protein/min, i.e. sevenfold higher than the corresponding capacity of neurons. Most of this hydrogen peroxidase activity was attributable to catalase. The protective role of astrocytes was due to its high clearance capacity of hydrogen peroxide rather than a possible release of protective compounds. Since the simultaneous inhibition of both hydrogen peroxidase activities did not completely suppress the clearance of H_2O_2 in either cell type, a nonenzymatic process, such as the Fenton reaction, could also contribute to the disappearance of hydrogen peroxide (Desagher et al., 1996).

Metabolism related to toxicity

In the aerobic cellular metabolism complete reduction of a molecule of oxygen to water requires four electrons, and in a sequential univalent process the superoxide anion radical (O_2^-), hydrogen peroxide and the hydroxyl radical ($OH\cdot$) intermediates are formed (Fridovich 1978; 1983). In the presence of reduced metal ions (Fe^{2+}; Cu^+) hydroxyl radicals may originate from hydrogen peroxide by the Fenton reaction. The chemical reactions involved in the generation of reactive oxygen species are shown below.

Molecular oxygen is reduced to water by four one-electron reduction steps:

$O_2 + e$	$\rightarrow$	$O_2^{-}\bullet$	(superoxide anion)
$O_2^{-}\bullet + e + 2H^+$	$\rightarrow$	H_2O_2	(hydrogen peroxide)
$H_2O_2 + e + H^+$	$\rightarrow$	$OH\bullet + H_2O$	(hydroxyl radical)
$OH\bullet + e + H^+$	$\rightarrow$	H_2O	(water)
Net: $O_2 + 4\ e + 4\ H^+$	$\rightarrow$	$2\ H_2O$	

Several enzymes are involved in the elimination of (reactive) oxygen species:

SOD $2\ O_2^{-}\bullet + 2H+$	$\rightarrow$	$H_2O_2 + O_2$	(SOD:superoxide dismutase)
GSPx $H_2O_2 + 2\ GSH$	$\rightarrow$	$2\ H_2O + GSSG$	(GSPx:glutathione peroxidase)
CAT $2\ H_2O_2$	$\rightarrow$	$2\ H_2O + O_2$	(CAT: catalase)

In the organism the highly reactive (and thus toxic) hydroxyl radical can also be produced non-enzymatically through catalysis by transition metal ions like Fe^{2+} and Cu^{+} (the so-called Haber-Weiss- and Fenton reactions):

metal ions $H_2O_2\ +\ O_2^{-}\bullet$	$\rightarrow$	$OH\bullet + OH^{-} + O_2$	(Haber-Weiss reaction)
$H_2O_2 + Cu^{+}/Fe^{2+}$	$\rightarrow$	$OH\bullet + OH^{-} + Cu^{2+}/Fe^{3+}$	(Fenton reaction)

In all likelihood the "full" Haber-Weiss reaction (i.e., the reduction of H_2O_2 by $O_2^{-}\bullet$) is as follows (showing that the Fenton reaction is representing one particular part of the Haber-Weiss reaction):

$O_2^{-}\bullet\ +\ Fe^{3+}/Cu^{2+}$	$\rightarrow$	$O_2 + Fe^{2+}/Cu^{+}$
$H_2O_2 + Fe^{2+}/Cu^{+}$	$\rightarrow$	$OH\bullet + OH^{-} + Fe^{3+}/Cu^{2+}$

Because iron is normally bound, free iron is maintained in the plasma at a very low level, and the cellular iron is not available to mediate a Fenton reaction *in vivo* (Gutteridge, 1994). Biological reducing or chelating agents, or acidic pH, may however promote the release of iron from transport and storage proteins (Vallyathan and Shi, 1997). Superoxide anion is transformed by superoxide dismutase to H_2O_2. Moreover, in the presence of traces of transition metal ions (iron salts may become available *in vivo*), superoxide anion and hydrogen peroxide undergo the so-called iron-catalyzed Haber-Weiss reaction which results in $OH\cdot$ formation. The hydroxyl radical is highly reactive and oxidises all organic chemicals, including biomolecules, when present in very close proximity to the place where the hydroxyl radical is formed. Superoxide and H_2O_2 are less reactive and can diffuse away from their site of formation, leading to $OH\cdot$ generation whenever they meet a "spare" transition metal ion. H_2O_2 also crosses all cell membranes easily. Thus, hydroxyl radicals are involved in H_2O_2 related toxic effects. Oxygen radical formation can lead to lipid peroxidation, destruction of proteins, including enzyme inactivation, or to DNA damage (Halliwell and Gutteridge, 1984; Vuillaume, 1987; Kappus, 1987).

A variety of in vitro cytotoxicity and genotoxicity studies (see Section 4.1.2.7) with exogenous hydrogen peroxide indicate that chelation of iron dramatically decreases the toxic response thus demonstrating the important role of hydroxyl radical generation in toxicity under those conditions.

Genetic polymorfism of enzymes involved in detoxification

In human populations there are genetically determined traits which determine the degradation capacity of hydrogen peroxide (catalase activity, level of reduced glutathione and hence the activity of the GSH redox cycle), notably in red blood cells. The distribution of blood catalase activity values was found to be trimodal, corresponding to the three phenotypes termed acatalasaemic, hypocatalasaemic and normal. Hypocatalasaemic individuals exhibited activities 36-55 per cent of the normal mean. About half of the individuals homozygous for acatalasaemia (blood catalase activities 0-3.2 per cent of normal) have clinical manifestations (Takahara's disease). In this disease, oral ulcerations develop mainly due to lack of catalase in blood and probably in tissues. Bacteria in the crevices of the teeth or tonsillar lacunas produce hydrogen peroxide. Since there is no catalase to decompose the H_2O_2 produced, haemoglobin is oxidised to methaemoglobin thus depriving the infected area of oxygen, and result in ulceration, necrosis and decay of the oral mucosa. In a Swiss population the frequency of homozygotes was about 0.04 per 1,000 (Aebi and Suter, 1972). The total number of reported patients of acatalasaemia worldwide (by 1989) was 107 belonging to 52 families. Acatalasaemia is assumed to be inherited as an incomplete autosomal recessive trait. Regarding Japanese acatalasaemia, the frequency of the recessive gene was estimated to be 0.00087, and the frequencies of heterozygotes and homozygotes were estimated to be $1.73 \cdot 10^{-3}$ and $4.23 \cdot 10^{-6}$, respectively. In typical acatalasaemia, there is a trace of catalase activity in somatic cells; in atypical acatalasaemia, there is less catalase activity in blood cells (about 4% of normal) and a reduced activity in somatic cells. The frequency of hypocatalasaemia among Asian population averaged 0.2-0.4%; it was highest among Koreans (1.29%) and lowest among Japanese (0.23%). In Japanese groups comprising 4-5 individuals, the mean ± SD blood catalase activity was 3,380±180 Pu/g Hb among normal persons, 1,520±350 Pu/g Hb for hypocatalasaemic cases, and 5.5±0.8 Pu/g Hb for acatalasaemic cases (Ogata, 1991).

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a genetic disorder of erythrocytes (over 300 hundred variants have been identified) in which the inability of affected cells to maintain NAD(P)H levels sufficient for the reduction of oxidised glutathione results in inadequate detoxification of hydrogen peroxide through glutathione peroxidase. Presumably hydroxyl radicals from the peroxide damage the plasma membrane and the cells are prone to haemolysis (Hochstein, 1988). Haemolysis is often associated with the oxidation of haemoglobin to methaemoglobin and the formation of denatured haemoglobin (Heinz bodies). It is estimated that about 400 million people throughout the world are deficient in G6PD. Since the defective gene locus is on the X-chromosome, the enzymopathy is more common in males than in females. Prevalence rates vary from 63% among Kurdish Jews to very low rates of 0.1% or less in Japan (Sodeinde, 1992). G6PD dependent haemolysis and anaemia have become manifest on using pharmaceuticals which generate hydrogen peroxide in the human body (such as the antimalarial primaquine). However, only a fraction of the enzymopathic persons develop the syndrome.

4.1.2.1.4 Conclusions on toxicokinetics and metabolism

Hydrogen peroxide is a normal metabolite in the aerobic cell, but there is uncertainty about the true levels of the substance in biological media due to analytical difficulties. The steady state level appears to depend on the balance between its generation and degradation. Hydrogen

peroxide passes readily across biological membranes (permeability constant corresponds to that of water) and, because it slowly reacts with organic substrates, it can diffuse at considerable distances in the cell. There are two main hydrogen peroxide metabolising enzymes, catalase and glutathione peroxidase, which control H_2O_2 concentration at different levels and in different parts of the cell as well as in the blood. At low physiological levels hydrogen peroxide is mainly decomposed by GSH peroxidase whereas the contribution of catalase increases with the increase of hydrogen peroxide concentration. Red blood cells remove hydrogen peroxide efficiently from the blood due to a very high catalase activity whereas in the serum catalase activity is low.

Both animal studies and human case reports indicate that at high uptake rates hydrogen peroxide passes the absorption surface entering the adjacent tissues and blood vessels where it is degraded liberating oxygen bubbles. One ml of 30% H_2O_2 yields approximately 100 ml of oxygen; thus mechanical pressure injury may be produced. The hazard of oxygen embolisation is particularly high if the substance is administered into closed body cavities where the liberated oxygen (under pressure) cannot freely escape. In most cases the consequences of venous embolisation are not catastrophic because the lung functions as an effective filter for microbubbles under normal conditions (Butler and Hills, 1979). However, in experiments with dogs, when the lungs were overloaded with a bolus injection of 30 ml of air, or when the animals were pretreated with a vasodilator (aminophylline) prior to venous infusion of microbubbles of air, embolisation was detected in the femoral artery with Doppler monitoring. Regarding hydrogen peroxide inhalation or skin contact at rates that would correspond to occupational exposures, there are no data on the systemic fate of the substance. In view of the high degradation capacity for hydrogen peroxide in blood it is however unlikely that the endogenous steady state level of the substance is affected. In biological systems, hydrogen peroxide may also undergo iron-catalyzed reactions (Fenton reaction, Haber-Weiss reaction) resulting in the formation of hydroxyl radicals. The cellular toxicity of hydrogen peroxide appears to depend largely on the generation of hydroxyl radicals. Genetically determined traits (acatalasaemia, glucose-6-phosphate dehydrogenase deficiency of the erythrocytes) render humans more susceptible to peroxide toxicity.

Further scientific data are desirable on the toxicokinetics of hydrogen peroxide. After exploring the feasibility of such studies industry has concluded that presently it seems impossible to measure the fate of exogenous hydrogen peroxide as any measurement will interfere with physiological equilibria.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

The salient data concerning acute toxicity studies in animals by the oral route, dermally, via inhalation and intravenously are summarised in Appendix C.

Oral studies

The oral LD_{50} values or lethal doses in rats range from about 800 mg/kg for 70% hydrogen peroxide (Du Pont, 1996) to more more than 5,000 mg/kg for 10% hydrogen peroxide (FMC, 1990), although Ito et al. (1976) found the dilute substance (9.6% H_2O_2) more toxic with an LD_{50} of about 1,500 mg/kg for male rats and 1,600 mg/kg for female rats. With 70% hydrogen peroxide most of the deaths occurred on the day of dosing. Clinical signs of toxicity were observed in all dose groups and included lethargy, immobility, irregular respiration and hunched

posture. Compound-related gross changes of the tongue, oesophagus, stomach and duodenum and adhesions in the peritoneal cavity were noted in male and female rats found dead. At all dose levels degenerative ulceration and regenerative hyperplasia of the pyloric antrum of the stomach were found. The ulcerative necrosis penetrated into the gastric epithelium (muscularis mucosa): the severity of the ulcerations was rated minimal to mild (Du Pont, 1996). In the study with 10% hydrogen peroxide, one female rat died on study day 1. Clinical signs noted included decreased or blackened feces, decreased locomotion, hypersensitivity to touch, hematuria, lacrimation, recumbency, cyanosis, ataxia, chromorhirnorrhea, nasal disharge and abdominogenital staining. The only necropsy findings noted were hemorrhagic, blood filled stomach and intestines and reddened lungs in the decedent.

Dermal studies

Acute dermal toxicity studies must be viewed with caution because the methods are mostly poorly described. Apparently dermal LD_{50} values for concentrated hydrogen peroxide solutions (90%) have a wide range (700-5,000 mg/kg) depending on the species, the rat being a resistant, and the rabbit a sensitive species (Hrubetz et al., 1951). For 70% H_2O_2 solution the dermal LD_{50} in rabbits is given as 9,200 mg/kg (FMC, 1979b). However, in another study with rabbits, 35% hydrogen peroxide solution under occlusive dressing for 24 hours did not kill any animals. Two animals out of ten were reported to show lacrimation and nasal discharge on days 4 and 5. At 24 hours after application all rabbits had erythema, oedema and blanching over the test sites. By day 4 of the study, all sites were necrotic. Eschar was present on all sites on day 7 and eschar and exfoliation was observed in all sites at termination. Seven rabbits gained weight and three rabbits lost weight during the study (FMC, 1983b). In a mouse study with 10% hydrogen peroxide signs of systemic poisoning (excitation and inhibition, ataxia, tremor and paresis of the limbs, and increased respiration rate) were reported to develop 5-10 minutes after skin application at a dose of 1,400 mg/kg. Death of some animals was observed on application of the 28% solution in doses exceeding 8,000 mg/kg (Liarskii et al., 1983). Another study in rats, which is poorly reported but probably involved a concentrated hydrogen peroxide solution, claimed that the cause of death was gas embolism (Kondrashov, 1977).

Inhalation studies

To study acute inhalation toxicity, exposures have been conducted with hydrogen peroxide aerosols and vapours. Aerosol studies, performed with mice, do not provide 4-hour LC_{50} values as the exposure durations have ranged form 5 minutes to 2 hours. Moreover, the particle size generated in two recent nose-only studies (Solvay Duphar, 1995a; 1995b) was not reported (but is presumed to represent the respirable range). Half of the mice died after 10-15-min exposure at 12,000-13,000 mg/m^3 of aerosol generated from 90% H_2O_2 (Punte et al., 1953), and in 2-hour exposures, levels ranging from 920 to 2,000 mg/m^3 (aerosol of 70% H_2O_2) were lethal to at least some mice; macroscopic findings in the dead animals (swelling and/or discolouration of the skin of the head, the tongue, neck, forepaws, and the nose, subcutaneous emphysema and haemorrhages, red lymph nodes, diffuse red lungs) were attributed to the bleaching and corrosive nature of the test substance (Solvay Duphar, 1995a). In a mouse study of respiratory irritancy, the RD_{50} value (decrease of respiration rate by 50%; 30-min exposure) was 665 mg/m^3 (aerosol of 70% H_2O_2) (Solvay Duphar, 1995b). Punte et al. (1953) reported in a mouse study that at concentrations from 3,600 to 5,200 mg/m^3 there were no deaths, but congestion of the lungs and necrosis of bronchial epithelium were found. At 9,400 mg/m^3 the lethality range was reached with death occurring 6 days following exposure. At 12,000-19,000 mg/m^3 for 10-15 min, the survival time was reduced in the majority of animals to less than an hour. The symptoms during

exposure to low concentrations consisted of a mild nasal irritation, blinking of the eyes, slight gasping, and loss of muscular coordination. These symptoms generally disappeared within 30 min. Pulmonary congestion was noted, and the surviving mice showed necrosis of bronchial epithelium. Gross opacities were present in the eyes of 4 animals exposed to the highest concentration (19,000 mg/m^3) and killed after 8 weeks. Microscopic lesions were found in the eyes of mice exposed to 9,400 mg/m^3 8 weeks after exposure, while those examined 5 weeks after exposure to this concentration showed no significant changes. These findings indicated that there was an insidious and slowly developing corneal damage subsequent to exposure to high aerosol concentrations of H_2O_2.

Mice and rats have been exposed (whole-body) to the vapour of hydrogen peroxide for 4-8 hours in two series of rat studies with a different experimental setup (1) to a calculated concentration of 4,000 mg/m^3 (the true concentration was probably much less, see the subsequent study) for 8 hours or, (2) to measured concentrations ranging from 338 to 427 mg/m^3 for 4 or 8 hours. In study (1) no deaths were reported and no signs of intoxication were observed. No abnormal signs were noted in rats other than scratching and licking themselves. Pathological examination revealed congestion in the trachea and lungs. Small localised areas of pulmonary edema without hemorrhage and areas of alveolar emphysema were present among the rats killed during the first three days. Most of the lungs exhibited many areas of alveolar emphysema in addition to severe congestion. All other organs examined appeared normal. In study (2) no deaths were reported from either the single four-hour or eight-hour exposure. Pathological examination of the animals showed results similar to those described in study (1) (Comstock et al., 1954; Oberst et al., 1954). Another poorly reported study which concerned a whole-body (shaved skin) exposure of rats to hydrogen peroxide vapour for 4 hours, gave an LC_{50} value of 2,000 mg/m^3 and noted that the primary cause of death in the animals was gas embolism (Kondrashov, 1977). Rats were exposed (whole body) for 4 hours to 170 mg/m^3 of hydrogen peroxide (the maximum attainable vapour concentration from 50% solution), and there were only minimal signs of treatment: nasal discharge and transient decrease in body weight (FMC, 1990).

Svirbely et al. (1961) found that the mouse was more susceptible to hydrogen peroxide vapour toxicity than the rat. Exposure for 4 hours at 110 mg/m^3 (78 ppm) was not lethal to the mouse; at 160 mg/m^3 (113 ppm) 1/10 mice died within 24 hours and 4/10 died within the 2-week observation period; at 321 mg/m^3 (227 ppm) 5/25 died within 24 hours and 22/25 died within 2 weeks. In another experiment at 320 mg/m^3 (226 ppm), 1/10 mice died within 24 hours and 5/10 within 2 weeks. A single prior exposure to hydrogen peroxide afforded a moderate degree of protection against otherwise lethal doses of H_2O_2 (Svirbely et al., 1961).

Intravenous studies

Concerning intravenous administration of hydrogen peroxide solutions, the maximum tolerated dose for rats in a prolonged (up to 30 min) infusion was approximately 50 mg/kg. The surviving rats did not show clear evidence of liver toxicity based on plasma enzyme levels (CEFIC, 1997a). In rabbits which were injected (it was not stated how rapidly the substance was injected but presumably the time scale was some minutes) into the marginal ear vein with more concentrated (3.6-90%) hydrogen peroxide solutions, the toxicity paradoxically increased with declining substance concentration. The LD_{50} dose for 3.6% hydrogen peroxide solution was about 3.2 mg/kg (Hrubetz et al., 1951).

4.1.2.2.2 Studies in humans

There are several reported cases of accidental hydrogen peroxide intoxications by the oral route but few reports have provided adequate information on the doses involved (Appendix D). An uncommon route of absorption from a cavity presumably lined by well-vascularised granulomatous tissue involved an obese 54-year-old male who underwent irrigation of an infected and fistulous herniorrhaphy wound with 5·20 ml volume of 3% hydrogen peroxide. Not all irrigating volume seemed to have drained from the wound. On the fifth irrigation the patient suddenly lost consciousness, showed cardiac shock and fell to coma which lasted for 15 min. There was no indication of red cell damage. ECG showed signs of transient myocardial ischaemia. The patient made a full recovery within 3 days. The authors attributed this occurrence to widespread embolisation of oxygen microbubbles, especially to the cerebral and coronary arteries (Bassan et al., 1982). If it is presumed that as much as one half of the volume of the irrigating solution was absorbed, the hydrogen peroxide dose would have been 1.5 g implying for an obese person (assumed weight of 100 kg) about 15 mg/kg bw. Two patients had their right thoracic cavity irrigated with 300 ml of 3% hydrogen peroxide during lung surgery (Konrad et al., 1997). After one of the patients had showed clinical signs of pulmonary embolism, the other patient was monitored with transoesophageal echocardiography. Within some seconds after the irrigation bubbles were detected in the right atrium and ventricle lasting for about 3 minutes. The patient did not show any haemodynamic or respiratory complications, however. The authors cited four further case reports of gas embolism in the context of surgical irrigation of body cavities with hydrogen peroxide.

An 84-year-old man sustained focal neurological deficits immediately after ingesting 30 ml of 35 % hydrogen peroxide solution (ingested dose about 10 g or approximately 150 mg/kg bw). Magnetic resonance imaging revealed multiple cerebral and cerebellar infarctions in the anterior, middle and posterior vascular territories. The presumed mechanism was cerebral oxygen gas embolisation (Sherman et al., 1994). In another case with uneventful recovery, a 40-year-old woman ingested mistakenly about 60 ml of 35% hydrogen peroxide solution. She had a burning sensation in the throat, epigastrium and substernal area and vomited. Radiography of the abdomen showed a large amount of gas in the stomach and gas in the venous system throughout the liver including the left lobe. There was also retroperitoneal gas along the psoas muscles and gas in the stomach wall. Oesophagogastroduodenoscopy revealed severe diffuse haemorrhagic gastritis; the pharynx, oesophagus and duodenum were normal (Luu et al., 1992). The calculated intake of hydrogen peroxide was 21 g, or about 350 mg/kg.

Regarding lethal doses by the oral route, two cases can be described. A 2-year-old boy ingested 4 to 6 oz (113 to 170 g) of 35% hydrogen peroxide. He rapidly became unresponsive and cyanotic, with stiffening of his left arm. On arrival at the hospital, a chest radiograph showed gas in the right ventricle, mediastinum, and portal venous system. He remained paralysed. Oesophagogastroduodenoscopy showed severe haemorrhagic gastritis without perforation. The eosophagus and duodenum appeared normal. He died on day 4. Autopsy showed marked diffuse cerebral oedema with cerebellar and uncal tonsillar notching (Christensen et al., 1992). The dose of hydrogen peroxide received was about 50 g and, assuming the weight of 13 kg, about 3,800 mg/kg bw. In the other case, A 16-month-old boy was found playing with an empty bottle that had contained about 230 g of 3% hydrogen peroxide solution. The container had a cracked lid that allowed the contents to be sucked. White foam emerged from the child's mouth and nose. He then walked to bed and was found dead 10 hours later. In a postmortem examination there was frothy blood in the right ventricle of the heart and the portal venous system. The gastric mucosa was red and the brain oedematous. Histopathological examination showed oedema in the lungs, and diffuse interstitial emphysema was evident. Gas emboli were found within the pulmonary

vasculature and gastric and intestinal lymphatics. Clear vacuoles were also found within the walls of the gastrointestinal tract, in the spleen, kidney and myocardium (Cina et al., 1994). The estimated dose of hydrogen peroxide ingested was 7 g, about 600 mg/kg/bw for a boy of 11.6 kg. Although the latter case is of note in that it involved a dilute (3%) hydrogen peroxide solution, it should be pointed out that even 1% solution may, when introduced into the newborn infant bowel, cause serious obstruction of mesenteric perfusion and ultimately result in gangrene (Shaw et al., 1967).

4.1.2.2.3 Other studies of acute organ toxicity

There are mechanistic reasons to suspect that hydrogen peroxide is operative in hyperoxic central nervous system toxicity (Piantadosi and Tatro, 1990; Zhang and Piantadosi, 1991), and in ischaemic/reperfusion injury of the myocardium (Cavarocchi et al., 1986; England et al., 1986; Byler et al., 1994; Voogd et al., 1994) and of other tissue models (Murthy et al., 1990). In the isolated perfused and ventilated guinea pig lung, hydrogen peroxide at a concentration of 50 μM (approximately 1.7 ppm) in the perfusion buffer decreased airway conductance, dynamic compliance and perfusion flow during a 5-min exposure. About a tenfold higher concentration was needed to cause a similar vascular and bronchial smooth muscle contraction in the rat lung. The pressor response was mediated by release of thromboxane A2. The vaso- and bronchoconstriction was believed to contribute to the acute pulmonary oedema observed in peroxide-induced injury of the lung (Bannenberg et al., 1993). Addition of alveolar macrophages to perfusates decreased the lung weight gain in isolated rat lungs perfused with the hydrogen peroxide generating system of beta-D-glucose and glucose oxidase; alveolar macrophages were as effective as the addition of erythrocytes or catalase in reducing the injury. The ability of alveolar macrophages to protect isolated lungs corresponded with their ability to reduce hydrogen peroxide concentrations in vitro. By comparison, azide-treated alveolar macrophages had decreased catalase activity, did not prevent injury to lungs perfused with the hydrogen peroxide generating system, and ineffectively decreased hydrogen peroxide in vitro (McDonald et al., 1991).

4.1.2.2.4 Conclusions on acute toxicity

There are a number of reported incidents of human poisoning by oral ingestion of hydrogen peroxide water solutions, but few reports have given data on the dose. The mechanism of systemic effect has been oxygen embolism. Even a dilute (3%) solution caused death in a 16-month-old boy when the ingested volume was large (dose approximately 600 mg/kg bw). Severe brain damage in an 84-year-old man ensued from ingestion of 35% hydrogen peroxide solution (dose approximately 150 mg/kg bw). In a more uncommon event arising from irrigation of an infected wound with 3% hydrogen peroxide, as low a dose as about 15 mg/kg bw caused transient shock and coma which was probably caused by systemic embolisation of oxygen microbubbles.

Based on all available information the classification of hydrogen peroxide is harmful by the oral route (R22) and harmful by inhalation (R20). For classification, see also Section 1.

4.1.2.3 Irritation

The irritancy/corrosivity of hydrogen peroxide solutions have been well outlined in studies of skin and eye irritancy, and the peculiar mechanism for the corrosive effect viz. blockage of the blood circulation has been demonstrated.

4.1.2.3.1 Skin

Studies in animals

According to modern skin tests with rabbits, hydrogen peroxide solution of 10% was slightly irritating (FMC, 1990a), while 50% and more concentrated solutions were severely irritating and corrosive (FMC, 1990b; 1989). Hydrogen peroxide solutions of 3% (Du Pont, 1972), 6% (Du Pont, 1973), and 8% (Du Pont, 1974) caused mild reactions in the rabbit skin in spite of occluded exposure for 24 hours, and were not rated irritating. Regarding a study on 35% hydrogen peroxide, six New Zealand White rabbits were treated on two skin sites with 0.5 ml of test substance for 4 hours under occlusive bandage. Slight to moderate erythema and/or oedema was observed in all rabbits at 4 and 24 hours; at 48 and 72 hours there were slight erythema and brown areas in the application sites. The brown areas developed into desquamation on day 6. At termination on day 14, desquamation was still present in two rabbits. Primary Irritation Score was 1.6/8.0 (FMC, 1983). Thus, the finding revealed moderate irritation by 35% hydrogen peroxide combined with delayed epidermal necrosis and sloughing.

Studies in humans

A retrospective review of all exposures reported to the Utah Poison Control Center over a 36-month period found that 325 cases (0.34%) were due to hydrogen peroxide. Ingestion was the most common route of exposure accounting for 83% of alla exposures. The next most common routes of exposure were ocular and dermal accounting for 8.0% and 7.7% of cases, respectively. The three chief dermatologic findings were paresthesias (60%), whiteness (56%), and blistering (16%). The most common skin and ocular exposure outcome was a minor, transient effect. There were no permanent sequelae from these exposures (Dickson and Caravati, 1994).

A group of 32 volunteers (18 men and 14 women, 23-37 years of age) exposed one hand to hydrogen peroxide vapour at variable concentrations and for variable durations. The threshold for skin irritant action was determined (the method is not disclosed). One hand of the subjects was placed inside an exposure chamber through an opening in a rubber membrane, the other hand served as a control. Immediately following the exposure the skin was washed, and the washings were analyzed (in both the exposed and the control area) to determine the deposition of H_2O_2. The threshold concentrations for skin irritation (apparent LOAELs) depended on the exposure time and were as follows: 20 mg/m^3 for 4-hour exposure, 80 mg/m^3 for 1 hour, 110 mg/m^3 for 30 min, 140 mg/m^3 for 15 min, and 180 mg/m^3 for 5-min exposure. The measured deposition of hydrogen peroxide at the threshold level exposures ranged 1.1-1.7 mg/dm^2, deposition ranging 0.5-0.8 mg/dm^2 was found to be ineffective (Kondrashov, 1977).

4.1.2.3.2 Eye

Studies in animals

Testing of eye irritancy for hydrogen peroxide with the Draize method indicated that 5% solution was slightly irritating (FMC, 1987a), 8% solution was moderately irritating (FMC, 1987b), and 10% solution was highly irritating (FMC, 1985). Interestingly, in the two latter studies washing of the eyes with tap water increased the severity of the irritation. In the study on 8% hydrogen peroxide, four New Zealand White rabbits were used. The eyes of two rabbits remained unwashed while the eyes of the remaining two rabbits were gently washed with 100 ml tap water approximately 20-30 sec after treatment. One hour after dosing, moderate conjunctivitis was noted in all eyes. Irritation worsened by the 24-hour scoring at which time unwashed eyes had slight corneal opacities, iritis and severe conjunctivitis. Washed eyes had severe corneal opacities, severe iritis and conjunctivitis. Irritation gradually resolved in unwashed eyes; washed eyes developed corneal vascularisation on study day 7 and bulging of the cornea (one rabbit) on day 13. At termination on day 22, one of the unwashed eyes had a slight corneal opacity and the remaining rabbit with washed eye had a slight corneal opacity, mild conjunctivitis and vascularisation (FMC, 1987b).

Sarver et al. (1996) studied the eye irritancy of 6% hydrogen peroxide solution with six New Zealand White rabbits. Approximately 20 seconds after the instillation of 0.1 ml of the test substance, the treated and control eyes of three rabbits were rinsed for about 1 minute with room temperature water. The eyes of the three remaining rabbits were not washed. The eyes were examined at 1, 24, 48, and 72 hours using the Draize technique. In the unwashed eyes, the test substance caused slight corneal opacity, moderate iritis, moderate and severe conjunctival redness, slight or mild chemosis and copious blood-tinged discharge. Biomicroscopic examinations revealed no corneal damage in the treated eyes. The treated eyes of two rabbits were clinically normal by 72 hours and the treated eye of the remaining rabbit was normal by 7 days following instillation. In the washed eyes, the test substance caused slight or mild corneal opacity, moderate iritis, mild or severe conjuctival redness, slight or moderate chemosis, and moderate or copious blood-tinged discharge. Blanching of the conjuctiva and conjuctival haemorrhaging with corneal vascularisation were observed in one rabbit. Biomicroscopic examination revealed moderate to severe corneal damage in this rabbit, but no corneal damage in the remaining two rabbits. The treated eyes of two rabbits were clinically normal by 48 or 72 hours. All irritation had resolved in the third rabbit by day 21, but corneal vascularisation was still evident.

In another, older series of eye irritancy studies on 8, 10 or 12% hydrogen peroxide with rabbits using the FHSA method, 10% and 12% solutions produced generalised, severe, penetrating, irreversible corneal injury (corrosion), severe iritis and severe conjunctivitis in rabbit eyes. Corneal damage was progressive and at 14 days, the corneas were grossly cloudy and distorted with heavily vascularised tissue changes. The washed eyes had moderate but penetrating corneal injury, severe to mild iritis, and severe conjunctivitis. Corneal damage was reversible and at 14 days, there was either no corneal injury or mild receding corneal injury. Hydrogen peroxide 8% produced a mild, reversible corneal damage and moderate to severe conjunctivitis with no significant iritic effect in a rabbit eye: Within seven days, the eye was normal. The washed eye had mild conjunctivitis with no significant corneal or iritic effect. This eye was normal within two days (Du Pont, 1972). The reason why in some studies washing of the eyes aggravated the irritant effect while in others it did not, is not clear. The purity of tap water (e.g. content of reduced metal ions) used in the eye wash could possibly influence the reaction. Hydrogen

peroxide 35% was corrosive to the rabbit eye. Washing the test eyes with tap water shortly after exposure had no significant effect on the irritation observed (FMC, 1983).

Five consecutive daily installations of 6 drops (total daily volume 0.3 ml) of 300 ppm hydrogen peroxide solution into the conjunctival sac of rabbit eyes resulted in a temporary increase in central corneal thickness by 10%; 100 ppm caused a 7% increase and 60 ppm caused no significant change. Maximal swelling was observed 2 hours after the final exposure and normal thickness was recovered after a further 4 to 6 hours (Yan and Pitts, 1991). Cytotoxicity studies with corneal epithelial cells have indicated that still lower levels (7-50 ppm) rapidly cause various toxic effects (Riley, 1990; Artola et al.; 1993; Hayden et al., 1990; Tripathi et al., 1992) clearly showing that the physiologic neutralisation mechanisms operating under *in vivo* conditions greatly attenuate local toxicity.

Studies in humans

In the retrospective review of all exposures reported to the Utah Poison Control Center over a 36-month period, 8% of the reports involving hydrogen peroxide concerned eye as the route of exposure. The most frequently encountered ocular symptoms included burning (65%), redness (50%), and blurry vision (19%). The most common ocular exposure outcome was a minor, transient effect and there were no permanent sequelae (Dickson and Caravati, 1994).

Historically 1 to 3% H_2O_2 (10,000-30,000 ppm) has been used topically as an on-eye antibacterial agent 3 to 5 times per day without causing significant injury (Grant, 1993). The effect of H_2O_2 is dose related with 0.5% (5,000 ppm) being used previously for treatment whereas 5 and 10% (50,000 and 100,000 ppm) are definitely known to cause cloudiness in the cornea, severe pain, and intraocular inflammation (Chalmers, 1989). A soft contact lens which had been stored in 3% hydrogen peroxide was placed in the eye of a 30-year-old woman without the appropriate catalase neutralisation. She had an immediate painful reaction with hyperaemia, tearing and eyelid spasm. The lens was removed at once, and the eye was treated with a topical anaesthetic. During the next 48 hours the eye became increasingly inflamed, despite the use of dexamethasone drops and the cornea began to show punctate staining. Thereafter the cornea began to clear, visual acuity was restored, and after several days there were no residual effects other than punctate keratopathy and mild discomfort (Knopf, 1984).

A controlled, randomised, double-blind study with eight human subjects was conducted to determine the threshold level of eye effects by hydrogen peroxide via a high water content hydrogel contact lens. Subjective comfort, conjunctival hyperaemia, corneal and conjunctival epithelial staining, and corneal oxygen uptake were assessed in response to 5-min wear of lenses that were presoaked in isotonic saline solutions containing 0, 25, 50, 100, 200, 400 or 800 ppm hydrogen peroxide. Higher levels of H_2O_2 (≥ 200 ppm) were associated with greater discomfort and increased conjunctival hyperaemia. The highest level (800 ppm) of H_2O_2 did not induce significant corneal or conjunctival epithelial staining or alter the corneal aerobic response (Paugh et al., 1988). In a single-masked, controlled study the eyes of 10 volunteers were exposed to drops of hydrogen peroxide solution or to contact lenses soaked for 2-4 hours in hydrogen peroxide solutions. The mean detection threshold for drops of dilute H_2O_2 was 812 ppm (range 400-1,500 ppm). The mean threshold was 267 ppm for 55% water lenses and 282 ppm for 38% water lenses. Removal of 50 ppm H_2O_2 from a hydrogel lens was completed within 30 seconds of human wear when the eyelids were held closed, and within 60 seconds during wide-open gaze, with blinking every 5 seconds. The corneal permeability to fluorescein was determined in 10 subjects after dosing with 50 ppm H_2O_2, 500 ppm H_2O_2, as well as negative and positive controls. There was no significant difference between the negative control and the two H_2O_2

concentrations. Hydrogen peroxide disinfection systems are designed to have residual H_2O_2 concentrations in the lens of no more than 50-60 ppm (Mc Nally, 1990).

4.1.2.3.3 Respiratory tract

Studies in animals

Aerosol generated from 70% hydrogen peroxide was studied for airway irritancy with the Alarie (mouse RD_{50}) method. The exposure concentration at which a 50% reduction of the respiratory rate was observed (RD_{50}) was 665 mg/m^3 (95% CI: 280-1,139 mg/m^3) and the exposure concentration at which a 50% reduction of the minute volume was observed was 696 mg/m^3 (95% CI: 360-1,137 mg/m^3). Hydrogen peroxide is a respiratory irritant at relatively high aerosol concentrations (Solvay Duphar, 1995).

Anaesthetised male Hartley guinea pigs were exposed to hydrogen peroxide aerosols for 5 min. Inhalation of 0.034, 0.34 or 3.4% hydrogen peroxide (0.01, 0.1 or 1 M) aerosol generated in a ultrasonic nebuliser (about 1 ml was consumed during 5 min which is calculated to have generated the maximum peroxide concentration of 42 mg/l, particle size is not given) caused a pontamine sky blue exudation (indicator of increased vascular permeability) in a concentration-dependent manner in the trachea and main bronchus. This effect was attenuated in a dose-dependent manner by a 5-min inhalatory pretreatment with catalase and deferoxamine (chelator of iron and inhibitor of hydrogen peroxide conversion to hydroxyl radical). Additionally, the high concentration of hydrogen peroxide caused a biphasic increase in ventilation overflow (demonstrating airway constriction) which was suppressed by inhalatory pretreatment with catalase but not with deferoxamine. The authors proposed that the observed inflammatory effect may be mediated not only by hydrogen peroxide itself but also by hydroxyl radical (Misawa and Arai, 1993).

Human observations

A group of 32 volunteers (18 men and 14 women, 23-37 years of age) were exposed to hydrogen peroxide vapour at variable concentrations and for variable durations through nose breathing (using a face mask). The threshold for respiratory irritation was determined (the method is not disclosed). Respiratory irritation depended primarily on the concentration of hydrogen peroxide, and only slightly on the duration of exposure. All exposures lasting from 5 min to 4 hours revealed a threshold concentration of 10 mg/m^3 (apparent LOAEL), and a no-effect level of 5 mg/m^3. The authors cite Russian industrial experience that workers complained respiratory irritation symptoms at hydrogen peroxide concentration of 10 mg/m^3, which is in agreement with the experimental results (Kondrashov, 1977). Kaelin et al. (1988) also reported that 7 dairy workers exposed to about 12 mg/m^3 of hydrogen peroxide (and possibly briefly to 41 mg/m^3), emitted from a milk packaging machine, experienced eye and throat irritation. Slight nasal irritation (and skin whitening upon contact) were observed in factory workers involved in drum and tank filling at a H_2O_2 production facility (CEFIC, 1996b). The maximum mean exposure level during the operations (1 hour) was 3.5 mg/m^3.

4.1.2.4 Corrosivity

As stated in the previous section, ≥35% hydrogen peroxide solutions cause epidermal necrosis, which becomes macroscopically discernible as brown or grey areas some days after application,

and results in desquamation and ulcer within a week. Histologically the formation of bullae caused by 50% hydrogen peroxide was observed by 48 hours (FMC, 1990). One anesthetised New Zealand White rabbit was treated with 0.5 ml of 70% hydrogen peroxide which was left in contact for approximately one hour, after which the test material was removed. At 4.5 hours the test site showed slight erythema, severe oedema and white bubbles under the skin. At 24 hours there was still mild erythema, oedema and white bubbles underneath the skin accompanied by several 1-2 mm brown spots. By 48 hours the findings were similar but the brown spots had enlarged to spotted areas. The corresponding Draize scores were 0.4/8.0, 0.3/8.0 and 0.3/8.0, respectively. Histopathological lesions were consistent with those occurring in third degree burns. The test material was judged to have caused extensive damage to the dermis, epidermis, blood vessels, connective tissue and adnexa (FMC, 1989).

Solutions of 50% or 70% hydrogen peroxide were evaluated in detail for acute skin corrosion potential in New Zealand White rabbits (Du Pont, 1994). Exposure to 50% hydrogen peroxide for 3 minutes caused moderate erythema and mild oedema by the end of the exposure period. Mild erythema and no to mild oedema were observed at 24, 48, and 72 hours after treatment. No dermal irritation was observed at 7 or 14 days. Blanching was observed at the time of dosing in the test site of the rabbit treated with 70% hydrogen peroxide. After 3 minutes of exposure, mild erythema and severe oedema were observed around the area of blanching. Moderate or mild erythema and moderate or mild oedema were observed at 24, 48, and 72 hours. Sloughing and fissuring were also observed in the test site. Superficial necrosis was observed at 24, 48, and 72 hours after treatment; full thickness necrosis was observed at 7 days. Scar tissue was observed at 14 days. Exposure to 50% hydrogen peroxide for 1 hour produced slight erythema, severe oedema and blanching. Mild erythema with mild, slight, or no oedema was observed through 7 days. No erythema or oedema was observed on day 14 after treatment. Superficial necrosis was observed in the test site at 72 hours after treatment, and full thickness necrosis and sloughing were observed at 7 days. Scar tissue was observed at 14 days**.** Exposure to 50% hydrogen peroxide for 4 hours produced mild erythema, moderate oedema and blanching by the end of the exposure period. Blanching was observed through 48 hours. Moderate, mild, or slight erythema and mild, slight, or no oedema was observed through 7 days after treatment. No erythema or oedema were observed at 14 days. Superficial necrosis was observed at 72 hours and full thickness necrosis and sloughing were observed at 7 days. Scar tissue and sloughing were observed at 14 days.

Conclusions on irritation and corrosivity

Available evidence from animal studies is sufficient to conclude on the irritancy/corrosivity of hydrogen peroxide in the eyes and the skin. Slight nasal irritation and skin bleaching upon contact were observed among workers exposed to the maximum mean level of 3.5 mg/m^3 during one-hour periods of drum and tank filling at a H_2O_2 production facility, and slight respiratory irritation was reported in volunteers exposed to 10 mg/m^3 of hydrogen peroxide vapours.

Hydrogen peroxide is highly corrosive (R35) and at lower concentrations irritating to eyes (R36) and skin (R38) and can cause severe damage to the eyes (R41). For classification, see Section 1.

4.1.2.5 Sensitisation

The skin sensitising property of nine different 3% hydrogen peroxide preparations was studied with guinea pigs using a modification of the Magnusson-Kligman procedure (Du Pont, 1953). For sensitisation five animals were given six intradermal injections of 0.1 ml 0.1% hydrogen

peroxide over a 2-week period; another group of five animals received six times one drop of 3% hydrogen peroxide to the abraded skin. After a 2-week rest period the animals were challenged with a single treatment of the previous type. The skin reactions were observed at 1, 24 and 48 hours. Primary irritancy of substance on intact skin was also studied in the ten animals before the sensitisation treatment and prior to the challenge. The study does not meet modern requirements due to few animals used and inadequate reporting. However, based on summary results, all the nine hydrogen peroxide substances appeared not to sensitise (ten animals used per substance).

There is one clinical report of two cases on positive patch tests to hydrogen peroxide (Aguirre et al., 1994). The first case was a 20-year-old woman, with no previous history of atopy and allergies, who had been working as a hairdresser for 4 years, the other case was a 27-year-old housewife, with no atopy or previous allergies, who had dyed her hair herself at home every 1 to 2 months for the last 6 years. In both cases the skin reactions to 3% hydrogen peroxide were strong; the former patient was positive also for nickel sulfate and 4-aminophenol, the latter for nickel sulfate, PPD, formaldehyde, 4-aminophenol, glyceryl monothioglycolate and cocamidopropylbetaine. The authors reported that 156 other hairdressers patch tested with the hairdresser's series of chemicals were all negative to hydrogen peroxide 3%. The Dermatological Department at the Finnish Institute of Occupational Health has since 1985 tested dermatitis patients having had exposure to hairdressing chemicals (mainly hairdressers) with a series of test substances containing 3% hydrogen peroxide in water. Computerised records were available concerning test results since 1991: 130 patients have been tested with no allergic reactions, one patient exhibited an irritant reaction. The Finnish Register of Occupational Diseases which was searched from 1975 through 1997 did not contain any cases of allergic dermatosis caused by hydrogen peroxide. The Dermatology Department of the University Central Hospital in Turku, Finland, patch tested 59 patients with 3% hydrogen peroxide during 1995-96, no positive reactions were found (Kanerva et al., 1998).

Conclusions on sensitisation

In spite of two reported cases of positive patch tests to hydrogen peroxide and the uncertainty surrounding an outdated animal study (with a negative result), and on recognition of the widespread occupational and consumer use over many decades, it may be confidently stated that the potential of hydrogen peroxide to cause skin sensitisation is extremely low and therefore do not meet the criteria for classification.

4.1.2.6 Repeated dose toxicity

The important features of, and main results from, repeated dose toxicity studies in mice, rats and dogs are summarised in Appendix E. Studies have been conducted by inhalation (to the vapour of hydrogen peroxide), and orally by gavage and via drinking water. In one study, hydrogen peroxide was administered in feed but there was much uncertainty what concentrations/doses actually entered the gastrointestinal tract (there were no effects reported). In another, poorly reported study, rats were whole-body exposed to airborne hydrogen peroxide vapour, and local effects in the shaved skin were assayed by enzyme determinations (Kondrashov, 1977).

4.1.2.6.1 Inhalation exposure

Studies in animals

There is one series of studies, conducted in the early 1950's, which involved whole body inhalation exposures of rats and mice for 7 weeks, and dogs for 6 months to the vapour of hydrogen peroxide (Comstock et al., 1954; Oberst et al., 1954). Due to the limited study methods (e.g. relatively imprecise analytical methods for hydrogen peroxide) and incomplete reporting it is difficult to draw firm conclusions; however, these unique experiments provide some important observations. A group of 23 rats was exposed to the mean level of 93 mg/m^3 (67 ppm) and groups of 10 mice to 79 mg/m^3 (57 ppm) or 107 mg/m^3 (77 ppm) of hydrogen peroxide, and mainly external effects by the treatment were noted: nasal discharge, oedematous feet, irritation of skin in the groin, hair loss. There was a slightly lower body weight gain (not significantly different) among the rats. Pathological/histopathological studies of the lungs, trachea, liver, kidneys, spleen, and cornea did not reveal significant changes.

Two dogs (one dog serving as a control) were exposed to the mean hydrogen peroxide concentration of 10 mg/m^3 (7 ppm) 6 hours daily, 5 days/week for 6 months (total 126 exposures). In this case there were both clear external signs of exposure as well as apparent changes in the respiratory system. During exposure the dogs showed obvious external skin irritation since the animals scratched themselves to the extent that several areas of the body were denuded. The hair was bleached. During exposures of the 24th week the dogs sneezed occasionally and lacrimation was also noted. The postmortem pathological studies showed changes only in the skin and in the respiratory system (the range of organs studied is not given). The skin was greatly thickened and, although there was a marked loss of hair, the hair follicles were not destroyed. In the lungs, there were patchy areas of atelectasis and emphysema. The small terminal bronchioles and respiratory bronchioles had hyperplastic muscular coats. Scattered throughout the lung tissue, mainly where the alveolar walls seemed to be fragmented, there were red staining circular areas composed of collagen, occasional muscle cells and strands of elastic tissue (Comstock et al., 1954; Oberst et al., 1954). The dog appears to be more sensitive to the vapour of hydrogen peroxide than the rat and mouse; it should be noted that the dog is a mouth breather. Because only one concentration level of hydrogen peroxide was used in the study, it is impossible to draw conclusions on the NOAEL. In view of the types of effect found in dogs (in comparison to rats and mice), 10 mg/m^3 is proposed as a tentative LOAEL.

Kondrashov (1977) conducted a subchronic study (exposure to 0.1-10.1 mg/m^3 hydrogen peroxide vapour for 4 months, 5 hours/day, 5 days/week) using whole-body (hair was clipped) exposure with rats. The respiratory organs and the exposed skin (see Section 4.1.2.6.2) were studied with histoenzymological methods. The threshold concentration of effect for H_2O_2 vapours in the respiratory system was reported to be 10 mg/m^3, the no-effect concentration was 1 mg/m^3. At 2 and 3 months of exposure to 10 mg/m^3 an increase was noted in the serum epoxidase activity (2.50 and 2.63, respectively, in the control animals 2.16 and 2.20). After 4 months the lungs showed a decrease of succinate dehydrogenase (SDH) activity (0.26 among exposed animals versus 0.34 in controls). After 4 months, the lungs revealed a decrease in the activities of SDH, monoamine oxidase (MAO), acid phosphatase, diesterase, and an increase in the activity of alkaline phosphatase. The study findings are difficult to interprete because of limited and unconventional methodology, and because of poor reporting, and no firm conclusions on the NOAEL can be drawn. On the basis of changes in tissue enzyme levels, 10 mg/m^3 of hydrogen peroxide might be regarded as a LOEL. The study findings may be supportive of the previously cited study with dogs.

After the hydrogen peroxide risk assessment was completed in Technical Meetings, the industry conducted a 28-day range finding inhalation toxicity study in rats (CEFIC Peroxygen Sector Group, 2002) towards fulfilling the data need requirement for a 90-day repeated inhalation toxicity study in rats. Groups of five male and female Alpk:AP_fSD (Wistar-derived) rats were exposed whole-body for 6 hours per day to 0 (control), 2.9, 14.6 or 33 mg/m^3 hydrogen peroxide vapour for 5 days per week, for a period of 28 days. Clinical signs which demonstrated respiratory tract irritation were seen at the exposure levels of 14.6 and 33 mg/m^3, but not at 2.9 mg/m^3. Regarding histopathology (**Table 4.12**), at the two higher levels concentration-related necrosis and inflammation of the epithelium in the anterior regions of the nasal cavity was found. In the larynx, mononuclear cell infiltration was seen in two females at the highest exposure concentration. Moreover, in the lungs, one male rat in each exposure group and two female rats in the top dose group exhibited perivascular neutrophil infiltration, and there was haemorrhage in some animals at the two lower dose levels. Control animals did not exhibit changes. The nasal localisation of the primary injury by peroxide is what can be expected from a water soluble oxidant vapour. As regards pathology in the lungs, the authors of the study considered it unlikely that the effects were treatment related due to the absence of a relationship with exposure concentration and the low incidence, and hence the NOAEL of the study would be 2.9 mg/m^3.

Table 4.12 Summarised microscopic findings of the respiratory system in the 28-day inhalation study in rats

	Microscopic findings			
Target organ	0 mg/m^3	2.9 mg/m^3	14.6 mg/m^3	33 mg/m^3
Nasal cavity	–	–	Necrosis* and inflammation (squamous epithelium, anterior regions of nasal cavity) 3/5 M, 2/5F	Rhinitis 1/5 M Necrosis* and inflammation (squamous epithelium, anterior regions of nasal cavity) 4/5M, 4/5F
Larynx	–	Inflammation 1/5F		Mononuclear cell infiltration 2/5F Epithelial erosion 1/5M
Lung	–	↑ Perivascular neutrophil infiltration 1/5M Haemorrhage 2/5M, 1/5F	↑ Perivascular neutrophil infiltration 1/5M Haemorrhage 2/5M	↑ Perivascular neutrophil infiltration 1/5M, 2/5F

- indicates no findings

* Necrosis in the context of this report means the more common type of cell death following external stimuli (cf. apoptosis), manifested by severe cell swelling or rupture, denaturation & coagulation of cytoplasmic proteins and breakdown of cell organelles

F - female; M - male

Human observations

A single report was located in the literature dealing with adverse effects in the context of long-term inhalation exposure to hydrogen peroxide. The report concerned a 41-year-old operator of a milk packaging machine who developed progressive dyspnoea and bilateral diffuse nodular infiltrates of the lungs. In the machine, cardboard was pulled through a bath of hydrogen peroxide solution; air measurements of H_2O_2 gave 41 mg/m^3 close to the machine and 12 mg/m^3 on the floor; thus the prevailing level of the day's exposure was of the order 12 mg/m^3 with transient elevations up to 41 mg/m^3. The patient had operated the machine for 3 years 2 days per week, followed by the most recent 6 months daily. The patient had smoked 2 packs of cigarettes daily for 25 years. His symptoms had developed within about one month prior to admission to the hospital. At work he had noticed (like the other 6 workers) eye and throat irritation and gradual bleaching of the hair. Pulmonary function testing and pulmonary gas exchange

measurements were consistent with interstitial lung disease. Transbronchial biopsy specimens revealed alveolar collapse, thickening of the alveolar walls, interstitial infiltration by mononuclear cells, and haemosiderin-laden macrophages within the alveoli. The patient was carefully examined with appropriate differential diagnostic methods. His erythrocyte catalase was found to be in the normal range. Withdrawn from the occupational exposure, the patient improved progressively without treatment, and by 1,5 months he no longer experienced dyspnoea. After subsequent oral corticosteroid medication the chest radiograph and lung function tests normalised. The authors attributed the clinical condition to the high hydrogen peroxide exposure; heavy smoking may have been a contributing factor (Kaelin et al., 1988).

Pulmonary function testing including FVC, FEV and PEF measurements were performed on all employees of a H_2O_2 production facility for a period of 3-5 years and showed no evidence of adverse effects attibutable to occupational exposure (CEFIC, 1996b). In the past, at the same plant there had been reports of hair bleaching, nose bleeds, and eye or respiratory irritation. Since the operating procedures were improved (typical exposure levels ranged from non detectable to 0.79 mg/m^3) there were few reported incidents.

One producer of hydrogen peroxide has recently conducted a survey of the health surveillance data on the production workers at four sites (Degussa-Huls, 1999). The survey encompassed 110 workers of whom 80 had been involved in the production for more than 10 years, (maximum 40 years). Collection of exposure data over the 1990's was targeted on loading and filling operations, packing drums, containers, trucks, railway cars with semi-automatic equipment, addition of stabilisers, and preparation of hydrogen peroxide solutions of various concentrations. The mean levels of hydrogen peroxide over the shift had been below the OEL of 1.4 mg/m^3 (see also Section 4.1.1.1.2) whereas short-term concentrations were up about 5 mg/m^3, and about 10 mg/m^3 in an accidental situation. The health examination data included some measurements of lung function (forced vital capacity and the peak expiratory flow), a symptom inquiry and other observations. No remarkable findings were reported in the lung function (smokers demonstrated a slightly descending curve of lung function values over the years which can be expected). At two plants occasional skin irritation and skin whitening after accidental contact with hydrogen peroxide was reported. Hair bleaching had occurred in one plant in the distant past. One case of acute throat irritation was also reported. The health surveillance data should dispel most fears of any clear clinical illness caused by hydrogen peroxide exposure but, since they are not derived from a properly conducted study, the health data cannot be used as solid evidence for the absence of adverse effects.

In line with endorsement by the Technical Meeting, the Finnish Institute of Occupational Health coordinated a worker health surveillance study in one company which concerned a small group of workers exposed to hydrogen peroxide vapours in aseptic packaging of fruit juices (Riihimäki et al., 2002). Fruit juice production in the plant had gradually started in the Spring of 1998, hence all the workers were engaged with hydrogen peroxide for 3 years or less. The company occupational health personnel was alerted in the Summer of 1999 by complaints among 6 operators/maintenance workers of two packaging machines situated at one end of the factory hall concerning irritation in the eyes and airways, headaches, temporary loss of olfaction, symptoms and signs in the skin, and blanching of hair. Peak exposures up to 11 mg/m^3 (8-hour TWA 2-3 mg/m^3) of H_2O_2 in air were measured in the breathing zone of the individuals, and intermittent skin contact ensued from amending breakdowns inside the machine. Workers who handled cartons inside the machine reported on burning and pricking of fingers, drying of the hands and face, decrease of skin elasticity, and dry, rough and bleached hair. At four other machines in the factory hall low peroxide levels were detected, and no complaints had emerged among the operators.

Measures were initiated to improve the situation and peroxide levels were monitored, however, it took several months until the targeted low levels (0.5-0.7 mg/m^3) were reached in the Spring of 2000. At that time symptoms were ascertained with a questionnaire indicating that every other person working with the two machines causing high exposure had experienced eye and airway irritation, and asthma symptoms. Clinical histories of respiratory illness were assessed from records of the company occupational health care unit and sick leave documents over time preceding and succeeding the reduction of H_2O_2 levels up until the Spring of 2001. Two machine operators and one maintenance worker exhibited a uniform course of recurring bronchitis-sinusitis which coincided with a 10-month period of high concentrations. Two patients, decribed in detail as case reports, exhibited even bronchoconstriction and made a full recovery only after administration of inhaled corticosteroids and the concurrent reduction of exposure.

The authors conclude that the results support the hypothesis that repeated exposures to high levels of hydrogen peroxide vapour induce sustained irritation and inflammation of the airway mucosa, increase susceptibility to respiratory infections, and may even cause irritant induced asthma. They note that there are clear similarities to the respiratory effects of oxygen (hyperoxia) and ozone which enhance the biological plausibility of the novel findings. However, as the study did not include specific examinations of the lungs, possible chronic lung changes by peroxide cannot be evaluated. Any remarkable effects were unlikely as the patients monitored in the study regained good health after the exposures were reduced. Moreover, the exposure duration was short for chronic effects to be manifested. From this limited study a LOAEL of 2 mg/m^3 (8-hour TWA) for the repeated inhalation toxicity by hydrogen peroxide (airway effects) can be derived. As the exposure concentrations fluctuated markedly it is possible that the peak levels (in one machine up to 11.3 mg/m^3, in the other machine up to 4.2 mg/m^3) played a significant role in the induction of effects.

4.1.2.6.2 Dermal exposure

A subchronic study (4 months, 5 hours/day, 5 days/week) using whole body exposure to hydrogen peroxide vapour at 0.1-10.1 mg/m^3 was conducted on rats with mechanically removed hair (Kondrashov, 1977). No details of study protocol are given. The threshold concentration of effect for H_2O_2 vapours on the rat skin was reported to be 1 mg/m^2, the no-effect concentration was 0.1 mg/m^3. After 2 months at 1 mg/m^3, histoenzymological studies of the epidermis in the back revealed an increase in the activity of MAO and NAD-diaphorase, and after 4 months, an increase in MAO, NAD-diaphorase, SDH, and lactate dehydrogenase. In addition the method of S.K. Rozental (method not described) revealed (after 4 months) a significant dysfunction of the horny layer of the skin. The study findings are difficult to interprete because of limited and unconventional methodology, and because of poor reporting, and no firm conclusions on the NOAEL can be drawn. On the basis of changes in tissue enzyme levels, 1 mg/m^3 of hydrogen peroxide may be regarded a LOEL. The author's main argument was that skin was more sensitive to hydrogen peroxide than the respiratory system (see Section 4.1.2.6.1). Previous studies in rats, mice and dogs seem to support that notion.

4.1.2.6.3 Oral administration

By gavage

There are two studies amenable for evaluation which deals with gavage administration of hydrogen peroxide daily for 40 to 100 days to Wistar rats. One used a fairly concentrated

hydrogen peroxide solution (5%) with a dose range of 56.2 to 506 mg/kg bw/day (Ito et al., 1976), the other used diluted solutions (0.06-0.6%) with a dose range of 6-60 mg/kg bw/day (Kawasaki et al., 1969). In the latter study, mainly the top dose seemed to be associated with effects: a significant reduction of the body weight gain after day 20 of administration, a slightly higher spleen weight on day 40 (but not at termination on day 100), a decreased haematocrit and plasma proteins on day 100. Plasma catalase was significantly decreased at the termination on day 100 in the 30 and 60 mg/kg bw/day dose groups. Thus NOAEL was 20 mg/kg bw/day. Ito et al. (1976) found a decreased body weight gain (and decreased feed intake and feed efficacy), and decreases in erythrocyte count, haemoglobin concentration and haematocrit in the high dose group (506.0 mg/kg). An increase of segmented neutrophils and monocytes, and a decrease of lymphocytes were seen in the high and medium dose (168.7 mg/kg) groups; S-GOT, S-GPT, alkaline phosphatase and blood urea nitrogen were also decreased, and S-GOT was decreased even in the low dose (56.2 mg/kg) group. The relative lung, spleen, adrenal and testis weights seemed to be increased in the high dose group but there were no treatment related histopathological findings. Gastric mucosal erosions, eschars as well as occasional infiltration of small round cells into the muscular layer were seen in the high dose group. It is notable that some types of effect (decreased liver enzymes, some haematological parameters) showed a dose-response. The authors attributed these effects to oxygen, however, local effects on the gastric and intestinal mucosa (no data were given on the duodenum and small intestine) should be considered as a complicating factor.

Via drinking water

Several studies have explored biological effects of hydrogen peroxide in drinking water experiments, but mostly with very limited objectives, and only one modern 90-day study in mice (FMC, 1997) fulfils the basic data needs for a toxicological evaluation. A common finding for rats and mice given ≥0.3% hydrogen peroxide in drinking water over several weeks is decreased water intake and growth retardation (Shapiro et al., 1960; Kihlström et al.; 1986a, 1986b; Hankin, 1958; Romanowski et al., 1960; Du Pont, 1995; FMC, 1997). In the study by Takayama (1980) even the lowest dose level, 0.15% hydrogen peroxide in drinking water, for 10 weeks seemed to result in slightly lower body weight gains among male and female F344 rats as compared to control animals. This was not the case with dd male mice (Aoki and Tani, 1972), or at a somewhat lower dose level (0.1%) with catalase-deficient C57BL/6NCrlBR mice (FMC, 1997). Higher concentrations of hydrogen peroxide in drinking water (1 and 1.5%) caused extensive carious lesions and pathological changes in periodontium in Holzman rats (Shapiro et al., 1960), and all rats which were given 2.5, 5, or 10% hydrogen peroxide in drinking water died within 43 days (Romanowski et al., 1960).

Groups of 10 male and female F344 rats were given 0, 0.15, 0.3, 0.6, 1.2, or 2.4% hydrogen peroxide in drinking water for 10 weeks (Takayama, 1980). Prominent weight losses and nasal bleeding were noted in the rats on the 2.4% solution starting immediately after initiation of the treatment. Also in the 1.2 and 0.6% dose groups weight losses were noted from an early stage of hydrogen peroxide treatment. Regarding body weight gain, a gain rate of 66.1% was achieved in the male controls, whereas a maximum gain of 53.3% was achieved in the hydrogen peroxide treated groups (0.6%), and a 45.9% weight loss occurred in males on 2.4% hydrogen peroxide. A gain rate of 37.2% was found in female controls, whereas a maximum gain of 29.7% was achieved in the low dose (0.15%) hydrogen peroxide group, and a weight loss of 30.4% in the top dose group. Nine of the males on the 2.4% solution and all rats at other dose levels survived the 10-week treatment. As in the male groups, nine of the 10 females at the top dose level and all animals at the other dose levels survived the treatment. Histopathology was performed on 5 rats

in each group. Pathological findings were made only at the top dose level: all males and females exhibited multiple gastric erosions and ulcer, 2 males showed atrophy of testis (in the whole group testis weights were reduced by 60% compared to controls), one rat showed congestion of the liver (died at week 7). The losses in weight of tissues other than the brain in the top dose males roughly corresponded to the body weight loss, the same applied for females. In view of the apparent effect on the weight gain even at the lowest dose level, no NOAEL can be determined.

In a modern 90-day drinking water study with catalase-deficient C57BL/6NCrlBR mice, 15 animals/sex/group received as drinking water 35% H_2O_2 diluted in distilled water to 100, 300, 1,000 and 3,000 ppm solutions for 90 days (FMC, 1997). Control animals were given distilled water. At term, ten males and ten females from each group were anesthetised, blood samples were collected and the animals were killed for macroscopic and histopathological examination. Five animals/sex/group continued on untreated distilled water for an additional 6-week recovery period.

Treatment period (Days 0-90): Clear treatment-related, dose-dependent effects were noted among both females and males receiving 300, 1,000 or 3,000 ppm of H_2O_2. Body weights were significantly reduced only in male and female animals receiving 3,000 ppm. Dose-related reductions in both food and water consumption were observed in female animals receiving 300 ppm and greater, while among the males consistent reductions were observed at the top dose level. Among females 300 ppm (103 mg/kg/day) was a LOAEL based on significant reduction in water consumption.

Recovery period (Days 91-134): The most notable effect was increased water consumption observed among males that had received 3,000 ppm, and among females that had received 300, 1,000 or 3,000 ppm.

Histopathology: Histological examinations were performed on all gross lesions, on the tongue, esophagus, stomach, duodenum, ileum, jejunum, caecum, colon, and rectum from all animals in all groups, and on all major organs including the sex organs in the high dose and control animals. Hydrogen peroxide related changes were observed only in the duodenum at terminal sacrifice in the 1,000 and 3,000 ppm groups of males and females, and in a single 300 ppm group male. Although the general architecture of the affected duodenum was normal, there was an increase in cross sectional diameter and a larger mucosal area with broader, more substantial villi when compared to those of control mice. The change was assessed as mucosal hyperplasia because of the increase in mucosal thickness and size of the villi. Mucosal hyperplasia was not found in 100 ppm group mice, neither among controls.

Mortality: There were no treatment-related deaths. One male mouse died in the control group (the cause of death was undetermined), and one male mouse in the 3,000 ppm group died on study day 43 (no histopathological findings). After the recovery period no hyperplasia was observed in any dose group.

Conclusion: NOAEL was 100 ppm (26 and 37 mg/kg/day) for males and females, repectively, based on dose-related reductions in food and water consumption, and on the observation of duodenal mucosal hyperplasia.

4.1.2.6.4 Other studies suggestive of organ toxicity

In a study on mechanistic events underlying the pathogenesis of chronic airway disease, quiescent bovine tracheal myocytes incubated for 2 to 60 min in 25 to 200 µM hydrogen peroxide exhibited mitogen-activated protein (MAP) kinase activation (Abe et al., 1994). The

authors suggested that the positive regulation of cell signaling caused by hydrogen peroxide may indicate a potential mechanism by reactive oxygen intermediates for the increased smooth muscle mass found in important inflammatory human airway disease (bronchopulmonary dysplasia and chronic severe asthma).

Growing database from experimental models and human brain studies suggest that oxidative stress, partly mediated by hydrogen peroxide, may play an important role in neuronal degenerative diseases such as Parkinson's disease, Alzheimer's disease and amyotrophic lateral sclerosis (Simonian and Coyle, 1996). While it is possible that individuals with deficient hydrogen peroxide neutralising mechanisms run increased risks, there is no firm hypothesis suggesting that exogenous exposure to hydrogen peroxide plays a role.

4.1.2.6.5 Conclusions on repeated dose toxicity

There is a sufficient database of animal studies available to characterise the repeated dose toxicity of hydrogen peroxide by the oral route. Decreased body weight gain was a typical finding in gavage studies in rats employing a dose range of 50-500 mg/kg bw/day; regarding other parameters examined, decreased erythrocyte count, haematocrit, plasma protein concentration, and plasma catalase were not uncommon observations. When administered in drinking water, 0.5% hydrogen peroxide consistently decreased the body weight gain (as well as intake of water) in rats and mice, and further studies at lower dose levels showed the same effect even at 0.15%=1,500 ppm in rats (Takayama, 1980) and at 3,000 ppm in mice (FMC, 1997). The latter, which is a well-conducted 90-day study with a catalase deficient strain of mice indicated that the NOAEL of hydrogen peroxide in drinking water was 100 ppm implying a daily dose of 26 mg/kg bw for males and 37 mg/kg bw for females. The LOAEL was 300 ppm (76 mg/kg bw for males, 103 mg/kg bw for females) based on dose-related reductions in food and water consumption, and on the observation of duodenal mucosal hyperplasia in one male. Hyperplasia was a consistent finding at the higher levels of 1,000 and 3,000 ppm both in males and females (corresponding daily doses were 239 mg/kg for males, 328 mg/kg for females and 547 mg/kg for males, 785 mg/kg for females, respectively), and it was completely reversible in the recovery period. At the top dose (3,000 ppm) plasma total protein and globulin concentrations were reduced.

Repeated exposure inhalation toxicity of hydrogen peroxide is not well elucidated and singular, limited studies with rats and dogs suggest that local effects in the skin, the respiratory tract, and the lungs may occur at about 10 mg/m^3 (Kondrashov, 1977; Comstock et al., 1954; Oberst et al., 1954; CEFIC Peroxygen Sector Group, 2002). These observations are notable in the light of a single reported human case of an interstitial lung disease which occurred in the context of occupational exposure to about 12 mg/m^3 of hydrogen peroxide for most of the workday, and transient exposures up to 41 mg/m^3 (Kaelin et al., 1988). Pulmonary function testing performed on all hydrogen peroxide production workers for a period of 3-5 years at one facility did not provide evidence for exposure-related harmful effects. Previously reported symptoms of eye and airway irritation and hair bleaching had been resolved when the peroxide concentrations were reduced to levels ranging from non detectable to 0.8 mg/m^3. A recent inquiry of clinical observations and symptoms among long-term exposed workers made in the occupational health monitoring programme of one company revealed incidental acute effects but did not suggest chronic pulmonary effects. However, since the health data were not derived from an appropriate study, they cannot be used as solid evidence for the absence of any adverse effects. Another health monitoring study involving a small group of workers (N = 6) exposed during about 10 months to relatively high levels (2-3 mg/m^3 8-hour TWA and up to 11 mg/m^3 STE) of peroxide vapour in aseptic packaging (Riihimäki et al., 2002) indicated that half of the group had

developed sustained airway irritation and inflammation, increased susceptibility to respiratory infections, and other symptoms, which were cleared after the exposures were strongly reduced. Further data, including human observations, are helpful to characterise and confirm the repeated dose toxicity of hydrogen peroxide by inhalation.

4.1.2.7 Mutagenicity

In vitro studies

Hydrogen peroxide is a mutagen and genotoxicant in a variety of in vitro test systems (see summarised data in Appendix F). In bacterial tests, most gene mutation assays (in the Ames test especially the strains sensitive to oxygen radicals), and DNA damage and repair assays have yielded positive results. With mammalian cells, positive results were mostly observed in gene mutation assays, DNA damage and repair assays, UDS assays, SCE assays, and cytogenetic assays for chromosomal aberrations. The responses were often, but not invariably (Abu-Shakra and Zeiger, 1990) modified by the amount of catalase present, which varies in bacteria and mammalian cells: bacterial strains lacking catalase activity seem to be especially sensitive (Abril and Pueyo, 1990), the hydrogen peroxide resistant Chinese hamster cell line R-8 had 10-fold higher catalase activity in comparison to the parental cells (Sawada et al., 1988). Although few tests have employed metabolic activation, it can be inferred from the results that the microsomal mix (like added catalase) markedly reduced or abolished the genotoxic response indicating that S9 contains hydrogen peroxide degrading enzymes (Mehnert et al., 1984a; 1984b; Speit et al., 1982; Procter & Gamble, 1985). Apart from protecting enzymes, other recognised variables of the cells determining their sensitivity to mutation were the extent of Fenton reaction (formation of hydroxyl radical) and the cells' repair abilities (Kruszewski and Szumiel, 1993).

In vivo studies

Concerning *in vivo* mutagenicity and genotoxicity, the studies available range from a Drosophila sex-linked recessive lethal test to modern *in vivo-in vitro* hepatocyte UDS and mouse bone marrow micronucleus assays (Appendix F). Additionally, there are two host mediated assays, one involving administration of 0.5 ml of 0.3% hydrogen peroxide twice by gavage to mice that had Salmonella indicator organisms inoculated intraperitoneally (Keck et al., 1980), the other involved intraperitoneal injections of different concentrations of hydrogen peroxide to mice which had previously received intraperitoneally inoculated tumour cells (Schöneich, 1967). In the former case, the positive mutagenicity result obtained suggested that hydrogen peroxide had been absorbed and come in contact with the bacteria. In the latter case, the positive result of chromosomal aberrations can be expected as a direct, local effect by hydrogen peroxide on the tumour cells. The intensity of response showed marked interindividual variance which the authors attributed to variable amounts of red blood cells (and hence catalase) in the peritoneal cavity.

In the *in vivo-in vitro* unscheduled DNA synthesis in rat liver study (CEFIC, 1997b) 5 male Wistar rats were treated with hydrogen peroxide at 25 or 50 mg/kg (0.1 or 0.2% solutions), by intravenous infusion at a dose rate of 0.2 ml/min, for the duration of approximately 30 min. Negative controls received water at the same dose rate and volume (25 ml/kg). Positive control animals (5 males) were dosed orally at 75 mg/kg with acetamidofluorene (2-AAF), suspended in corn oil (12-14-hour experiment). Dimethylnitrosamine (DMN, dissolved in water) was used as the positive control for the 2-4-hour experiment (dosing orally 10 mg/kg). Liver was perfused

with buffers, isolated hepatocytes were exposed to [^{3}H] thymidine for the determination of UDS. In the livers from the hydrogen peroxide infused rats, the group mean net grain count was not greater than –2.1 and not more than 0.7% cells were found in repair at either dose. The group mean NNG count for the vehicle-treated animals was <0 (-2.6 and -2.7) with only 0-0.3% cells in repair. The positive control chemicals 2-AAF and DMN increased the group mean NNG counts to 9.4 and 10.4, respectively, and 50% or more cells (84.7% and 83.7%, respectively) were found to be in repair. Thus the test system was sensitive to two known DNA damaging agents. The study was appropriately conducted, and relevant for genotoxicity evaluation with the limitation that the intravenous administration of hydrogen peroxide was restricted to approximately 30 min. Both positive control substances were given orally.

Two micronucleus studies with modern methodology have been conducted, one with the catalase deficient C57BL/6NCr1BR mouse (Du Pont, 1995), the other with Swiss OF1/ICO:OF1 (IOPS Caw) mouse (CEFIC, 1995b). In the first case, a micronucleus evaluation was included as part of the 2-week drinking water toxicity study of hydrogen peroxide. On study day 14, bone marrow smears were prepared from ten male and ten female mice in each of the 0, 200, 1,000, 3,000, and 6,000 ppm exposure groups. Additional groups of 5 male and 5 female mice were administered a single intraperitoneal injection of 20 mg/kg cyclophosphamide (positive control) 24 hours prior to harvest. Polychromatic erythrocytes from the negative control, 6,000 ppm, and positive control groups were evaluated for micronuclei; 2,000 PCEs from each animal were scored. No statistically significant increases in the frequency of micronucleated PCEs were observed in the 6,000 ppm dose group, neither was any decreased ratio polychromatic/normochromatic erythrocytes noted. Animals receiving cyclophosphamide responded as expected (Du Pont, 1995).

In the study by CEFIC (1995b), six groups of 5 male and 5 female mice were treated with a single i.p. injection of hydrogen peroxide. The doses were selected on the basis of preceding acute toxicity tests: 1%, 2% or 4% solutions were given in a volume of 25 ml/kg (250, 500 or 1,000 mg/kg, respectively). Two groups of 5 males and 5 females received i.p. injection of water (negative controls). Positive controls received cyclophosphamide orally at a volume of 10 ml/kg. Time of sacrifice was 24 hours or 48 hours. For each animal, the micronuclei were counted in 2,000 polychromatic erythrocytes; the polychromatic (PE) and normochromatic erythrocyte (NE) ratio was established by scoring of 1,000 erythrocytes. No clinical signs and no mortality were observed after treatment in the animals of both sexes given 250 or 500 mg/kg or in females given 1,000 mg/kg. 1/16 male mouse died at the dose of 1,000 mg/kg, hypoactivity and/or piloerection were noted in the remaining males. Under the experimental conditions, the test substance did not induce cytogenetic damage in the bone marrow cells at any dose level. In the hydrogen peroxide mouse groups the PE/NE ratios were significantly lower ($p<0.05$) than in the vehicle control group at the 24-hour harvest, and in 250 and 1,000 mg/kg dose groups at the 48 hours harvest, showing that the test substance affected the bone marrow. Cyclophosphamide induced a highly significant increase ($p<0.001$) in the number of micronucleated polychromatic erythrocytes, indicating the sensitivity of the test system. The PE/NE ratio decreased significantly ($p<0.05$) showing the toxic effect of this substance on the bone marrow cells. In the preceding range-finding study, the top dose level of 2,000 mg/kg, administered in 4-8% solutions, caused in several animals convulsions followed by death or hypoactivity and piloerection among the survivors. The study was appropriately conducted, and is relevant for genotoxicity evaluation; however, the negative outcome should be viewed with caution because of the presumably very short lifetime of hydrogen peroxide. It should be noted that the authors concluded that hydrogen peroxide somehow affected the bone marrow (because the PE/NE decreased) but the mechanism is not clear.

Two additional mouse bone marrow micronucleus assays, both with a negative outcome, are mentioned in scientific reports (Keck et al., 1980; Liarskii et al., 1983), but due to incomplete reporting they cannot be evaluated.

A recent study explored target tissue (mouse skin) genotoxicity and mutagenicity as a pre-screen for carcinogenicity (Society for Plastic Industry, 1997). Hydrogen peroxide 70% was applied to the skin of 10 female Sencar mice per dose group at dose levels of 10, 100, or 200 μmol in 200 μl of ethanol twice weekly for 4 weeks. Mice treated under the same conditions with DMBA (10 or 100 μmol/animal) or ethanol (200 μl) acted as positive and negative controls, respectively. The animals were killed on days 2 or 4 after the last administration (5 mice on each day). The application sites were removed, and after fixation and staining epithelial and dermal thickness, and dermal cellularity were determined visually by light microscopy. Non-phenol extraction of fresh frozen tissue was used to isolate DNA from animals killed 2 days after last dosing, and following digestion to nucleosides, 8-OH-2'-deoxyguanosine (8-OH-dG) was quantified by HPLC. Mutations in codon 61 of c-Ha-ras gene were determined using DNA isolated from paraffin blocks of whole skin. Treatment with hydrogen peroxide at all dose levels gave negative responses in all effect endpoints. The positive control DMBA induced DNA damage, c-Ha-ras mutations, epidermal hyperplasia and dermal cellularity changes. Calculation of the H_2O_2 concentrations used in the experiment gives 0.2, 1.6 or 3.2%. The inference can be made that at low non-irritating concentrations, and with a low application rate, hydrogen peroxide did not cause detectable cellular proliferation or *in vivo* mutagenicity in the Sencar mouse skin and hence were not suggestive of significant potential of carcinogenicity in this tissue model. Regarding the analysis of 8-OH-dG, the time lapse of two days between the last treatment and sampling may imply a certain uncertainty, as the damage may have been repaired.

Mechanistic studies

Hydroxyl radicals may attack on DNA bases (causing lesions such as 8-OH-dG) or on the sugar-phosphate backbone of DNA, causing fragmentation of deoxyribose. The oxidant damage to DNA typical of hydrogen peroxide under *in vitro* conditions, viz. single-strand and, less frequently, double-strand breakage have been demonstrated in a variety of mammalian cells: rat hepatocytes (Olson, 1988), mouse lymphoma cells (Garberg et al., 1988), bovine lens epithelial cells (Kleiman et al., 1990), Chinese hamster V79-379A cells (Prise et al., 1989), V79 Chinese hamster fibroblasts, SV40 transformed human fibroblasts and primary human fibroblasts (Mello Filho and Meneghini, 1984), P388D1 murine macrophages, aortic endothelial cells and human peripheral lymphocytes (Schraufstatter et al., 1986; Van Rensburg et al., 1992). While a single treatment of JB6 cells with H_2O_2 (10^{-6}-10^{-4} M) induced DNA single-strand scissions, it did not induce anchorage independent growth (Gensler and Bowden, 1983). In *Salmonella typhimurium* TA100 cells, hydrogen peroxide dose-dependently increased the content of 8-hydroxydeoxyguanosine in the DNA (Kasai et al., 1986).

To study the relative sensitivity of rat tracheal epithelial and mesothelial cell DNA to oxidant damage, the comet assay, a gel microelectrophoresis that allows visual determination of DNA strand breaks on a cell-by-cell basis was used to evaluate damage after H_2O_2 exposure. Freshly isolated rat tracheal epithelial cells and mesothelial cells were exposed to 1-50 μM of H_2O_2 for 10 min; in some experiments catalase or deferoxamine were added to the cell suspension before hydrogen peroxide. Using the comet assay, both cell types showed, with a dose-response, similar increase in the number of cells with strand breaks and the number of breaks per cell after exposure to hydrogen peroxide; however, even at the highest concentration some cells failed to show damage. By contrast, 100% of cultured V79 lung fibroblasts showed evidence of strand

breaks at 25 and 50 μM of H_2O_2. Catalase largely prevented the formation of strand breaks, deferoxamine (an iron chelator) afforded only partial protection against 50 μM of hydrogen peroxide. To evaluate DNA repair, cells were exposed to 10 μM hydrogen peroxide for 10 min, washed and maintained in culture medium; by 2 hours the proportion of mesothelial and epithelial cells showing comets had returned to control levels for both cell types. The mechanism of hydrogen peroxide-induced damage to DNA of both cell types was presumed to relate to the iron-catalyzed formation of hydroxyl radical (Churg et al., 1995).

Exposure of human mononuclear leukocytes to H_2O_2 (up to 300 μM) induced DNA damage demonstrated by activation of ADP ribosylation and by nucleoid sedimentation assays. Unscheduled DNA synthesis was only slightly induced suggesting that either the DNA lesions are repaired by a short patch mechanism involving little UDS, or the repair was inhibited, or some combination of both. Repair of DNA lesions induced by N-acetoxy-2-acetylaminofluorene, an inducer of large patch DNA repair, was inhibited in a dose-dependent manner by exposure to H_2O_2 (25 or 100 μM) and the inhibition was dependent on ADP ribosylation. In contrast, the repair of DNA strand breaks induced by H_2O_2 was complete within about 8 hours and the repair was independent of ADP ribosylation (Pero et al., 1990).

In another study, pre-exposure of freshly prepared human peripheral mononuclear leukocytes to H_2O_2 (25-200 μM for 1 hour) significantly inhibited DNA repair activities in response to damage induced by N-methyl-N'-nitro-N-nitrosoguanidine, measured as unscheduled DNA synthesis. The responses to H_2O_2 were compared in four healthy human subjects with two sample preparations on different days. H_2O_2 significantly inhibited DNA repair in a dose-dependent manner after adjustment for between- and within-subject variability. There was also substantial variability in DNA repair activities for the same individual sampled on different days regardless of the hydrogen peroxide dose level. Thus, H_2O_2 not only can induce DNA damage, but may also have suppressive effects on DNA repair (Hu et al., 1995).

Conclusions on mutagenicity

Hydrogen peroxide is a mutagen and genotoxicant in a variety of *in vitro* test systems. The responses observed were modified by the presence of degrading enzymes (catalase), the extent of formation of hydroxyl radicals by Fenton reaction, and the cells repair abilities. Regarding *in vivo* genotoxicity, studies employing modern methodologies have explored DNA repair in liver cells of rats administered hydrogen peroxide by intravenous infusion for 30 minutes (CEFIC, 1997b), as well as micronucleus formation in mice in the context of a 2-week drinking water exposure (Du Pont, 1995), or after a single intraperitoneal injection (CEFIC, 1995b), all with a negative outcome. Intravenous administration of hydrogen peroxide in the *in vivo-in vitro* unscheduled DNA synthesis study ensured that the substance had a fair chance to reach the target (liver) cells, although the duration of exposure was limited (CEFIC, 1997b). In the micronucleus study by oral drinking water exposure (Du Pont, 1995), the systemic fate of hydrogen peroxide was uncertain, and there was no decrease in the ratio of polychromatic/normochromatic erythrocytes in the bone marrow. In the other micronucleus study (CEFIC, 1995), a single intraperitoneal injection of a large dose of hydrogen peroxide somehow affected the bone marrow (because the PE/NE decreased), but the absence of micronucleus formation must be viewed with caution because of the presumably very short lifetime of hydrogen peroxide. With a view to exploring target tissue *in vivo* genotoxicity and mutagenicity as a pre-screen for carcinogenicity, hydrogen peroxide 0.2-3.2% solutions in ethanol were applied to the skin of Sencar mice twice weekly for 4 weeks (Society for Plastic Industry, 1997). There was no indication of induced DNA damage (increased 8-OH-dG), c-Ha-

ras mutations, epidermal hyperplasia and dermal cellularity changes. Thus at low concentrations, and with a low application frequency, hydrogen peroxide did not induce local mutagenicity in this tissue model. In conclusion, the available studies are not in support of a significant genotoxicity/mutagenicity for hydrogen peroxide under *in vivo* conditions. A wider database of genotoxicity and mutagenicity observations on other relevant target tissues in direct contact with hydrogen peroxide is however desirable. Mechanistic studies suggest that cells are adapted to repair DNA damages caused by oxidants; on the other hand there is some evidence that hydrogen peroxide may inhibit the repair of DNA lesions inflicted by other types of reactive chemicals (Churg et al., 1995; Pero et al., 1990; Hu et al., 1995).

According to the principles followed in the EU, hydrogen peroxide is not classified as a mutagen.

4.1.2.8 Carcinogenicity

The salient data of carcinogenicity studies performed with hydrogen peroxide are summarised in Appendix G. Two relevant carcinogenicity studies with hydrogen peroxide have been conducted via the oral route (drinking water), one on C57BL mice (Ito et al., 1981a;b), the other on F344 rats (Takayama, 1980); in both cases the study reports are incomplete. Furthermore, hydrogen peroxide has been studied for its tumour initiating and promoting effect in the skin of Sencar mice (Klein-Szanto and Slaga, 1982; Kurokawa et al., 1984) and in the skin of ICR Swiss mouse (Bock et al., 1975), for tumour promoting effect in the rat duodenum and small intestine (Hirota and Yokoyama, 1981; Takahashi et al., 1986), and for carcinogenicity and tumour promotion in Syrian hamster buccal mucosa (Weitzman et al., 1986; Marshall et al., 1996),

Carcinogenicity or tumour promotion studies by the oral route

Ito et al. (1981a, 1981b) gave hydrogen peroxide to groups of 50 catalase-deficient C57BL/6J mice of each sex in 0.1 or 0.4% distilled water solutions as drinking water (*ad lib.)* from week 8 to week 108. The control mice received distilled water. Fresh solution was prepared every other morning. All mice were observed on every day and weighed once a month. The experiment was terminated at 108 weeks, and all animals were subjected to complete autopsy. In mice treated with 0.4% hydrogen peroxide the survival rate was 63%, in the 0.1% hydrogen peroxide group it was 61%, and in the control mice 54%. The body weight gain in the high dose females was lower than in the controls. The incidence of erosion and ulcer in the glandular stomach, most frequently prepylorically on the lesser curvature, increased dose dependently (high dose 42%, low dose 20 %, control 4%), as did single or multiple duodenal nodules. The nodules were classified into hyperplasia, adenoma or carcinoma by their histopathological appearance. The incidence of duodenal hyperplasia was significantly increased by treatment (high dose 62%, low dose 4%, control 9%). The earliest occurrence of duodenal hyperplasia was found on the 60th day after H_2O_2 administration. Typical duodenal adenomas were found at a frequency of less than 6% in all groups. Localised duodenal carcinomas were found only in H_2O_2 administered mice (5% in high dose, 1% in low dose and none among the controls). Carcinomas invaded the muscular layer and the small vessels but did not metastasise. The findings concerning other tumours were unremarkable. Only two dose levels were used in the study; even the low dose level (1,000 ppm) gave a clear effect of gastric and duodenal lesions. The authors do not give the doses received, but an estimation would predict roughly 300 mg/kg bw/day.

The authors subsequently extended their study to other strains of mouse but with more limited objectives. C57BL/6N, DBA/2N, BALB/cAnN mice of variable group sizes (2-29) were

provided 0, 0.1, or 0.4% hydrogen peroxide in drinking water (the vehicle was distilled water) for variable time periods up to 740 days (Ito et al., 1982). After 140 days of H_2O_2 administration, H_2O_2 was replaced with distilled water for 10, 20 or 30 days. In other groups of animals, hydrogen peroxide was given for 120 to 180 days and then changed to distilled water for 30 days. A fresh solution of H_2O_2 was prepared every other day. The stomach and the duodenum were the only organs studied. In C57BL mice, gastric lesions in the forestomach occurred in over 67% of the mice treated with H_2O_2 for 120 days and duodenal lesions were noted in over 80% of the mice that received hydrogen peroxide for 60 days. After the cessation of H_2O_2 treatment the lesions mostly regressed and even disappeared. Among mice given 0.4% and 0.1% H_2O_2 for 420 days to 740 days, 5% and 1% of them, respectively, had duodenal cancer by histological criteria though they did not show any distant metastases. In the control group, no duodenal cancer was noted in the same observation period. While the total incidence of the lesions was not very different among the three strains of mice, the average number of lesions per mouse was much higher in C57BL mice then in DBA or BALB mice; C57BL mice were more sensitive to the noduligenic effect of H_2O_2 than the other strains. Another important finding from this study concerned the behaviour of the duodenal lesions which showed a marked tendency of regression after the cessation of hydrogen peroxide treatment.

The third study used four strains of mice: C3H (high catalase activity), C57BL (low catalase activity), their F1 hybrid: B6C3F1 and C3H/C_s^b (a hypocatalasaemic mutant strain). Groups of 9-12 male and female animals were given 0.4% hydrogen peroxide as drinking water throughout the experiment. All mice were autopsied at 6 to 7 months after start of administration. Incidence of duodenal tumours (= hyperplasia or neoplasia) and the mean number of tumours per mouse were 11.1% and 0.11 in C3H mice; 31.8% and 0.36 in B6C3F1 mice; 100% and 3.91 in C57BL mice; 91.7% and 2.63 in C3H/C_s^b mice, respectively. There was a strong negative correlation between the incidence of duodenal tumours and catalase activities in duodenal mucosa, blood and liver among the different strains of mice (Ito et al., 1984).

Takayama (1980) has reported on an oral carcinogenicity study of hydrogen peroxide with F344 rats. Groups of 50 animals of either sex were given 0.6% solution, or 0.3% solution of hydrogen peroxide as drinking water, and the control group received tap water for 18 consecutive months. Thereafter all the groups were given tap water and, after an observation period of 6 months, killed for autopsy. Fresh H_2O_2 solutions were prepared four times weekly. The dosed animals showed lower weight gains than the controls; the treated groups started gaining weight again after the treatment was stopped. The 18-month survival rate was 97%, and there was no significant difference between the dose groups. Nasal bleeding was noted in some animals at an early stage of the study. Organ weights (not tumour bearing organs) were measured (relative weights were not given), and a wide battery of serum biochemistry parameters were analyzed from 10 randomly selected rats per group at termination. There seemed not to be any differences in absolute or relative organ weights, but testis weights appeared to be slightly increased dose-dependently. (The tables do not indicate any statistically significant differences but it is not clear if testing was done.) No significant differences were found in the spectrum of tumour bearing organs, incidence of tumours, or the tumour-developing stage between the treated and control groups. Almost all male rats had tumours, notably Leydig cell tumours and endocrine tumours. Compared to historical F344 controls, the present controls had a higher incidence of tumours, partly because of the long study period. No differences were noted among the type of tumour bearing organs. Tumours of the gastrointestinal tract were not found at all. The test substance proved not to be carcinogenic to rats. The study appears to be appropriately designed (only two dose levels were used, however) and carefully conducted, and therefore relevant for the evaluation of carcinogenicity, but any firm conclusions are restricted by the incomplete

reporting. The daily intake of hydrogen peroxide for male rats was 433 mg/kg/day (0.6% H_2O_2) and 195 mg/kg/day (0.3% H_2O_2), and for female rats 677 mg/kg/day and 306 mg/kg/day, respectively. For comparison, the human intake of hydrogen peroxide in Japan (apparently from diet) was estimated as 4.3 µg/kg/day.

In a study of promoting effects in intestinal carcinogenesis, groups of 3 or 8 male F344 rats were administered 1.5% H_2O_2 in drinking water either with or without methylazoxymethanol acetate (MAM) treatment (three i.p. injections of 25 mg/kg bw every other week) for 10 or 21 weeks; 3 control rats received water. Rats given H_2O_2 four weeks prior to MAM injections, during intervals between injections, and until the termination of the study showed higher incidences of duodenal (8/8) and jejunal (5/8) carcinomas when compared to rats otherwise similarly treated but not given H_2O_2 subsequent to MAM injections (2/8 and 2/8, respectively). The three rats given H_2O_2 alone throughout the study period did not develop carcinomas in the studied organs; there was no group of animals receiving MAM alone. Only gross tumours of the g-i tract were reported (Hirota and Yokoyama, 1981). In another study with similar objectives, male Wistar rats were given either N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and a diet supplemented with 10% sodium chloride over 8 weeks as a tumour initiation procedure (30 rats), 1% H_2O_2 in drinking water for 32 weeks subsequent to initiation by MNNG (21 rats), or only 1% H_2O_2 for 32 weeks (10 rats). Only gastroduodenal tumours were investigated. Hydrogen peroxide did not enhance the tumour development in the glandular stomach, although adenomatous hyperplasia in the fundic region was frequent (38% of animals). In the forestomach, the incidence of squamous cell papilloma was significantly increased irrespective of prior initiation (100% incidence in MNNG+H_2O_2 rats and 50% incidence in H_2O_2 rats). Duodenal adenocarcinoma was induced as expected by the initiation done (10% of animals), but it was not affected by the subsequent treatment with H_2O_2 (Takahashi et al., 1986).

Carcinogenicity and tumour promotion studies in oral cavity

Groups of 5-11 male Syrian hamsters were painted on the left buccal pouches twice weekly with 9,10-dimethyl-1,2-bentzanthracene (DMBA) (0.25% solution in heavy mineral oil) alone, or additionally, on two other days each week at the same site either with 3% hydrogen peroxide, or with 30% hydrogen peroxide. A fourth group of 9 hamsters was painted on the left buccal mucosa twice weekly only with 30% hydrogen peroxide. In animals treated with 30% H_2O_2 alone, histopathological examination after 22 weeks revealed hyperkeratosis and hyperplasia in all animals with hyperchromatic cells and a mild dysplasia in 4/9 animals; no tumours were found. DMBA treatment alone caused an incidence of 43% (3/7) epidermoid carcinomas, while 55% (6/11) of animals treated with DMBA plus 3% H_2O_2 and 100% (5/5) of animals treated with DMBA plus 30% H_2O_2 developed carcinomas (Weitzman et al., 1986). The volumes (doses) of substances applied were not given. Only tumours at the application site were studied. The hamster cheek pouch was used as a model for human oral carcinogenesis. Although the size of the study is limited, the promoting effect seems clear.

A more recent study explored the oral cavity carcinogenic and cocarcinogenic potential of dentifrices containing hydrogen peroxide and sodium bicarbonate (Marshall et al., 1996). Two experiments were conducted with groups of 25 male and female Syrian hamsters employing the method of application to cheek pouch. In Study A, 0.5% DMBA (0.1 ml) and 0.75% H_2O_2 / 5% $NaHCO_3$ in dual phase dentifrice (0.2 ml) were applied to the cheek pouch alone or in combination, five times per week for 20 weeks. In Study B, the corresponding treatments were 0.5% or 0.25% DMBA (0.1 ml) alone or in combination with 1.5% H_2O_2 / 7.5% $NaHCO_3$ in dual-phase dentifrice (0.2 ml), or 0.25% DMBA + 3% H_2O_2 / $NaHCO_3$ (0.1 ml + 0.2 ml). DMBA was applied three times per week and hydrogen peroxide preparations were applied five

times per week, over 16 weeks followed by a 4-week observation period. Mineral oil used for wetting the swabs was used as a control treatment in Study A, moreover, the untreated contralateral cheek pouch was used for comparison. In Study A, the H_2O_2 releasing dual-phase dentifrice was not carcinogenic, and in combination with DMBA it did not cause any observed acceleration of tumour development compared with DMBA alone. In Study B, in the context of treatment with 0.5% DMBA (but not 0.25% DMBA) combined with the H_2O_2 releasing dual-phase dentifrice, the latency period for tumour formation increased, compared to DMBA alone. Animals receiving 0.25% DMBA and 3% H_2O_2 / $NaHCO_3$ had a significantly lower rate of tumour formation and overall mass incidence. Croton oil (1%) also reduced the rate of tumour formation when applied with 0.25% DMBA. In animals not receiving DMBA, no abnormalities other than slight keratosis in one or two animals per group were found. Hydrogen peroxide alone was not studied. The authors noted that the combination of substances may result in chemical interactions, e.g. the dual-phase dentifrice used may have reduced hydroxyl radical formation.

Carcinogenicity and tumour promotion studies in the skin

Three studies have explored the tumour promotion or complete carcinogenicity potential of hydrogen peroxide in the mouse skin. In the first study, after initiation with 125 µg 9,10-dimethyl-1,2-bentzanthracene (DMBA), 0.2 ml 3% water solution of H_2O_2 was applied to the skin of 30 female ICR Swiss mice 5 times a week over 56 weeks; none of the animals developed skin tumours (Bock et al., 1975). Klein-Szanto and Slaga (1982) performed a tumour promotion and complete carcinogenicity study with female Sencar mice. Groups of 60 mice were treated on the dorsal skin with (a) 9,10-dimethyl-1,2-bentzanthracene (DMBA) followed by 0.2 ml of 30% H_2O_2, or H_2O_2 (30%) and acetone 1:1, or H_2O_2 and acetone 1:2, or H_2O_2 and acetone 1:5, once or twice weekly over 25 weeks, (b) one dose of H_2O_2 (30%) and acetone 1:1 followed by TPA (12-O-tetradecanoyl-phorbol-13-acetate) promotion, or (c) H_2O_2 (30%) and acetone 1:1 twice weekly; the total duration of the complete carcinogenicity study was 50 weeks. Control animals received the vehicle. H_2O_2 was ineffective as an initiator or as a complete carcinogen but, according to the authors, it functioned as "an extremely weak" promoter. In the third study, groups of 20 female Sencar mice were treated on the dorsal skin with (a) DMBA (9,10-dimethyl-1,2-bentzanthracene) followed by 0.2 ml of 5% H_2O_2 in acetone twice weekly, or 0.2 ml of 5% H_2O_2 in acetone twice weekly for 51 weeks. Control animals received the vehicle. Hydrogen peroxide showed neither promoting nor complete carcinogenic activity. Epidermal hyperplasia was observed in 45% of the mice in the promotion test while in the complete carcinogenicity test with hydrogen peroxide, only one mouse (5%) showed epidermal hyperplasia (Kurokawa et al., 1984).

Conclusions on carcinogenicity

A drinking water study in a catalase-deficient mice strain showed that hydrogen peroxide caused with a dose response duodenal hyperplasia (at a high frequency) and localised duodenal carcinomas (at a low frequency) (Ito et al., 1981a;b; Ito et al., 1982). A subsequent study with different strains of mice showed that there was a strong negative correlation between the indicence of duodenal tumours (hyperplasia or neoplasia) and catalase activities in duodenal mucosa, blood and the liver (Ito et al., 1984). In a comparable study with rats, drinking water administration of hydrogen peroxide seemed not to be associated with the occurrence of tumours, and there were no tumours in the gastrointestinal tract at all (Takayama, 1980). In carcinogenicity and tumour promotion studies, treatment with hydrogen peroxide demonstrated a promoting effect in rat intestinal carcinogenesis inititated by methylazoxymethanol acetate (Hirota and Yokoyama, 1981), in Syrian hamster buccal pouch carcinogenesis inititated by 9,10-dimethyl-

1,2-bentzanthracene (DMBA) (Weitzman et al., 1986), and "extremely weakly" in the Sencar mouse skin after DMBA treatment (Klein-Szanto and Slaga, 1982). Other studies of similar design have not shown carcinogenic or promotion acitivity (Takahashi et al., 1986; Marshall et al., 1996; Bock et al., 1975; Kurokawa et al., 1984). However, 1% hydrogen peroxide in drinking water for 32 weeks induced sqamous cell papillomas of the forestomach in rats (Takahashi et al., 1986).

While it is clear that hydrogen peroxide has the potential, even if weak, to induce local carcinogenic effect in the duodenum of a sensitive mouse strain, it is notable that the lesions showed a marked tendency of regression and even disappearance after the cessation of treatment. The mechanism of carcinogenic effect is unclear. Given that hydrogen peroxide causes DNA damage, a genotoxic mechanism cannot be excluded. Unfortunately, no cytogenetic studies have been available on the target tissue in various stages of histopathological injury. As regards tumour promotion, several mechanisms might be operative: direct genotoxicity, impairment of DNA repair, and chronic inflammation.

The special nature of the demonstrated carcinogenicity of hydrogen peroxide, and the overall evidence available at this time, cast some doubt on whether hydrogen peroxide should be regarded as a carcinogen of practical significance. The weak effect found in complete carcinogenesis studies in mice as well as in some promotion studies suggest promotion type of activity and possible underlying genotoxic mechanisms. Given the fact that mammalian cells have of necessity built defences against reactive oxygen species arising in endogenous metabolism, the injuries caused by hydrogen peroxide may well be non-stochastic, i.e. have a dose/dose rate threshold. This evidence however is not sufficient to trigger classification.

4.1.2.9 Toxicity for reproduction

Fertility

There were no reproductive toxicity studies available employing appropriate study methods. Wales et al. (1959) gave 0.33, 1 or 3% hydrogen peroxide in drinking water to three groups of 12 male albino mice . Solutions were changed twice weekly. The mice on the high level of peroxide (3%) refused to drink and after 5 days were removed from the experiment having lost about 20% of their body weight. The remaining two groups were each divided at random into four subgroups of 3 animals. Two female mice were placed with each male of the first subgroup on day 7 and again (with two other females) on day 28 after starting hydrogen peroxide. Two subgroups of males were placed with females on day 21: the animals in one of the groups continued on hydrogen peroxide, for the other group hydrogen peroxide was replaced with tap water (ensuring no consumption of hydrogen peroxide by the females). The fourth subgroup of three male mice was killed on day 21 and the epididymal spermatozoa were examined. The drinking water of three albino rabbits was also replaced with 0.33, 1 or 3% hydrogen peroxide and the semen was examined at weekly intervals for 6 weeks. All female mice mated to treated males became pregnant within a few days and in each case healthy young were born in litters of normal size. Pregnant mice that continued to consume 1% H_2O_2 in water up until near term showed some delay in parturition compared to dams using tap water (the effect was, however, small and inconsistent). The concentration, morphology and motility of the mouse spermatozoa (in three mice) after 3 weeks of treatment appeared normal. There were no detectable abnormalities in the sperm of the three rabbits exposed for 6 weeks either. No firm conclusions can be drawn from this limited study which did not use any control animals, although any major deleterious effects by the treatment on reproduction seem to be excluded.

The same researchers (Wales et al., 1959) also demonstrated in an *in vitro* experiment that rabbit semen was more resistant to exogenous hydrogen peroxide (even 3,000 ppm failed to immobilise the spermatozoa completely) than semen from bull, fowl, dog, ram, mouse and human. Rabbit seminal plasma had a particularly high capacity to decompose hydrogen peroxide, presumably due to catalase.

In another old study, three weanling Osborne-Mendel female rats were given 0.45% H_2O_2 in drinking water and maintained on it for 5 months. Thereafter they were given tap-water and mated with normal males. Six normal male litter mates were divided into two equal groups: one received 0.45% H_2O_2 while the other received tap water. These animals were maintained on their respective regimens for 9 months. Normal litters were produced, and thus long-term treatment with peroxide did not appear to affect the reproduction in female rats. Regarding observations made on the six male offspring that were followed for 9 months, the only noticeable effect was a difference in body weight: an average of 521 g for those on tap water against 411 g for those on H_2O_2 (Hankin, 1958). No firm conclusions can be drawn from this restricted study with few animals.

There is a brief account of experimental studies with hydrogen peroxide involving even observations on reproductive effects (Antonova et al., 1974). Male and female rats were administered hydrogen peroxide daily by gavage at doses of 1/10-1/5 LD_{50} (which is not specified) for 45 days. At the high dose, females showed modifications of the oestrus cycle and males reduced mobility of spermatozoa, without an effect on the testis weight. In another experiment male and female rats received daily doses of 0.005, 0.05, 0.5, 5, or 50 mg hydrogen peroxide/kg bw by gavage for 6 months, and were mated. Variations of the oestrus cycle in females were observed during treatment at 50 and 0.5 mg/kg but not at 5 mg/kg. Reduced mobility of spermatozoa in males was observed at 50 mg/kg. No changes were found in the morphology and weight of the testes. Among the high dose females, 3/9 produced litters, compared to 7/9 in the control group. In addition, litter size and bodyweight gain of the offspring of the high dose females were reduced relative to those of control females. Due to inadequate reporting the study findings cannot be assessed.

Developmental toxicity

One study which addresses developmental toxicity has been conducted with Wistar rats (Moriyama et al., 1982). Aqueous solutions of hydrogen peroxide were mixed with powdered feed to 10, 2, 0.1, or 0.02% and administered to groups of 5-8 pregnant rats for one week during “the critical period of pregnancy”. The foetuses were removed on day 20 for examinations (Study A). Separate dose groups of 2-3 rats were similarly treated but the rats were allowed to go through normal delivery, and the offspring were followed-up for about four weeks (Study B). In Study A, at the high dose level the dam body weight did not increase markedly. Food consumption was reduced to about one third as compared to the other dose groups, for which there was no difference from controls. Foetal resorptions were increased and the foetal body weight was decreased; most of the foetuses were close to death. No external malformations were found in any of the dose groups. Haemorrhaging of internal organs (eye, parietal region of the brain, cardiopulmonary region, torso) was dose dependently increased in the dose range 0.1-10% H2O2. Skeletal hypoplasias occurred dose dependently at the two highest levels. In Study B, all the neonates of the 10% treatment group died within 1 week post partum, the body weights were low and the number of live births was decreased. In the other dose groups there was no major effect on the development of neonates. There are major uncertainties about the exposure and effect mechanism which cast doubt on the relevance of the study. H2O2 concentration in feed was reported to decrease to 1/10 after 24 hours and to virtually nil by 72 hours. The authors state that “the amount of residue was determined and consumption was estimated”; however, it is not stated how frequently fresh feed

was prepared. Nevertheless, it seems likely that the dams indeed ingested hydrogen peroxide, and there was not much of an increase in dam body weight at the top dose level. There was no marked difference between the groups in placental weight. The authors proposed that the observed effects on foetal development were due to the breakdown of essential nutrients in food by hydrogen peroxide.

Hydrogen peroxide has also been tested, together with 7 organic peroxides, with the three-day chicken embryo air chamber method (Korhonen et al., 1984). The total effective (ED_{50}) dose (including all deaths and malformations) was 2.7 mmol H_2O_2/egg. In the series of eight peroxides studied, hydrogen peroxide exhibited a low potency of embryotoxicity. Overall, the peroxides were judged not to be (comparatively) very effective in causing malformations.

Conclusions on reproductive toxicity

No appropriate animal studies were available for a complete evaluation of reproductive and developmental toxicity. Two limited studies with mice and rats exposed to hydrogen peroxide in drinking water suggested no grave disturbances on the male or female reproductive functions (Wales et al., 1959; Hankin, 1958). Moreover, an appropriate 90-day drinking water study with catalase-deficient mice (FMC, 1997), and carcinogenicity studies with catalase-deficient mice (Ito et al., 1981a;b) and F344 rats (Takayama, 1980) did not identify testes or ovaries as target organs for toxicity. The only available developmental toxicity study in Wistar rats which were fed on powdered feed mixed with hydrogen peroxide did show foetotoxic effects (Moriyama et al., 1982), but the study contains major uncertainties about the exposure and effect mechanisms (the authors proposed that the deleterious effect was due to the breakdown of essential nutrients in food by hydrogen peroxide). Although raising some further questions, the study cannot be used for an evaluation.

Thus there is a clear data gap regarding studies of developmental toxicity for hydrogen peroxide. Industry had however requested a derogation for reproductive toxicity screening which was consented at the Technical Meeting level. The decision was reached on the presumption that conventional study protocols (e.g. administration in drinking water) were unlikely to show specific embryonal or foetal effects firstly, because it is doubtful whether hydrogen peroxide (as opposed to its degradation products oxygen and water) would reach the foetus and secondly, because local effects in the mother, possibly causing nutritional disturbances and general toxicity, are expected.

4.1.3 Risk characterisation

4.1.3.1 General aspects

Hydrogen peroxide is a normal metabolite in the aerobic cell, and occurs under most conditions at submicromolar concentrations. Due to the many applications of hydrogen peroxide in industry, disinfection and personal care, there is potential exposure to the exogenous substance for workers, consumers and the population at large.

Toxicokinetics and metabolism

Hydrogen peroxide readily passes across biological membranes (permeability coefficient corresponds to that of water) and, because it slowly reacts with organic substrates, it can diffuse considerable distances in the cell. There are two main hydrogen peroxide metabolising enzymes, catalase and glutathione peroxidase, which control H_2O_2 concentration at different levels and in different parts of the cell as well as in the blood. At low physiological levels hydrogen peroxide is mainly decomposed by GSH peroxidase whereas the contribution of catalase increases with the increase of hydrogen peroxide concentration. Red blood cells remove hydrogen peroxide efficiently from the blood due to a very high catalase activity whereas in the serum, catalase activity is low.

Both animal studies and human case reports (mainly) of large ingested doses of hydrogen peroxide indicate that at high uptake rates hydrogen peroxide enters the surrounding tissues and blood vessels where it is degraded liberating oxygen bubbles, which may cause oxygen embolism. Because embolic effects have occurred in the heart muscle and the brain, it is apparent that hydrogen peroxide or, more probably, oxygen microbubbles thereof may be carried in the venous circulation and that sometimes (such as in the event of serious overload) they may pass through the lungs. Occupational experience in disinfection from handling concentrated hydrogen peroxide solutions or peracetic acid containing 15-30% hydrogen peroxide showed that white spots appeared on the skin of hands and arms of the workers on contact with the substance if the skin was not properly protected. The spots disappeared during some hours, which is in keeping with the hypothesis that the skin whitening was due to oxygen microbubbles.

There are no studies concerning the systemic fate of the substance after administration into the body at different rates and via different routes of uptake. It can be presumed that at low rates of absorption, mimicking e.g. occupational inhalation exposures, the ample bodily defences against reactive oxygen species likely maintain hydrogen peroxide at physiological levels. Regarding severe exposures, the question remains open whether exogenous hydrogen peroxide may increase the normal steady state levels of the substance in circulating blood. Although such an outcome is less likely, the data gap makes it impossible to preclude entirely the possibility of systemic effects.

In biological systems, hydrogen peroxide may also undergo reactions catalyzed by iron and other transition metals (via Haber-Weiss and Fenton reactions) resulting in the formation of highly reactive hydroxyl radicals. The cellular toxicity of hydrogen peroxide appears to depend largely on the generation of hydroxyl radicals.

From the viewpoint of the identification of vulnerable population groups it is notable that genetically determined traits (acatalasaemia, glucose-6-phosphate dehydrogenase deficiency of the erythrocytes) render humans more susceptible to peroxide toxicity.

Health effects

Acute toxicity

Concerning acute toxicity there are a number of reported incidents of human poisoning by oral ingestion of hydrogen peroxide water solutions, but few reports have given data on the dose. The mechanism of systemic effect has been oxygen embolism. Even a dilute (3%) solution caused death in a 16-month-old boy when the ingested volume was large (dose approximately 600 mg/kg bw) (Cina et al., 1994). Severe brain damage in an 84-year-old man ensued from ingestion of 35% hydrogen peroxide solution (dose approximately 150 mg/kg bw) (Sherman et al., 1994). In a clinical incident arising from irrigation of an infected wound with 3% hydrogen peroxide, as low a dose as about 15 mg/kg bw caused transient shock and coma which was probably caused by systemic embolisation of oxygen microbubbles (Bassan et al., 1982). Several other cases of surgical patients with oxygen embolism after irrigation with hydrogen peroxide have been described.

The acute toxicity of hydrogen peroxide vapours by inhalation has been explored in animal studies. Rats exposed to 338-427 mg/m^3 for 4-8 hours showed few symptoms other than scratching and licking themselves, and none of the animals died (Comstock et al., 1954; Oberst et al., 1954). Pathological examination revealed congestion in the trachea and lungs, and the lungs exhibited many areas of alveolar emphysema. Rats were exposed (whole body) for 4 hours to 170 mg/m^3 of hydrogen peroxide (the maximum attainable vapour concentration from 50% solution) with only minimal signs of treatment: nasal discharge and transient decrease in body weight (FMC, 1990). Another poorly reported study which concerned a whole-body (shaved skin) exposure of rats to hydrogen peroxide vapour for 4 hours, gave an LC_{50} value of 2,000 mg/m^3 and noted that the primary cause of death in the animals was gas embolism (Kondrashov, 1977).

Svirbely et al. (1961) found that the mouse was more susceptible to hydrogen peroxide vapour toxicity than the rat. Exposure for 4 hours at 110 mg/m^3 (78 ppm) was not lethal to the mouse; at 160 mg/m^3 (113 ppm) 1/10 mice died within 24 hours and 4/10 died within the 2 week-observation period, at 321 mg/m^3 (227 ppm) 5/25 died within 24 hours and 22/25 died within 2 weeks. In another experiment at 320 mg/m^3 (226 ppm), 1/10 mouse died within 24 hours and 5/10 within 2 weeks. A single prior exposure to hydrogen peroxide afforded a moderate degree of protection against otherwise lethal doses of H_2O_2 (Svirbely et al., 1961).

Concerning hydrogen peroxide aerosols, 2-hour exposures to levels ranging from 920 to 2,000 mg/m^3 (aerosol of 70% H_2O_2) were lethal to at least some mice; macroscopic findings in the dead animals (swelling and/or discolouration of the skin of the head, the tongue, neck, forepaws, and the nose, subcutaneous emphysema and haemorrhages, red lymph nodes, diffuse red lungs) were attributed to the bleaching and corrosive nature of the test substance (Solvay Duphar, 1995a). Punte et al. (1953) reported in a mouse study that at concentrations from 3,600 to 5,200 mg/m^3 there were no deaths, but congestion of the lungs and necrosis of bronchial epithelium were found. At 9,400 mg/m^3 the lethality range was reached with death occurring 6 days following exposure. At 12,000-19,000 mg/m^3 for 10-15 min, the survival time was reduced in the majority of mice to less than an hour. The symptoms of the animals during exposure to low concentrations consisted of a mild nasal irritation, blinking of the eyes, slight gasping, and loss of muscular coordination. These symptoms generally disappeared within 30 min. Pulmonary congestion was noted, and surviving animals showed necrosis of bronchial epithelium. Gross opacities were present in the eyes of 4 mice exposed to the highest concentration (19,000 mg/m^3) and killed after 8 weeks.

Concerning intravenous administration of hydrogen peroxide solutions, the maximum tolerated dose for rats in a prolonged (up to 30 min) infusion was approximately 50 mg/kg. The surviving rats did not show clear evidence of liver toxicity based on plasma enzyme levels (CEFIC, 1997b). In rabbits which were injected (it was not stated how rapidly the substance was injected but presumably the time scale was some minutes) into the marginal ear vein with more concentrated (3.6-90%) hydrogen peroxide solutions, the toxicity paradoxically increased with declining substance concentration. The LD_{50} dose for 3.6% hydrogen peroxide solution was about 3.2 mg/kg (Hrubetz et al., 1951).

Irritation

To study irritant effects in the skin, a group of 18 men and 14 women exposed one hand to hydrogen peroxide vapour at variable concentrations and for variable durations. The threshold for skin irritant action was determined (the method is not disclosed). One hand of the subjects was placed inside an exposure chamber through an opening in a rubber membrane, the other hand served as a control. Immediately following the exposure the skin was washed, and the washings were analyzed (in both the exposed and the control area) to determine the deposition of H_2O_2. The threshold concentrations for skin irritation (apparent LOAELs) depended on the exposure time and were as follows: 20 mg/m^3 for 4-hour exposure, 80 mg/m^3 for 1 hour, 110 mg/m^3 for 30 min, 140 mg/m^3 for 15 min, and 180 mg/m^3 for a 5-min exposure. The measured deposition of hydrogen peroxide at the threshold level exposures ranged 1.1-1.7 mg/dm^2, deposition ranging 0.5-0.8 mg/dm^2 was found to be ineffective (Kondrashov, 1977). The mean detection threshold in the eye was examined by dropping hydrogen peroxide solutions to the eyes of 10 volunteers in a single-masked controlled study (Mc Nally, 1990); the mean threshold was 812 ppm (0.08%) with a range of 400-1,500 ppm. To study irritation in the respiratory system a group of 18 men and 14 women were exposed to hydrogen peroxide vapour at variable concentrations and for variable durations through nose breathing (using a face mask). The threshold for respiratory irritation was determined (the method is not disclosed). Respiratory irritation depended primarily on the concentration of hydrogen peroxide, and only slightly on the duration of exposure. All exposures lasting from 5 min to 4 hours revealed a threshold concentration of 10 mg/m^3 (apparent LOAEL), and a no-effect level of 5 mg/m^3. The authors cite Russian industrial experience that workers complained respiratory irritation symptoms at hydrogen peroxide concentration of 10 mg/m^3, which is in agreement with the experimental results (Kondrashov, 1977). Workers involved with drum and tank filling in a H_2O_2 production facility and exposed to the maximum substance concentration of 3.5 mg/m^3, reported slight nasal irritation (CEFIC, 1996b). Kaelin et al. (1988) also reported that 7 dairy workers exposed to about 12 mg/m^3 of hydrogen peroxide (and possibly briefly to 41 mg/m^3), emitted from a milk packaging machine, experienced eye and throat irritation.

Appropriate animal tests show that 6% hydrogen peroxide solution was already irritating, 8% solution was moderately irritating, and ≥10% hydrogen peroxide was highly irritating and corrosive to the eye. In the skin, 10% hydrogen peroxide was slightly irritating whereas ≥35% solutions, although causing only moderate irritation at the lower concentration limit, were found to result in epidermal necrosis, and ≥50% were corrosive. Hydrogen peroxide 70% solution caused full thickness necrosis after 3 minutes of exposure. Apparently, the main mechanism for the necrotic effect caused by hydrogen peroxide is blood circulation impairment due to oxygen bubbles but direct cytotoxicity can also be envisaged. In the mouse RD_{50} test for airway irritancy, aerosol generated from 70% hydrogen peroxide proved irritating at relatively high concentrations (the mean RD_{50} value was 665 mg/m^3) (Solvay Duphar, 1995).

Sensitisation

Based on human epidemiological data it may be confidently stated that the potential of hydrogen peroxide to cause skin sensitisation is extremely low.

Repeated dose toxicity

There is a sufficient database of animal studies available to characterise the repeated dose toxicity of hydrogen peroxide by the oral route. Decreased body weight gain was a typical finding in gavage studies on rats employing a dose range of 50-500 mg/kg bw/day; regarding the other parameters examined, decreased erythrocyte count, haematocrit, plasma protein concentration, and plasma catalase were not uncommon observations. When administered in drinking water, 0.5% hydrogen peroxide consistently decreased the body weight gain (as well as intake of water) in rats and mice, and further studies at lower dose levels showed the same effect even at 1,500 ppm in rats (Takayama, 1980) and at 3,000 ppm in mice (CEFIC, 1997a). The latter, which is a well-conducted 90-day study with a catalase deficient strain of mice indicated that the NOAEL of hydrogen peroxide in drinking water was 100 ppm implying a daily dose of 26 mg/kg bw for males and 37 mg/kg bw for females. LOAEL was 300 ppm based on dose-related reductions in food and water consumption among females, and on the observation of duodenal mucosal hyperplasia in one male. Hyperplasia was a consistent finding at the higher levels of 1,000 and 3,000 ppm both in males and females, and it was completely reversible in the recovery period. At the top dose (3,000 ppm) plasma total protein and globulin concentrations were reduced.

Repeated exposure inhalation toxicity of hydrogen peroxide is not well elucidated and singular studies with rats (Kondrashov, 1977) and dogs suggest that local effects in the skin (thickening, bleaching, loss of hair), airways (hyperplastic muscular coats in distal bronchioles), and the lungs (fragmentation of alveolar walls, patchy areas of atelectasis and emphysema) may occur at about 10 mg/m^3 (Comstock et al., 1954; Oberst et al., 1954). A recent 28-day range finding inhalation toxicity study in the rat (CEFIC Peroxygen Sector Group, 2002) showed respiratory tract irritation and concentration-related necrosis and inflammation of the epithelium in anterior regions of the nasal cavity at 14.6 mg/m^3 and 33 mg/m^3 but not at 2.9 mg/m^3 (the apparent NOAEL). These limited observations are notable in the light of a single reported human case of an interstitial lung disease which occurred in the context of occupational exposure to about 12 mg/m^3 of hydrogen peroxide for most of the workday, and transient exposures to 41 mg/m^3 (Kaelin et al., 1988). Industrial experience from health surveillance of H_2O_2 production workers suggested no exposure-related effects on simple respiratory functions at airborne levels up to 0.8 mg/m^3 (CEFIC, 1996b) or less than 1.4 mg/m^3 with short-term peaks up to about 5 mg/m^3 (Degussa-Hüls, 1999). The latter study disclosed occasional skin irritation and skin whitening after accidental contact, hair bleaching in the past, and one case of acute throat irritation. Since the previous observations were not derived from properly conducted studies, the health data cannot be used as solid evidence for the absence of adverse pulmonary effects.

Another health monitoring study of six aseptic packaging workers which involved an 10-month period of high exposure (2-3 mg/m^3 8-hour TWA, peaks up to 11 mg/m^3) due to machine malfunction and, after repairs, a one-year follow up at a reasonably low and stable exposure (0.5-0.7 mg/m^3 8-hour TWA) indicated that three of the workers experienced eye and airway irritation, headache, and a uniform course of recurring bronchitis-sinusitis which coincided with the high exposure (Riihimäki et al., 2002). Two of the workers even exhibited bronchoconstriction and made a full recovery only after administration of inhaled corticosteroids and the concurrent reduction of exposure. The study did not include specific examinations on the

lungs. Further data, including human observations, are helpful to characterise and confirm the repeated dose toxicity of hydrogen peroxide by inhalation.

Mutagenicity

To conclude on genotoxicity/mutagenicity, hydrogen peroxide is a mutagen and genotoxicant in a variety of *in vitro* test systems. The responses observed were modified by the presence of degrading enzymes (catalase), the extent of formation of hydroxyl radicals, and the cells' repair abilities. Regarding *in vivo* genotoxicity, studies employing modern methodologies have explored DNA repair in liver cells of rats administered hydrogen peroxide by intravenous infusion for 30 minutes (CEFIC, 1997b), as well as micronucleus formation in mice in the context of a 2-week drinking water exposure (Du Pont, 1995), or after a single intraperitoneal injection (CEFIC, 1995b), all with a negative outcome. Intravenous administration of hydrogen peroxide in the *in vivo-in vitro* unscheduled DNA synthesis study ensured that the substance had a fair chance to reach the target (liver) cells, although the duration of exposure was limited (CEFIC, 1997b). In the micronucleus study by oral drinking water exposure (Du Pont, 1995), the systemic fate of hydrogen peroxide was uncertain, and there was no decrease in the ratio of polychromatic/normochromatic erythrocytes in the bone marrow. In the other micronucleus study (CEFIC, 1995b), a single intraperitoneal injection of a large dose of hydrogen peroxide somehow affected the bone marrow (because the PE/NE decreased), but the absence of micronucleus formation must be viewed with caution because of the presumably very short lifetime of hydrogen peroxide. In a study exploring target tissue *in vivo* genotoxicity and mutagenicity as a pre-screen for carcinogenicity, hydrogen peroxide 0.2-3.2% solutions in ethanol were applied to the skin of Sencar mice twice weekly for 4 weeks (Society for Plastic Industry, 1997). There was no indication of induced DNA damage (increased 8-OH-dG), c-Ha-ras mutations, epidermal hyperplasia and dermal cellularity changes. Thus at low concentrations, and with a low application frequency, hydrogen peroxide did not induce local mutagenicity in this tissue model. In conclusion, the available studies are not in support of a significant genotoxicity/mutagenicity for hydrogen peroxide under *in vivo* conditions. A wider database of genotoxicity and mutagenicity observations on other relevant target tissues is however desirable. Mechanistic studies suggest that cells are well adapted to repair DNA damages caused by oxidants; on the other hand there is some evidence that hydrogen peroxide may inhibit the repair of DNA lesions inflicted by other types of reactive chemicals (Churg et al., 1995; Pero et al., 1990; Hu et al., 1995).

Further scientific data are desirable for the evaluation of the *in vivo* genotoxic and mutagenic potential of exogenous hydrogen peroxide in target tissues, especially those in direct contact with the substance during exposure.

Carcinogenicity

A carcinogenicity study in catalase deficient mice, which were given hydrogen peroxide in drinking water, showed that the substance caused dose-related duodenal hyperplasia (at a high frequency) and localised duodenal carcinomas (at a low frequency) (Ito et al., 1981a; 1981b; 1982). A subsequent study with different strains of mice showed that there was a strong negative correlation between the indicence of duodenal tumours and catalase activities in duodenal mucosa, blood and the liver (Ito et al., 1984). In a comparable study with rats, drinking water administration of hydrogen peroxide seemed not to be associated with the occurrence of tumours, and there were no tumours in the gastrointestinal tract at all (Takayama, 1980). In carcinogenicity and tumour promotion studies, treatment with hydrogen peroxide demonstrated a promoting effect in rat intestinal carcinogenesis inititated by methylazoxymethanol acetate

(Hirota and Yokoyama, 1981), in Syrian hamster buccal pouch carcinogenesis inititated by 9,10-dimethyl-1,2-bentzanthracene (DMBA) (Weitzman et al., 1986), and "extremely weakly" in the Sencar mouse skin after DMBA treatment (Klein-Szanto and Slaga, 1982). Other studies of similar design have not shown carcinogenic or promotion acitivity (Takahashi et al., 1986; Marshall et al., 1996; Bock et al., 1975; Kurokawa et al., 1984). However, 1% hydrogen peroxide in drinking water for 32 weeks induced squamous cell papillomas of the forestomach in rats (Takahashi et al., 1986).

While it is clear that hydrogen peroxide has the potential, even if weak, to induce local tumourigenic and carcinogenic effect in the duodenum of a sensitive mouse strain, it is notable that the lesions showed a marked tendency of regression after the cessation of treatment. The mechanism of carcinogenic effect is unclear. Given that hydrogen peroxide causes DNA damage on contact with cells, a genotoxic mechanism cannot be excluded. Unfortunately, no cytogenetic studies *in vivo* have been available on the target tissue in various stages of histopathological injury. As regards tumour promotion, several mechanisms might be operative: direct genotoxicity, impairment of DNA repair, and chronic inflammation. The special nature of the demonstrated carcinogenicity of hydrogen peroxide, and the overall evidence available at this time cast some doubt on whether hydrogen peroxide should be regarded as a carcinogen of practical significance. The weak effect found in complete carcinogenesis studies in mice as well as in some promotion studies suggest promotion type of activity and possible underlying genotoxic mechanisms. Given the fact that mammalian cells have of necessity built defences against reactive oxygen species arising in endogenous metabolism, the injuries caused by hydrogen peroxide may well be non-stochastic, i.e. have a dose/dose rate threshold.

Toxicity for reproduction

No appropriate animal studies were available for the evaluation of reproductive and developmental toxicity. While there was no indication of adverse effects on reproductive organs in a catalase-deficient strain of mice which received hydrogen peroxide in drinking water for 90 days, thus providing some assurance that the substance is not a reproductive toxicant, there is a gap in the basic data requirement for developmental effects. However, it was presumed that because of the rapid degradation of the substance on absorption and due to local effects, a further study would be unlikely to reveal any specific developmental effects. Since reproductive effects by hydrogen peroxide are not deemed to cause any concern they are not considered any further in the risk characterisation.

Conclusion

The outstanding feature of the known adverse effects by hydrogen peroxide is that they (mainly) occur locally at the site of contact. The exception is exposure resulting in such high uptake rates of the substance that oxygen bubbles liberated in the blood stream cause embolism. It should be noted that, based on human case reports, the hazard of embolism may arise at fairly low doses (15-150 mg/kg bw) when hydrogen peroxide is introduced into body cavities. There is no firm evidence in repeated dose toxicity studies pointing to hydrogen peroxide toxicity in remote organs (haematological and clinical chemical effects may be secondary to changes in the gastrointestinal tract); however, lack of toxicokinetic observations do not allow the preclusion of the possibility of systemic effects entirely.

An assessment of the critical effects for hydrogen peroxide can be based on human observations supported by animals studies. Concerning single exposures, notable effect endpoints are acute toxicity (by the oral route: LOAEL approximately 100 mg/kg bw) and, for hydrogen peroxide

vapours, irritant effects in the eyes and airways (LOAEL 3.5-10 mg/m^3), irritant effects in the skin (LOAEL 20 mg/m^3), for hydrogen peroxide solutions, eye irritation (detection threshold about 0.1% [in contact lenses about 0.02%]; mild irritation 6%, moderate irritation 8%, severe irritation and corrosion ≥10%) and skin irritation/corrosivity (slight irritation 10%, moderate irritation 35%, corrosion ≥50%). Concerning repeated exposures, oral administration (drinking water) in mice gave NOAELs of 26 mg/kg bw/day in males and 37 mg/kg bw/day in females based on a dose-related reduction of food and water consumption and local effect (duodenal mucosal hyperplasia). Although a local carcinogenic effect (observed at higher doses) by a genotoxic mechanism cannot be excluded, the weight of evidence at this time does not suggest that carcinogenicity should be regarded as the critical effect. However, further studies exploring the possible *in vivo* genotoxicity and mutagenicity in the target tissue on contact with hydrogen peroxide would help to refine the evaluation and are encouraged. There were no valid and reliable studies on reproductive effects by hydrogen peroxide, but these effect endpoints were presumed not to be critical for human health.

The hazards of repeated inhalation exposures to hydrogen peroxide are not adequately defined. A recent 28-day range finding study in rats showed that hydrogen peroxide vapour at 14.6 mg/m^3, but not at 2.9 mg/m^3, caused respiratory tract irritation as well as necrosis and inflammation of the epithelium in anterior regions of the nasal cavity. This was not an unexpected finding for a water soluble oxidant in an obligate nose breathing species. There is, however, suggestive evidence from a study with dogs causing some concern that levels of about 10 mg/m^3 may be associated with local changes in the lungs as well as local effects in the skin. A search of the published literature located a single human case of presumed H_2O_2 induced pulmonary affection (interstitial lung disease) involving an exposure concentration of the same magnitude, thus providing some support for the hypothesis that hydrogen peroxide vapour could cause lung toxicity when breathed through the mouth. In search for further human evidence, industry reports of occupational health surveillance of hydrogen peroxide production workers, who were exposed to levels well below 1.4 mg/m^3 did not suggest impairment of lung function or remarkable respiratory irritancy. However, health surveillance reports cannot be used as solid evidence for the absence of adverse pulmonary effects. In contrast a health monitoring study of a small group of aseptic packaging workers linked sustained airway irritation and inflammation, susceptibility to respiratory infections, and asthma symptoms to airborne peroxide exposure at 2-3 mg/m^3 (apparent LOAEL) as a time-weighted average over the whole shift with peaks up to 11 mg/m^3. The peak levels may have played a significant role in the causation of effects. Although the study is limited, the findings seem a clear indication of hazard, as regards airway effects by hydrogen peroxide vapour, and can be used as guidance for a preliminary risk characterisation for workers exposed repeatedly by inhalation.

Acknowledging the uncertainties especially involving pulmonary effects, a careful follow up of relevant future studies in workers exposed to peroxide vapours, as well as all possible information on repeated inhalation toxicity on sodium perborate would be desirable.

4.1.3.2 Workers

4.1.3.2.1 Introduction

Workers are exposed to hydrogen peroxide by inhalation of vapours or aerosols, by skin deposition, and through accidental but not uncommon skin contact or, infrequently, splashes to the eye. Toxicokinetic evaluation of hydrogen peroxide suggests that only under conditions of

high uptake rates the substance might enter the systemic circulation. Moreover, findings from a limited set of relevant animal studies with hydrogen peroxide have not indicated systemic effects. Thus, apart from the demonstrated possibility of oxygen embolism in accidental exposure, the presently available database provides solid evidence for local effects only. It is concluded that it is especially unlikely that the substance deposited on the skin is systemically absorbed to a meaningful degree.

Although acute toxicity through the mechanism of oxygen embolism can be significant orally, or if the substance is introduced into body cavities, such routes (and the associated high uptake rates) are not deemed relevant for the occupational setting: c**onclusion (ii)**. Because only two human cases of skin sensitisation to hydrogen peroxide have been reported in the world literature in spite of widespread use over decades and frequent contact to the skin, it may be concluded that the skin sensitising potential of hydrogen peroxide is extremely low and therefore not of concern to human health: **conclusion (ii)**.

In view of the positive genotoxicity and mutagenicity of hydrogen peroxide in a comprehensive set of *in vitro* tests, whereas four *in vivo* tests each with experimental limitations did not show genotoxicity/mutagenicity, it is important to have an adequate database to judge on the potential for local genotoxicity in target tissue *in vivo*. A recent study exploring the potential of repeated local applications of hydrogen peroxide to induce sustained skin hyperplasia, DNA damage and c-Ha-ras mutations in the Sencar mouse did not show evidence of cell proliferation and local genotoxicity. However, the low concentration of hydrogen peroxide solution (at most 3.4%), the low application frequency, and the tissue model used, limit the inferences that can be made from the study, and a wider database of studies on other relevant target tissues is desirable. Regarding carcinogenicity, hydrogen peroxide induced local duodenal tumours including a low frequency of carcinomas in a drinking water experiment in a catalase-deficient strain of mice. In rats, a higher concentration of hydrogen peroxide in drinking water induced squamous cell papillomas in the forestomach. No indications of increased tumour yields in remote organs were found in mice and rats. In the light of present knowledge, mutagenicity and carcinogenicity are likely not of practical significance at low levels of exposure and via the exposure routes relevant for workers (**conclusion (ii)**), although improved database on local genotoxicity and mutagenicity would allow a refinement of this evaluation.

The adverse effects of hydrogen peroxide which are of main concern in the risk characterisation for workers are irritation/corrosivity and local toxicity in the repeated exposure situation.

In appropriate eye irritation tests with rabbits, hydrogen peroxide water solutions of ≥10% in strength caused severe irritation and irreversible damage (corrosion) and 6% solution was already irritating. Past experience from clinical practice with humans indicates that 1-3% solutions of hydrogen peroxide topically applied to the eye as an antibacterial did not cause significant injury; however, 5 and 10% solutions are definitely known to cause cloudiness in the cornea, severe pain, and intraocular inflammation. Consequently, the handling of concentrated H_2O_2 solutions (≥5%) without adequate eye protection causes a risk of serious eye effects, and solutions in excess of 3% may cause irritation. In reality, such effects must be uncommon because no human reports of irreversible eye injury were located. In a retrospective review of 325 exposures to hydrogen peroxide reported to the Utah Poison Control Center over a 36-month period, 8% concerned the eye and the symptoms reported included burning (65%), redness (50%), and blurry vision (19%). The typical outcome was a minor, transient effect, and there were no permanent sequelae.

Regarding acute effects in the skin, irritancy testing of 35% hydrogen peroxide with rabbits (4-hour exposure under occlusion) caused only slight to moderate signs of inflammation, but a delayed development of epidermal necrosis ensued obviously due to obstruction of blood circulation by oxygen bubbles. With more concentrated (50%, 70%) hydrogen peroxide solutions a corrosive effect through the full skin thickness became clear and followed from shorter durations of exposure. It can be anticipated that splashes of concentrated hydrogen peroxide solutions to the unprotected skin of a worker would be rapidly removed thus mitigating any possibility of marked local effects. However, anecdotal data of white spots in the skin of workers following contact to H_2O_2 which disappear after some hours and leave no injury can best be explained by cutaneous oxygen bubbles but of a magnitude which does not impair blood circulation critically. The previously cited review from the Utah Poison Control Center reported that 7.7% of the 325 exposures to hydrogen peroxide involved skin effects, the main findings being paresthesias (60%), whiteness (56%), and blistering (16%). Thus, skin corrosion appears to be possible under the worst conditions, i.e. high concentration substance and failure to remove the substance rapidly from the skin.

Irritation symptoms caused by airborne hydrogen peroxide in the eyes and throat have been complained by Russian industrial workers (concentration about 10 mg/m^3) and Swiss dairy workers (about 12 mg/m^3, peaks up to 41 mg/m^3), and irritation of the nose was reported by workers exposed to 3.5 mg/m^3 during drum and tank filling. Although not clearly documented it is presumed that exposures involved both aerosols and vapours. In a poorly documented volunteer study, 10 mg/m^3 of hydrogen peroxide vapour was the threshold concentration of respiratory irritation (irritation criteria are unkown). Aerosol of 70% hydrogen peroxide was tested for respiratory irritation in the mouse Alarie method and proved to have a moderate potency (RD_{50} value was 665 mg/m^3). The 3% rule proposed by Alarie would give a tentative occupational exposure limit of 20 mg/m^3. Hence the complaints of irritation among workers at about 3.5-10 mg/m^3 likely pertain to slight effects. The rapporteurs (one female and one male) had the opportunity to make their own observations in premises where malfunctioning machinery generated exceptionally high concentrations (up to 11 mg/m^3) of hydrogen peroxide vapour. The feelings of dryness and occasional pricking in the eyes and upper airways were mild.

Repeated dose toxicity by the oral route is not deemed to cause risk for workers due to limited intake by ingestion of substance deposited in the upper airways: **conclusion (ii)**. Effects by repeatedly inhaled vapours or aerosols of hydrogen peroxide in the lungs are of some concern based on suggestive, limited evidence of hazard. Recent health monitoring of workers has uncovered chronic airway irritancy and inflammation at airborne peroxide levels which are slightly above the OEL of 1.4 mg/m^3 adopted in many countries. These findings, although based on individuals rather than populations, seem clear enough to be used for a preliminary risk characterisation for workers. On the other hand, since there is no evidence that exposure to airborne hydrogen peroxide at levels well below the OEL causes adverse effects in the respiratory system, it is provisionally considered that peroxide concentrations in excess of the OEL (1.4 mg/m^3 for 8-hour TWA) cause risk. Adverse effects of airborne hydrogen peroxide in the skin were also suggested in animal experiments, and at about the same levels as lung effects, however, there are no reports of such chronic effects (skin changes can be expected to draw the attention of the involved worker and the occupational health personnel). Therefore chronic skin effects are not considered a concern for human health: **conclusion (ii)**. There is anecdotal evidence of hair bleaching among hydrogen peroxide exposed workers but the dose-response for airborne substance is not known and even hand contact to the hair may play a role.

To characterise the risks for workers, the following 19 exposure scenarios were chosen: (1) production of hydrogen peroxide, (2) synthesis of other chemicals, (3) loading operations, (4)

pulp and paper bleaching, (5) bleaching of textiles, batch process, (6) bleaching of textiles, automated process, (7) industrial laundering, (8) aseptic packaging: immersion bath process, old type, (9) aseptic packaging: other types, (10) hydrogen peroxide and peracetic acid use: brewery, (11) peracetic acid use: meat processing, (12) etching of circuit boards, modern process, (13) etching of circuit boards, old process, (14) metal plating, (15) production of modified starch, (16) degrading of proteins, (17) drinking water treatment, (18) wastewater treatment, and (19) hairdresser's work.

4.1.3.2.2 Chemical manufacture

Hydrogen peroxide production is an automated, closed, continuous process. Some exposure to the compound may incidentally occur during distillation, stabilisation, dilution, sampling and laboratory work. Small leaks may also occur. A report from the industry reviewed personal 8-hour measurement data during synthesis, distillation and stabilisation, and gives mean levels over the work-shift of 0.24-0.8 mg/m^3. Similar exposures were measured for the laboratory personnel. Appropriate equipment for eye and skin protection is usually available, and the trained personnel are aware of the hazards of hydrogen peroxide.

The reasonable worst-case exposure to hydrogen peroxide via air in production was chosen as 0.8 mg/m^3 (TWA, full-shift). The risk of repeated inhalation toxicity is not significant: **conclusion (ii)**. Because direct handling does not occur, the potential of splashes to the eye and skin contact is low. The risks of eye, skin and airway irritancy/corrosivity are considered low: **conclusion (ii)**.

4.1.3.2.3 Synthesis of other chemicals

In the production of other peroxides, epoxidised compounds and modified starches, the processes are either closed, continuous or to a minor degree small batch processes. Mechanical general ventilation and local exhausts are common. Process data for the large-scale production of sodium perborate and sodium percarbonate indicate that there is little possibility of exposure to the workers due to the closed system. A single measurement available showed air concentration of 0.07 mg/m^3. EASE predicts low concentrations (0-0.14 mg/m^3. Production of peracetic acid is similarly a closed system. Syntheses in smaller plants mainly use batching processes. During weighing and mixing operations the measured airborne concentrations of H_2O_2 varied between 0.14 and 0.7 mg/m^3 (mean 0.3 mg/m^3). EASE predicted that exposure during this charging phase may amount to 1.4 mg/m^3. Therefore, it was concluded that the RWC for short-term exposure is 2 mg/m^3, and that for the full-shift exposure is 0.5 mg/m^3. Workers' exposure may also result from incidental splashes during charging the batches or filling of containers, and from leaks in the pipework. It can be expected that appropriate equipment for eye and skin protection is available and that it is used.

The reasonable worst-case inhalation exposure for this scenario (full-shift) for closed systems is 0.2 mg/m^3, and for batching process 0.5 mg/m^3. For short-term exposure during batching RWC is 2 mg/m^3.

The risk of repeated inhalation toxicity is not significant: **conclusion (ii)**. Because direct handling does not occur (regarding loading operations, see the next scenario), the potential of splashes to the eye and skin contact is low. The risks of eye, skin and airway irritancy/corrosivity are considered low: **conclusion (ii)**.

4.1.3.2.4 Loading operations

Loading was reviewed as a separate scenario although it takes place at the production site. The highest exposures are likely to occur at drum filling. The 8-hour measured area concentrations had a mean of 1.21 mg/m^3 and the short-term area measurements gave the mean of 1.58 mg/m^3. The highest single short-term area value measured was 3.5 mg/m^3. The personal 8-hour exposures had a mean of 0. 44 mg/m^3 (n = 3), whereas the personal short-term exposure had a mean of 1.8 mg/m^3 (n = 3), and the highest personal short-term value measured was 2.83 mg/m^3. All the personal exposures were measured in different occasions or workplaces. Thus, the given personal mean 8-hour exposure value for drum filling appears to be too low when compared both with the area and short-term measurements. The reasonable worst-case personal 8-hour exposure during drum filling was judged to be 2 mg/m^3; the exposure may be composed of repeated variably high peak concentrations, and short-term levels up to 5 mg/m^3 have been measured. As for production personnel, it can be expected that personal protective equipment is made available and used, and that the level of awareness concerning hazards is high.

No exposure data were found for transportation or unloading, but it can be anticipated that the 8-hour exposure would be lower than that for loading. Higher exposures could occur in accidental events.

The reasonable worst-case inhalation exposure over a work shift is 2 mg/m^3. There is a risk of repeated inhalation toxicity: **conclusion (iii)**. Loading type of work is associated with significant potential for vapour formation and for splashes and spills of concentrated (up to 70%) hydrogen peroxide solutions, therefore local irritancy/corrosivity in the eye and skin, and airway irritation may ensue unless PPEs are strictly used. While the latter cannot be anticipated for all loading operations (**conclusion (iii)**), sufficient measures to mitigate the risks may already be in place in many production sites.

4.1.3.2.5 Pulp and paper bleaching

Pulp and paper mills are today highly automated continuous processes. Process workers exposure conditions are well under control and they spend most of the time in well-ventilated control rooms. In the flowing mass, H_2O_2 concentration is relatively low (from 4% down to 0.5%). Therefore even during maintenance operations at the process lines the airborne exposure is unlikely to be high. Some exposure may occur in the very beginning of the process where H_2O_2 is diluted and fed into the process lines. Such occurrences would however be incidental because the facilites are unmanned. If incidental situations caused by leaks are not accounted for, the reasonable worst-case airborne exposure is no higher than 0.7 mg/m^3 (TWA, full-shift).

Workers are equipped with protective equipment of relevant material, and they are also trained to act in case of accidents.

Irritancy/corrosivity (eye, skin, respiratory tract): **conclusion (ii)**.
Repeated inhalation toxicity: **conclusion (ii)**.

4.1.3.2.6 Bleaching of textiles, batch process

Concerning the use of hydrogen peroxide in textile bleaching there were no measurement data on exposure. Small-scale textile bleaching is performed in small enterprises employing e.g. normal washing machines. The peroxide (35%) is normally charged manually to the machine, and may

cause short-term peak exposure. After the machine is closed further exposure is deemed minimal. Only dilution ventilation is anticipated. The short-term exposure was modelled using the EASE WIN 2.0 programme, and the predicted hydrogen peroxide vapour exposure was 14.1-28.2 mg/m^3 over 30 minutes per shift. Transformation to a concentration over the full shift (rest of the time 0.1 mg/m^3) gives 1-1.8 mg/m^3. However, because the level is suspected to be an overestimation (e.g. the charging time may be excessive), the lower end of the range seems appropriate. PPE may be used, especially gloves, but not invariably.

The reasonable worst-case inhalation exposure over a work shift is about 1 mg/m^3. The risk of repeated inhalation toxicity is not significant: **conclusion (ii)**. Manual batching is associated with significant potential for splashes and spills of concentrated (35%) hydrogen peroxide solutions, therefore local irritancy/corrosivity in the eye and skin may ensue unless PPEs are strictly used. As the latter is not guaranteed, the conclusion for irritancy/corrosivity (eye, skin) is a **conclusion (iii)**. EASE predicted for the charging phase very high (14-28 mg/m^3) airborne concentrations. This prediction is in conflict with actual measurements during manual transfer of 35% hydrogen peroxide in disinfection use, which gave about 2 mg/m^3. It is concluded that acute irritancy by the vapour in the airways is not a concern: **conclusion (ii)**.

4.1.3.2.7 Bleaching of textiles, automated process

In large plants, bleaching is a continuous and automated process in practically closed systems with local exhausts and mechanical general ventilation. Although no measurement data are available airborne hydrogen peroxide concentrations are expected to be low. Modelling with the EASE WIN 2.0 programme predicted <0.14 mg/m^3 as the reasonable worst-case inhalation exposure. As there is no manual handling of hydrogen peroxide, the likelihood of contact to the eye or skin is low.

Irritancy/corrosivity (eye, skin, respiratory tract): **conclusion (ii)**.
Repeated inhalation toxicity: **conclusion (ii)**.

4.1.3.2.8 Industrial laundering

Hydrogen peroxide bleaching is used in large industrial laundries washing clothing and linen. The washing machines are automated and practically closed washing lines (tube machines). A modern laundry with good general ventilation and local exhausts at the machines did not show detectable levels (<0.07 mg/m^3) of hydrogen peroxide in air. EASE modelling also predicted very low levels (0-0.14 mg/m^3). As there is no manual handling of hydrogen peroxide, the likelihood of contact to the eye or skin is low.

Irritancy/corrosivity (eye, skin, respiratory tract): **conclusion (ii)**.
Repeated inhalation toxicity: **conclusion (ii)**.

4.1.3.2.9 Aseptic packaging

Measured exposures at both types of machines (immersion bath, spray-type) give the overall personal 8-hour mean value of 0.76 mg/m^3 which is thus less than the OEL level. However, the measurements also show that some workers have encountered exposures at or even above the OEL. For short periods of working time (at the maintenance level) the exposure was on the average 2.35 mg/m^3. The creamery processes are continuous with little variation in the process

during working shifts. Generally, the machines are situated in large halls, which are equipped with mechanical ventilation, and the semi-open packing machines are equipped with local exhausts. The exposure in the vicinity of the machines is quite stable. The reasonable worst-case personal exposure to hydrogen peroxide over a work shift (8-hour TWA) for a disinfection machine operator was judged as 1.5 mg/m^3. In an old type of immersion bath process, the worker filled the reservoir with 35% hydrogen peroxide manually a few times a day. However, modern machines are equipped with pumps and therefore the likelihood of eye or skin contact is low.

Conclusion for repeated inhalation toxicity is a **conclusion (iii)** for the operator of aseptic packaging machines. Sufficient measures to mitigate the risks may already be in place in many packaging facilities. Regarding irritancy/corrosivity, risk of eye or skin effects should be considered significant for old types of immersion bath machines (**conclusion (iii)**) whereas such risks are already reduced in other types (**conclusion (ii)**). Regarding respiratory tract irritancy, there is no concern for this scenario: **conclusion (ii)**.

4.1.3.2.10 Hydrogen peroxide and peracetic acid use: brewery

There is widespread use of diluted 35% hydrogen peroxide and peracetic acid for disinfection of equipment and premises in the food industry. In the brewery, the worst-case exposure situations involved short-term exposures when hydrogen peroxide/peracetic acid was handled in greater amounts as concentrated products, especially in the brewing cellar and during dilution operations in the juice departments. The short-term exposure concentration in the cellar had a mean value of 0.47 mg/m^3, with peak exposures at 2.8 mg/m^3 (OEL_{stel}3 mg/m^3). In the juice departments, the manual transfer of concentrated peracetic acid caused daily short-term exposures at 1.4 mg/m^3. Although the observations were limited to short-term measurements, the reasonable worst-case exposure was judged as 0.5 mg/m^3 over the full shift. The previous assignments may lead to skin contact, and the workers reported occasional occurrence of white spots in the hands and forearms. Splashes to the eye are also possible. Since the substance used is a mixture of hydrogen peroxide, peracetic acid and acetic acid, its irritating/corrosive potency may be higher than that of hydrogen peroxide of similar strength alone.

Conclusion for repeated inhalation toxicity is a **conclusion (ii)**. Regarding irritancy/corrosivity, risks of eye or skin effects are significant: **conclusion (iii)**. Regarding respiratory tract irritancy, there is no concern for this scenario: **conclusion (ii)**.

4.1.3.2.11 Peracetic acid use: meat processing

In the meat product factory, the cleaning with diluted peracetic acid (0.5%) concerns the machines and pipework and large open surfaces (floors, tables, conveyors). The cleaning process is partly automated and partly the solution is also sprayed manually. After handling with the disinfectant, the pipes, equipment and surfaces are still rinsed out with sterile water. The whole factory is cleaned and disinfected every night.

When the dilution of the disinfectant is done on site by automatic instruments the exposure to splashes is minimal. Spraying of the diluted product occurs at low pressure, therefore, also the aerosol generation is minimal. The disinfection per operation area lasts about 30 min; the exposure period per work shift has the maximum of 2 hours. During a site visit in a Finnish meat product factory, the exposure measured with Dräger tubes amounted to 0.07-0.14 mg/m^3 (n = 15) of H_2O_2. The highest concentration of 0.14 mg/m^3 (n = 5 was measured during the spraying

operation. As PPE the worker used rubber gloves and boots and a plastic apron. No published or registered data were found for disinfection with peracetic acid in meat processing factories. A Dutch survey of similar work utilising a different disinfection chemical found somewhat higher concentrations. In view of the possibility that other methods of application could generate more aerosol of hydrogen peroxide, the reasonable worst-case exposure over the full work shift is judged to be 0.5 mg/m^3.

Irritancy/corrosivity (eye, skin, respiratory tract): **conclusion (ii)**.
Repeated inhalation toxicity: **conclusion (ii)**.

4.1.3.2.12 Etching of circuit boards, modern process

In the electronics industry, hydrogen peroxide (30-60%) is used for acidic (micro)etching baths to make circuit boards. The baths are of varying sizes (60-1,000 l) and contain 1-20% H_2O_2 solutions. Temperature is elevated (40°C) due to an exothermic process. In large-scale modern production, the system is practically closed and automated, and causes little possibility of exposure to the worker.

Although no measurement data were available, according to Finnish experts airborne hydrogen peroxide exposure remains low in modern automatic continuous closed etching systems. Modelling with EASE predicts airborne levels of 0-0.14 mg/m^3. The likelihood of eye or skin contact is low.

Irritancy/corrosivity (eye, skin, respiratory tract): **conclusion (ii)**.
Repeated inhalation toxicity: **conclusion (ii)**.

4.1.3.2.13 Etching of circuit boards, old process

Older types of circuit board production use open baths which are often equipped with local exhausts but not invariably. At older batch baths the measured mean airborne 8-hour area concentration of hydrogen peroxide was 0.83 ± 0.33 (sem) mg/m^3 [3 factories] and the highest measured value was 1.5 mg/m^3. The concentrations were measured at points of emission which means that the concentration was lower further away in the hall. During the etching process the workers moved around in the hall visiting the batches now and then. The personal exposure may therefore have been slightly lower. Neither personal nor short-term exposure data were available.

Based on the highest 8-hour area mean value (1.5 mg/m^3), the reasonable worst-case full-shift exposure concentration at etching was chosen as 1.5 mg/m^3. Maintenance of the baths is presumed to involve manual handling of concentrated (20-60%) hydrogen peroxide. Therefore, unless PPE is strictly used, eye or skin contact may occur. Risk of eye and skin irritancy/corrosivity cannot be excluded for this scenario: **Conclusion (iii)**. Concerning respiratory tract irritation there is no concern: **conclusion (ii)**. Conclusion for repeated inhalation toxicity is a **conclusion (iii)**.

4.1.3.2.14 Metal plating

Hydrogen peroxide (50%, diluted 1:3) is added once per month or a few times per year to metal (Cr, Zn) plating basins for the purpose of cleaning. The substance is handled either with small pumps or manually with pails. Inhalation exposure modelled with EASE WIN 2.0 programme for the brief (about 30 minutes) workphase gave excessively high values compared to actual

measurements during manual transfer of 35% hydrogen peroxide in disinfection, which yielded about 2 mg/m^3. Transformation of the latter to a mean exposure over the full shift (rest of the time concentration is 0.07 mg/m^3) gives 0.14 mg/m^3. It must be noted, however, that the exposure is very infrequent. Thus repeated inhalation toxicity is not a relevant effect endpoint. On the other hand manual handling of concentrated hydrogen peroxide is expected to cause potential for contact to the eye or the skin. Thus the conclusions for irritancy/corrosivity for the eye and skin are **conclusions (iii)**. Concerning respiratory tract irritation, there is no concern: **conclusion (ii)**.

4.1.3.2.15 Production of modified starch

Production is performed in automated continuously functioning reactors which are situated outdoors. Therefore, although there are no measurement data available, exposure is presumed to be low. Modelling with EASE WIN 2.0 predicts inhalation exposure of 0-0.14 mg/m^3. No contact to the substance is expected except under accidental circumstances.

Irritancy/corrosivity (eye, skin, respiratory tract): **conclusion (ii)**.
Repeated inhalation toxicity: **conclusion (ii)**.

4.1.3.2.16 Degrading of proteins

No representative measured exposure data of hydrogen peroxide were found for this type of uncommon industry. Observations made at one factory suggested potential short-term inhalation exposure and skin (potentially eye) contact due to manual handling of 50% solution and open process. The assignment involved manual transfer of hydrogen peroxide with pails 4-6 times a day (each lasting about 10 minutes) to the reactors. Measurements of airborne concentration of hydrogen peroxide were performed only 5 hours after the batches were charged, and the levels were low (about 0.14 mg/m^3). Modelling with EASE WIN 2.0 for the charging phase (1 h) gave excessively high values compared with actual measurements during manual transfer of 35% hydrogen peroxide in disinfection (about 2 mg/m^3). When the latter was used for calculation of the mean concentration over the full shift (assuming the level of 0.14 mg/m^3 during the remaining 7 hours) 0.27 mg/m^3 was derived. Due to manual handling of hydrogen peroxide without any PPE, splashes to the eye and skin contact were clearly possible; the workers confirmed the not uncommon occurrence of white spots in the skin.

Irritancy/corrosivity (eye, skin): **conclusion (iii)**.
Repeated inhalation toxicity: **conclusion (ii)**. Respiratory tract irritation: **conclusion (ii)**.

4.1.3.2.17 Drinking water treatment

The use of hydrogen peroxide for water treatment is not well known; in Finland the use appears to be very limited. Only one measurement result (<0.02 mg/m^3) was available concerning treatment of raw water. EASE estimation predicted a low (<0.14 mg/m^3) exposure.

Irritancy/corrosivity (eye, skin, respiratory tract): **conclusion (ii)**.
Repeated inhalation toxicity: **conclusion (ii)**.

4.1.3.2.18 Wastewater treatment

No measurement data were made available. EASE predicted up to 7 mg/m^3 which can be regarded as a short-term RWC value. The corresponding full-shift RWC concentration is 1 mg/m^3.

Irritancy/corrosivity (eye, skin, respiratory tract): **conclusion (ii)**.
Repeated inhalation toxicity: **conclusion (iii)** based on the high predicted short-term value. The uncertainties related to this conclusion should be noted because no descriptions of the process and no measurements were available.

4.1.3.2.19 Hairdressers work

The use of hydrogen peroxide solutions (up to 12% diluted 1:1 for use in the hair with other hairdressing chemicals) in hair dyeing and bleaching is commonplace. Based on actual workplace measurements done in the frame of this risk assessment, and earlier measurements from Germany, the full-shift reasonable worst-case hydrogen peroxide exposure concentration for the hairdresser was estimated as 0.5 mg/m^3. A peak concentration of 0.6 mg/m^3 has been measured over 5 minutes.

Based on the known substance concentrations handled, splashes to the eye could be of some concern for irritancy/corrosivity (**conclusion (iii)**) whereas the regular use of gloves precludes the relatively minor irritant effects that might arise from skin exposure (**conclusion (ii)**). There is no concern for respiratory tract irritation and for repeated inhalation toxicity: **conclusion (ii)**.

4.1.3.2.20 Summary of the risk characterisation for workers

Based on the available, incomplete dataset for the various effect endpoints, irritation/corrosivity in the eyes, skin and airways and repeated dose toxicity by inhalation are the most relevant adverse effects for workers. From the risk viewpoint these effect endpoints were evaluated for each of the 19 scenarios. All other endpoints: acute toxicity, sensitisation, repeated oral toxicity, repeated dermal toxicity, mutagenicity, carcinogenicity and reproductive toxicity were not considered to cause concern for human health in the occupational setting (**conclusion (ii)**). The summary of the conclusions is shown in **Table 4.13**.

Table 4.13 Summary of conclusions for the risk characterisation for workers

Scenario	Irritancy/corrosivity			Repeated inhalation toxicity	Acute toxicity, sensitisation, repeated oral toxicity, repeated dermal toxicity, mutagenicity, carcinogenicity
	Eye	Skin	Airways		
Production of H_2O_2	ii	ii	ii	ii	ii
Synthesis of other chemicals	ii	ii	ii	ii	ii
Loading operations	**iii**	**iii**	**iii**	**iii**	ii
Pulp and paper bleaching	ii	ii	ii	ii	ii
Bleaching of textiles, batch process	**iii**	**iii**	ii	ii	ii
Bleaching of textiles, automated process	ii	ii	ii	ii	ii
Industrial laundering	ii	ii	ii	ii	ii
Aseptic packaging: immersion bath process, old type	**iii**	**iii**	ii	**iii**	ii
Aseptic packaging: other types	ii	ii	ii	**iii**	ii
Hydrogen peroxide and peracetic acid use: brewery	**iii**	**iii**	ii	ii	ii
Peracetic acid use: meat processing	ii	ii	ii	ii	ii
Etching of circuit boards, modern process	ii	ii	ii	ii	ii
Etching of circuit boards, old process	**iii**	**iii**	ii	**iii**	ii
Metal plating	**iii**	**iii**	ii	not relevant	ii
Production of modified starch	ii	ii	ii	ii	ii
Degrading of proteins	**iii**	**iii**	ii	ii	ii
Drinking water treatment	ii	ii	ii	ii	ii
Wastewater treatment	ii	ii	ii	**iii**	ii
Hairdresser's work	**iii**	ii	ii	ii	ii

4.1.3.3 Consumers

4.1.3.3.1 Introduction

Many consumer products, such as tooth bleaching agents, mouthwashes, disinfectants, cleaning and bleaching agents, foods, hair dyeing and bleaching products, and contact lens disinfectants contain hydrogen peroxide. These products cause exposure via the gastro-intestinal tract and via inhalation, by deposition on the skin, eye exposure, and exposure to the gingiva and the tooth pulp in some specific scenarios.

Toxicokinetic evaluation of hydrogen peroxide suggests that only under condition of high exposure rates the substance might enter the systemic circulation. When accidental swallowing is excluded, it is unlikely that such high exposure rates could be reached in any realistic scenario

concerning consumer exposure. It is concluded that it is especially unlikely that the substance deposited on the skin is systemically absorbed to a meaningful degree.

Local irritation and, in extreme and uncommon cases, corrosion of the skin, eye, gingivae or the teeth are the critical adverse effects caused by consumer exposure to hydrogen peroxide. Most of the effects reported (e.g. eye irritation, irritation of the gingivae and the throat, irritation, sensitivity and inflammation in the tooth pulp, and the morphological changes in tooth surface) are transient or are considered mild. However, even rather dilute solution of hydrogen peroxide (3%) may cause danger, if swallowed accidentally. Furthermore, effects of splashes of strong solutions to the eye (≥5%) and skin (≥35%), and resorption of the teeth occasionally reported after tooth bleaching by the dentist (≥35%), represent some serious scenarios which are relevant in terms of consumer exposure.

Effect endpoints that are similarly relevant for worker and consumer exposures are described and discussed in detail in Section 4.1.3.2.1 Introduction. Thus, the conclusions regarding sensitisation, mutagenicity and carcinogenicity are **conclusions (ii)**. Repeated inhalation exposures to hydrogen peroxide do not occur in consumer exposure scenarios, therefore this endpoint is not relevant. On the other hand, the effects on the gingiva and the tooth pulp, and the oral exposure caused by food, mouthwash and toothpastes are relevant only for consumers and are covered in this chapter.

To characterise the risks for consumers, the following scenarios were chosen: (1) hair dyeing and bleaching, (2) textile bleaching, (3) cleaning, (4) contact lens disinfection, (5) tooth bleaching, (6) ingestion in food, and (7) mouth care products.

Only food and use of mouth care products cause repeated oral dosage of hydrogen peroxide. Thus, for the other four scenarios, toxicity caused by repeated oral exposure is not relevant: **conclusion (ii)**. Similarly, some endpoints/risks are considered not relevant for certain scenarios and are not assessed (see **Table 4.15**). For example, since the small residues of hydrogen peroxide in contact lenses could only cause effects in the eye, it is unnecessary to assess other routes of exposure and other endpoints.

4.1.3.3.2 Hair dyeing and bleaching

In most applications/uses, the risk associated with consumer exposure to hydrogen peroxide is low. During hair bleaching and dyeing the customer is normally exposed to levels ranging from <0.07 to 0.2 mg/m^3 (see **Table 4.14**). When a solution with higher concentrations of hydrogen peroxide (up to 12%, mixed 1:1 with dye) is occasionally used at a higher temperature (about 40°C), concentration of hydrogen peroxide in the hair salon may transiently reach a higher level (peaks up to 0.6 mg/m^3). However, the duration of such exposure is short and no irritation of the eyes and/or mucous membranes by the vapour could be anticipated. Thus there is no concern for irritation in respiratory tracts: **conclusion (ii)**.

It is estimated that in the reasonable worst-case deposition on the scalp is 12 mg of hydrogen peroxide/kg of body weight. Presumably, a part of this is percutaneously absorbed (especially as the scalp skin is rather permeable). Although at the present time there is no conclusive interpretation for the skin absorption of hydrogen peroxide in terms of systemic dose, it is likely that the substance is broken down in the skin when the deposition rate is low. The current data strongly suggest that systemic dose due to skin absorption is negligible [acute toxicity: **conclusion (ii)**], and that repeated dermal toxicity is irrelevant due to infrequent exposure: **conclusion (ii)**.

Complaints of hairdressers' clients concerning stinging or irritation in the scalp are not uncommon after hair dyeing or bleaching. The symptoms are probably caused by the combined effect of ammonium persulphate, hydrogen peroxide and other chemicals used in the mixture. Permanent or serious effects on the scalp skin have not been reported (oral communication 1998, expert of the Finnish Association of Hairdressers). In the light of the previous data, it was concluded that skin irritation which might occur at or below the normal (regulated) levels resulting in 6% hydrogen peroxide in hair cannot be clearly attributed to this substance (**conclusion (ii)**). According to hairdressers' reports dyeing of eyelashes is performed with 1.5% hydrogen peroxide solution (3% solution diluted 1:1 with the dye) whereas for eyebrows at most 3% hydrogen peroxide solution is used. While the present practices, at the mentioned concentrations, of dyeing of eyelashes and eyebrows probably imply no significant risk of eye irritation, application of higher concentrations (≥5%) for dyeing of hair (approved up to 6%), would constitute a risk for eye irritation in case of a spill: **conclusion (iii)**.

4.1.3.3.3 Household textile bleaching

Some exceptional products used for bleaching of textiles in households may contain relatively high concentrations of hydrogen peroxide (according to product information one contained 35%). Industry has claimed that hydrogen peroxide concentrations ≥8% are not used for consumer products; however previous data suggest that this may not always be the case. Information given by the importer of the products indicates that usually the bleaching takes place in a washing machine, and thus inhalation exposure is likely to remain low. When bleaching is done manually, protective gloves are recommended.

Modelling of the air concentrations of hydrogen peroxide in this scenario shows that airway irritation is unlikely: **conclusion (ii)**. Apart from accidental ingestion, which is beyond the scope of this risk assessment, the routes of exposure and dose levels involved preclude acute toxicity: **conclusion (ii)**. The relevant endpoints are eye irritancy caused by splashes if consumer products contain ≥5% hydrogen peroxide (**conclusion (iii)**), conclusion for skin irritation is a **conclusion (ii)**. Hazards of eye and skin effects would naturally be more severe (corrosion) if the product should contain higher hydrogen peroxide concentrations than 8%.

4.1.3.3.4 Cleaning agents

Considering cleaning agents, the adverse effects of main concern are irritation/corrosivity in the eye. Other effects and routes of exposure can be summarised as follows:

- The possible skin whitening effect and irritation is assessed to be unlikely, since the products are diluted and gloves are often used: **conclusion (ii)**.
- It is assessed that the skin exposure level caused by textile bleaching agents (0.6 mg/kg bw, occasionally), which was regarded safe, is not exceeded, when "all purpose cleaners" and toilet cleaners are used (acute toxicity: **conclusion (ii)**).
- The air concentrations measured in rather similar (slightly worse) scenario of hair bleaching are well below the OEL value (1.4 mg/m^3) and below the level, which was found harmful in a recent worker health surveillance (3-4 mg/m^3) (respiratory tract irritation: **conclusion (ii)**).
- The risk caused by accidental swallowing of the products is relevant, but formally not within the scope of this assessment.

Two other consumer scenarios described, i.e. textile bleaching and hair dyeing/bleaching resemble the cleaning agent scenario. In all these uses, solution of hydrogen peroxide is manually handled, sometimes without gloves and eye protection. It is the experience of the industry that since peroxide can cause some mild and reversible "skin whitening", many consumers use gloves. Many product instructions recommend use of gloves, especially if using neat product for certain tasks.

The adverse effects of these products are dependent on the concentration of hydrogen peroxide in the preparation. At least some of the "all purpose cleaners" contain less that 5% of hydrogen peroxide, and these are considered to be safe. When the percentage is 5-8% the product may irritate the eyes, when splashes occur and when the product contaminates users fingers. When the concentration is 8% or higher (as in the case of one toilet cleaner identified in the Finnish market) there is a risk of serious damage to eyes if undiluted products come into contact with the eyes.

The Poison Information Centre of Finland was consulted for information on complaints of consumers and workers. The calls to the Poison Information Centre are recorded primarily on the base of the product category, and not the chemical content of the product. Thus, in some cases other constituents of the product (e.g. ammonium compounds in hair bleaching agents) may have caused the symptoms reported. In **Table 4.14**, the calls to the Centre received in one and a half years are summarised. This summary includes only few cases caused by cleaning agents containing H2O2, since this product group is relatively new in Finland. If the concentration of H2O2 is high enough, some of the symptoms listed in **Table 4.14** are possible. In the case of cleaning agents, exposure via inhalation is unlikely and oral exposure may concern the children only.

Table 4.14 Calls to the Poison Information Centre of Finland in about 1,5 years concerning products of and/or exposures to hydrogen peroxide
(Unpublished registry data submitted by Ilmarinen and Hoppu, the Poison Information Centre of Finland, 6/8/2001)

Route of exposure	Products	Number of cases/those with symptoms	Children involved/ those with symptoms	Percentage of in H_2O_2 the product	Symptoms
Oral	Usually 3% H_2O_2 used for disinfection of small wounds or as mouthwash	31/7	12/3	<9% except in one case	Numbness of mouth and oesophagus, cough, vomiting, inappetence, nausea
Dermal	Products used in industry	6/4	0	>9% in all cases	White spots on the skin, stinging, redness of the skin
Eyes	Two hair bleaching/ dyeing agents, one toilet cleaner	3/3	0	<9% in all cases	Transient stinging and itching
Inhalation	Products used in industry	3/3 [1)]	0	>9% in all cases	Stinging of mucous membranes of nose and oesophagus, coughing, laboured breathing, faintness, dizziness, headache, nausea

1) All the exposed individuals were workers

Several cases of accidental hydrogen peroxide intoxication have been reported. In one case, ingestion of 230 g of 3% hydrogen peroxide, which induced gas emboli, caused the death of a 16-month-old boy. Other cases of serious poisoning have been caused by strong solution (35%) and medical uses of hydrogen peroxide (see "Conclusions on acute toxicity"). Formally, accidents are not within the scope of risk reduction based on the regulation 793/93 and the issue is not discussed here in detail. Tentative recommendations, which may be taken up by other regulatory frameworks, will be considered in the Risk Reduction Strategy document to be finalised after approval of this risk assessment report.

Experimental data and data from poison control centres have provided evidence on the hazard of the irritation/corrosion of eyes caused by hydrogen peroxide. As recently revised classification of hydrogen peroxide indicates, solution which contains:

< 5% does not cause concern,
≧ 5% irritates the eyes, (Xi; R36), and
≧ 8% causes risk of serious damage to eyes (Xn-; R22-41).

The data from product registers in Finland, Sweden and Norway and the market information from Spain indicate that all purpose cleaners contain up to 8% of hydrogen peroxide. Thus, there is a risk of eye irritation, when splashes of the undiluted product reach the eyes: **conclusion (iii)**. This risk has been reduced in some cases by the product formulation. Furthermore, in many "all purpose cleaners", the concentration of hydrogen peroxide is kept below 8%. These measures, however, do not completely eliminate the risk identified.

Toilet cleaners may contain up to 20-35% of H_2O_2. While in most products the concentration is likely to be lower, there are products, which cause a risk of serious damage to eyes, if splashes of undiluted product reach the eye and when the agent is taken to the area of eyes by the contaminated hands: **conclusion (iii)**. There is also a risk of skin irritation, if the product contains ≥ 35% of hydrogen peroxide. According to the information provided by the industry, many if not all currently marketed toilet cleaners have child resistance closures (CRCs), which preclude accidental contact by children with the cleaning solution.

4.1.3.3.5 Contact lens disinfectants

Contact lens disinfectants leave some residual hydrogen peroxide in lenses, which occasionally may have high enough concentration to cause mild eye irritation. The residual concentration in lenses is normally below 15 mg/l. The critical concentration for eye discomfort, stinging and conjunctival hyperaemia is 100-267 mg/l with short exposure times (Paugh et al., 1988; Janoff, 1990; McNally, 1990). McNally reported that at the threshold level (about 300 mg/l) the stinging sensation was mild and transient.

According to other studies, (Riley and Wilson, 1993) the threshold for corneal damage or penetration to the aqueous humour for short-term (10 minutes of less) hydrogen peroxide exposure lies above 700 mg/l for contact lenses and 2,000 mg/l for drops. Because these concentrations are two or three-fold above the sensitivity levels for discomfort reported for both lenses and drops, such exposures would not be expected. Moreover, *in vivo* neutralisation of hydrogen peroxide seems to be rapid when the concentration is moderate. Removal of 50 mg/l hydrogen peroxide from a hydrogel lens was completed within 30-60 seconds (McNally, 1990). It has been concluded that the cornea and the palpebral tissues, together with the tear film, form a highly effective barrier and detoxifying system which except under extreme, accidental

circumstances prevents both extra- and intra-ocular damage by the hydrogen peroxide used in contact lens care (Riley and Wilson, 1993).

Whether repeated exposure to low levels of hydrogen peroxide in contact lenses could cause any adverse long-term outcomes is not known. While systematic surveys on chronic effects are not available, it is probable that any marked effects (e.g. chronic inflammation, hyperaemia, opacity) would have been observed and reported by ophthalmologists having the clinical experience of various types of contact lenses and their disinfectants.

For this scenario, the only relevant endpoint is eye irritation (acute or chronic). Based on clinical experience, this application of hydrogen peroxide does not cause risk: **conclusion (ii)**.

4.1.3.3.6 Tooth bleaching

Several *in vivo* and *in vitro* experiments show that 35% hydrogen peroxide can penetrate the enamel and dentine (Bowles and Ugwuneri, 1987) and affect the tooth pulp causing temperature sensitivity, pulp irritation, or inflammatory response; moreover, morphological changes in tooth surface, odontoblast destruction and resorption of nonvital teeth have been observed (Marshall et al., 1995; Goldstein and Schumacher, 1993; Zalkind et al., 1996). Some years after the bleaching treatment, 58 non-vital teeth were examined and four cases of resorption were found, two of them progressive (Friedman et al., 1988). Higher temperatures used to enhance bleaching increase the permeability of dental hard tissues (Bowles and Ugwuneri, 1987). In the current practice of bleaching non-vital teeth, the filling of the pulp is made more impermeable by using protective intracoronal (e.g. a glass ionomer) isolation.

In most cases the effects of hydrogen peroxide on the tooth pulp are reversible (Marshall et al., 1995; Goldstein and Schumacher, 1993). Pulpal necrosis has been observed only under exceptional conditions (Haywood and Heymann, 1991). According to US data home bleaching systems contain 2-10% of H2O2 and there is no evidence of severe effects on the tooth pulp (Marshall et al., 1995). Mild and transient gingival irritation has been described by patients (Haywood and Heymann, 1991). Some patients have also reported burning palate, throat and gingivae (Howard, 1992). Similarly, some users of the home bleaching systems (probably 10% carbamide peroxide) have informed the National Consumer Administration of Finland about irritation of gingivae and sore throat (Personal communication, Eeva-Liisa Sainio, National Consumer Administration). Our estimate for the amount of bleaching gel used per application is about 0.6 g.

Although new techniques are applied to protect the tooth pulp, it is likely that there is no margin of safety, and the use of 35% hydrogen peroxide for tooth bleaching has caused some concern among the professionals in dental health The EU Commission has established in the cosmetics directive that in consumer oral hygiene products the concentration of hydrogen peroxide is limited to 0.1%. A recent opinion of the Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (September 2002) stated that tooth whitening products containing more than 0.1% hydrogen peroxide should exclusively be administered under supervision of a dentist and that the content of hydrogen peroxide in tooth whitening products should not exceed 6% (present or released) with a limitation of maximum 50 mg hydrogen peroxide per day. The use of tooth whitening products is not recommended prior to or immediately after dental restoration. Conditions such as pre-existing tissue injury or concurrent use of tobacco and/or alcohol may exacerbate the toxic effects of hydrogen peroxide at present, this recommendation has not yet been implemented.

Due to decomposition and efficient removal of hydrogen peroxide in the gel only minor amounts (less than 1 mg) come into contact with gingival surfaces and/or is ingested. The partial vapour pressure of hydrogen peroxide in the gel is low and thus there is no risk of airway irritancy or acute toxicity: **conclusions (ii)**. Repeated oral toxicity is not considered relevant, because of limited exposure duration and low dose: **conclusion (ii)**. SCCNFP even considered enhancement of cancer risk in the oral cavity among frequent users of bleach products who are smokers and habitual users of alcohol, and judged the risk unlikely: **conclusion (ii**).

The use of 35% hydrogen peroxide by the dentist for tooth bleaching apparently carries some risk of injury to the tooth pulp: **conclusion (iii)**. The safety of the practice should be considered in an appropriate forum for eventual risk reduction.

4.1.3.3.7 Ingestion in food

It is estimated that dietary intake caused by natural and residual hydrogen peroxide in food is 2 mg at the most. For an adult (60 kg), dose of 2 mg causes an exposure of 0.033 mg/kg/day, whereas for a child (15 kg) the exposure is 0.13 mg/kg/day. These are compared with the NOEAL of 100 ppm in drinking water (daily doses 26 and 37 mg/kg bw for males and females, respectively) derived from a 90-day study catalase-deficient mice, where duodenal mucosal hyperplasia was seen at higher levels. The comparison gives a safety margin of 200-1,121.

Duodenal hyperplasia observed in mice should be considered together with other evidence suggesting that duodenal tumours may develop in sensitive (catalase-deficient) animals exposed to high levels of hydrogen peroxide. However, mucosal cells seem to have well-developed defences and repair mechanisms for damages induced by hydrogen peroxide. In the light of present knowledge, carcinogenicity is probably not of practical significance at low levels of exposure.

The relevant effect endpoints are local effects in the gastrointestinal after repeated daily exposures. Based on the wide safety margin there is no risk of repeated oral toxicity: **conclusion (ii)**. For local carcinogenicity, there is also no concern: **conclusion (ii)**.

4.1.3.3.8 Mouth care products

Soft tissues exposed to hydrogen peroxide for prolonged periods may show changes consistent with inflammation or hyperplasia. Two case reports showed that hydrogen peroxide might occasionally be harmful to oral tissues at 3% solution as a mouth rinse. Soft tissue irritation can occur when the material is used even for short periods, and injury (such as ulcerations on the tongue and or the alveolar and labial mucosa) may become more severe with chronic use. However, in the cases reported, there had been previous tissue injury and the mouth rinse was used to prevent oral inflammation and bacterial growth.

According to the EU cosmetics directive, mouth care preparations for consumer use should not contain more that 0.1% hydrogen peroxide. According to the TGD, the typical amount of mouthwash used per application is 10 g. COLIPA has estimated that the daily exposure to hydrogen peroxide via ingested mouthwash is 5 mg/day, i.e. about 0.08 mg/kg of bw per day for an adult. This estimate should be considered preliminary, since no accurate information on mouthwash products on the market in the Europe was available. In Finland, these products were not identified.

In view of the low concentration of hydrogen peroxide permitted in mouthwash products there should be no concern for local mucous membrane irritancy: **conclusion (ii)**. Concerning repeated dose oral toxicity, based on current provisions and estimates the margin of safety is sufficient: **conclusion (ii)**.

Toothpastes may contain the maximum of 0.1% hydrogen peroxide. According to the TGD, typical amount per application is 1.4 g of which 17% is assumed to be ingested. The total dose amounts to 0.48 g per day (two applications per day), or about 0.008 mg/kg bw per day (SCCNFP/0119/99). The conclusions concerning use of toothpastes are as presented above for mouthwash products.

Recently, the Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) has given its opinion on the hydrogen peroxide in oral care products (draft report dated 23.4.1999, SCCNFP). SCCNFP was asked whether increase of the limit concentration of hydrogen peroxide to 3.6% in oral hygiene products (tooth whiteners, mouth rinses or toothpastes) should be allowed. Exposure to mouthwash containing 3.6% of hydrogen peroxide would be 3.0 mg of H_2O_2 /kg bw day. The Committee concluded that the margin of safety for chronic/sub-chronic toxicity is not sufficient, and did not approve the proposed higher limit concentration for mouth care preparations.

4.1.3.3.9 Combined consumer exposure

Estimation of combined systemic exposure, i.e. total exposure via the gi-tract, via inhalation and through the skin is not justified, since it is unlikely that the amount of hydrogen peroxide swallowed, inhaled or deposited on the skin would be systemically distributed.

The oral exposure caused by food, mouthwash products and toothpastes are 0.033-0.13, 0.08 and 0.008 mg/kg of body weight, respectively. It is realistic to assume that consumers may have repeated daily exposure to hydrogen peroxide from these three sources. In such a case the combined oral exposure would be 0.12-0.22 mg/kg bw per day. A part of hydrogen peroxide in toothpaste and mouthwash are likely to be decomposed before the remaining amount in the mouth is swallowed. The oral exposure from tooth bleaching agents is occasional and therefore it is not added to the daily oral exposures. This combined oral exposure is compared with the NOEAL of 100 ppm H_2O_2 in drinking water (daily doses 26 and 37 mg/kg bw for male and female mice, respectively) derived from a 90-day study with mice. The comparison gives a safety margin of 118-308. This safety margin is considered sufficient for repeated oral toxicity: **conclusion (ii)**.

Table 4.15 Comparison between NOAEL/lOAEL values for specific effects and the consumer exposures

Scenario	Route of exposure & Duration	Measured/estimated exposure	NOAEL/lOAEL and the effect concerned	MOS
Hair dyeing and bleaching	Inhalation 30 min [1)] Skin of scalp	0.07-0.2 mg/m^3 6% peroxide with dye	LOAEL: 2-3 mg/m^3, (human) effects on respiratory track Sensitive users demonstrate signs of irritation (erythema, small vesicles) not solely attributable to peroxide	50-143 none
Textile bleaching	Eye Splash/accidental contact with 5-8% hydrogen peroxide		Eye Irritation	none
Cleaning agents	Eye Splash/accidental contact with 0.2-35% hydrogen peroxide When 8% is exceeded, risk of serious damage to eyes		Eye Irritation	none
Contact lens disinfectants	Eye 1-5 min	15 mg/l in the lens	LOAEL: 100-267 mg/l, eye discomfort, stinging and conjunctival hyperaemia	6.6-27
Tooth bleaching	Local application (exposure of tooth surface pulp and gingivae) 30 min-10 h over up to 2 weeks	Concentration of the gel is 2-35%	Effects on gingivae: 1% solution (LOAEL) causes pathological changes in the periodontium after three weeks (rat) Effects on pulp: current use (with 35 % gel) has caused adverse effect: sensitivity, pulp irritation, inflammatory response, morphological changes in tooth surface, odontoblast destruction and resorption of nonvital teeth (human)	none
Ingestion in food (natural and residual H_2O_2)	Ingestion Daily	0.033-0.13 mg/kg bw/day	NOAEL: 26-37 mg/kg bw/day, duodenal hyperplasia in a repeated oral toxicity study (mice)	200-1121
Mouth care products (mouthwash & toothpaste)	Ingestion 5/day	0.088 mg/kg bw/day	NOAEL: 26-37 mg/kg bw/day, duodenal hyperplasia in a repeated oral toxicity study (mice)	295-420

1) Assuming that respiratory volume is 0.75 m^3/hour the dose per application is 0.0025 mg/kg bw. The peroxide used for hair dyeing causes a dermal deposition of 12 mg/kg bw per application. However, this is not regarded to result in any significant systemic dose.

4.1.3.3.10 Summary of the risk characterisation for consumers

Table 4.16 Summary of conclusions for consumers

Scenario	Irritancy/corrosivity			Repeated dose toxicity, oral	Acute toxicity; sensitisation; mutagenicity; carcinogenicity others
	Eye	Skin	Airways		
Hair dyeing and bleaching	**iii** 1)	ii 2)	ii	ii	ii
Textile bleaching	**iii** 3)	ii	ii	ii	ii
Cleaning agents	**iii** 3)	ii	ii	ii	ii
Contact lens disinfection	ii	ii	ii	ii	ii
Tooth bleaching	ii	ii	ii	ii	**iii** 4)
Ingestion in food	ii	ii	ii	ii	ii
Mouth care products	ii	ii	ii	ii	ii

1) Eye irritancy is of concern if the concentration of hydrogen peroxide in the substance used is ≥5%.
2) Skin irritation has been observed. It is likely that not H_2O_2 alone, but the combined exposure with ammonium persulphate and dye compounds, e.g. amines causes irritation or allergic symptoms when hydrogen peroxide concentration in the applied mixture is as regulated (6% or lower).
3) Current data suggest that textile bleaching products and cleaning agents available for consumers normally contain less than 8% of hydrogen peroxide. Eye irritancy is of concern if the concentration of hydrogen peroxide in the substance used is ≥5%. When 8% is exceeded, there is a risk of serious damage to eyes.
4) After treatment with 35% of hydrogen peroxide by dentists, effects on tooth pulp, odontoblast destruction and resorption of non-vital teeth have been observed. Risk reduction should be considered in an appropriate forum.

4.1.3.4 Humans exposed via the environment

According to EUSES modelling, indirect exposures of humans to hydrogen peroxide via ambient air and drinking water resulting from local releases are low, and do not cause a concern (for all endpoints: **conclusion (ii)**).

Compared to other recognised sources of oral exposure (notably endogenous content in food), EUSES predicted a rather high oral intake from leaf crops (0.28 mg/kg bw per day) in a local scale, caused by releases from a local point source. When this oral exposure is compared with the NOAEL of 100 ppm H_2O_2 in drinking water (daily doses 26 and 37 mg/kg bw for male and female mice, respectively), derived from a 90-day study with mice, a safety margin of 93-132 is derived. This safety margin is considered sufficient for repeated oral toxicity: **conclusion (ii)**.

4.1.3.5 Combined exposure

Combined exposure needs to be addressed regarding oral intake of hydrogen peroxide from consumer sources and from indirect environmental sources. The combined intakes may amount to 0.4-0.5 mg/kg bw per day. Compared to the repeated dose toxicity NOAELs of 26 and 37 mg/kg bw per day in male and female mice, respectively, obtained in a drinking water study, a safety margin of 52-93 is derived. This safety margin is considered sufficient for repeated oral toxicity: **conclusion (ii)**.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

4.2.1.1 Occupational exposure

Exposure of workers to hydrogen peroxide was discussed in Section 4.1.1.1. Exposure to high enough levels of H_2O_2 to present a potential physico-chemical hazard under normal handling and use could arise during production, transportation, storage and industrial use.

The production and major industrial uses (pulp and paper bleaching, manufacture of chemicals, textile bleaching) take normally place in automated, closed or partially closed systems and stringent exposure and hazard controls are mostly in place. Containers used for transportation and storage meet special safety requirements. Exposure of workers to high levels of hydrogen peroxide causing physico-chemical hazards could occur in accidental situations only.

The small industries use hydrogen peroxide often as diluted solutions (disinfection purposes in the dairy, refreshment and foodstuff industries), although concentrated solutions are also used (metal pickling, electronics industry, degrading organic materials). The small industries obtain the peroxide in smaller containers. Feeding of the substance to the process, or further dilution, is mainly done manually or at least partly manually (by decanting, or with siphons or small movable pumps). The danger of leaks and spills during manual handling is high. Even transportation and storage of the small containers need special attention (containers should be kept in an upright position and without stacking, avoiding bumping, and stored in a dark, well-ventilated space on concrete floor with water availability for flushing). In the small factories, workers awareness of the dangerous properties of hydrogen peroxide seems to be insufficient.

4.2.1.2 Consumer exposure

Exposure of consumers to hydrogen peroxide was discussed in Section 4.1.1.2. An accident may occur if hydrogen peroxide (even diluted) is stored in a glass bottle with a tight stopper. In the course of time, overpressure will be generated in the bottle due to slow decomposition of the peroxide, and the bottle may break. Larger spills of the concentrated peroxide (≥25%) on materials such as clothing, wood or paper may, after some delay, cause danger of fire if the substance remains unwashed.

4.2.1.3 Humans exposed via the environment

Humans are not exposed indirectly via the environment to levels of hydrogen peroxide causing any physico-chemical hazards.

4.2.2 Effects assessment

Hydrogen peroxide is a reactive unstable chemical. Its decomposition is highly exothermic (heat of decomposition is –105.8 kJ/mol gas and –98.3 kJ/mol liquid; Goor et al., 1989). During its application, it will react or decompose producing oxygen and water steam. In case of spillage or

accident, rapid decomposition will take place in every natural compartment producing gaseous reaction products (Degussa AG; IUCLID).

Concerning the reactivity of aqueous concentrations of H_2O_2 used in industry [> ca.8% (Solvay Interox), 10-35% (FMC Corporation, Canada), 20-52% (Degussa AG)], all major producers warn that contamination by many substances including heavy metals and their salts, reducing agents, strong oxidisers, alkalis, dust particles and dirt will cause its decomposition. The rate of decomposition increases with increasing concentration and temperature, and in reduced pressure. The decomposition of concentrated solutions may be very vigorous with rapid generation of large volumes of oxygen and water steam.

4.2.2.1 Explosivity

Hydrogen peroxide does not fulfil the criteria for classification as an explosive (CEFIC Peroxygen Sector Group). At high concentrations, hydrogen peroxide alone (in the absence of organic materials) has however explosion potential. At concentrations above 26 vol %, the vapour is explosive by means of decomposition. Thus hydrogen peroxide aqueous solutions of 74 w/w % strength or higher can produce explosive vapours at elevated temperature and/or at decreased pressure. At concentrations above 86 w/w % which is the maximum commercial strength in the EU, the liquid itself can be made to explode.

Lower concentrations may cause spontaneous fire on contact with combustible materials.

4.2.2.2 Flammability

Autoignition and flammable limits, lower or upper, are not applicable (Brenntag Ltd; Degussa AG; Solvay Interox; IUCLID), and the compound is non-combustible (FMC Corporation).

While pure H_2O_2 does not burn, it can initiate spontaneous ignition of organic materials such as paper, wood or cloth. Ignition may be rapid but it can also be delayed for several hours. Spontaneous ignition and fire can occur in the event of leaks or spills of even diluted (≥25%) solutions if the peroxide solution is allowed to remain in the combustible material. The mechanism is that water is first volatilised thus causing the peroxide to concentrate, wherafter the peroxide sets the material on fire. Rapid oxygen evolution from decomposing H_2O_2 may increase the intensity of fire especially in closed unventilated spaces. (Degussa AG; Solvay Interox; FMS Corporation; CCINFO 1997; Stellman 1998).

4.2.2.3 Oxidising potential

Owing to its potential exothermic decomposition and high molecular oxygen content, hydrogen peroxide is a powerful oxidiser. Hydrogen peroxide solutions containing ≥60 w/w % of the substance are classified as oxidisers according to Directive 67/548/EEC. The compound is also classified as an oxidising agent for shipping (Brenntag Ltd; Kemira Peroxides B.V. Rozenburg; Degussa AG; FMS Corporation). According to UN classification, aqueous solutions of H_2O_2 (UN no 2014) ≥8% belong to class 5.1, i.e. oxidisers.

4.2.3 Risk characterisation

4.2.3.1 Workers

The assessment of physico-chemical hazards indicates that hydrogen peroxide is highly unstable, and its concentrated solutions are oxidising and apt to decompose gradually or even explosively if not free from contaminants, well stabilised, and if not used at normal temperature and pressure. The spontaneous exothermic decomposition presents a high risk of fire when the concentrated substance comes in contact with combustible materials: **conclusion (iii)**.

The major industrial uses in closed automated production systems, employment of specially-made containers with safety valves for storage and shipping, and stringent safety controls, imply that the potential risk of physico-chemical hazards to workers in the major industries is minimal under conditions of normal handling and use. Even the highest measured peak levels of exposure (in the event of leaks: 9-15 ppm) are far below the levels that may cause explosion hazard. The risk of fire and explosion is also addressed in the safety data sheets provided by the major producers (e.g. Ausimont Spa; Degussa-Huls AG; Solvay Interox S.A.).

In minor industrial uses, hazards may be involved in manual operations with hydrogen peroxide. The peroxide is manually delivered from small containers with cans or pails or by the use of siphons or movable pumps to the processes. Spills and leaks are commonplace. Workers knowledge about the oxidative (fire hazard) property of H_2O_2, and about the hazard of rupture of the container due to spontaneous decomposition was not deemed sufficient. There were no safety management systems implemented for either the process use, or for storing or transporting the substance inside the factory. On the other hand the delivery of hydrogen peroxide to the customer in Finland is carried out competently by the producer or the importer.

4.2.3.2 Consumers

Hydrogen peroxide products for consumer use are more diluted than the products used in the industry. However, exceptionally, products may contain higher concentrations of hydrogen peroxide and spills on combustible materials may involve a fire hazard, if the substance is not removed by washing. Thus, **conclusion (iii)** is appropriate. Storing the substance in a bottle with a tight stopper may also result in increased pressure inside the vessel due to spontaneous decomposition, and violent rupture.

4.2.3.3 Humans exposed via the environment

There is no risk of physico-chemical hazard for the population due to exposure to hydrogen peroxide indirectly via the environment.

5 RESULTS

5.1 ENVIRONMENT

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion is reached because of:

- concerns for effects on the aquatic compartment as a consequence of exposure arising from four production sites and use in manufacture of other chemicals.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to:

- the aquatic compartment for 19 production sites, pulp bleaching, textile bleaching, environmental applications and consumer use.
- microorganisms in the sewage treatment plant, the terrestrial environment and the atmosphere for production, all processing scenarios and consumer use.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

With the exception of reproductive toxicity, the hazardous properties of hydrogen peroxide have been studied and evaluated in humans and/or animals to the extent that the minimum data requirements according to Article 9(2) of Regulation 793/93 have been met. Results obtained from repeated dose studies are considered sufficient to draw the conclusion that hydrogen peroxide is unlikely to cause adverse effects on fertility. Regarding developmental toxicity of hydrogen peroxide, it is not possible to draw firm conclusions, but it was deemed doubtful that hydrogen peroxide would reach the foetus and that further studies were unlikely to reveal specific developmental effects. Inhalation of hydrogen peroxide vapours is the primary route of exposure for workers. Limited studies indicated that repeated inhalation exposure to hydrogen peroxide may cause local effects in the respiratory system. Human evidence of sustained airway irritation and inflammation was considered sufficient for risk characterisation, but a follow up of relevant future studies is desirable.

5.2.1.1 Workers

Irritation/corrosivity in the eye, skin and respiratory tract and repeated inhalation toxicity are the most relevant adverse effects of hydrogen peroxide for workers. Appropriate procedures of safe handling and personal protection are required to prevent risks of irritation/corrosivity regarding all scenarios which involve handling of the more concentrated (≥5%) solutions of hydrogen peroxide. Appropriate technical arrangements of containment, automation and ventilation should be applied to machines and processes employing hydrogen peroxide to reduce airborne exposure of workers.

Results of the risk characterisation for workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion is reached because of:

- concerns for skin, eye and respiratory tract irritation and/or corrosivity, depending on concentration as a consequence of exposure arising from loading operations;
- concerns for skin and eye irritation and/or corrosivity, depending on concentration, as a consequence of exposure arising from bleaching of textiles (batch process), aseptic packaging (old types of immersion bath machines), hydrogen peroxide and peracetic acid use in breweries, etching of circuit boards (old process), metal plating, degrading of proteins;
- concerns for eye irritation and/or corrosivity, depending on concentration, as a consequence of exposure arising from hairdresser's work;
- concerns for repeated inhalation toxicity in loading operations and aseptic packaging (all types of machines), etching of circuit boards (old process) and wastewater treatment.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to:

- acute toxicity, sensitisation, repeated oral toxicity, repeated dermal toxicity, mutagenicity and carcinogenicity for all exposure scenarios;
- skin, eye and respiratory tract irritation and/or corrosivity in production of H_2O_2, synthesis of other chemicals, pulp and paper bleaching, bleaching of textiles (automated process), industrial laundering, aseptic packaging (other than old types of immersion bath processes), peracetic acid use in meat processing, etching of circuit boards (modern process), production of modified starch, drinking water treatment, and wastewater treatment;
- respiratory tract irritation in bleaching of textiles (batch process), aseptic packaging (old types of immersion bath machines), hydrogen peroxide and peracetic acid use in breweries, etching of circuit boards (old process), metal plating, degrading of proteins;
- both skin and respiratory tract irritation in hairdresser's work;
- repeated inhalation toxicity in production of hydrogen peroxide, synthesis of other chemicals, pulp and paper bleaching, bleaching of textiles (batch and automated processes), industrial laundering, hydrogen peroxide and peracetic acid use in breweries, peracetic acid use in meat processing, etching of circuit boards (modern process), production of modified starch, degrading of proteins, drinking water treatment, and hairdresser's work.

5.2.1.2 Consumers

Certain ≥5% hydrogen peroxide containing consumer products may cause irritant and corrosive effects. Hair bleaching and dyeing products may cause irritation in the eyes, textile bleaching products may cause hazards for the eyes and, if they should contain more than 35% hydrogen peroxide, even for the skin, and tooth bleaching products applied by the dentist may cause

hazards for the treated teeth. "All purpose cleaners" and toilet cleaners containing ≥ 5% of hydrogen peroxide may cause irritation in the eyes and serious damage to the eyes if the concentrations is ≥ 8%. The method for limiting the risks is to reduce the concentration of hydrogen peroxide in consumer use to safe levels.

Results of the risk characterisation for consumers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion is reached because of:

- concerns for eye irritation as a consequence of exposure arising from hair dyeing and bleaching and concerns for eye irritation/corrosivity in use of textiles bleaches and cleaning agents, if the actual concentration of hydrogen peroxide is >5%;
- concerns for specific adverse effects on tooth pulp and teeth as a consequence of exposure arising from tooth bleaching with 35% of hydrogen peroxide by a dentist;

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to:

- acute toxicity, sensitisation, repeated oral toxicity, repeated dermal toxicity, mutagenicity and carcinogenicity for all exposure scenarios;
- skin, eye and respiratory tract irritation in the context of contact lens disinfection, tooth bleaching, ingestion in food, and use of mouth care products,
- both skin and respiratory tract irritation in hair dyeing and bleaching, in textile bleaching and use as a cleaning agent.

5.2.1.3 Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

This conclusion applies to:

- all effect endpoints for humans exposed to hydrogen peroxide via the environment.

5.2.1.4 Combined exposure

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

5.2.2 Human health (risks from physico-chemical properties)

Assessment of physico-chemical hazards indicates that hydrogen peroxide is highly unstable, and its concentrated solutions are oxidising and apt to decompose gradually or even explosively

if not free from contaminants, well stabilised, and if not used at normal temperature and pressure. The spontaneous exothermic decomposition presents a high risk of fire when the concentrated substance comes in contact with combustible materials.

5.2.2.1 Workers

Due to the closed production processes, and stringent safety controls in place in the major industrial uses of hydrogen peroxide, physico-chemical hazards only arise in accidents. In minor industrial uses, the manual methods of handling cause a high risk of spills and leaks. The awareness of the workers about fire hazards resulting from contact of hydrogen peroxide with combustible materials is deemed insufficient.

Results of the risk characterisation for workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies to the workers and to the consumers because of:

- concerns for the risk of fire hazard caused by spills of the more concentrated (≥ 25%) hydrogen peroxide solutions on combustible materials.

5.2.2.2 Consumers

Hydrogen peroxide products for consumer use are more diluted than the products used in the industry, and fire hazards are unlikely. However, in case of an exceptional textile bleach containing up to 35% hydrogen peroxide, spills on combustible materials may involve a fire hazard, if the substance is not removed by washing. Storing the substance in a bottle with a tight stopper may also result in increased pressure inside the vessel due to spontaneous decomposition, and violent rupture.

Results of the risk characterisation for consumers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies to the workers and to the consumers because of:

- concerns for the risk of fire hazard caused by spills of the more concentrated (≥ 25%) hydrogen peroxide solutions on combustible materials.

5.2.2.3 Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

There is no risk of physico-chemical hazard for the population due to exposure to hydrogen peroxide indirectly via the environment.

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biochemical Oxygen Demand
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 90 percent dissipation / degradation

E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)

IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidising (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic

P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	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
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
ThOD	Theoritical Oxygen Demand

UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

Appendix A EUSES calculations

EUSES Summary report **Single substance**

Printed on	22.8.2000 13:55:07
Study	H_2O_2 final 08/00
Substance	Hydrogen peroxide
Defaults	Standard
Assessment types	1A, 1B
Base set complete	No

Euses Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

Appendix B Measured environmental concentrations

SOURCE: CEFIC, PEROXYGEN SECTOR GROUP, HYDROXEN PEROXIDE, Draft three 18 September 1997

Table B.1 Measured environmental concentrations in sea water

	Method	Detection limit (µg/l)	Mean (µg/l)	Conc. (µg/l)	Reference	Val.
Sea Water						
Mediterranean sea water surface	LUM	0.3		4	Price et al. (1994)	1
Sargasso Sea	POPHA	0.1	3	2.5-6	Miller and Kester (1994)	1
Seto Island bay	POPHA		7	0.7-14	Fujiwara et al. (1993)	1
Atlantic ocean				1-6	Weller and Schrems (1993) 2)	1
Eastern Caribbean				2-14	Sikorski and Zika (1993) 2)	1
Eastern Caribbean	SCOPO	0.2	5	3-14	Moore et al. (1993) 2)	1
Great barrier reef, Australia				1-4	Szymczak and Waite (1991) 2)	1
Western Mediterranean Sea	ALPS	0.4		3-5	Johnson et al. (1989)	1
Sargasso Sea				4-5	Palenik and Morel (1988) 2)	1
Mediterranean sea water surface	ALPS	0.4		3-10	Johnson et al. (1987)	1
Gulf of Mexico	SCOPO			2-7	Cooper et al. (1987)	1
Gulf of Mexico	SCOPO	0.2		3-8	Zika et al. (1985a)	
Gulf of Peru	SCOPO	0.2		0.3 -2	Zika et al. (1985b)	
Gulf of Mexico	SCOPO			0.5 -7	Van Baalen and Marier (1966)	3
Texas coastal waters	SCOPO			0.5-6	Van Baalen and Marier (1986) 1)	3
	IODO					
North Atlantic				1-5	Zika (1978) 1)	2
Biscayne Bay/Florida				3-7	Zika (1980) 1)	2
Bahama bank				2-7	Zika (1980) 1)	2

1) Quoted in Cooper et al. (1988b)
2) Quoted in Miller and Kester (1994)

Table B.2 Measured environmental concentrations in estuarine surface waters and freshwater

	Method	Detection limit (µg/l)	Mean (µg/l)	Conc. (µg/l)	Reference	Val.
Estuarine surface waters						
Chesapeake Bay	SCOPO		68	10-58	Helz and Kieber (1985)	1
Patuxent estuary	SCOPO			1-3	Helz and Kieber (1985)	1
Patuxent estuary	SCOPO	0.07		0.4 -12	Kieber and Helz (1995)	1
Freshwater						
Lakes Ontario, Erie, Jacks	SCOPO	0.3	3.4	0.3 - 27	Cooper et al. (1989)	1
Lakes Ontario, Erie, Jacks	SCOPO	0.2	3.4	4-7	Cooper and Lean (1989) Cooper et al. (1994)	1
New Zealand lakes	DPD		1.5	3-30	Herrmann (1996)	1
Southestem US				3-11	Cooper and Zika (1983)	3
Volga River				44-109	Sinei'nikov (1971) [1)]	4
reservoir, Russia				24 -44	Sinei'nikov (1971) [1)]	4
Lake Greigensee (CH)				max 14	Sturzenegger (1989)	
Lakes (CH)				3.4-6.8	Sturzenegger (1989)	
River Glatt (CH)				0.3-14	Sturzenegger (1989)	
River Grieshbach (CH)				14-27	Sturzenegger (1989)	

1) Quoted in Cooper et al. (1988)
2) Quoted in Miller and Kester (1994)

Table B.3 Measured environmental concentrations in rainwater

	Method	Detection limit (µg/l)	Mean (µg/l)	Conc. (µg/l)	Reference	Val.
Rainwater						
California L.A. Basin 1985-1988	SCOPO			3-3230	Sakugawa and Kaplan (1992)	1
L.A. Basin 1985-1990	POPHA			0.3-4930		
L.A. Basin 1989 (winter)	LUM			3-224		
L.A. Basin 1989 (winter)				75-2380		
L.A. San Bemardino Mountains 1988-1989 (May-October)				306-3060		
Rarotonga (Cook islands) (7/8-1-1995)	DPD			986-2040	Herrmann (1996)	1
New Zealand 09/94-12/94	DPD	3		44-925	Herrmann (1996)	1
Elk Mountain, WY 1987-1988 winter	POPHA			up to 340	Snider, quoted in Gunz (1990)	3
Strasbourg France	AMPERO	0.2		2-38	Lagrange and Lagrange (1990)	1
Dortmund Germany, 1983-84, summer	TCPO	0.3	340	25-2200	Klockow and Jacob (1986)	1
winter			30	0-290		
Netherlands, Apr.-Jun. 1986	POPHA			280	Keuken et al. (1987)	1
	AMPERO	5				
North Sea, summer 1982	LUM			17-2414	Roemer et al. (1985)	1
winter 1981				0.3-7		
Florida and Bahama Islands, 1981	SCOPO			340-2380	Zika et al. (1982)	1
California, LA basin 1978-79	LUM			40-1590	Kok (1980)	1
Gulf of Mexico	SCOPO		1367	390-2800	Cooper et al. (1987)	1
Florida Keys - Western Atlantic Ocean	SCOPO		431	285-700	Cooper et al. (1987)	1
Summit of Whitetop Mountain, VA (1,689m), spring-autumn 1986	POPHA		333	<1-1353	Oiszyna et al. (1988)	1
Eastern USA, summer 1982-83	POPHA			3-2142	Kelly et al. (1985)	1
Ontario, Canada, Jan.-Feb. 1984	POPHA			<17-170	Daum (1990)	
Brazil, Mar.-Apr. 1988	TCPO	2		578-6766	Jacob et al. (1990)	1
Tokyo, Japan, 1981-82	LUM	0.1		7-1064	Yoshizumi et al. (1984)	1

Table B.4 Measured environmental concentrations in cloudwater

	Method	Detection limit (µg/l)	Mean (µg/l)	Conc. (µg/l)	Reference	Val.
Cloudwater						
California L.A. Basin 1985-1988 May-Oct. 1989	POPHA		850	306-2108	Sakugawa and Kaplan (1992)	1
California San Pedro Hills, July 87	POPHA			102-1666	Munger et al. (1989)	1
Canada, Ontario, Summer 88, Spring 90	POPHA			51-4760	Mac Donald et al. (1995)	1
Cumbria, Great Dun Fell,	POPHA			805-3400	Dollard et al. (1988)	1
North Sea, summer 1982, (150-3,000m)	LUM					
Eastern US, summer 1982-83, (< 3,000m)	LUM			< 41-2000	Roemer et al. (1985)	1
Eastern US, 1982-83,(450-1,500m)	POPHA	2		3-3400	Kelly et al. (1985)	1
California, LA basin, May 1982	POPHA	3		< 2550	Daum et al. (1984)	1
California, LA basin, May-Jun. 1985				31-2992	Richards et al. (1983)	1
Carolina coast, US, Jan.-Mar. 1986				408-5678	Richards (1989)	1
Summit of Whitetop Mountain, VA, spring-autumn 1986, (1,689m)	POPHA	10		10-3808	Barth et al. (1989)	1

Table B.5 Measured environmental concentrations in ambient air

	Method	Detection limit (ppb)	Mean (ppb)	Conc. (ppb)	Reference	Val.
Ambient air						
Los Angeles and its vicinity				0.02-5	Sakugawa and Kaplan (1992)	1
Anholt island, Denmark, Jun. 1992,40 m	POPHA	0.05	1	0-2.2	Granby et al. (1994a)	1
Lille Valby, Zealand, July 1 99@, ground	POPHA	0.05	0.8	0-2	Granby et al. (1994a)	1
Greenland Arctic, Aug. 1993, ground	POPHA	0.05	0.3	0.17-0.33	Granby et al. (1994a)	1
Northeastern US, Aug-Sept. 1988,	POPHA	0.2	0.2-1.3		Tremmel (1993)	1
troposphere (1 00-3500 m)				0.40-1.80		
Meadview, AZ, Summer 1992, ground,						
Total peroxides	POPHA			1-5	Tanner and Schorran (1995)	1
Mountain fields sites, Germany,						
June 1990-May 1991 : 1780 m	POPHA	0.06	0.8	0.06-3	Junkerman et al. (1993)	1
1175 m		0.9		0.06-4		
Western Atlantic Ocean, Jan. 1986	POPHA	0.03	0.12	0.26-1.24	Heikes et al. (1988)	1
Appalachian region, Aug. 1988	POPHA			0.6-2.3	Van Valin et al. (1994)	1
ground and 500-1 000 m						
Rural Southern England, Jan. 1987-July 1990,	LUM.	0.1	0.7	0-4	Dollard and Davies (1992)	1
ground						
Southern England, April 1987, 2 m	LUM.	0.04		< 2.5	Dollard et al. (1989)	1
Hawaii, Spring 1988,3200 m	POPHA		1.2		Heikes et al. (1991)	1
Australia, Samoa, Fiji, Jan. 1987 <91 m	POPHA	0.1	0.4	0.4	Heikes et al. (1991)	1
900-3300 m				0.8		
5600 m				0.2		
Canada, Ontario, summer 1988	POPHA	0.1	6		Mac Donald et al. (1995)	1
Spring 1990				2		1
Swiss plateau, Summer 90, ground	POPHA	0.1		0.1-3	Dommen et al. (1995)	1
Summer 90, balloon (0-2000 m)	DS syst	0.1		0.6		1
Summer 91	POPHA	0.1		0.1-6		1
Marine atmosphere (pacific), 1990	POPHA			0.45-0.65	Thompson (1994)	1

Table 5 continued overleaf

Table B.5 continued Measured environmental concentrations in ambient air

	Method	Detection limit (ppb)	Mean (ppb)	Conc. (ppb)	Reference	Val.
Ambient Air						
North pacific, 1991 Highest value, near Philipines (300 m-1 3 km)	POPHA	0.03	1	0.1-6	Heikes et al. (1996)	1
Tasmania (Cape Grim), total peroxides, Summer	POPHA	0.03		1.4-2	Ayers et al. (1996)	1
1991-1992 Winter				0-0.2		
East Greenland Sea, Summer 1994, troposphere	POPHA	0.05	0.4	0.1-1	Welter and Schrems (1996)	1
Central Greenland, summit 3200 m				3.5	quot. in Welter and Schrems	1
Glendora, CA, Aug. 1996,	TDLAS	0.14		0.1-2.4	Tanner and Shen (1990)	1
Azusa, CA, Aug. 1986	POPHA	0.03		0.03-2	Dasgupta (1990)	1
Glendora, CA, Aug. 1986	TDLAS	0.15		0.1-2	Mac Kay et al. (1990)	1
Munich, Germany, april 1988	TCPO	0.025		0-0.5	Kins (1990)	1
sept. 1989				0.2-1.5		
Denmark, Aug 1991 -Jan. 1992	POPHA	0.06	0.1 (jan)	0-1	Granby et al. (1993)	1
	TI(IV)	0.13		0.2 (aug)		
Rural air, day, ground				0.3-3	Das et al. (1983)	1
night, ground				< 0.01		
Canada,Ontario, summer 1984-85, ground	TDLAS		0,1- 0,2	0.1-2.1	Slemr et al. (1986)	1
Upton, NY, summer-autumn 1985, ground	POPHA	0,1		0.1-1.2	Tanner et al. (1986)	1
Carolina coast, Jan.-Mar. 1986, cloud	POPHA	0,2		0.2-2.4	Barth et al. (1989)	1
Whiteface Mountain, NY, (1,500m),	POPHA		0.6	2.7	Mohnen and Kadlecek (1989)	1
summer 1986 (463 samples)			0.8	6.1		
summer 1987 (673 samples)						
Rome, Italy, Jan.-Mar. 1988, ground	Ti (IV)	0,035	0,1	0,05-0,15	Possanzini et al. (1988)	1
Southern California, summer-autumn, 1985, ground	POPHA			0,02-1,2	Sakugawa and Kaplan (1987)	1
Southern Califonia 1985-88, ground	POPHA				Sakugawa and Kaplan (1989)	1
Westwood (LA)			0.36	0,03-1,35		1
Duarte (LA)			0.42	0,12-0,78		
Dagett(Mojave Desert)			1.19	0,2-2,04		
San Bemardino Mountains			1.02	0,43-1,72		

Table 5 continued overleaf

Table B.5 continued Measured environmental concentrations in ambient air

	Method	Detection limit (ppb)	Mean (ppb)	Conc. (ppb)	Reference	Val.
Ambient Air						
Dortmund, Germany, Oct. 1984-Jul. 1985, ground	TCPO		0.03		Jacob et al. (1987)	1
Brazil, Mar.-Apr. 1988, ground	TCPO	0,3		0.2-3.9	Jacob et al. (1990)	1
Eastern USA, autumn 1984, cloud (1 50-3,700m)	POPHA			0.2-4.1	Heikes et al. (1987)	1
South central USA, Feb. 1987, cloud (1,700-2,600m)	POPHA			0.1-1	Van Valin et al. (1987)	1
Central USA, Jun. 1987, ground to 5.5km	POPHA	0.2		0.2-7	Daum et al. (1990)	1
Northeastern USA, Jun. 1987, ground to 4km	POPHA	0.05		0.6-3.6	Van Valin et al. (1990)	1
Summit of Whitetop Mountain, VA, (1,689m),	POPHA		0.8	0.02-2.6	Oiszyna et al. (1988)	1
summer 1986			0.15	0.02-0.57		
fall 1986						
Central USA, 1957, (1,450-2,450m)	POPHA			0.3-4.8	Boatman et al. (1989)	1
Riverside CA; Hoboken NJ, summer 1970, ground (smog)	Ti (IV)			180; 40	Bufalini et al. (1972) *	4
California, south coast, summer 1970, ground (smog)	LUM	0.4		10-30	Kok et al. (1978a) *	4

* possible artefact formation H202 within collectors

TDLAS : Tunable Diode Laser Absorption Spectroscopy
POPHA: peroxidase-catalyzed dimerisation of p-hydroxyphenylacetic acid (POPHA) and fluorescence detection
LUM: chemiluminescenceoxidation of luminol (5-amino-2,3-dihydro-1,4phthalazinedione)
TCPO : peroxyoxalate chemiluminescence TCPO ((2,4,5-trichioro-6-phenyl-oxalate method
DPD : enzyme-catalyzed oxidation of N,N diethyl-p-phenylenediamine
SCOPO: peroxidase-mediated depletion of scopoletin (6-methyl-7-hydroxy-1,2-benzopyrone) fluorescence
Ti(IV): formation of colored TI(IV) complex
IODO: iodometric titration
AMPERO: amperometric titration with Pt electrode
ALPS: photometric determination with N-ethyl-N-(sulfopropyl) anilinesodium salt

Appendix C Acute toxicity studies in animals

Table C.1 Acute toxicity (oral)

Species and strain	Type of study	Substance	Result	Remark	Reference
Rat Strain not known	oral LD50	70% H_2O_2	LD_{50} males: 75 mg/kg	doses: 50, 75 or 100 mg/kg	FMC (1979)
Rat CRL:CD®BR	oral LD50	70% H_2O_2	LD_{50} combined: 805 mg/kg (634-1,018 mg/kg 95% CI) males: 1026 mg/kg (95% CI not defined) females: 694 mg/kg (427-960 mg/kg 95% CI)	doses males: 500, 1,000 or 5,000 mg/kg females: 500, 750 or 1,000 mg/kg	Du Pont (1996)
Rat Wistar	oral LD50	60% H_2O_2	LD_{50} males: 872 mg/kg (744-1013 mg/kg 95% CI) females: 801 mg/kg (635-1010 mg/kg 95% CI)	doses males: 0, 0.351, 0.535, 0.734, 1.019 or 1.296 ml/kg females: 0, 0.213, 0.323, 0.426, 0.659, 0.879, 1.236 or 1.647 ml/kg	Mitsubishi (1981)
Rat Sprague-Dawley	acute oral toxicity Screen	50% H_2O_2	LD_{50} not determined	undiluted substance at dose level of 225 mg/kg, no deaths among female rats 1/5 male rat died on day one	FMC (1986)
Rat Sprague-Dawley	oral LD50	35% H_2O_2	LD_{50} males: 1,193 mg/kg (773-1,612 mg/kg 95% CI) females: 1270 mg/kg (1088-1453 mg/kg 95% CI)	doses males: 630, 797, 1,000, 1,260, 1,588 or 2,000 mg/kg females: 794, 1,000, 1,260 or 1,588 mg/kg	FMC (1983)
Rat Sprague-Dawley	limit test	10% H_2O_2	LD_{50} not determined (lethal dose >5,000 mg/kg)	Undiluted substance at dose level of 5000 mg/kg. One rat died on day 1	FMC (1990)
Rat Wistar-JCL	oral LD50	9.6% H_2O_2	LD_{50} males: 1518 mg/kg (1,358-1,696 mg/kg 95% CI) females: 1,617 mg/kg (1,432-1,826 mg/kg 95% CI)	doses: a range of 7 volumes with a stepwise increase by 1.2. males: 0.88-2.63 ml/100g females: 0.92 - 2.75 ml/100g	Ito et al. (1976)

Table C.2 Acute toxicity (inhalation) (aerosols)

Species	Type of study	Exposing substance	Exposure	Result	Remark	Reference
Mouse Strain unkown	acute inhalation toxicity	aerosol generated from 90% H_2O_2	5-15 min study 1: 3,600-5,200 mg/m^3 study 2: 9,400-19,000 mg/m^3 aerosols, mass median particle size: appr. 3.5 microns	LC_{50} not determined, LCLo 9,400 mg/m^3 lethality: min. conc. mortal. 10 13,200 5/10 15 11,800 5/10 15 16,700 9/10	not 4-hour exposure	Punte et al. (1953)
Mouse Male	acute inhalation toxicity	aerosol generated from 70% H_2O_2	7.5-120 min 880 – 4,960 mg/m^3 aerosol: particle size not given	LC_{50} not determined lethality: time, min. conc. mortality 60 <2,170 0/4 60 3,013 4/4 120 920 ¾ 120 2,000 2/4 120 1,450 1/4	nose-only not 4-hour exposure	Solvay Duphar (1995a)
Mouse Swiss male	inhalation RD_{50} (respiratory irritancy)	aerosol generated from 0% H_2O_2	30 min 300, 616, 1,135, 1,856 mg/m^3 aerosols, particle size not given	RD_{50} (respiratory rate): 665 mg/m^3, (95% CI: 280-1,139 mg/m^3) RD_{50} (minute volume): 696 mg/m^3 (95% CI: 360-1,137 mg/m^3)	nose-only not 4-hour exposure	Solvay Duphar (1995b)

Table C.3 Acute toxicity (inhalation) (vapours)

Species	Type of study	Exposing substance	Exposure	Result	Remark	Reference
Rat Sprague Dawley, Male and Female	acute inhalation toxicity (screen)	vapour (generated from 50% H_2O_2)	4 hour whole-body exposure at 170 mg/m^3 (maximum attainable level)	no deaths. Minimal signs of treatment (nasal discharge). Following the exposure body weights were transiently decreased		FMC (1990)
Rat Strain unknown	acute inhalation toxicity	vapour (generated from 90% H_2O_2)	4 hour or 8 hour whole-body exposure at 338-427 mg/m^3	no deaths. Few signs during treatment (scratching and licking). In animals killed within 3 days, the trachea and lungs were congested with localized areas of pulmonary oedema. Later killings showed many areas of alveolar emphysema	three groups of ten rats, one exposed for 4 hours and two for 8 hours.	Comstock et al. (1954) Oberst et al. (1954)
Mouse Swiss, male	acute inhalation toxicity	vapour (generated from 90% H_2O_2)	4 hour whole-body exposure at 16.1, 37.4, 78.1, 113, 194 or 227 ppm	no deaths at 78 ppm or less. Within the 2 wk observation period, at 113 ppm (160 mg/m^3) 4/10, at 227 ppm 22/25, and at 226 ppm (another exp.) 5/10 mice died		Svirbely et al. (1961)
Rat Strain unknown	LC_{50} study	"vapour of H_2O_2", no further details	4 hour whole-body exposure, no further data given	LC_{50} given as 2,000 (1,690-2,360) mg/m^3	data briefly mentioned in a review of author's own studies	Kondrashov (1977)

Table C.4 Acute toxicity (intravenous)

Species	Type of study	Substance	Result	Remark	Reference
Rat Wistar	i.v. (MTD =maximum tolerated dose)	i.v. 35% H_2O_2 0 mg/kg (water) 12.5 mg/kg (0.05%) 25 mg/kg (0.1%) 50 mg/kg (0.2%) 125 mg/kg (0.5%) 250 mg/kg (1%)	MTD: appr. 50 mg/kg (0.2%)	Graded dilutions of 35% H_2O_2 (in water) were given as single intravenous adminstration (by infusion for appr. 30 min at a rate of 0.2 ml/min). AST, ALT, γ-GT measured in plasma samples taken from the animals 12-24 h after treatment did not unequivocally demonstrate toxic effects in the liver. Animals died 15 and 6 min after the start of dosing with 0.5 and 1% solutions, respectively (which actually corresponds to 65 and 55 mg/kg).	CEFIC (1997a)
Rabbit	i.v. LD50	i.v. 90% H_2O_2 58.6% H_2O_2 36.0% H_2O_2 14.4% H_2O_2 3.6% H_2O_2	LD50: 15.0 cu.mm/kg (= ~ 21 mg/kg) 12.6 cu.mm/kg (= ~ 15 mg/kg) 8.9 cu.mm/kg (= ~ 10 mg/kg) 5.0 cu.mm/kg (= ~ 5 mg/kg) 3.2 cu.mm/kg (= ~ 3.2 mg/kg)	I.v. injections were given into the marginal ear veins of rabbits.	Hrubetz et al. (1951)

Table C.5 Acute toxicity (dermal)

Species and strain	Type of study	Substance	Result	Remark	Reference
Rat White	dermal LD50	90% H_2O_2	appr. 3.5 cc/kg (= ~ 5,000 mg/kg)	method not well described. 4/12 died at 3.55 cc./kg 9/12 died at 4.0 cc./kg	Hrubetz et al. (1951)
Rat Black	dermal LD50	90% H_2O_2	-	0/6 died at 5.0 cc./kg 2/6 died at 6.0 cc./kg	Hrubetz et al. (1951)
Rabbit	dermal LD50	90% H_2O_2	appr. 0.5 cc./kg (= ~ 700 mg/kg)	6/12 died at 0.5 cc./kg	Hrubetz et al. (1951)
Cat	dermal LD50	90% H_2O_2	-	no deaths at 2-3 cc/kg (= ~ 2,800-3 200 mg/kg)	Hrubetz et al. (1951)
Pig	dermal LD50	90% H_2O_2	appr. 2.0 cc/kg (= ~ 2,800 mg/kg)	2/5 died at 2.0 cc/kg (= ~ 2,800 mg/kg)	Hrubetz et al. (1951)
Rabbit	dermal LD50	70% H_2O_2	9,200 mg/kg	method not well described.	FMC (1979b)
Rabbit	dermal LD50	35% H_2O_2	>2,000 mg/kg	limit dose study, 24 h exposure under occlusion. No deaths.	FMC (1983b)
Mouse	dermal toxicity	10% H_2O_2 (a) 28% H_2O_2 (b)	(a) 1,400 mg/kg caused signs of systemic toxicity (b) >8,000 mg/kg killed some animals	method not well described.	Liarskii et al. (1983)
Rat	dermal LD50	H_2O_2 % not given	4,060 mg/kg (3,000-5,480 mg/kg)	method not well described. single application to 1 dm^2 of the back skin. Death by gas embolism.	Kondrashov (1977)

Appendix D Occupational exposure measurements

Table D.1 Studies in humans

Subjects	Exposure	NOAEL	Effect concentration / dose	Effect	Remark	Reference
18 males 14 females	H_2O_2 vapour inhalation E 5 min - 4 h exposure	5 mg/m^3	10 mg/m^3	respiratory irritation threshold (all exposure times)	The volunteers inhaled H_2O_2 vapours from a chamber through the nose using a face mask. The method for assessing respiratory irritation is not described. Results from this volunteer study agreed with cited industrial experience.	Kondrashov (1977)
18 males 14 females	H_2O_2 vapour dermal single 5 min – 4 h exposure	10 mg/m^3	20 mg/m^3	dermal irritation threshold (4 h)	One hand was placed inside the H_2O_2 containing chamber through an opening in a rubber membrane, the other hand served as a control. The method for assessing skin irritation is not described. Threshold concentrations (vapour) for various exposure durations: 60 min - 80 mg/m^3 30 min - 110 mg/m^3 15 min - 140 mg/m^3 5 min - 180 mg/m^3	Kondrashov (1977)

Table D.1 continued overleaf

Table D.1 continued Studies in humans

Subjects	Exposure	NOAEL	Effect concentration / dose	Effect	Remark	Reference
Male dairy worker, age 41	vapour and aerosol of H_2O_2 measured as 41 mg/m^3 close to UHT milk products packaging machine and 12 mg/m^3 on the floor. duration: For 3 years 2 d/wk, followed by 6 months daily.		12 mg/m^3 most of the time, transiently 41 mg/m^3	interstitial lung disease	During work the patient experienced bleaching of hair, increased cough and dyspnea on exertion. Pulmonary function testing, gas exchange measurements, tracheobronchial biopsy findings, and the radiographic picture were consistent of an interstitial lung disease. Withdrawn from exposure the patient improved progressively during 1.5 months, and after one more month of prednisone treatment, the chest radiograph and lung fuction tests normalised. The patient was carefully examined with appropriate differential diagnostic methods. The patient was a heavy smoker (2 packs of cigarettes daily for 25 years) which may have been a contributing factor. The patient's erythrocyte catalase was within the normal range.	Kaelin et al. (1988)
Altogether 110 hydrogen peroxide production workers	mean levels of airborne H_2O_2 were well below 1.4 mg/m^3 and transiently up to 5 mg/m^3. Duration: 80/110 workers had been in the production over 10 years.			No evidence of peroxide related change in lung function over time	lung function monitoring was based on forced vital capacity and peak expiratory flow measurements. A symptom inquiry disclosed occasional skin irritation, skin whitening after accidental contact, hair bleaching in the past, and one case of acute throat irritation.	Degussa-Hüls (1999)

Table D.1 continued overleaf

Table D.1 continued Studies in humans

Subjects	Exposure	NOAEL	Effect concentration / dose	Effect	Remark	
A group of 6 aseptic packaging/maintenance workers, three males and three females, mean age 50, range 40-55	due to packaging machine malfunction TWA peroxide levels in air over the shift were 1.7-3.4 mg/m^3 with peaks up to 11.3 mg/m^3 for 8 months, and subsequently after repairs 0.5-0.7 mg/m^3 without much fluctuation.		LOAEL about 2 mg/m^3	sustained irritancy and inflammation in the airways	Half of the workers experienced irritation in the eyes and airways, headache, temporary loss of olfaction, symptoms and signs in the skin and blanching of hair. Three workers exhibited a uniform course of recurring bronchitis-sinusitis which coincided with the period of high exposure. Two of them showed bronchoconstriction and made a full recovery only after administration of inhaled corticosteroids and the concurrent reduction of exposure.	Riihimäki et al. (2002)
10 volunteers	topical application to the eye		812 ppm for solutions, 267 ppm for 55% hydrogel lenses, 282 ppm for 38% hydrogel lenses	mean discomfort threshold to the eye	A single-blind controlled study. Either drops of H_2O_2 solutions or hydrogel contact lenses soaked for 2-4 h in test solutions were applied. Eye comfort responses were assessed after 1 and 10 min for the drop threshold, and after 1, 3 and 30 min for the lenses. While the mean threshold for drops was 812 ppm, individual values ranged from 400 to 1500 ppm.	McNally (1990)

Table D.1 continued overleaf

Table D.1 continued Studies in humans

Subjects	Exposure	NOAEL	Effect concentration / dose	Effect	Remark	
54-year-old male	irrigation of an infected and fistulous herniorrhaphy wound with 3% H_2O_2		up to 1.5 g, appr. 15 mg/kg bw	Shock and coma for 15 min with full recovery	an obese patient had an infected and fistulous wound after a right inguinal herniorrhaphy. After the wound was drained, irrigation under pressure with 3% H_2O_2 in 20 ml volumes was performed five times. Not all irrigation volume seemed to have drained from the wound. On the fifth irrigation the patient suddenly lost consciousness, showed signs of cardiac shock and fell to coma. There was no indication of RBC damage. ECG showed transient myocardial ischaemia. apparently there was a widespread systemic embolisation of oxygen microbubbles, especially to the cerebral and coronary arteries.	Bassan et al. (1982)
84-year-old man	ingestion of 30 ml of 35% H_2O_2 solution (about 10 g H_2O_2) diluted with 100-300 ml water.		about 10 g, appr. 150 mg/kg	multiple cerebral infarction	within 3 min after ingestion of hydrogen peroxide (as a self-prescribed remedy for arthritis) the patient slumped over and became unresponsive. In the emergency department, he was noted to have a decreased level of consciousness and a dense left hemiparesis. On the 5th hospital day, a cranial magnetic resonance imaging scan showed multiple, bilateral areas of infarction. After initial improvement in the level of consciousness, severe neurological deficits remained. The likely cause was oxygen gas embolism in cerebral arteries.	Sherman et al. (1994)
16-month-old boy	ingestion of about 230 g of 3% H_2O_2 solution (about 7 g H_2O_2)		appr. 600 mg/kg bw	death by gas (oxygen) embolism	lowest concentration of H_2O_2 solution ingested reported in a case with a deadly outcome. The child was found dead 10 h after ingestion. On postmortem, the gastric mucosa was red, there was frothy blood in the right ventricle and the portal venous system, and the brain was oedematous. Histopathology showed oedema and diffuse interstitial emphysema in the lungs, gas emboli were detected in the pulmonary vasculature as well as gastric and intestinal lymphatics. Clear vacuoles were found in the gastrointestinal tract wall, in the spleen, kidney and myocardium.	Cina et al. (1994)

Appendix E Repeated dose toxicity studies

Table E.1 Repeated dose toxicity (inhalation)

Species, strain and sex	Group size	Route of exposure	Exposure data	NOAEL	LOAEL	Effects	Remark	Reference
Rat No data No data	single group of 23 rats (13 for pathology, 10 for mortality) controls:10 rats	inhalation (whole body)	93 mg/m^3 (67 ppm) H_2O_2 vapour for 6 weeks (180 h of exposure, over 7 weeks), 6 h daily, 5 d per week	-	93 mg/m^3	after week 2: nasal discharge, oedematous feet, irritation of skin in the groin region after week 5: hair loss	conclusions are restricted by the limited study design and incomplete reporting.	Comstock et al. (1954) Oberst et al. (1954)
Mouse No data No data	two groups of 10 mice controls*:* no data	inhalation (whole body)	79 mg/m^3 (57 ppm) or 107 mg/m^3 (77 ppm) H_2O_2 vapour for 6 weeks (180 h exposure over 7 weeks), 6 h daily, 5 d per week	-	79 mg/m^3	after week 2: nasal discharge, oedematous feet, irritation of skin in the groin region after week 5: hair loss	conclusions are restricted by the limited study design and incomplete reporting	Comstock et al. (1954) Oberst et al. (1954)
Dog No data No data	2 dogs control: 1 dog	inhalation (whole body)	10 mg/m^3 (7 ppm) H_2O_2 vapourfor 6 months, 6 h daily, 5 d per week (total 126 exposures)	-	10 mg/m^3	sneezing, lacrimation, external skin irritation, bleaching of hair, loss of hair, greatly thickened skin. hyperplastic muscular coats in terminal and respiratory bronhioles, buds of fibrotic tissue scattered in the lungs, patchy areas of atelectasis intermingled with emphysematous areas	conclusions are restricted by the limited study design and incomplete reporting	Comstock et al. (1954) Oberst et al. (1954)
Rat Alpk: AP_fSD Male and Female	5 rats	inhalation (whole body)	0 (control), 2.9, 14.6 or 33 mg/m^3 of H_2O_2 vapour 6 h daily, 5 d per week for a period of 28 d	2.9 mg/m^3	14.6 mg/m^3	at the two higher levels concentration related respiratory tract irritation, necrosis and inflammation of the epithelium in the anterior regions of the nasal cavity	the study was designed for range finding purposes	CEFIC Peroxygen Sector Group (2002)
Rat No data No data	no data controls*:* no data	inhalation (whole body)	0.1 mg/m^3 – 10.1 mg/m^3 H_2O_2 vapour for up to 4 months	1 mg/m^3 (NOEL)	10 mg/m^3 (LOEL)	after 2-4 months: increase in serum epoxidase, decrease in pulmonary SDH, MAO, acid phosphatase, diesterase activities	Unconventional methodology, no details, study poorly reported	Kondrashov (1977)

Table E.2 Repeated dose toxicity (dermal & via stomach tube)

Species, strain and sex	Group size	Method of adminis-tration	Exposure data	NOAEL	LOAEL	Effects	Remark	Reference
Rat No data No data	no data controls: no data	dermal deposition from air (shaved skin)	0.1 mg/m^3 – 10.1 mg/m^3 H_2O_2 vapour for up to 4 months	0.1 mg/ m^3 (NOEL)	1 mg/m^3 (LOEL)	after 2-4 months increase in epidermal MAO, NAD-diaphorase, SDH, LDH activities	unconventional methodology, no details, study poorly reported.	Kondrashov (1977)
Rat Wistar-JCL Male	12 rats per group controls: 12 rats	oral stomach tube	0 (physiol. saline solution), 56.2 mg/kg bw/d (0.112 ml/100g) 168.7 mg/kg bw/d (0.34 ml/100g) 506.0 mg/kg bw/d (1.01 ml/100g) (5% H_2O_2 solution) 6 d per week, 12 weeks	-	56.2 mg/kgbw/d	high dose only: decreased body weight gain, erythrocyte count, haemoglobin concentration, Hct medium and high doses: increased segmented neutrophils and monocytes, decreased lymphocytes, decreased S-GOT, S-GPT, alkaline phosphatase, BUN low dose level: decreased S-GOT. Histopathology: gastric mucosal erosions, eschars and occasional round cell infiltration were found in the high dose level group. no deaths reported.	dose response was seen in several parameters. fairly high concentration of H_2O_2 (5%) was administered.	Ito et al. (1976)
Rat Wistar Male	9-12 rats per group controls: 9-12 rats	oral stomach tube	0 (water), 0, 6, 10,20, 30 or 60 mg/kg bw/d (0.6, 1, 2, 3 or 6 mg/100g bw/d) (30% H_2O_2 diluted to 0.6-6 mg/ml = 0.06-0.6% solution) 40 d (half of the rats) daily 100 d (half of the rats) daily	20 mg/kg bw/d	60 mg/kg bw/d	60 mg/kg bw/d (at 100 days of adm.), significant reduction in the body weight gain after 20 days of administration. slightly higher spleen weight at 40 days (5% significance level), but no difference after 100 days. Decreased haematocrit, plasma protein values and plasma catalase activities (5% level of significance). Plasma catalase was lower also in the 30 mg/kg bw group. No difference in liver or kidney weights. No deaths reported	no clear dose-response (effects mainly at top dose level). Statistical analysis not reported.	Kawasaki et al. (1969)

Table E.3 Repeated dose toxicity (via stomach tube and in feed)

Species, strain and sex	Group size	Method of administration	Exposure data	NOAEL	LOAEL	Effects	Remark	Reference
Rat Male and Female	no data	oral stomach tube	0.005-50 mg H_2O_2/ kg bw/d 6 months 85-90% H_2O_2 diluted to 0.00001, 0.0001, 0.001, 0.01 or 0.1% H_2O_2 solution	0.1 mg/l (0.005 mg/kg bw/d) (NOEL??)	-	at 50 mg/kg bw/d: decrease in body weight gain and blood lymphocyte concentration, increase in the number of reticulocytes and haemolysis, decrease in hepatic catalase activity, increase in hepatic SDH activity, changes in enzyme activities of the stomach, duodenum, and cerebrum; albuminuria, structural changes in gastrointestinal mucosa at 5 mg/kg bw/d: same effects as above, but no decrease in body weight gain, catalase activity of the liver or histopathological changes in the stomach.	unconventional methodology. methods lack important information, incomplete reporting of results. Effects cannot be assessed.	Antonova et al. (1974)
Rat Wistar Male	6 rats per group controls: 6 rats	Oral in feed	0, 0.6, 1, 3, or 6 mg H_2O_2 per 20 g feed/d 90 d	6.0 mg/20g feed	-	no effects reported.	H_2O_2 was added to feed which likely resulted in rapid H_2O_2 degradation. It is uncertain what concentration actually entered the g-i tract	Kawasaki et al. (1969)

Table E.4 Repeated dose toxicity (oral in drinking water)

Species, strain and sex	Group size	Method of administration	Exposure data	NOAEL	LOAEL	Effects	Remark	Refetence
Rat Holzman Male	study I 24 rats per dose group controls: 24 rats study II: 5 groups of 10 rats	oral drinking water	study I: 0, 0.5, 1 or 1.5% H_2O_2 8 weeks *(ad lib.)* study II: 1 or 1.5% H_2O_2 standard diet, but differences in frequency of feeding and form of feed (pellets or ground feed)	-	0.5% H_2O_2	study I: growth retardation in all groups, 7/24 rats died at the high dose (1.5%). extensive carious lesions and pathological changes in periodontium (1 and 1.5%). study II: growth retardation in all groups. extensive carious lesions and pathological changes in periodontium (1 and 1.5%).	conclusions are restricted by the limited study design.	Shapiro et al. (1960)
Rat Wistar male	8 rats controls: 8 rats	oral drinking water	0 (water), 0.5% H_2O_2 56 d *(ad lib.)*	-	0.5%	decreased intake of water and body weight gain. Se-dependent glutathione peroxidase decreased in skeletal muscle, kidney and liver. muscle catalase decreased. water deprivation caused similar effects. no deaths reported.	conclusions are restricted by the limited study design.	Kihlström et al. (1986)
Mouse NMR1 Male	8 mice controls: 8 mice	oral drinking water	0 (water), 0.5 % H_2O_2 40 d *(ad lib.)*	-	0.5%	decreased intake of water. H_2O_2 or water deprivation decreased the body weight gain. no changes in peroxide metabolising enzymes in the studied organs. No deaths reported.	conclusions are restricted by the limited study design.	Kihlström et al. (1986)
Rat Osborne-Mendel Male	no data	oral drinking water	0.45% H_2O_2 3 weeks *(ad lib.)* (study included control animals, no further data provided)	-	0,45%	decreased intake of water, decreased body weight	limited methods, no details, study poorly reported.	Hankin (1958)

Table E.4 continued overleaf

Table E.4 continued Repeated dose toxicity (oral in drinking water)

Species, strain and sex	Group size	Method of administration	Exposure data	NOAEL	LOAEL	Effects	Remark	Ref.
Rat F344 Male/female	10 rats per group	oral drinking water	0, 0.15, 0.3, 0.6, 1.2 or 2.4% H_2O_2 for 10 weeks (*ad lib.*)	-	0.15% (males) 0.15% (females)	body weight gain among male controls was 66.1%, whereas the max. Gain among H_2O_2 treated males (0.6% group) was 53.3%. Body weight gain among female controls was 37.2% while the highest gain in the treated females was 29.7% in the 0.15% group. One male and one female in the top dose group died. Histopathology was performed on 5 rats in each group with abnormal findings only at the top dose: all males & females exhibited multiple gastric erosions and ulcer, 2 males showed atrophy of testis. The lower tissue weights in organs other than the brain at the top dose level roughly corresponded to the body weight loss in both males and females.	NOAEL could not be determined.	Takayama (1980)
Rat No data Male	no data	oral drinking water	normal rats: 0 (water), 0.25, 0.5, 2.5, 5 or 10% H_2O_2 artifically hypertensive rats: 1% saline, 0.25, 0.5 or 2.5% H_2O_2 in saline 290 d	-	0.5%	normal rats: all animals died within 43 days in groups receiving 2.5, 5 or 10% H_2O_2 dose level 0.25% at 146 d: Normal body weight, no deaths dose level 0.5%, at 290 d: reduced body weight slight increase in blood pressure. 8 deaths reported artifically hypertensive rats: Both 0.25% and 0.5% of hydrogen peroxide had a marked effect in reducing the blood pressure and prolonging the life of hypertensive animals with 1 and 2 deaths, respectively	conclusions are restricted by the limited study design. method description lacks important details.	Roma-nowski et al. (1960)

Table E.4 continued overleaf

Table E.4 continued Repeated dose toxicity (oral in drinking water)

Species, strain and sex	Group size	Method of administration	Exposure data	NOAEL	LOAEL	Effects	Remark	Ref.
Mouse dd strain Male	preliminary study: no data main study: 4 groups of 4 mice 2 groups of 4 mice as controls	oral, drinking water *(ad lib.)*	preliminary study: 0, 0.15, 0.3, 0.6, 1.0, 2.0, 4.5 and 9% H_2O_2 no data on duration main study: 0 or 0.15% H_2O_2 for 35 weeks	0.15% -	- 0.15%	preliminary study: the NOAEL concentration was chosen for the main study main study: at week 13 (4 mice): no histopathological changes in the tissues studied (liver, kidney, spleen, small intestine, stomach) at week 16 (2 mice): sporadic, local necrotic foci in the liver, some hyperplastic changes of gastric mucosa at week 22 (1 mouse)*:* clear changes were visible in all organs at week 28 (1 mouse)*:* hydropic degeneration of liver tissue and epithelium of the kidney tubule, slight necrosis, inflammation and irregularities of tissue structure in stomach wall, marked sedimentation of haemosiderin in the spleen. at week 35 (2 mice)*:* hypertrophy of lymphoid tissue of the small intestine wall. no deaths reported.	there was normal body weight gain. by 13 weeks, no changes in histopathology were found in the studied organs. conclusions are severely restricted by the limited design of the study (e.g. the few animals used), and incomplete reporting.	Aoki and Tani (1972)

Table E.4 continued overleaf

Table E.4 continued Repeated dose toxicity (oral in drinking water)

Species, strain and sex	Group size	Method of administration	Exposure data	NOAEL	LOAEL	Effects	Remark	Ref.
Mouse C57BL/6NCr 1BR male and female	5 groups of 10 mice per sex including control group	oral, drinking water	0, 200, 1,000, 3,000 or 6,000 ppm male: 0, 42.4, 164, 415 or 536 mg/kg bw/d female: 0, 48.5, 198, 485 or 774 mg/kg bw/d 14 d	1,000 ppm		at 3,000 and 6,000 ppm dose related decrease in water consumption. decreased body weight gain and food consumption. degenerative and regenerative alterations in the mucosa of the stomach and duodenum	One female in 200 ppm group found dead, but the reason could not be determined.	Du Pont (1995)
Mouse Charles River Catalase deficient C57BL/6NCrl BR Male and Female	5 groups of 15 mouse per sex including control group	oral, drinking water	treatment period (days 0-90) 0, 100, 300, 1,000 or 3,000 ppm male: 26, 76, 239 or 547 mg/kg bw/d female: 37, 103, 328 or 785 mg/kg bw/d recovery period (days 91-134) (5 animals/sex/group continued on untreated distilled water for additional 6 weeks)	100 ppm males: 26 mg/kg/d females: 37 mg/kg/d	300 ppm	3,000 ppm, during/after treatment decreased body weight gain. Males: significant reductions of total protein and globulin levels in the blood 3,000 ppm, recovery period significantly reduced body weights (on day 105, recovery week 2) but no difference in body weight gain at the end of the study 300 ppm and higher dose levels dose-related reductions of food and water consumption (LOAEL) esp. among females males 300 ppm and females 1,000 ppm and higher Duodenal mucosal hyperplasia after treatment; no hyperplasia after recovery in any dose group.	A modern, well-conducted repeated dose study. Histopathology was performed for all animals on different parts of the g-i tract as well as on gross lesions found in any organs, and on the complete set of tissues for high dose and control animals.	FMC (1997)

Appendix F Mutagenicity studies

Table F.1 Mutagenicity (gene mutation assays (*in vitro*), bacteria and yeasts)

Species	Strain	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
Salmonella typhimurium	TA97 TA102 TA104 SB1111 SB1106 SB1106p	ames test - plate incorporation assay - preincubation	H_2O_2 doses: 1, 2 or 4 µM/plate doses: 0.3, 0.6 or 1.2 µM/plate	* TA97 + TA102 + TA104 * SB1111 * SB1106 + SB1106p	NT	Abu-Shakra and Zeiger (1990)
Salmonella typhimurium	TA102	ames test - a liquid incubation assay	H_2O_2 concentrations: 0 or 400µM (without Na_2S) concentrations: 0, 40 or 50 µM (with 100 µM Na_2S)	+	NT	Carlsson et al. (1988)
Salmonella typhimurium	TA97 TA102	ames test	H_2O_2 concentrations: no data	*	*	De Flora et al. (1984)
Salmonella typhimurium	TA92 TA97 TA100 TA102 TA104 TA1535 TA1537	ames test - standard plate incorporation assay	H_2O_2 doses: 0, 0.15, 0.30, 0.60, 1.20 or 2.40 µM/plate	- TA92 - TA97 - TA100 + TA102 + TA104 - TA1535 - TA1537	NT	Glatt (1989)
Salmonella typhimurium	TA92 TA94 TA98 TA100 TA1535 TA1537	ames test - preincubation	H_2O_2 doses: 0.2 mg/plate (max)	- TA92 - TA94 - TA98 + TA100 - TA1535 - TA1537	NT	Ishidate et al. (1984)

Table F.1 continued overleaf

Table F.1 continued Mutagenicity (gene mutation assays (*in vitro*), bacteria and yeasts)

Species	Strain	Measured endpoint	Test conditions	Results without activation	Results with activation	Ref.
Salmonella typhimurium	TA97 TA98 TA100 TA102 TA1537 TA1538	ames test - standard plate incorporation assay - preincubation assay - liquid incubation assay	H_2O_2 concentrations: up to 6 mM concentrations: up to 340 μM concentrations: up to 4.5 μM	+ TA97 + TA98 - TA100 + TA102 + TA1537 - TA1538	- TA97 - TA98 - TA100 - TA102 - TA1537 - TA1538	Kensese and Smith (1989)
Salmonella typhimurium	TA98 TA100 TA1535 TA1537 TA1538	ames test	H_2O_2 doses (-S9): 0.0033 - 0.67 mg/plate (TA98, TA1535, TA1538), 0.001 - 0.33 mg/plate (TA100, TA1537) doses (+S9): 0.010 - 3.3 mg/plate (all five TA strains)	- TA98 + TA100 - TA1535 - TA1537 - TA1538	- TA98 + TA100 - TA1535 - TA1537 - TA1538	Prival et al. (1991)
Salmonella typhimurium	BA9 BA13	bacterial forward mutation - l-arabinose forward mutation test (l-arabinose resistant)	H_2O_2 concentrations: 2941, 5882, 11765 or 17647 nM/ml	+	NT	Ruiz-Rubio et al. (1985)
Salmonella typhimurium	TA100	ames test	H_2O_2 doses: 0.5, 1.0, 1.5, 3.0, 4.5 or 7.5 μM/plate	*	NT	Winquist et al. (1985)
Salmonella typhimurium	TA102	ames test - plate incorporation assay	H_2O_2 doses: 0, 50, 75, 100, 150, 175, 200 or 300 μg/plate	+	NT	Wilcox et al. (1990)
Salmonella typhimurium	TA102 TA2638	ames test	H_2O_2 dose: 100 μg/plate	+ TA102 + TA2638	NT	Levin et al. (1982)
Salmonella typhimurium	TA98 TA100 TA1535 TA1537 TA1538	ames test	H_2O_2 doses 1.0-3333.3 μg/plate (-S9 & +S9)	- TA98 + TA100 - TA1535 - TA1537 - TA1538	- TA98 + TA100 - TA1535 - TA1537 - TA1538	SRI International (1980)

Table F.1 continued overleaf

Table F.1 continued Mutagenicity (gene mutation assays (*in vitro*), bacteria and yeasts)

Species	Strain	Measured endpoint	Test conditions	Results without activation	Results with activation	Ref.
Salmonella typhimurium	TA98 TA100	ames test	H_2O_2 concentration not given, with or without Cu^{2+} (10^{-5} M)	* TA98 * TA100	NT	Stich et al. (1978)
Escherichia coli	WP2 (uvrA)	ames test	H_2O_2 doses 1.0-3333.3 μg/plate (-S9 & +S9)	-	-	SRI International (1980)
Escherichia coli	WP2 uvrA (pKM101) WP2 (pKM101)	*Escherichia coli* reverse mutation	H_2O_2 doses: 0, 50, 75, 100, 150, 175, 200 or 300 μg/plate	+	NT	Wilcox et al. (1990)
Escherichia coli	K12 (katG, katE, katF)	bacterial forward mutation assay (catalase deficient strains) - L-arabinose resistance	H_2O_2 dose levels up to 900 nM/plate	+	NT	Abril and Pueyo (1990)
Escherichia coli	DB2	bacterial forward mutation assay - ampicillin-resistance, preincubation	H_2O_2 concentrations: 0, 20/24, 40, 60 or 80 μg/ml	+	NT	Bosworth et al. (1987)
Escherichia coli	WP2	*Escherichia coli* reverse mutation	H_2O_2 doses (-S9): 0.033 - 3.3 mg/plate doses (+S9): 0.0010 - 30 mg/plate	-	-	Prival et al. (1991)
Bacillus subtilis		bacterial forward mutation - multigene sporulation test	H_2O_2 concentrations: 0.0005, 0.001, 0.002 or 0.003%	+	NT	Sacks and MacGregor (1982)
Saccharomyces cerevisiae	ade2 (induction of respiratory deficient mutations)	Yeast gene mutation	H_2O_2 concentration: 2 mg/ml	*	NT	Thacker and Parker (1976)

Table F.2 Mutagenicity (genetic toxicity (*in vitro*), beacterial DNA damage and repair)

Species	Strain	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
Salmonella typhimurium	TA1535/pSK1002	DNA damage and repair	H_2O_2 concentration: 45 µg/ml	+	NT	Nakamura et al. (1987)
Escherichia coli	PQ37	DNA damage and repair assay (SOS chromotest)	H_2O_2 concentrations: 0, 5, 10, 20, 50, 100, 200 or 500 µM	+	NT	Zhou et al. (1991)
Escherichia coli	WP2 WP67 CM871	DNA damage and repair	H_2O_2 concentrations: no data	+ WP2 + WP67 + CM871	+ WP2 + WP67 + CM871	De Flora et al. (1984)
Escherichia coli	WP2	DNA damage and repair - lambda prophage induction	H_2O_2 doses: 0.78 - 100 µg/well	+	NT	Rosman et al. (1991)
Escherichia coli	PQ37	DNA damage and repair (SOS chromotest)	H_2O_2 concentrations: 0, 0.1, 0.3 or 1.0 mM	+	NT	von der Hude et al. (1988)

Table F.3 Mutagenicity (mammalian cell gene mutation assays (*in vitro*))

Species	Strain /cells	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
Chinese hamster	CHO cells clone K1-BH4, transformat AS52	HGPRT (GPT assay)	H_2O_2 concentrations: 0, 0.2 or 0.4 µM	+	NT	Hsie et al. (1993)
Chinese hamster	V-79 cells	HGPRT	H_2O_2 concentrations: 10, 20, 30 or 40 µM	+	NT	Nassi-Calò et al. (1989)
Chinese hamster	V-79 cells, CHO cells	HGPRT	H_2O_2 concentrations: 0, 10, 20, 40, 60 or 80 µM	*	NT	Speit (1986)
Chinese hamster	V-79 cells	HGPRT	H_2O_2 concentrations: 27.5-585 µM	-	NT	Bradley and Erickson (1981)
Murine leukaemic lymphoblasts	L5178Y-S (LY-S) L5178 (LY-R)	HGPRT	H_2O_2 concentrations: 03 - 5.0 µM	+	NT	Kruzewski Szumiel (1993)
Chinese hamster	V-79 cells	mammalian cell gene mutation - (6-thioguanine resistance)	H_2O_2 concentrations: 353 µM	-	NT	Bradley et al. (1979)
Chinese hamster	V-79 CHC	mammalian cell gene mutation - (8-azaguanine and ouabain resistance)	H_2O_2 concentrations: 0, 0.1, 0.2, 0.3, 0.5 or 1.0 mM	-	NT	Tsuda (1981)
Chinese hamster	V-79 cells	mammalian cell gene mutation - (6-thioguanine resistance (Tg^r clones)	H_2O_2 concentrations: 0.5 - 4.0 mM	+	NT	Ziegler-Skylakakis and Andrae (1987)
African green monkey	kidney cells (CV-1)	mammalian cell gene mutation - (supF locus of the pZ189 plasmid mutations)	H_2O_2 concentrations: 0.5 - 10 mM	+	NT	Moraes et al. (1990)

Table F.3 continued overleaf

Table F.3 continued Mutagenicity (mammalian cell gene mutation assays (*in vitro*))

Species	Strain /cells	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
African green monkey	kidney cells (CV-1)	Mammalian cell gene mutation - (supF locus of the pZ189 plasmid mutations)	H_2O_2 concentrations: 0.5 - 10 mM	+	NT	Moraes et al. (1990)
Mouse	L5178Y lymphoma cells	TK-locus assay	H_2O_2 without S9: 0.0018 – 0.1 μg/ml (15 dose levels) with S9: 2.3 – 30 μg/ml (10 dose levels)	+	-	Procter & Gamble (1986)
Mouse	L5178Y lymphoma cells	TK-locus forward mutation	H_2O_2 concentrations: 18.6, 37.2, 79.5, 199.0 or 496 μM	+	NT	Wangenheim and Bolcsfoldi (1988)

Table F.4 Mutagenicity (genetic toxicity (*in vitro*), mammalian cell DNA damage and repair)

Species	Strain /cells	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
Chinese hamster	V79, lung fibroblasts	DNA damage and repair degradation of cccDNA	H_2O_2 concentrations: 5 µl of 2M H_2O_2	+	NT	Tachon and Giacomoni (1989)
Chinese hamster	V-79 cells	DNA damage and repair	H_2O_2 concentrations: 353 µM	+	NT	Bradley et al. (1979)
Chinese hamster	V79-379A cells	DNA damage and repair - DNA single- and double-strand breaks	H_2O_2 concentrations: 10–1,000 µM	+	NT	Prise et al. (1989)
Chinese hamster	V79 fibroblasts	DNA damage and repair	H_2O_2 concentrations: 200 or 300 µM	+	NT	Mello Filho and Meneghini (1984)
Mouse	lymphoma cells (L5178/TK+/-)	DNA damage and repair - DNA single- and double-strand breaks	H_2O_2 concentrations: 0, 200, 218, 233 or 251 µM	+	NT	Garberg et al. (1988)
Mouse	mouse-mouse hybridoma cell line HyHEL-10	DNA damage and repair	H_2O_2 concentrations: 0, 5, 15 or 40 µM	+	NT	Cacciuttolo et al. (1993)
Murine	$P388D_1$ murine macrophages	DNA damage and repair	H_2O_2 concentrations: 0–1,000 µM	+	NT	Schraufstatter et al. (1986)
Rat	hepatocytes	DNA damage and repair	H_2O_2 concentrations: 100–100,000 µM	+	NT	Beales and Suter (1989)
Rat	hepatocytes	DNA damage and repair - (DNA single- and double-strand breaks)	H_2O_2 concentrations: 0, 10, 50, 100, 200, 500 or 1,000 µM	*	NT	Olson (1988)

Table F.4 continued overleaf

Table F.4 continued Mutagenicity (genetic toxicity (*in vitro*), mammalian cell DNA damage and repair)

Species	Strain /cells	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
Bovine	lens epithelial cells	DNA damage and repair - DNA single- strand breaks (alkaline and neutral filter elution)	H_2O_2 concentrations: 10-200 µM	*	NT	Kleiman et al. (1990)
Human	mono-nuclear leucocytes	DNA damage and repair - DNA single-strand breaks (nucleoid sedimentation technique)	H_2O_2 concentrations: 12-100 µM	+	NT	Van Rensburg et al. (1992)
Human	diploid fetal lung cells (WI-38 CCL75)	DNA damage and repair	H_2O_2 concentrations: 0, 0.15, 0.6, 2.3, 9.4, 37.5, 150 or 600 µg/ml	+	NT	Coppinger et al. (1983)
Human	peripherial lymphocytes	DNA damage and repair	H_2O_2 concentrations: 0-1,000 µM	+	NT	Schraufstatter et al. (1986)
Human	fibroblasts (strain N1)	DNA damage and repair	H_2O_2, % not given concentrations: 28-300 µM	+	NT	Mello Filho and Meneghini (1984)
Human	SV40 transformed fibroblast cell line (VA13)	DNA damage and repair	H_2O_2 concentration: 2.8 µm	+	NT	Mello Filho and Meneghini (1984)

Table F.5 Mutagenicity (genetic toxicity (*in vitro),* mammalian cell unsceduled DNA synthesis)

Species	Strain /cells	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
Rat	hepatocytes	unscheduled DNA synthesis	H_2O_2 concentrations: 1,900-3,200 µM	+	NT	Cattley and Smith-Oliver (1988)
Rat	hepatocytes	unscheduled DNA synthesis	H_2O_2 concentrations: first experiment : 0, 10, 30, 100, 300, 1,000 or 3,000 µg/ml Repeat experiment: 0.78125, 1.5625, 3.125, 6.25, 12.5, 25, 50 or 100 µg/ml	 - +	 NT NT	CEFIC (1997b)
Human	diploid fetal lung cells (WI-38 CCL75)	Unscheduled DNA synthesis	H_2O_2 concentrations: 0, 0.6, 2.4, 9.0, 36, 150, 600 or 2400 µg/ml	+	NT	Coppinger et al. (1983)

Table F.6 Mutagenicity (genetic toxicity (*in vitro*), sister chromatid exchange)

Species	Strain /cells	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
Chinese hamster	V-79 cells, CHO cells	SCE	H_2O_2 concentrations: 0, 10, 20, 40, 60 or 80 µM	+	NT	Speit et al. (1982)
Chinese hamster	V-79	SCE	H_2O_2 concentrations: 10-20 µM	+	NT	Tachon (1990)
Chinese hamster	CHO	SCE	H_2O_2 concentrations: 0.31-130 µM (24h exp) 5-100 µM (3h exp)	+	NT	MacRae and Stich (1979)
Chinese hamster	CHO-AUXB1	SCE	H_2O_2 concentrations: 0, 40, 80, 120, 160, 200 or 240 µM	+	NT	Tucker et al. (1989)
Chinese hamster	V-79	SCE	H_2O_2 concentrations: 353 µM	+	NT	Bradley et al. (1979)
Chinese hamster	V79 cells CHO cells	SCE	H_2O_2 concentrations: 0, 10, 20 or 40 µM	+	- (V79) * (CHO)	Mehnert et al. (1984a)
Chinese hamster	CHO (Don-6)	SCE	H_2O_2 concentrations: 0, 0.5, 1 or 2 mM (0, 0.017, 0.034 or 0.068 mg/ml)	+	NT	Sasaki et al. (1980)
Chinese hamster	CHO	SCE	H_2O_2 concentrations: 0.5, 1, 10 or 100 mM	+[1)]	NT	Wilmer and Natarajan (1981)
Human	D98/AH2 cells (a HeLa variant)	SCE	H_2O_2 concentration added or generated as a photoproduct: 1.3 - 2 µg/ml	+	NT	Estervig and Wang (1984)
Human	WBC (whole blood culture, PLC (purified lymphocyte culture)	SCE	H_2O_2 concentrations: 20-2000 µM	- WBC + PLC	- WBC + PLC (reduced)	Mehnert et al. (1984b)

Table F.7 Mutagenicity (genetic toxicity (*in vitro*), cytogenetic assays)

Species	Strain /cells	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
Chinese hamster	CHL (R-8) parental cells	chromosomal aberrations	H_2O_2 concentrations: 56 µg/ml (R-8), 6 µg/ml (parental)	+	NT	Sawada et al. (1988)
Chinese hamster	CHO	chromosomal aberrations	H_2O_2 concentrations: not given	+	NT	Stich et al. (1978)
Chinese hamster	CHO	chromosomal aberrations	H_2O_2, % not given concentrations: without S9: 25.31, 33.75 or 45.00 nl/ml with S9: 10, 50 or 100 µl/ml	+	+	Procter & Gamble (1985)
Chinese hamster	fibroblasts	chromosomal aberrations	H_2O_2 concentrations: 0.25 mg/ml	+	NT	Ishidate et al. (1984)
Chinese hamster	CHO	choromosomal aberrations (CA) chromatid translocations (CT) micronuclei (M)	H_2O_2 concentrations: 0-25 µmol	+ CA + CT + M	NT	Stich and Dunn (1986)
Chinese hamster Syrian hamster Mouse	CHO-K1 V-79 and CHC cells BALB/c newborn mouse back skin cells	chromosomal aberrations	H_2O_2 concentrations: 0, 0.1, 0.2, 0.3, 0.5 or 1.0 mM	+	NT	Tsuda (1981)
Mouse (C57BL/6J)	splenocytes	micronucleus	H_2O_2 concentrations: 0, 10 or 20 µM	*	NT	Dreosti et al. (1990)

Table F.7 continued overleaf

Table F.7 continued Mutagenicity (genetic toxicity (*in vitro*), cytogenetic assays)

Species	Strain /cells	Measured endpoint	Test conditions	Results without activation	Results with activation	Reference
Chinese hamster	V79 cells	micronucleus	H_2O_2 concentrations: 10–20 μM	+	NT	Tachon (1990)
Human	D98/AH2 cells (variant of HeLa)	chromosome aberrations	H_2O_2 0–3 μg/ml	- (H_2O_2 only) + (H_2O_2 generated as a photoproduct)	NT	Estervig and Wang (1984)
Human	embryonic fibroblasts	chromosomal aberrations	H_2O_2 concentrations: 10-1,000 μM	+	NT	Oya et al. (1986)

Table F.8 Mutagenicity (genetic toxicity (*in vivo)*)

Species and strain	Type of study Measured endpoint	Exposure data Test conditions	Result	Remark	Reference
Mouse Swiss HIM/OG1	Host mediated assay with intraperitoneally inoculated *Salmonella typhimurium* strains TA1530, G46	dosing: 0.003, 0.3 or 3.0% H_2O_2 in milk for one week. 0.5 ml 0.3% H_2O_2 twice by gavage with a 2 h interval	- H_2O_2 in milk + pure H_2O_2	a strong positive response for TA1530, a weak one for G46.	Keck et al. (1980)
Mouse inbread strain AB Jena Gat.	cytogenetic assay with intraperitoneally inoculated tumour cells (S2 sarcoma, Ehrlich ascites, sarcoma 180)	dosing: 1 ml of 0.01, 0.05, 0.1 or 0.5 M H_2O_2 i.p. 48 h after the implantation of the tumour cells. chromosomes were studied 48 h after the treatment.	increased chromatid aberrations	local effect; response presumed to depend on the presence or absence of RBCs.	Schöneich (1967)
Rat Wistar, male	*In vivo - in vitro* hepatocyte unscheduled DNA synthesis (UDS)	H_2O_2 dosing: 0, 25 or 50 mg/kg by intravenous infusion of 0%, 0.1% or 0.2% water solution at a rate of 0.2 ml/min during approximately 30 min (=MTD)	negative	exposure duration limited to 30 min.	CEFIC (1997b)
Mouse Swiss HIM/OF1	micronucleus assay of bone marrow polychromatic erythrocytes	dosing: 0.003, 0.3 or 3.0% H_2O_2 in milk for 32 h (apparently also in water, % not given)	negative	oral route, reporting unclear and incomplete.	Keck et al. (1980)
Mouse strain unkown	micronucleus assay of bone marrow polychromatic erythrocytes	single intraperitoneal injection of ½, 1/5, 1/25 or 1/100 LD_{50} dose of H_2O_2	negative	no experimental details given	Liarskii et al. (1983)
Mouse C57BL/6NCr1BR	micronucleus assay of bone marrow polychromatic erythrocytes	H_2O_2 in drinking water at 0, 200, 1,000, 3,000 or 6,000 ppm for 2 weeks. Doses males: 0, 42.4, 164, 415 or 536 mg/kg bw/day; females: 0, 48.5, 198, 485 or 774 mg/kg bw/day.	negative, P/N ratio was not changed	oral route	Du Pont (1995)
Mouse Swiss OF1/ICO:OF1 (IOPS Caw)	micronucleus assay of bone marrow polychromatic erythrocytes	dosing: 0, 250, 500 or 1,000 mg/kg i.p. (25 ml/kg: 0, 1, 2 or 4% H_2O_2, respectively) Time of harvest 24 or 48 h	negative, P/N was lower at 24 h, and at 48 h in the 250 and 1,000 mg/kg groups	Single i.p. injection	CEFIC (1995b)
Drosophila melanogaster	drosophila SLRL test	single dose of 3% H_2O_2 injected into male larvae	negative		Di Paolo (1952)

Table F.8 continued overleaf

Table F.8 continued Mutagenicity (genetic toxicity (*in vivo)*)

Species Strain sex	Type of study measured endpoint	Test conditions	Result	Remark	Reference
Mouse Sencar Female	pre-screen for carcinogenicity in target tissue (mouse skin) quantity of 8-OH-2'-deoxyguanosine (DNA damage) mutations in codon 61 of c-Ha-ras gene epidermal hyperplasia and dermal cellularity changes	hydrogen peroxide 70% was applied to the skin of 10 female Sencar mice per dose group at dose levels of 10, 100, or 200 μmol in 200 μl of ethanol (i.e. 0.2-3.2% solutions) twice weekly for 4 weeks. Mice treated under the same conditions with DMBA (10 or 100 μmol/animal) or ethanol (200 μl) acted as positive and negative controls, respectively. The animals wer killed on days 2 or 4 after the last administration (5 mice on each day). The application sites were removed and after fixation and staining, epithelial and dermal thickness and dermal cellularity were determined visually by light microscopy. Non-phenol extraction of fresh frozen tissue was used to isolate DNA from animals killed 2 days after last dosing, and following digestion to nucleosides, 8-OH-2'-deoxyguanosine (8-OH-dG) was quantified by HPLC. mutations in codon 61 of c-Ha-ras gene were determined using DNA isolated from paraffin blocks of whole skin.	negative for all enpoints	at the relatively low concentrations used hydrogen peroxide did not induce local in vivo genotoxicity and mutagenicity in the skin.	Society for Plastic Industry (1997)

\+ positive result
\- negative result
* ambiguous result
+[1)] weak positive result
NT not tested

Appendix G Carcinogenicity studies

Table G.1 Carcinogenicity (oral drinking water studies)

Species Strain Sex	Group size	Exposure	Organ with excess tumours type of tumour	Lowest effective dose for significant increase in tumours	Remark	Reference
Mouse C57BL Male/female	50	oral, drinking water 0, 0.1 or 0.4% H_2O_2 100 weeks	localised duodenal carcinomas: in high dose group 5%, in low dose group 1% and none among controls ($p<0.05$)	0.1% H_2O_2	occurrence of tumours in tissues other than stomach and duodenum was unremarkable.The incidence of erosions and ulcer in the glandular stomach increased dose dependently [high dose 42%, low dose 20%, control 4% ($p<0.005$)], as did the incidence of duodenal hyperplasia [high dose 62%, low dose 40%, control 9%] ($p<0.005$).	Ito et al. (1981a) Ito et al. (1981b)
Mouse C57BL DBA/2N BALB/cAnN Male/female	variable, 2-29	oral, drinking water 0, 0.1% or 0.4% H_2O_2 30-740 days (up to 105 weeks)	among C57BL mice given 0.4% or 0.1% H_2O_2 for 420 days to 740 days, 5 or 1%, respectively, had duodenal carcinomas by histological criteria though they did not show any distant metastases. In the control group, no duodenal cancer was noted in the same observation period. the average number of lesions per mouse were higher in C57BL mice then in DBA or BALB mice.	0.1% H_2O_2	only stomach and duodenum were studied. In C57BL mice, gastric lesions in the forestomach occurred in over 67% of the mice treated with H_2O_2 for 120 days and duodenal lesions were observed in over 80% of the mice that received H_2O_2 for 60 days. After the cessation of H_2O_2 for 10-30 days the frequency and number of lesions mostly decreased and even disappeared.	Ito et al. (1982)
Mouse C3H C57BL B6C3F1 C3H/C Male/female	 18 22 21 24	oral, drinking water 0.4% H_2O_2 6 months	Incidence of duodenal tumours (hyper-plasia or neoplasia) and the mean number of tumours per mouse were: 11.1% and 0.11 in C3H mice; 31.8% and 0.36 in B6C3F1 mice; 100% and 3.91 in C57BL mice; 91.7% and 2.63 in C3H/C mice	0.4% H_2O_2	a strong negative correlation was found between the incidence of duodenal tumours and catalase activities in duodenal mucosa, blood and liver among the different strains of mice.	Ito et al. (1984)

Table G.1 continued overleaf

Table G.1 continued Carcinogenicity (oral drinking water studies)

Species Strain Sex	Group size	Exposure	Organ with excess tumours type of tumour	Lowest effective dose for significant increase in tumours	Remark	Reference
Rat F344	50	oral, drinking water 0, 0.3 or 0.6% H_2O_2 males: 0, 195 or 433 mg/kg bw/d females: 0, 306 or 677 mg/kg bw/d 18 months, followed by 6 months of observation period			during treatment the animals had lower weight gains than the controls; the treated groups started gaining weight again in the follow up period. The 18 month survival rate was 97%, and there was no significant difference between the dose groups. no significant differences were found among the groups in the spectrum of tumour bearing organs, incidence of tumours or the tumour developing stage. Almost all male rats had tumours, notably Leydig cell tumours and endocrine tumours. Compared to historical F344 controls, the present controls had a higher incidence of tumours, partly because of the long study period; no difference was noted in tumour bearing organs. umours of the gastrointestinal tract were not found at all. The study appears to be a carefully conducted, appropriate carcinogenicity study but the available reporting is incomplete.	Takayama (1980)

Table G.2 Carcinogenicity (tumour promotion studies, oral drinking water)

Species Strain Sex	Group size	Exposure	Organ with excess tumours type of tumour	Lowest effective dose for significant increase in tumours	Remark	Reference
Rat Fischer 344 Male	8 combined treatment 3 H_2O_2 alone	oral, daily drinking water 1.5% H_2O_2 10 or 21 weeks with or without MAM (methylazoxy-methanol acetate) (three i.p. injections every other week)	rats given H_2O_2 four weeks prior to MAM injections, during intervals between injections, and until the termination of the study showed higher incidences of duodenal (8/8) and jejunal (5/8) carcinomas as compared to rats not given H_2O_2 subsequent to MAM injections (2/8 and 2/8, respectively).	1.5% H_2O_2 (for promotion)	a tumour promotion study with MAM (an intestinal carcinogen in rats via i.v. injection). only gross tumours of the g-i tract were reported. the three rats given H_2O_2 alone throughout the study period did not develop carcinomas in the duodenum or upper jejunum.	Hirota and Yokoyama (1981)
Rat Wistar Male	21 or 10	oral drinking water 32 weeks (a) 4 groups of 21 rats were given 1% H_2O_2 for 32 weeks subsequent to initiation by MNNG (N-methyl-N'-nitro-N-nitrosoguanidine) in drinking water and a diet supplemented with 10% sodium chloride over 8 weeks (b) 5 groups of 10 rats were given 1% H_2O_2 for 32 weeks (without initiation)	duodenal adenocarcinoma was induced by the initiation with MNNG (10% of animals), but it was not affected by subsequent H_2O_2.		only gastroduodenal tumours were reported. hydrogen peroxide did not enhance the tumour development in the glandular stomach, although adenomatous hyperplasia in the fundic region was frequent (38% of animals). In the forestomach, the incidence of squamous cell papillomas was significantly increased irrespective of prior initiation.	Takahashi et al. (1986)

Table G.3 Carcinogenicity (tumour promotion studies, oral cavity)

Species Strain Sex	Group size	Exposure	Organ with excess tumours type of tumour	Lowest effective dose for significant increase in tumours	Remark	Reference
Hamster Syrian golden Male	5-11	groups of 5 - 11 hamsters in a group were painted on the left buccal pouches twice weekly with DMBA (9,10-dimethyl-1,2-bentzanthracene) (0.25% solution in heavy mineral oil), and (a) with 3% hydrogen peroxide on two other days each week, or (b) with 30% hydrogen peroxide. 9 hamsters were painted on the left buccal mucosa twice weekly only with 30% hydrogen peroxide.	DMBA treatment alone caused an incidence of 43% (3/7) epidermoid carcinomas, while 55% (6/11) of animals treated with DMBA plus 3% H_2O_2 and 100% (5/5) of animals treated with DMBA plus 30% H_2O_2 developed carcinomas. in animals treated with 30% H_2O_2 alone, histopathological examination after 22 weeks revealed hyperkeratosis and hyperplasia in all animals with hyperchromatic cells and mild dysplasia in 4/9 animals; no tumours were found.	see remarks	only tumours at the application site were studied. although the size of the study is limited the promoting effect seems clear. Concentrations but not volumes of H_2O_2 applied are given. the hamster cheek pouch was used as a model for human oral carcinogenesis.	Weitzman et al. (1986)
Syrian hamster Male/female		application to cheek pouch (a): 20 weeks; 5 times per week; (b) 16 weeks; 3 times per week with DMBA, 5 times per week with H_2O_2 solutions a) 0.5% DMBA (0.1 ml); 0.75% H_2O_2 / 5% $NaHCO_3$ in dual phase dentifrice (0.2 ml) alone or in combination b) 0.5% or 0.25% DMBA (0.1 ml); 1.5% H_2O_2 / 7.5% $NaHCO_3$ in dual-phase dentifrice (0.2 ml), DMBA alone and in combination with H_2O_2 releasing preparation; 0.25% DMBA + 3% H_2O_2 / $NaHCO_3$ (0.1 ml + 0.2 ml)			hydrogen peroxide alone was not studied. Combination of substances may result in chemical interactions, e.g. the dual-phase dentifrice used may reduce hydroxyl radical formation. a): H_2O_2 releasing dual-phase dentifrice was not carcinogenic, and in combination with DMBA resulted in no observed acceleration of tumour onset, compared with DMBA alone b): With 0.5% DMBA (but not 0.25% DMBA) combined with H_2O_2 releasing dual-phase dentifrice the latency period for tumour formation increased, compared to DMBA alone. Animals receiving 0.25% DMBA and 3% H_2O_2 / $NaHCO_3$ had a significantly lower rate of tumour formation and overall mass incidence.	Marshall et al. (1996)

Table G.4 Carcinogenicity (carcinogenicity and tumour promotion studies, skin)

Species Strain Sex	Group size	Exposure	Organ with excess tumours type of tumour	Lowest effective dose for significant increase in tumours	Remark	Ref.
Mouse Sencar Female	60	dermal 25 week, 50 weeks for a complete carcinogenicity study mice were treated on the dorsal skin with: (a) DMBA (9,10-dimethyl-1,2-bentzanthracene) followed by 0.2 ml of 30% H_2O_2, or H_2O_2 (30%) and acetone 1:1, or H_2O_2 and acetone 1:2, or H_2O_2 and acetone 1:5, once or twice weekly (b) one dose of H_2O_2 (30%) and acetone 1:1 followed by TPA promotion (c) H_2O_2 (30%) and acetone 1:1 twice weekly	H_2O_2 was ineffective as an initiator or as a complete carcinogen but it functioned as "an extremely weak" promoter	see remark.	only treated skin was studied. the authors speculated that repetitive treatments with concentrated H_2O_2 solutions possibly were too toxic to permit the survival of a large population of initiated cells, whereas the low concentration solutions possibly were too weak to unfold the necessary proliferative reactions which accompany tumour promotion.	Klein-Szanto and Slaga (1982)
Mouse ICR Swiss Female	30	dermal 0.2 ml 3% H_2O_2 (after DMBA initiation) 5 applications per week 56 weeks	no tumours		only treated skin studied	Bock et al. (1975)
Mouse Sencar Female	20	dermal 51 weeks mice were treated on the dorsal skin with (a) DMBA (9,10-di-methyl-1,2-bentz-anthracene) followed by 0.2 ml of 5% H_2O_2 in acetone twice weekly or(b) 0.2 ml of 5% H_2O_2 in acetone twice weekly			hydrogen peroxide (5%) showed neither promoting nor complete carcinogenic activity locally in the skin. epidermal hyperplasia was observed in 45% of the mice treated with H_2O_2 in the promotion test, but only in 5% of the H_2O_2 treated mice in the complete skin carcinogenicity study.	Kurokawa et al. (1984)

Appendix H Product register data

Use categories of products containing hydrogen peroxide in Sweden.

In the table below, the uses and functions of the products containing hydrogen peroxide according to the Swedish product register are presented. The total amount of products is 77. Some of these products could cause exposure to consumers.

Uses/functions (More than 3 products/function)	Tonnage/year	
Bleaching agents, mostly pulp bleaching	20 544	also consumer products
Hardeners for paints	0	
Hardeners of plastics	16-47	also consumer products
Laboratory chemicals	985-986	
Metal surface treatment agents	1	
Pickling agents (metals)	511	
Oxidising agents	943	
Process regulators	920	
Cleaning agents	15	also consumer products
Disinfectants	1043- 044	also consumer products

Uses/functions (Less than 3 products/functions, tonnage's of these products are confidential)

Motor fuels
Emulsifiers
Corrosion inhibitors
Catalysts
Detergents and cleaning agents additives
Carbonisation agents
Diluents (paints etc.)
Intermediates, (raw materials and plastic manufacture)

Appendix I SCIES estimation

The SCIES (Screening Consumer Inhalation Exposure Software) provided by the US EPA was used to estimate the concentration of hydrogen peroxide in the breathing zone of customers in hair salons. The products of interest contain 1.75-12% of H_2O_2. The input data are based on recent studies carried out in a representative sample (20) of hair salons in Helsinki by Leino et al. (in press).

The partial vapour pressure of hydrogen peroxide in 10% water solution at 22°C (11 Pa) was extrapolated from the plot of the vapour pressures of products with higher weight fractions (35% -90%, vapour pressures 48 and 333 Pa, respectively).

Taking into account that much of the hydrogen peroxide will react in hair quickly and will not cause inhalation exposure, it was assumed that 50% of hydrogen peroxide in the product will actually generate vapour during the treatment

Concentration of hydrogen peroxide in hair salons during bleaching or dyeing; estimated using the SCIES model on two scenarios

Normal use	Worst case	
Input data		
Amount of product used	40 g (· 0.5)	80 g (· 0.5)
Room volume of the salon	200 m3	40 m3
Air exchange rate (/hour)	3	1
Weight percentage of H_2O_2 in the product	5%	10%
Results		
Concentration in the zone of release (mg/m3)		
During use	0.008	0.2
After use	0	0.015
Concentration in zone 2		
During use	0.001	0.007
After use	0	0.008

Appendix J Concentration limits of hydrogen peroxide from various legislation

Table J.1 Concentration limits of hydrogen peroxide from various legislation (November 1999)

Use or source	Concentration limit
Hair care preparations*	12% (40. vol) present or released
Skin-care products*	4% present or released
Nail hardening preparations*	2% present or released
Oral hygiene products*	0.1% present or released
Food packaging materials**	No detectable amounts in hotwater extract
Drinking water***	0,1 mg/l (Germany) and 0,5 mg/l (France) (residual conc.)

* Council Directive 76/768/EEC of July 1976 on the approximation of the laws of the Member States relating to cosmetic products
** National legislation in Finland (and in some other EU countries) (EU-legislation on H_2O_2 in food packaging materials does not exist)
*** National legislation in Germany and France

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Environment and quality of life series

The report provides the comprehensive risk assessment of the substance hydrogen peroxide. It has been prepared by Finland 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 humans 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 environmental risk assessment for hydrogen peroxide concludes that there is concern for the aquatic ecosystem arising from four production sites and use in manufacture of other chemicals. There is no concern for the atmosphere, the terrestrial ecosystem and microorganisms in the sewage treatment plant.

The human health risk assessment for hydrogen peroxide concludes that there is concern for workers and consumers while no concern was identified for humans exposed via the environment.

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) N. 793/93.

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