Environmental Health Criteria 56

PROPYLENE OXIDE

Published under the joint sponsorship of
the United Nations Environment Programme,
the International Labour Organisation,
and the World Health Organization

World Health Organization
Geneva, 1985

The International Programme on Chemical Safety (IPCS) is a joint venture the United Nations Environment Programme, the International Labour Organis tion, and the World Health Organization. The main objective of the IPCS is carry out and disseminate evaluations of the effects of chemicals on human hea and the quality of the environment. Supporting activities include the developm of epidemiological, experimental laboratory, and risk-assessment methods that cou produce internationally comparable results, and the development of manpower i the field of toxicology. Other activities carried out by IPCS include the develo ment of know-how for coping with chemical accidents, coordination of laborato testing and epidemiological studies, and promotion of research on the mechanis of the biological action of chemicals.

ISBN 92 4 154196 2

PRINTED IN FINLAND
Vammalan Kirjapaino Oy
85/6655 — VAMMALA — 5800

CONTENTS

Page

WHO TASK GROUP ON PROPYLENE OXIDE

Members

Dr R. Bruce, Environmental and Criteria Assessment Office, US Environmental Protection Agency, Research Triangle Park, North Carolin, USA (Rapporteur)

Mr T.P. Bwititi, Hazardous Substances and Articles Department, Ministry of Health, Harare, Zimbabwe

Dr B. Gilbert, CODETEC, University City, Campinas, Brazil

Prof P. Grasso, Robens Institute, University of Surrey, Guildford, Surrey, United Kingdom

Prof M. Ikeda, Department of Environmental Health, Tohoku University School of Medicine, Sendai, Japan (Chairman)

Dr T. Lewis, US National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA

Dr B. Malek, Prague Hygiene Station, Department of Industrial Hygiene, Prague, Czechoslovakia

Prof N.C. Nayak, Department of Pathology, All-India Institute of Medical Sciences, New Delhi, India

Prof M. Noweir, Occupational Health Research Centre, High Institute of Public Health, Alexandria, Egypt (Vice-Chairman)

Dr G.J. Van Esch, Bilthoven, The Netherlands

Members of Other Organizations

Dr A. Berlin, Health and Safety Directorate, Commission of the European Communities, Luxembourg

Dr R. Steger, International Commission on Occupational Health, Geneva, Switzerland

Mme M.Th. Van der Venne, Health and Safety Directorate, Commission of the European Communities, Luxembourg

Observers

Dr E. Longstaff (European Chemical Industry Ecology and Toxicology Centre), ICI Central Toxicology Laboratory, Genetic Toxicology Section, Macclesfield, United Kingdom

Dr M. Martens, Institute of Hygiene and Epidemiology, Division of Toxicology, Brussels, Belgium

Dr W. Moens, Institute of Hygiene and Epidemiology, Division of Toxicology, Brussels, Belgium

Dr M. Wooder (European Chemical Industry Ecology and Toxicology Centre), Shell International Petroleum Company, Health, Safety and Environment Division, London, United Kingdom

Secretariat

Prof F. Valić, Andrija Stampar School of Public Health, University of Zagreb, Zagreb, Yugoslavia (Secretary)[a]

Dr T. Vermeire, National Institute of Public Health and Environmental Hygiene, Bilthoven, The Netherlands (Temporary Adviser)

Mr J. Wilbourn, International Agency for Research on Cancer, Lyons, France

---

[a] IPCS Consultant.

PREFACE

Although only key references essential for the evaluation of the risks for human health and the environment are cited, this document is based on a comprehensive search of the available original scientific literature, while valuable information has also been obtained from various reviews.

A detailed data profile on propylene oxide can be obtained from the International Register of Potentially Toxic Chemicals (UNEP/IRPTC, Palais des Nations, CH-1211 Geneva 10, Switzerland, telephone number 988400 - 985850).

The document focuses on describing and evaluating the risks of propylene oxide for human health and the environment.

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors, which may have occurred, to the Manager, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

ENVIRONMENTAL HEALTH CRITERIA FOR PROPYLENE OXIDE

The WHO Task Group for the Environmental Health Criteria for Propylene Oxide met at the Institute of Hygiene and Epidemiology, in Brussels, Belgium, on 21-26 October 1985. Dr G. Thiers, who opened the meeting, welcomed the participants on behalf of the host government, and Dr F. Valic welcomed them on behalf of the heads of the three IPCS co-sponsoring organizations (ILO/WHO/UNEP). The Group reviewed and revised the second draft criteria document and made an evaluation of the health risks of exposure to propylene oxide.

The efforts of DR T. VERMEIRE, of the NATIONAL INSTITUTE OF PUBLIC HEALTH AND ENVIRONMENTAL HYGIENE, Bilthoven, the Netherlands, who was responsible for the preparation of the draft, and of all who helped in the preparation and the finalization of the document are gratefully acknowledged.

* * *

Partial financial support for the publication of this criteria document was kindly provided by the United States Department of Health and Human Services, through a contract from the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA - a WHO Collaborating Centre for Environmental Health Effects.

1. SUMMARY

Propylene oxide is a colourless, highly volatile, and flammable liquid at room temperature and normal atmospheric pressure. It is very reactive towards nucleophiles. The compound can be determined in air, by gas chromatography, with a detection limit of 0.06 μg/m³ and, in food, with a limit of 0.1 mg/kg. Detection limits of various other methods include 0.3 μg/litre in biological fluids and 30 mg/kg in synthetic materials.

World production of propylene oxide exceeds 2000 kilotonnes per year, most of which is used as a chemical intermediate. Small amounts are used for the sterilization of medical equipment and for the fumigation of foodstuffs. About 0.07% of all the propylene oxide used is lost to the atmosphere. The compound can be removed from the atmosphere by slow oxidation and by rain. It evaporates from water and is not expected to bioaccumulate. Aerobic biodegradation is slow.

The main route of human exposure is through inhalation at the work-place. No published data have been found on ambient levels away from point sources. Eight-hour time-weighted average occupational exposure levels are normally less than 5 mg/m³. However, peak exposures of up to 9010 mg/m³ have been recorded.

Analyses of fumigated foodstuffs revealed that the propylene oxide derivatives, chloropropanols and 1,2-propanediol, were present at levels ranging from 4 to 47 mg/kg and 29 to 2000 mg/kg, respectively. However, in pure lipids, where degradation is minimal, levels of propylene oxide of over 4000 mg/kg have been determined. Levels of up to 6260 mg/kg have been found in wrapping materials.

Available LC_{50} values for propylene oxide in various fish species range between 89 and 215 mg/litre for a 96-h exposure.

From *in vitro* studies, it would appear that propylene oxide is metabolized by glutathione epoxide transferase to S-(2-hydroxy-1-propyl)glutathione. It is converted to 1,2-propanediol by epoxide hydrolase and non-enzymic hydrolysis, but both of these reactions are slow. The diol can be oxidized to lactic and pyruvic acid.

The oral LD_{50} has been reported to be 630 mg/kg body weight for the mouse, 660 mg/kg for the guinea-pig, and from 520 to 1140 mg/kg for the rat. Damage to the stomach mucosa and liver was observed in rats exposed to such levels.

The 4-h LC_{50}s for the rat and the mouse via inhalation were 9500 and 4100 mg/m³, respectively. At these concentrations, there was severe eye and nose irritation, laboured breathing, and central nervous system depression.

With repeated exposure (6 h/day, 5 days/week, for 2 weeks) to propylene oxide concentrations ranging from 110 - 3400 mg/m^3 (rats) and 50 - 1150 mg/m^3 (mice), dyspnoea was observed in rats exposed to 3400 mg/m^3 and in mice exposed to 460 mg/m^3 and 1150 mg/m^3. Reduced activity was observed in both species, and irregular limb movement was seen in rats. After exposure to concentrations of propylene oxide of 240, 460, or 1080 mg/m^3 for 112 - 218 days (7 h/day, 5 days/week), monkeys and rabbits did not show any adverse effects, but irritation of the eyes and respiratory passages was observed in rats and guinea-pigs at 1080 mg/m^3. Internally, changes were found only in the lungs in both species and consisted of oedema and haemorrhage. In addition, an increase in lung weight was observed in female guinea-pigs exposed at 460 mg/m^3.

A dose-related increase in the incidence of inflammatory lesions and proliferative lesions in the nasal epithelium was observed in Fischer 344/N rats and B6C3F1 mice exposed to 470 or 940 mg/m^3, for 6 or 7 h per day, 5 days/week, for 2 years. Similar inflammatory lesions and hyperplasia were also observed at 240 mg/m^3 in another study on Wistar rats exposed for 6 h/day, 5 days per week, for 124 weeks. Non-neoplastic effects were not observed in the nasal mucosa or internal organs of rats exposed to 70 mg/m^3.

Axonal dystrophy was observed in the nucleus gracilis in cynomolgus monkeys, 2 per group, exposed to 237 and 717 mg propylene oxide/m^3 (7 h/day, 5 days/week) for 2 years. One of two untreated monkeys also showed such changes. The changes in the treated groups were more pronounced than those in the controls.

A dose-related increase in the incidence of squamous cell carcinoma of the forestomach was observed in rats treated by gavage for 112 weeks with 0, 15, or 60 mg propylene oxide/kg body weight dissolved in salad oil. The numbers of rats affected were 0 (controls), 2, and 19, respectively. When propylene oxide, dissolved in trycaprylin, was administered subcutaneously to mice, once a week, for 106 weeks, only local sarcomas were induced. The numbers of animals exhibiting sarcomas were 0/200 in untreated controls, 4/200 in tricaprylin controls, and 3/100, 2/100, 12/100, and 15/100 in mice treated with 0, 0.1, 0.3, 1.0, and 2.5 mg per injection, respectively.

The carcinogenicity of propylene oxide inhalation exposure has been investigated in rats and mice. Two studies have been conducted on Fischer 344 rats using groups of 80 - 100 animals, for 2 years. In one study, exposure was to concentrations of 470 and 940 mg/m^3, 6 h/day, for 5 days per week, over 103 weeks; in the second, exposure was to concentrations of 237 - 717 mg propylene oxide/m^3, for

7 h/day, 5 days/week, over 2 years. A few adenomas were observed in the nasal cavity in both studies at the highest level of treatment. When Wistar rats were treated with 70, 242, or 712 mg/m^3, 6 h/day, 5 days per week, for 124 weeks, no nasal tumours were reported, but a dose-related increase in the incidence of multiple mammary fibroadenoma was observed. There was no increased incidence of brain tumours.

In mice, malignant nasal tumours were induced. Groups of 50 B6C3F1 mice of each sex were exposed to 470 and 940 mg/m^3 propylene oxide, for 6 h/day, 5 days/week, over 103 weeks. Tumours in the nasal cavity occurred in both sexes. Haemangiosarcomas were observed in the nasal cavity of 5 male and 2 female mice at the higher concentration, and haemangiomas appeared in 5 males and 3 females at the same site. In addition, one squamous cell carcinoma and one papilloma appeared in high-dose males and 2 adenocarcinomas in high-dose females, at the same site. No treatment-related tumours were observed at the lower dose.

No teratogenic or fetotoxic effects were observed when pregnant New Zealand rabbits were exposed through inhalation to 1190 mg propylene oxide/m^3, for 7 h/day, during days 1 - 19 or days 7 - 19 of gestation. An increase in the number of resorptions was found when Sprague Dawley rats were exposed to 1190 mg propylene oxide/m^3, for 7 h/day, during days 7 - 16 of gestation. Some reduction in ossification in vertebrae and ribs and wavy ribs were found when pregnant Sprague Dawley rats were similarly exposed on days 1 - 16 of gestation. When rats were exposed for 3 weeks prior to mating and on days 1 - 16 of gestation, the numbers of corpora lutea, implantations per dam, and live fetuses were decreased compared with those in the other groups.

Propylene oxide is mutagenic to microorganisms and insects and produced mutations, DNA damage, and chromosomal effects in mammalian cells *in vitro*. Negative results in such studies have never been reported. *In vivo*, propylene oxide induced a 5-fold increase in micronuclei in mice, when given intraperitoneally (ip) at a concentration of 300 mg/kg body weight, but not at 150 or 75 mg/kg body weight, nor when administered orally. No dominant-lethal effects were observed, when propylene oxide was administered via inhalation to male rats at 720 mg/m^3 for 5 days prior to mating, or, when it was administered daily, by the oral route, to male mice at 50 or 250 mg/kg body weight for 2 weeks prior to mating. No increase in chromosome aberrations or sister chromatid exchanges in peripheral lymphocytes were observed in male Cynomolgus monkeys exposed to 237 or 717 mg propylene oxide/m^3 air, for 7 h/day, 5 days per week, for 2 years.

No sperm head abnormalities were detected in mice after exposure for 7 h/day, for 5 days, to 720 mg propylene

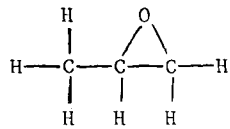
oxide/m^3 or in cynomolgus monkeys exposed to 240 or 710 mg/m^3 for 2 years.

There are no adequate epidemiological studies to assess the toxic effects of propylene oxide on man. Taking into account the body of available data - the alkylating nature of propylene oxide, the formation of DNA adducts, the positive responses in in vitro mutagenesis assays, the carcinogenic effects in animals at sites of entry into the body, and the absence of adequate data on cancer in human beings - propylene oxide should be considered as a possible human carcinogen. Therefore, propylene oxide should be regarded, for practical purposes, as presenting a carcinogenic risk for man, and levels in the environment should be kept as low as feasible.

2. PROPERTIES AND ANALYTICAL METHODS

2.1 Identity

Structural formula:



Molecular formula: C_3H_6O

Abbreviation: PO

Common synonyms: 1,2-epoxypropane, methyl ethylene oxide, methyl oxirane (IUPAC and CAS name), propene oxide, propylene epoxide, 1,2-propylene oxide

CAS registry number: 75-56-9

RTECS registry number: TZ2975000

2.2 Chemical and Physical Properties of Propylene Oxide

Propylene oxide is a colourless, highly volatile liquid at room temperature and normal atmospheric pressure. It is highly flammable. The vapour will form an explosive mixture with air. The substance may polymerize violently. Ring opening occurs in reactions with nucleophiles, such as water, alcohols, amines, halides, and sulfhydryl compounds. Propylene oxide is very reactive, particularly with chlorine, ammonia, strong oxidants, and acids. Some physical and chemical data on propylene oxide are given in Table 1.

Conversion factor: 1 ppm = 2.37 mg/m^3 air at 25 °C and 101.3 kPa (760 mm Hg)

2.3 Analytical Methods

A summary of methods for the sampling and determination of propylene oxide in air, water, food, synthetic materials (including, e.g., medical equipment), and biological media is presented in Table 2. However, the methods for the determination in water, synthetic materials, or biological media are not specific for propylene oxide.

It was proposed that, as for ethylene oxide (Ehrenberg et al., 1974; Osterman-Golkar et al., 1976, 1983), the determin-

Table 1. Some physical and chemical data on propylene oxide

physical state	liquid
colour	colourless
odour	ethereal
odour threshold	20 mg/m³ for perception and 80 - 470 mg/m³ for recognition[a]
relative molecular mass	58.08
melting point	-104 °C
boiling point	34 °C
water solubility	405 g/litre, 20 °C
log n-octanol-water partition coefficient	-0.13
density	0.83 g/ml, 20 °C
relative vapour density	2.0
vapour pressure	59 kPa (445 mm Hg), 20 °C
flash point	-37 °C (open-cup)
flammable limits	2 - 37% by volume in air

[a] From: Jacobson et al. (1956) and Hellman & Small (1974).

ation of the degree of alkylation of amino acids, and specifically histidine, in haemoglobin could be used for monitoring the tissue doses of propylene oxide. Assuming even distribution, dose is defined as the integral of the calculated concentration of free propylene oxide in the tissues over a specified period of time (Farmer et al., 1982; Svensson & Osterman-Golkar, 1984). Methods for the determination of N³-(2-hydroxypropyl)histidine in rat haemoglobin have been described using gas chromatography with mass spectrometry (Farmer et al., 1982) and high-performance liquid chromatography after derivatization with fluorescamine (Svensson & Osterman-Golkar, 1984). In rats, the alkylation of haemoglobin was found to increase linearly with the level of exposure to propylene oxide vapour, with a detection limit of 0.002 mg alkylated histidine/kg haemoglobin (Farmer et al., 1982). Human haemoglobin has a lifespan of about 4 months and, therefore, will integrate the dose of propylene oxide over a long period. The method was applied to samples from

Table 2. Sampling, preparation, analysis

Medium	Sampling method	Analytical method	Detection limit	Comments	Reference
Air	adsorption on Tenax-GC, thermal desorption, cryofocusing	gas chromatography with mass spectrometric detection	0.06 $\mu g/m^3$	suitable for analysis of ambient air	Krost et al. (1982)
Air (work-place)	adsorption on coconut charcoal, desorption by carbon disulfide	gas chromatography with flame ionization detection		recommended for the range 25 - 720 mg/m^3; suitable for personal and area sampling	NIOSH (1977)
Air	adsorption on Tenax or Porapak N, thermal desorption	gas chromatography with flame ionization detection	2 $\mu g/m^3$		Russell (1975)
Water		colorimetry using cadmium iodide after hydrolysis and reaction with periodate in the solvent system 1,2-dimethoxyethane-water	detection limit in the nmole range	the method is not specific	Mishmash & Meloan (1972)

Table 2 (contd).

Medium	Sampling method	Analytical method	Detection limit	Comments	Reference
Water		potentiometric titration using hydrochloric acid after reaction with sodium sulfite		the method is not specific	Swan (1954)
Food	extraction by 5:1 acetone-water by volume for 24 h	gas chromatography with beta-ionization detection	0.1 mg/kg wet weight	sample size 5 - 10 g	Heuser & Scudamore (1969)
Synthetic materials	distillation of samples in monochlorobenzene into glacial acetic acid	titration using hydrogen bromide in glacial acetic acid	30 mg/kg	sample size 2 g; the method is not specific	Gunther (1965)
Biological media (blood, urine)		fluorimetry employing alkylation of nicotinamide followed by a reaction with acetophenone to a fluorescent compound	0.3 mg/litre	sample size 0.1 ml; direct analysis; interference by other alkylating agents	Nelis & Sinsheimer (1981)

industrial workers by Osterman-Golkar et al. (1984). A low background level of alkylation was observed, which may limit the resolving power of detection at average exposures below 0.7 mg/m^3. More work is needed to establish the relationship between propylene oxide exposure and haemoglobin alkylation in human beings.

3. SOURCES IN THE ENVIRONMENT, ENVIRONMENTAL TRANSPORT AND DISTRIBUTION

3.1 Production, Uses, Disposal of Wastes

3.1.1 Production levels and processes

Propylene oxide is produced in the USA, western Europe, Japan, and several other countries. In the USA, production increased from 800 kilotonnes in 1974 to 1020 kilotonnes in 1979. However, production in 1983 was estimated to be 720 kilotonnes (Bogyo et al., 1980; Webber, 1984; IARC, 1985). In western Europe, 850 kilotonnes were produced in 1979 and 810 kilotonnes in 1982; in Japan, 130 kilotonnes were produced in 1974 and 190 kilotonnes in 1982 (IARC, 1976, 1985).

Propylene oxide can be produced by the chlorohydrin process or by peroxidation. In the first of these processes, 1-chloro-2-propanol and 2-chloro-1-propanol react with potassium hydroxide or calcium oxide to form propylene oxide. In the second process, propylene oxide is synthesized through a catalysed reaction between propene and tertiary butyl hydroperoxide. Tertiary butyl hydroperoxide is prepared by the oxidation of isobutane (WHO, 1978). Common impurities, that may be present in small amounts include water, acetic acid, chloride, and aldehydes. Small amounts of monochloroacetone, 1,2-dichloro-3-propanol, and propylene dichloride can occur in propylene oxide, produced by the chlorohydrin process (IARC, 1985).

3.1.2 Uses

Most propylene oxide produced is used as an intermediate in the production of various chemicals. In order of importance, in the USA, these chemicals are: polyether polyols for urethanes, propylene glycol, mainly for polyester fibres, polypropylene glycol, dipropylene glycol, glycol ethers, glycerin, and surfactants. Minor quantities are used for the (antimicrobial) sterilization or (insecticidal) fumigation of medical equipment and foodstuffs (IARC, 1976; WHO, 1978). Small quantities are also used in the production of modified food starch and alginate and as a stabilizer in dichloromethane.

3.1.3 Disposal of wastes

The emission of propylene oxide through process vents appears to be the most important source of atmospheric pollution. However, the waste gas can be removed from air by

scrubbing, and emission from liquid wastes can be controlled by incineration. Little, if any, propylene oxide seems to be released in waste water in the chlorohydrin process, but an environmental problem is created by large amounts of by-products such as calcium chloride and chlorinated organic compounds. No specific solid wastes are associated with the manufacture of propylene oxide (Bogyo et al., 1980).

3.2 Transport and Fate in the Environment

Propylene oxide enters the environment mainly through evaporation and in vented gases during production, handling, storage, transport, and use. Most of the propylene oxide applied as a sterilant or fumigant will finally enter the atmosphere (Bogyo et al., 1980). In the USA, in 1981, a total loss to the atmosphere of almost 600 tonnes of propylene oxide was estimated, or approximately 0.07% of total production (Storck, 1981; US EPA, 1981).

The major removal of propylene oxide from the atmosphere will occur rapidly via oxidation by hydroxyl radicals. On the basis of a theoretical rate constant for this reaction, the atmospheric residence time of propylene oxide was calculated to be 8.9 days (Cupitt, 1980), but by analogy with ethylene oxide (WHO, 1985), the real value is probably an order of magnitude greater. Because of its high solubility in water, propylene oxide levels in air can also be reduced via washout by rain (Bogyo et al., 1980). No data were found concerning the rate of evaporation of propylene oxide from water. However, because of its lower vapour pressure and high water solubility, it can be assumed that the rate is slower for propylene oxide than that for ethylene oxide, for which, under certain specified conditions, a half-life of 1 h has been determined (Conway et al., 1983). Chemical degradation in water via ionic reactions appears a slow process under environmental conditions. In neutral fresh water, at 25 °C, propylene oxide will react to form 1,2-propanediol with a half-life of approximately 12 days (Koskikallio & Whalley, 1959). This reaction is acid catalysed. In marine waters, 1- and 2-halopropanols are also formed. In neutral marine water, there is a preference for the formation of 1-halopropan-2-ol (Addy & Parker, 1963). Bogyo et al. (1980) estimated the relative importance of the reaction of propylene oxide with water and that with chloride at 25 °C in neutral sea water of 3% salinity. According to these calculations, approximately 80% of the propylene oxide present will react to form chloropropanol; the remainder will react to form 1,2-propanediol. The overall half-life with respect to these reactions is 4 days.

Microorganisms from the effluent of a biological sanitary waste treatment plant were found to degrade propylene oxide very slowly. The biological oxygen demand (BOD) over 5 days was 8% of the theoretical oxygen demand (Bridié et al., 1979b). In another study, the biological oxygen demand of microorganisms from activated sludge was 20% of the chemical oxygen demand (COD) over 4 h, after 1 month of acclimation (Hatfield, 1957). The aerobic bacteria Nocardia A60 also oxidized propylene oxide after adaptation. It has been established that the first step in bacterial metabolism is the conversion of propylene oxide to 1,2-propanediol by epoxide hydrolase (EC 3.3.2.3), followed by dehydration and oxidation (Bont et al., 1982).

4. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

4.1 Occurrence in the Environment

The only available information on atmospheric concentrations of propylene oxide are estimates of levels in the vicinity of production plants. The lowest annual average concentration occurring within 20 km of a specific point source was estimated, using dispersion models, to be less than 4.836×10^{-8} mg/m^3 (Anderson, 1983). No data are available indicating that propylene oxide occurs as a natural product.

4.2 General Population Exposure

Exposure via food

The residue levels in food after fumigation or sterilization by propylene oxide will depend on factors similar to those investigated by Scudamore & Heuser (1971) in their studies on ethylene oxide. Important factors are: the total amount and concentration of propylene oxide, the composition of the treatment mixture, temperature, aeration and storage conditions after treatment, the type of commodity and its moisture content, pH, permeability, and particle size, and the method of packaging.

Few residue data exist on propylene oxide. In Japan, propylene oxide residues of up to several thousands mg/kg wet weight were measured in a variety of foodstuffs. For example, after 24 h of aeration, at 37 °C, levels of over 4000 mg/kg were found in lard and oleic acid (Oguma et al., 1968, 1969). Food wrappings and containers were also found to contain propylene oxide residues, after fumigation. Depending on the materials, these levels fluctuated between 0 and 6260 mg/kg, 3 h after fumigation (Hirashima et al., 1970). No migration studies were reported.

Propylene oxide can react with water and chloride in commodities to form 1,2-propanediol and chloropropanol, respectively. In commercially fumigated walnut meat, flour, cocoa, glacé cherries, and glacé citrons, 4 - 47 mg 1-chloropropan-2-ol/kg wet weight were measured in the USA (Ragelis et al., 1968). When dehydrated mashed potatoes were sterilized, residues of 12.1 mg chloropropanol, mostly 1-chloropropan-2-ol, and 29 mg 1,2-propanediol/kg wet weight were measured. There was no detectable reaction of propylene oxide with the starch (Steele & Hadziyev, 1976). Residues of propylene oxide in packed prunes were no longer detectable, 7 days after treatment. At this time, over 50% of the propylene oxide added appeared to be converted to 1,2-propanediol; residue

levels of this product exceeded 2000 mg/kg wet weight for many months (Mestres & Barrois, 1964). Residues of 1,2-propanediol of 190 - 900 mg/kg wet weight were reported for flour, when wheat was treated with propylene oxide, before milling at room temperature. The amount of residue increased with the moisture content. When the flour was treated after milling, 1000 mg/kg wet weight was found (Vojnovich & Pfeifer, 1967).

4.3 Occupational Exposure

Levels of propylene oxide were measured by personal sampling in 8 plants in the Federal Republic of Germany, where alkene oxides were produced between 1978 and 1980. In each case, the time-weighted averages were reported to be far below 240 mg/m^3, though higher concentrations were measured for brief periods (Thiess et al., 1981a).

More detailed results were reported for a propylene oxide-producing plant in the USA in 1979, where daily, time-weighted average exposures were found to range from 0.5 to 4.7 mg/m^3. Peak air concentrations in that year were 24 - 9010 mg/m^3 (Flores, 1983).

In a factory in Sweden, in 1981, where starches were alkylated with propylene oxide, the time-weighted average for 5 of the workers, potentially exposed to the highest levels of propylene oxide during their work, varied between 1.4 and 28 mg/m^3. The work with propylene oxide occupied 25 - 75% of the total working time. Short-term exposures of up to 2370 mg/m^3 were recorded for some workers (Pero et al., 1982).

5. KINETICS AND METABOLISM

5.1 Absorption

No experimental data on the absorption of propylene oxide are available.

5.2 Distribution, Metabolic Transformation, and Excretion

There are no *in vivo* data on the distribution and metabolism of propylene oxide. On the basis of *in vitro* experiments, 2 metabolic pathways have been suggested (Tachizawa et al., 1982). Propylene oxide was found to be a substrate for rat liver glutathione epoxide transferase (EC 4.4.1.7), while nonenzymic conjugation was negligible (Fjellstedt et al., 1973). It was also observed to be hydrolysed to 1,2-propanediol by epoxide hydrolase (EC 3.3.2.3) from rat liver microsomes, but at a low rate (Guengerich & Mason, 1980; Dent & Schnell, 1981). Propylene oxide was found to be a poor substrate for human liver epoxide hydrolase (Oesch, 1974). The nonenzymatic hydrolysis to 1,2-propanediol is rather slow. At 37 °C, the half-life for the uncatalysed reaction in a neutral medium was found to be 87 h (Ross, 1950).

Propanediol can be excreted unchanged via the kidneys and can be oxidized to lactic and pyruvic acid (Ruddick, 1972). The data are summarized in Fig. 1.

Propylene oxide is a direct-acting agent, and *in vitro* alkylation of DNA deoxynucleosides has been found. A total of 15 different calf thymus DNA adducts of propylene oxide were detected, which altered 1.3% of the nucleosides in the DNA molecule (Randerath et al., 1981). Guanosine and, to a lesser extent, adenosine were alkylated to N^7-(2-hydroxypropyl)-guanosine and N^3- or N^6-(2-hydroxypropyl)adenosine, respectively (Lawley & Jarman, 1972; Walles, 1974; Hemminki et al., 1980). In rats, haemoglobin alkylation was established at the amino acids, cysteine, valine, and histidine (Farmer et al., 1982; Svensson & Osterman-Golkar, 1984). Histidine alkylation was found to increase linearly with the level of vapour exposure. Exposure of rats for 4 h to 3080 mg/m^3 resulted in 10.5 mg hydroxypropylhistidine/kg haemoglobin (Farmer et al., 1982).

On the basis of the haemoglobin alkylation data of Farmer et al. (1982), a half-life of approximately 40 min can be calculated for the elimination of propylene oxide from rat tissues, assuming 100% alveolar absorption and first order kinetics.

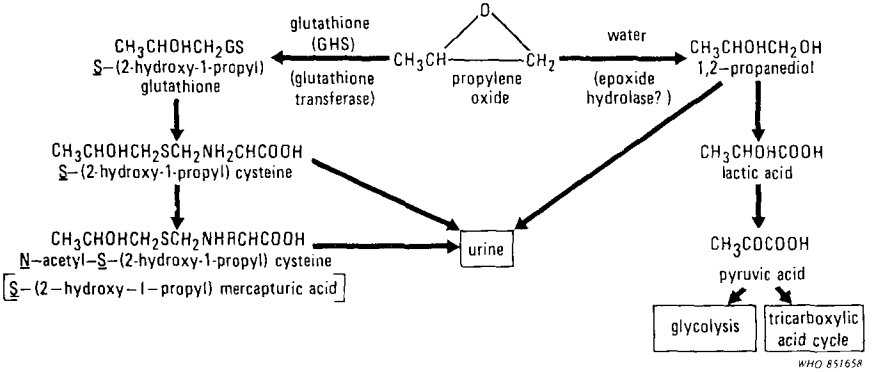


Fig. 1. Proposed metabolic pathways for propylene oxide.
GSH = glutamylcysteinylglycine.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

In an acute toxicity test on goldfish (Carassius auratus), in static fresh water, at 20 °C, pH between 6 and 8, and a dissolved oxygen content greater than 4 mg/litre, the 24-h LC_{50} for propylene oxide was 170 mg/litre (Bridié et al., 1979a). In other static tests, with the fresh water species bluegill sunfish (Lepomis machrochirus) and mosquito fish (Gambusia affinis), 96-h LC_{50} values for propylene oxide were 215 and 141 mg/litre, respectively, at 23 °C. For the common mullet (Mugil cephalus), a marine fish, a static 96-h LC_{50} for propylene oxide of 89 mg/litre was determined at 23 °C and a water salinity of 1.5% (no water analysis was reported) (Crews, 1974). The 24-h LC_{50} for 1,2-propanediol (a product of propylene oxide) for goldfish was over 5000 mg/litre (Bridié et al., 1979a). Propylene oxide is very soluble in aqueous media; the log n-octanol water partition coefficient was reported to be -0.13 (Radding et al., 1977) and, therefore, it is not expected to bioaccumulate.

7. EFFECTS ON ANIMALS

7.1 Single Exposures

7.1.1 Oral exposure

In 2 studies, the oral LD_{50}s for the rat were reported to be 1140 mg/kg body weight and 520 mg/kg body weight for males, and 540 mg/kg for females (Smyth et al., 1941; Antonova et al., 1981); the difference between 16 and 84% mortality was caused by a dose of only approximately 300 mg/kg body weight, indicating a rather steep dose-effect relationship. In one of these studies, oral LD_{50}s for male mice and guinea-pigs were 630 and 660 mg/kg body weight, respectively (Antonova et al., 1981).

At lethal oral doses, necrosis of the stomach mucosa was observed in rats. Succinate dehydrogenase (EC 1.3.99.1) activity was reported to be decreased in the stomach mucosa. The liver cells showed oedema and fatty changes. In serum, alanine aminotransferase (EC 2.6.1.2) and aspartate aminotransferase (EC 2.6.1.1) activity and histamine levels were increased. Kidney function was disturbed. Mature lymphocytes were reduced in the spleen (Antonova et al., 1981).

7.1.2 Skin and eye irritation

Solutions of 100 or 200 g propylene oxide/litre water, applied under a plastic cover on the intact skin of rabbits produced hyperaemia, oedema, and finally scars after 6 or more min of exposure. The intensity of the effects was proportional to the exposure time (Rowe et al., 1956).

No, or only slight, irritation was observed when undiluted 1,2-propanediol, a possible reaction product of propylene oxide in water, was applied to the skin of various animals under occlusive conditions for 24 or 72 h (Davies et al., 1972).

When 5 µl of undiluted propylene oxide was applied once on the centre of the cornea of rabbits, a severe burn resulted with necrosis (Weil et al., 1963).

7.1.3 Inhalation exposure

In inhalation studies, the 4-h LC_{50}s for rats and mice were 9500 and 4100 mg/m^3, respectively (Jacobson et al., 1956). The lowest lethal concentration (US NTP, 1984) or the 0.1% mortality level (Jacobson et al., 1956) for 4-h exposures was approximately 5250 mg/m^3 for rats and 900 mg/m^3 for mice. In both species, 100% mortality was reached after 4 h of exposure at levels above 17 000 mg/m^3 (Jacobson et al.,

1956). In rats, 100% mortality was also reported after a 30-min exposure to 38 000 mg/m^3 or a 7-h exposure to 9500 mg/m^3 (Rowe et al., 1956).

After inhalation of propylene oxide, rodents showed eye and nose irritation, nasal discharge, dyspnoea, and depression of the central nervous system, the severity of which increased with increasing level and length of the exposure (effect levels not specified) (Rowe et al., 1956). Gross pathology revealed distension of the stomach only at lethal concentrations (Jacobson et al., 1956). No organ damage was observed in rats exposed to 2370 mg/m^3 for 7 h, 4740 mg/m^3 for 4 h, or 9480 mg/m^3 for 0.5 h (Rowe et al., 1956). In 4 groups, each containing 3 dogs, exposed for 4 h to propylene oxide concentrations of 3230, 4750, 4810, or 5880 mg/m^3, lachrymation, salivation, nasal discharge, and vomiting occurred. Congestion in the lungs and trachea, oedema of pulmonary tissues, and necrosis of bronchiolar epithelium were observed at 4810 and 5880 mg/m^3. Deaths occurred in the groups exposed to concentrations of 4750 mg/m^3 or more (Jacobson et al., 1956).

7.2 Repeated Exposures

7.2.1 Oral exposure

Propylene oxide was administered in the drinking-water to 4 groups of rats of both sexes at dose levels calculated by the authors to be 0.52, 5.2, 52, or 520 µg/kg body weight per day, over a 26-week period. At the highest dose level, polyuria, haematological abnormalities, lowering of serum-albumin, increased serum-beta-globulin levels, and increased activity of gastrointestinal mucosal enzymes were observed. Mild haematological abnormalities occurred at the next lower dose, while no adverse effects were noted at the two lowest doses (Antonova et al., 1981).

7.2.2 Inhalation exposure

In range-finding tests for a carcinogenicity study, groups of 5 male and 5 female Fischer 344/N rats were exposed to 0, 110, 230, 460, 1150, or 3400 mg propylene oxide/m^3 air for 5 days per week, and 6 h per day, during a 2-week exposure period. B6C3F1 mice were exposed for the same period to 0, 50, 110, 230, 460, or 1150 mg/m^3. All animals were necropsied on the 12th day. No pathological effects were observed. Body weights were not affected. Dyspnoea and gasping were observed in rats, one of which died at 3400 mg/m^3. Mice showed dyspnoea at 460 and 1150 mg/m^3. Both species were less active at the highest exposure. Rats also showed irregular limb movements and diarrhoea. After 13

weeks of a similar exposure regime up to concentration of 1150 mg/m^3, rats and mice did not show any gross- or histopathological effects. Body weights were reduced at 1150 mg/m^3 only (US NTP, 1984).

Groups of 10 - 20 rats, 8 guinea-pigs, 1 or 2 rabbits of both sexes, and 1 or 2 female Rhesus monkeys were exposed to 0, 240, 460, or 1080 mg propylene oxide/m^3 air for 112 - 218 days, for 7 h per day, and 5 days per week. Rabbits and monkeys did not show any adverse effects with regard to appearance, behaviour, mortality rate, growth, organ weights, and gross- and histopathology. Rats showed irritation of the eyes and respiratory passages and an increased mortality rate due to pneumonia at 1080 mg/m^3. Guinea-pigs also showed irritation of the eyes and respiratory passages at this exposure level, but no increase in mortality rate. In addition, the growth of the female guinea-pigs was reduced. Livers exhibited slight fatty degeneration in male guinea-pigs. The relative weights of the lungs of the guinea-pigs were slightly, but significantly, increased in both sexes at 1080 mg/m^3, and in females at 460 mg/m^3. It should be noted that control lung weights were low. Histopathological findings were alveolar haemorrhages and oedema, and interstitial oedema and hyperaemia in the lungs of guinea-pigs after 157 days of exposure to 1080 mg/m^3. After 37 - 39 days of exposure to 1080 mg/m^3, these histopathological effects had also been observed in rats (Rowe et al., 1956).

The possibility of the induction of neuropathological effects by propylene oxide was investigated in groups of 12 male Cynomolgus monkeys. The animals were exposed to actual concentrations of 0, 237, and 717 mg/m^3 propylene oxide, for 7 h per day, 5 days per week, for 2 years. In 2 monkeys per group, brain, ulnar and sciatic nerves, and spinal cord were examined histologically after exposure. No clinical signs were reported. The only treatment-related neuropathological lesions found were in the medulla oblongata of the brain. Axonal dystrophy was observed in the nucleus gracilis in all of the 4 treated monkeys examined, without any apparent dose-effect relationship. The same lesion was observed in one of the two control monkeys (Sprinz et al., 1982).

7.3 Mutagenicity and Related End-Points

A summary of mutagenicity tests with positive results is presented in Table 3. Propylene oxide is mutagenic in bacteria, fungi, and insects; no such studies with negative results have been reported.

Propylene oxide causes single-strand breaks in isolated calf thymus DNA, probably by alkylation of the phosphodiester bond (Walles, 1974). Single-strand breaks were observed in

Table 3. Mutagenic tests for propylene oxide with positive results[a]

Test description	System description: Organism	Strain/cell type	Reference
Gene mutations			
Forward mutations	virus	Bacillus subtilis phage φ 105	Garro & Phillips (1980)[b]
Reverse mutations (base-pair substitutions)	bacterium	Escherichia coli WP2	McMahon et al. (1979)[c]
		Escherichia coli WP2	McMahon et al. (1979)[c]
		Escherichia coli WP2	Hemminki & Falck (1979)
		Escherichia coli WP2 CM871, CM891	Bootman et al. (1979)[c]
		Bacillus subtilis	Phillips et al. (1980)
		Salmonella typhimurium TA 1535, TA 100	Wade et al. (1978)
			McMahon et al. (1979)[c]; Bootman et al. (1979)[c]; Pfeiffer & Dunkelberg (1980)[d]
Reverse mutations	bacterium	Escherichia coli SD4	Hussain & Osterman-Golkar (1984)
Forward mutations		Klebsiella pneumoniae	Voogd et al. (1981)
Reverse mutations	fungus	Neurospora crassa W40 macroconidia	Kolmark & Giles (1955)
		Schizosaccharomyces pombe	Heslot (1962)
Forward mutations	fungus	Schizosaccharomyces pombe P1	Migliore et al. (1982)[c]
Sex-linked recessive lethals	insect	Drosophila melanogaster	Hardin et al. (1983)
Forward mutations on specific locus	mammal (in vitro)	Chinese hamster ovary cells	Zamora et al. (1983);

Table 3 (contd).

Test description	System description: Organism	Strain/cell type	Reference
DNA damage			
Single-strand breaks	bacterium	Bacillus subtilis	Phillips et al. (1980)[b]
	mammal(in vitro)	rat hepatocytes	Sina et al. (1983)
		calf thymus DNA	Walles (1974)
Chromosome damage			
Chromatid gaps and breaks, Chromosome breaks, fragments	mammal(in vitro)	human lymphocytes	Bootman et al. (1979)
Chromatid gaps, deletions, exchanges	mammal (in vitro)	epithelial rat liver cells	Dean & Hodson-Walker (1979)[c]
Micronuclei	mammal (ip) (2 x 300 mg/kg)	mouse polychromatic erythrocytes	Bootman et al. (1979)

[a] For details of these studies, see text and data profile (IRPTC, 1984).
[b] Treatment of isolated DNA in vitro, followed by transformation (bacteria) or transfection (virus).
[c] A similar or slightly reduced effect after metabolic activation by S9 rat or mouse liver fraction.
[d] Chloropropanols were also mutagenic, but not as mutagenic as propylene oxide; 1,2-propanediol was not mutagenic.

the DNA of isolated rat hepatocytes at concentrations that were not toxic (Sina et al., 1983).

Propylene oxide caused chromosome aberrations in mammalian cells in vitro, in particular, chromatid gaps and breaks (Bootman et al., 1979; Dean & Hodson-Walker, 1979). However, no increases in chromosome aberrations or sister-chromatid exchanges were found in peripheral lymphocytes of male Cynomolgus monkeys, after long-term vapour exposure, in vivo. The animals were exposed in groups of 12 to concentrations of 0, 237, and 717 mg propylene oxide/m^3 air, for 7 h per day, 5 days per week, for 2 years (Lynch et al., 1984b).

Two oral doses of up to 500 mg propylene oxide/kg body weight, in gum tragacanth, administered within 24 h to mice, did not induce micronuclei in the polychromatic erythrocytes. In contrast, 2 intraperitoneal doses of 300 mg/kg body weight in water, administered within 24 h, gave a 5-fold increase over controls. No effects were observed following ip administration of 2 doses of 75 mg/kg or 150 mg/kg (Bootman et al., 1979).

The results of the dominant-lethal assay were negative when male rats were exposed, for 7 h per day, to propylene oxide vapour at a concentration of 720 mg/m^3, for 5 days prior to mating (Hardin et al., 1983). A negative result was also obtained in a dominant lethal assay in which male mice received, once a day, 0, 50, or 250 mg propylene oxide/kg body weight in gum tragacanth, by gavage, for 2 weeks prior to mating (Bootman et al., 1979).

No increased frequency of abnormal sperm heads was observed, 1 - 9 weeks after exposure of mice for 5 days to propylene oxide vapour at a concentration of 720 mg/m^3, for 7 h per day (Hardin et al., 1983). Similarly, no increase was observed in the frequency of abnormal sperm heads in the groups of Cynomolgus monkeys exposed for 2 years (Lynch et al., 1984c). These monkeys were used by Sprinz et al. (1982) (section 7.2.2) and Lynch et al. (1984b) (section 7.3).

7.4 Carcinogenicity

7.4.1 Oral exposure

Groups of 50 female Sprague Dawley rats received 2 doses of 15.0 or 60.0 mg propylene oxide/kg body weight per week, by gavage, for a total of 112 weeks. The compound was dissolved in salad oil and administered to fasting rats. Two groups of 50 female rats served as vehicle controls or untreated controls. There was an exposure-free period between the 79th and 82nd week because of an outbreak of pneumonia. The rats were observed up to 150 weeks. No statistical analysis of the results was reported. Mortality rates were not affected by

the exposures. There was a dose-related incidence of squamous cell carcinoma of the forestomach. In addition, one early carcinoma of the forestomach was observed. The numbers of rats affected were 0, 2, and 19 in animals receiving 0, 15, and 60 mg/kg body weight, respectively. The combined incidences of hyperkeratosis, hyperplasia, and papillomas were 0, 7, and 17 at 0, 15, and 60 mg/kg body weight, respectively. At the highest dose level, one adenocarcinoma of the pylorus was also observed. There was no treatment-related increase of any other tumour type (Dunkelberg, 1982).

7.4.2 Inhalation exposure

The following studies have been reported by the US NTP (1984). Groups of 50 Fischer 344/N rats and 50 B6C3F1 mice of each sex were exposed to average propylene oxide vapour concentrations of 0, 470, and 940 mg/m^3 air, for 6 h per day, 5 days per week, over a 103-week period. Three accidental overexposures at the highest exposure level occurred. The concentrations did not exceed 15 300 mg/m^3 for a maximum of 12 min during these periods.

In rats, survival rate was not affected and was over 58% at the end of the study, at all exposure levels. Growth was slightly reduced from week 20 onwards. The respiratory epithelium of the nasal turbinates showed a dose-related increase in the incidence of suppurative inflammation of the mucosae, hyperplasia, and squamous cell metaplasia. At 940 mg/m^3, 2 out of 50 male and 3 out of 50 female rats had papillary adenomas involving the respiratory epithelium and the underlying submucosal glands of the nasal turbinates. No such tumours were observed in controls or low-dose animals. In the thyroid of the female rats, a dose-related increase in the combined incidences of C-cell adenomas and carcinomas occurred, which was significant at 940 mg/m^3. The combined incidence of endometrial stromal polyps and sarcomas was reported to have increased, at both exposure levels, in a dose-related manner. According to the authors, the C-cell adenomas and C-cell carcinomas were not related to treatment. The incidences of polyps and sarcomas were within the historical control range for the species tested. In males, an increase in skin keratoacanthomas was observed, with a statistically-significant positive trend. Induced non-neoplastic lesions further included testicular atrophy, acinar cell atrophy in the pancreas of males, cytomegaly in the adrenal cortex of females, and cystic endometrial hyperplasia (US NTP, 1984).

The survival rate in mice was decreased at 940 mg/m^3, from week 60 onwards and was 58 and 20% for male and female mice, respectively, at the end of the study, compared with 84

and 76% for male and female controls. Growth was slightly reduced from week 29 onwards. In the nasal turbinates, a dose-related increased incidence of inflammation occurred. Squamous cell metaplasia was observed in 1 male at 470 mg/m^3 and 2 females at 940 mg/m^3. At 940 mg/m^3, haemangiosarcomas were found in the nasal cavity of 5 males and 2 females. Haemangiomas were also observed in the nasal cavity of 5 males and 3 females at this dose level. The increases in the incidence of haemangiosarcomas in the males and of haemangiomas in both sexes were statistically-significant.

One squamous cell carcinoma and one papilloma were induced in the nasal cavity of male mice at 940 mg/m^3 and 2 adenocarcinomas were induced in the nasal cavity of females at 940 mg/m^3. None was observed in controls or low-dose animals. The incidence of adenocarcinomas of the mammary gland was increased at 940 mg/m^3, but did not exceed the historical control range for the species tested. Induced non-neoplastic lesions further included ovarian atrophy and suppurative inflammation, mainly of the uterus and peritoneum (US NTP, 1984).

In a combined NIOSH toxicity-carcinogenicity study, groups of 80 male Fischer 344 rats were exposed to 237 or 717 mg propylene oxide/m^3, for 7 h per day, 5 days per week, over 2 years. A control group contained 80 rats. There was an exposure-free period of 2 weeks in month 16 because of a pulmonary infection, which contributed to the mortality rate. The mortality rate was increased at both exposure levels, and the increase was significant at 717 mg/m^3. The mean survival was 96 weeks at this exposure level, compared with 103 weeks for control rats. Body weights were reduced from the 2nd week at 717 mg/m^3 and from the 39th week at 237 mg/m^3. After 2 years, at both concentrations, the relative weights of lungs, adrenals, and brain were increased and those of the testes decreased. The only altered biochemical parameters were increased haemoglobin concentrations in blood at both exposure levels and increased activities of serum aspartate aminotransferase (EC 2.6.1.1) and serum sorbitol dehydrogenase (EC 1.1.1.14) at 237 mg/m^3. Dose-related increases in the incidence and severity of inflammatory lesions in the lungs, nasal cavity, trachea, and middle ear were observed. In the nasal passages, there was a dose-related increased incidence of complex epithelial hyperplasia that was significant at 717 mg/m^3. Metaplasia was not observed. Two rats showed nasal-cavity adenomas at 717 mg/m^3. At this concentration, there was also an increased incidence of multifocal areas of atrophy and degeneration of skeletal muscles. No lesions were observed in the nerves. The only statistically significant neoplastic change observed was an increased incidence of adrenal phaeochromocytomas at

both concentrations. The incidences were 8/78 in controls, 25/78 in the low-dose group, and 22/80 in the high-dose group (Lynch et al., 1984a).

Another study on the possible toxic and carcinogenic properties of inhaled propylene oxide was performed on randomly bred Wistar rats. Groups of 100 rats of each sex were exposed to propylene oxide concentrations of 70, 242, or 712 mg/m^3, for 6 h per day, 5 days per week, over a period of 123 - 124 weeks. Groups of 100 rats of each sex served as controls. Ten rats per sex and per group were killed for examination after 12, 18, and 24 months of exposure. No adverse effects were observed on general health, behaviour, food intake, biochemistry, urinalysis, and haematology in comparison with control rats. The mortality rate was increased at the highest exposure level from week 73, in males, and from week 109, in females, and at the end of the exposure to 242 mg/m^3 in females. Rats of both sexes gained less weight than controls at 712 mg/m^3, though the difference compared with controls became smaller towards the end of the exposure. The relative and absolute weights of adrenals, spleen, liver, and lungs of males were increased at 712 mg/m^3, but no pathological lesions were observed in these organs. Male rats showed a lower incidence of pale exorbital lachrymal glands at this exposure level. In both sexes, the incidences of basal cell hyperplasia and atrophy of the olfactory epithelium and the incidence of nest-like infolds of the respiratory epithelium were increased mainly at the 2 highest exposure levels. These changes were also noted at interim kills. The severity of the changes increased only slightly, if at all, with increasing length of exposure and with age. Squamous metaplasia was not observed. One rat was found with squamous cell carcinoma of the nose. In female rats, the incidence of benign tumours of the mammary glands, mostly fibroadenomas, was increased at 712 mg/m^3 in comparison to both the concurrent controls and the historical controls. Moreover, the number of females bearing 2 or more mammary fibroadenomas increased in a dose-related manner from the lowest exposure level onwards when compared with controls. The increased incidence of tubulopapillary mammary carcinomas at 712 mg/m^3 was within the range of historical controls. With the exclusion of mammary tumours, the total incidence of primary tumours in females and the number of malignant tumour-bearing rats of both sexes was increased at the highest exposure level (Reuzel & Kuper, 1983). Following reports that ethylene oxide had induced brain tumours in rats, the histopathological investigation of the brain of the rats was extended. There was no evidence that propylene oxide induced such tumours (Reuzel & Kuper, 1984).

7.4.3 Subcutaneous exposure

Groups of 100 female NMRI mice received subcutaneous doses of 0.1, 0.3, 1.0, or 2.5 mg propylene oxide per animal in tricaprylin once a week, for 106 weeks. These groups were compared with 200 controls receiving tricaprylin and 200 untreated controls. In the second year of exposure, mice were not treated for 11 weeks. Body weights and survival rates were not affected by treatment. At the site of injection, a dose-related increase in the incidence of sarcomas (mainly fibrosarcomas) occurred. The numbers of mice affected were 0/200 in untreated controls, 4/200 in tricaprylin controls, and 3/100, 2/100, 12/100, and 15/100 at the 0.1, 0.3, 1.0, and 2.5 mg dose levels, respectively. The increases in incidence at the 2 highest dose levels were statistically significant. The first tumour appeared in week 38 (Dunkelberg, 1981).

7.5 Effects on Reproduction and Teratogenicity

When B6C3F1 mice of both sexes were exposed repeatedly for 2 years to propylene oxide at concentrations of 470 and 940 mg/m^3 air (section 7.4.2), the incidence of ovarian atrophy was increased at the higher exposure level (US NTP, 1984). In F344 rats, similarly exposed, higher incidences of testicular atrophy were found at both exposure levels, but they were not dose-related (US NTP, 1984). Decreased relative weights of the testes were reported by Lynch et al. (1984a), when male F344 rats were exposed repeatedly for 2 years to propylene oxide at levels of 240 and 720 mg/m^3 air.

Sperm head abnormalities were not detected in mice after exposure for 5 days, 7 h per day, to 720 mg propylene oxide/m^3 (Hardin et al., 1983), or in groups of 12 Cynomolgus monkeys, exposed for 2 years to 240 and 710 mg propylene oxide/m^3, for 7 h per day, 5 days per week. In monkeys, at both exposure levels, sperm counts and sperm motility were reduced, and the sperm drive range was elevated (Lynch et al., 1984c).

In a reproduction-teratogenicity study, groups of 41 - 44 female Sprague Dawley rats were exposed to 1190 mg propylene oxide/m^3 air, for 7 h per day, during days 7 - 16 of gestation (Group 1), days 1 - 16 of gestation (Group 2), or for 3 weeks (5 days/week) before mating and on days 1 - 16 of gestation (Group 3). A group of 46 rats served as controls. The dams were sacrificed on day 21. No deaths of dams occurred, their histology was normal, and the percentage of pregnant rats was not affected by the exposure. Toxic effects in dams were expressed as decreased body weights and food consumption and increased relative weights of kidneys in all exposed groups. The numbers of corpora lutea, implantations

per dam, and live fetuses were lower in group 3, compared with those in the other groups. In group 1, the number of resorptions was increased compared with that in group 2. The body weights and lengths of fetuses were decreased in all exposed groups compared with controls, but more so in group 3. In group 2, increases in wavy rib and in reduced ossification, primarily of the vertebrae and ribs, were observed (Hackett et al., 1982).

Groups of New Zealand rabbits were also exposed to 1190 mg/m^3, for 7 h per day, during days 1 - 19 or days 7 - 19 of gestation. No evidence of toxicity was observed in the mothers, fetuses, or embryos, and no developmental defects were noted (Hacket et al., 1982).

Female rats administered a single oral dose of 260 mg/kg body weight of propylene oxide showed disturbance of the estrus cycle.

Pregnant female rats administered an identical dose during the first 2 weeks of gestation exhibited higher embryotoxicity and lower offspring body weight compared with the controls. Male rats exposed to a single oral LD_{50} (520 mg/kg) dose of propylene oxide showed reduced sperm motility and damage to primary spermatocytes. When such rats were mated with normal female rats, between 2 and 10 weeks after exposure, 50% of the males were infertile. The fertility of the first generation was reduced by 23% (Antonova et al., 1981).

8. EFFECTS ON MAN

8.1 Exposure of Skin and Eyes; Skin Sensitization

Accidental exposure of the eyes of 3 persons to propylene oxide (it was not reported whether this was liquid or vapour) resulted in alterations in the cornea and conjunctiva (McLauglin, 1946).

Allergic contact dermatitis was diagnosed in 3 cases of exposure to solutions of propylene oxide (Ketel, 1979; Jensen, 1981). Biopsy on the skin of these patients revealed spongiosis in the epidermis, oedema in the cutis, and dense perivascular infiltrates with mononuclear cells.

8.2 Accidental Inhalation Exposure

No data are available.

8.3 Occupational Inhalation Exposure

In the Federal Republic of Germany, 279 employees from 8 plants where alkene oxides were produced or processed, were examined during 1978. They were employed for an average of 10.8 years. No clinical abnormalities were found that could be related to exposure to alkene oxides. Propylene oxide levels were measured by personal sampling over 1 - 10 h, but levels of exposure were not reported. The workers were exposed to many other chemicals, including ethylene oxide (Stocker & Thiess, 1979). Because of the mixed exposure and unavailability of propylene oxide exposure data, the Task Group was unable to evaluate this study.

8.4 Mortality Studies

In the Federal Republic of Germany, 602 workers were investigated for mortality over the period 1928-80. The workers had been employed for at least 6 months in 8 plants producing ethylene oxide and propylene oxide, the latter produced only since 1959. A subcohort of 351 workers was observed for more than 10 years. Control data came from a styrene plant and from national statistics. Propylene oxide levels, measured by personal sampling (number of samples not reported), from 1978 to 1980, were far below a time-weighted average of 240 mg/m^3 over a working shift of 12 h (Thiess et al., 1981a). Higher levels were measured for brief periods. The workers were also exposed to many other chemicals, some of which might be carcinogenic for human beings. There were 56 deaths compared with 76.6 expected. No significant excess of

deaths could be found due to any cause in the cohort of 602 workers. In the sub-cohort of 351 workers, there was a significant increase in mortality rate due to kidney disease (3 compared with 0.4 expected). There was 1 death from gall-bladder cancer, 1 death from urinary-bladder cancer, 1 death from brain cancer, and 1 death from myeloid leukaemia. Two stomach tumours were observed compared with 1.8 expected (Thiess et al., 1981b). Since the workers were also exposed to many other chemicals, such as butylene oxide, epichlorohydrin, dioxan, dichloropropane, and chlorohydrins, the Task Group was unable to evaluate this study in relation to propylene oxide.

8.5 Mutagenicity and Related End-Points

In 43 male workers from the cohort of 602 workers discussed in section 8.4 (Thiess et al., 1981b), no increase in chromosome aberration rate was found in 2 groups of workers exposed to alkene oxides for average periods of either 12.5 or 17.6 years; in addition, workers in the latter group had at least one accidental high exposure to ethylene oxide. The results were also negative in a group of workers exposed once for a brief period following an accident. On the other hand, the aberration rate was significantly elevated in workers exposed for more than 20 years (Thiess et al., 1981a).

For the reason mentioned in section 8.4, the Task Group was unable to evaluate this study in relation to propylene oxide.

Unscheduled DNA synthesis, induced *in vitro* by the mutagen *N*-acetoxy-2-acetylaminofluorene, was inhibited in the lymphocytes of 23 workers from a factory in Sweden, where starch was modified with propylene oxide. The workers had been exposed for 1 - 20 years. At the time of the study, exposure was generally below a time-weighted average of 28 mg/m^3. However, short-term exposures of up to 2370 mg/m^3 were recorded for some workers (Pero et al., 1982).

9. EVALUATION OF THE HEALTH RISKS FOR MAN AND EFFECTS ON THE ENVIRONMENT

Exposure of man to propylene oxide mainly occurs through inhalation at the work-place.

Data are insufficient to estimate the exposure to propylene oxide residues in food after fumigation and sterilization. The main conversion products in foodstuffs are chloropropanols and 1,2-propanediol, which are more persistent than the parent compound (section 4.2). No adverse effects have been reported due to the ingestion of propylene oxide and its reaction products in food.

No ambient air monitoring data are available, but the lowest annual average concentration at distances of up to 20 km from production plants has been assessed, by modelling, to be less than 4.836×10^{-8} mg/m^3 (section 4.1). The risk for human health under such conditions of exposure is likely to be negligible.

Propylene oxide is highly soluble in water but is likely to evaporate to a great extent. However, no data on the rate of evaporation are available. In neutral fresh water, propylene oxide is converted to 1,2-propanediol and, in marine waters, to halopropanols, but, even in the presence of micro-organisms, these processes are slow (section 3.2). Because of the low log n-octanol water-partition coefficient, propylene oxide and its conversion products are unlikely to bio-accumulate (Table 1). The toxicity of propylene oxide for aquatic organisms is low. The available LC_{50}s are above approximately 90 mg/litre (section 6). Thus, the probability of an adverse impact on the aquatic environment is considered low.

Eight-hour time-weighted occupational exposure in propylene oxide production and use is normally below 5 mg/m^3, with occasional peak exposures up to 9000 mg/m^3 (section 4.3).

Inhaled propylene oxide is probably readily absorbed, distributed throughout the body, and rapidly metabolized. The half-life in rat tissues has been estimated to be 40 min (section 5.2). There are no data on skin absorption.

An aqueous solution of propylene oxide (100 or 200 g/litre) is irritating to rabbit skin when applied under occlusive cover (section 7.1.2). In man, corneal and conjunctival damage, and allergic contact dermatitis have been reported through accidental exposure to propylene oxide vapour (section 8.1).

The 4-h LC_{50}s for the rat and the mouse were 9500 mg/m^3 and 4100 mg/m^3, respectively. Dogs exposed by inhalation, once for 4 h, to a concentration of 3230 - 5880 mg/m^3 showed salivation, lachrymation, nasal discharge,

and vomiting. Deaths were observed at 4750 - 5880 mg/m^3 but not at 3230 mg/m^3 (section 7.1.3).

On repeated exposure of various species to propylene oxide vapour, 7 h per day, 5 days per week, for 112 - 218 days, at concentrations of 0, 240, 460, and 1080 mg/m^3, rabbits and monkeys did not show any adverse effects on appearance, mortality, growth, and histopathology of internal organs. Rats and guinea-pigs showed irritation of the respiratory passages and lung damage histologically at 1080 mg/m^3. An increase in lung weight was observed in female guinea-pigs at concentrations of 460 mg/m^3 or more. No effect was observed in any species at a concentration of 240 mg/m^3. A concentration of 3400 mg/m^3 administered for 2 weeks, 6 h/day, 5 days per week, resulted in dyspnoea and death in rats. In the same study, mice showed dyspnoea at 460 and 1150 mg/m^3 (section 7.2.2).

Rats and mice exposed for 2 years showed increased incidences of inflammatory and proliferative lesions of the nasal epithelium from an exposure level of 470 mg/m^3. In rats, the inflammatory lesions and hyperplasia were also observed at an exposure level of 240 mg/m^3, but not at 70 mg/m^3 (section 7.4.2).

Depression of the central nervous system, the severity of which increased with increasing level and length of exposure, was observed when rats and mice were exposed by inhalation to single high concentrations of propylene oxide (section 7.1.3). Although no clinical central nervous system effects were reported when monkeys were exposed to 237 and 717 mg/m^3 for 2 years, some histopathological changes were observed in the treated animals (section 7.2.2). It should be noted that these data cannot be evaluated for estimating hazard for man, since only 2 monkeys were examined in each of the exposed groups, and the lesion appeared also in one of the 2 controls.

Summarizing the results of animal studies (excluding mutagenic, carcinogenic, and reproduction effects) the no-observed-adverse-effect level for prolonged repeated 6- to 7-h daily exposure is 70 mg/m^3.

Propylene oxide administered by inhalation for 2 years produced ovarian atrophy in mice at 940 mg/m^3. Testicular atrophy was found at 240 and 720 mg/m^3 in rats (section 7.5).

No sperm head abnormalities were detected in mice after exposure for 5 days to 720 mg/m^3 or in Cynomolgus monkeys exposed to 240 or 710 mg/m^3 for 2 years, but sperm count and motility were reduced, and sperm drive range (time to traverse a linear path) increased in the monkeys. A reduced sperm motility and damage to spermatocytes were observed in male rats treated with an oral LD_{50} (520 mg/kg body weight) dose. A reduced fertility was observed when these males were

mated between 2 and 10 weeks after exposure with normal females (sections 7.3, 7.5).

Reduced fetal ossification of vertebrae and ribs and wavy ribs were observed when pregnant Sprague Dawley rats were exposed to 1190 mg propylene oxide/m^3, 7 h per day, on days 1 - 16 of gestation. When rats were additionally exposed for 3 weeks before mating, the numbers of corpora lutea, implantations per dam, and live fetuses were decreased. No teratogenic or fetotoxic effects were found in New Zealand rabbits exposed to 1190 mg/m^3 (section 7.5).

Propylene oxide is mutagenic in microorganisms and insects and produces DNA damage and chromosomal aberrations in mammalian cells in vitro. It produced micronuclei in mouse erythrocytes after parenteral injection of 2 doses of 300 mg/kg body weight but not after oral exposure. No chromosomal aberrations or sister chromatid exchanges occurred in monkeys exposed by inhalation to 237 and 717 mg/m^3, for 7 h/day, 5 days/week, for 2 years. No dominant-lethal effects were observed in rats or mice following inhalation or oral exposure, respectively, in 2 studies (section 7.3). No adequate data on chromosomal effects in human beings are available.

In studies on the carcinogenicity of propylene oxide in rats and mice, malignant tumours were mainly observed at the site of entry into the body: for stomach, at 15 and 60 mg/kg body weight; for subcutaneous tissues, at 1.0 - 2.5 mg; and, for nasal passages, at 940 mg/m^3. At the dose levels at which these tumours were induced, propylene oxide produced tissue damage. This damage may have played a role in the appearance of the tumours. Propylene oxide also produced an increase in the incidence of multiple benign mammary tumours in female rats following inhalation exposure (section 7.4). No adequate epidemiological studies on cancer incidence in exposed human populations have been carried out.

Taking into account the body of available data - the alkylating nature of propylene oxide, the formation of DNA adducts, the positive responses in in vitro mutagenesis assays, the carcinogenic effects in animals at the sites of entry into the body, and the absence of adequate data on cancer in human beings - propylene oxide should be considered as a possible human carcinogen. Thus, for practical purposes, propylene oxide should be regarded as if it presented a carcinogenic risk for man, and levels in the environment should be kept as low as feasible.

10. RECOMMENDATIONS FOR FURTHER RESEARCH

1. A thorough detailed study on the absorption, distribution, and metabolism of propylene oxide should be conducted.

2. Biological indicators should be developed that quantify both the incidence and severity of human exposure.

3. The epidemiological studies indicating an increased risk of cancer in workers exposed to propylene oxide in combination with other chemicals suggest that additional studies should be conducted on populations whose exposure has been primarily to propylene oxide. The adequate quantification of past exposures should be a part of these studies.

11. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

An International Agency for Research on Cancer Working Group (IARC, 1985) evaluated the carcinogenicity of propylene oxide and concluded that:

"There is sufficient evidence for the carcinogenicity of propylene oxide to experimental animals; there is inadequate evidence for its carcinogenicity to humans. It is noted that, in the absence of adequate data in humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in experimental animals as if they represented a carcinogenic risk to humans."

REFERENCES

ADDY, J.K. & PARKER, R. (1963) The mechanism of epoxide reactions. V. The reaction of 1,2-epoxypropane with chloride ions in water under neutral and acidic conditions. J. Chem. Soc., 915-921.

ANDERSON, G.E. (1983) Human exposure to atmospheric concentrations of selected chemicals. Vol. II, Research Triangle Park, North Carolina, US Environmental Protection Agency, pp. 574-601 (Prepared by Systems Applications, Inc., San Rafael, California, No. SA1/EF81-156R2).

ANTONOVA, V.I., ZOMMER, E.A., KUZNETSOVA, A.D., & PETROVA, N.A. (1981) [Toxicology of propylene oxide and regulation for surface water.] Gig. i Sanit., 46: 76-79 (in Russian).

BOGYO, D.A., LANDE, S.S., MEYLAND, W.M., HOWARD, P.H., & SANTODONATO, J. (1980) Investigation of selected potential environmental contaminants: Epoxides, Syracuse, New York, Centre for Chemical Hazard Assessment, Syracuse Research Corporation (Prepared for US EPA) (US EPA 560/11-80-005, PB 80-183197).

BONT, J.A.M. DE, DIJKEN, J.P. VAN, & GINKEL, K.G. VAN (1982) The metabolism of 1,2-propanediol by the propylene oxide utilizing bacterium Nocardia 60. Biochem. Biophys. Acta, 714: 465-470.

BOOTMAN, J., LODGE, D.C., & WHALLEY, H.E. (1979) Mutagenic activity of propylene oxide in bacterial and mammalian systems. Mutat. Res., 67: 101-112.

BRIDIE, A.L., WOLFF, C.J.M., & WINTER, M. (1979a) The acute toxicity of some petrochemicals to goldfish. Water Res., 13: 623-626.

BRIDIE, A.L., WOLFF, C.J.M., & WINTER, M. (1979b) BOD and COD of some petrochemicals. Water Res., 13: 627-630.

CALLEMAN, C.J., EHRENBERG, L., JANSSON, B., OSTERMAN-GOLKAR, S., SEGERBACK, D., SVENSSON, K., & WACHTMEISTER, C.A. (1978) Monitoring and risk assessment by means of alkyl groups in haemoglobin in persons occupationally exposed to ethylene oxide. J. environ. Pathol. Toxicol., 2: 247-442.

CONWAY, R.A., WAGGY, G.T., SPIEGEL, M.H., & BERGLUND, R.L. (1983) Environmental fate and effects of ethylene oxide. Environ. Sci. Technol., 17: 107-112.

COOKSON, M.J., SIMS, P., & GROVER, P.L. (1971) Mutagenicity of epoxides of polycyclic hydrocarbons correlates with carcinogenicity of parent hydrocarbons. Nature (New Biol.), 234: 186-187.

CREWS, R.C. (1974) Effects of propylene oxide on selected species of fishes, Florida, Air Force Armament Center, Eglin Air Force Base (US NTIS AD/A003637).

CUPITT, L.T. (1980) Fate of toxic and hazardous materials in the environment, Research Trianlge Park, North Carolina, US Environmental Protection Agency, Environmental Sciences Laboratory, Office of Research and Development (US EPA 600/3-80-084, PB 80-221948).

DAVIES, R.E., HARPER, K.H., & KYNOCH, S.R. (1972) Inter-species variation in dermal reactivity. J. Soc. Cosmet. Chem., 23: 371-382.

DEAN, B.J. & HODSON-WALKER, G. (1979) An in vitro chromosome assay using cultured rat liver cells. Mutat. Res., 64: 329-337.

DENT, J.G. & SCHNELL, S.R. (1981) Inhibition of microsomal membrane-bound and purified epoxide hydrolase by C2-C8 1,2-alkene oxides. Biochem. Pharmacol., 30: 1712-1714.

DUNKELBERG, H. (1981) [Carcinogenic activity of ethylene oxide and its reaction products 2-chloroethanol, 2-bromoethanol, ethylene glycol, and diethylene glycol. I. Carcinogenicity of ethylene oxide in comparison with 1,2-propylene oxide after subcutaneous administration in mice.] Zbl. Bakt. Hyg. (I. Abt. Orig. B), 174: 383-404 (in German).

DUNKELBERG, H. (1982) Carcinogenicity of ethylene oxide and 1,2-propylene oxide upon intragastric administration to rats. Br. J. Cancer, 46: 924-933.

EHRENBERG, L., HIESCHE, K.D., OSTERMAN-GOLKAR, S., & WENNBERG, I. (1974) Evaluation of genetic risks of alkylating agents: Tissue doses in the mouse from air contaminated with ethylene oxide. Mutat. Res., 24: 83-103.

FAO/WHO JOINT EXPERT COMMITTEE ON FOOD ADDITIVES (1974) WHO Food Add. Ser., 5: 491-497 (Toxicological Monographs arising

from the Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives).

FARMER, P.B., GORF, S.M., & BAILEY, E. (1982) Determination of hydroxypropylhistidine in haemoglobin as a measure of exposure to propylene oxide using high resolution gas chromatography mass spectrometry. Biomed. Mass Spectrometr., 9: 69-71.

FEDERAL REGISTER (1971) Paragraph 121.1076, propylene oxide, subpart D, food additives, Washington DC, US Environmental Protection Agency, Food and Drug Administration, p. 33.

FJELLSTEDT, T.A., ALLEN, R.H., DUNCAN, B.K., & JAKOBY, W.B. (1973) Enzymatic conjugation of epoxides with glutathione. J. Biol. Chem., 248: 3702-3707.

FLORES, G.H. (1983) Reducing plant pollution exposure: controlling exposure to alkene oxides. Chem. Eng. News, 79: 39-43.

GARRO, A.J. & PHILLIPS, R.A. (1980) Detection of mutagen-induced lesions in isolated DNA by marker rescue of Bacillus subtilis phage stopb105. Mutat. Res., 73: 1-13.

GUENGERICH, F.P. & MASON, P.S. (1980) Alcohol dehydrogenase-coupled spectrophotometric assay of epoxide hydratase activity. Anal. Biochem., 104: 445-451.

GUNTHER, D.A. (1965) Determination of adsorbed ethylene and propylene oxides by distillation and titration. Anal. Chem., 37: 1172-1173.

HACKETT, P.L., BROWN, M.G., BUSCHBOM, R.L., CLARK, M.L., MILLER, R.A., MUSIC, R.L., ROWE, S.E., SCHIRMER, R.E., & SIKOV, M.R. (1982) Teratogenic study of ethylene and propylene oxide and N-butyl acetate, Richland, Washington, Batelle Pacific Northwest Laboratories (Prepared for NIOSH) (PB 83-258038).

HARDIN, B.D., SCHULER, R.L., MCGINNIS, P.M., NIEMEIER, R.W., & SMITH, R.J. (1983) Evaluation of propylene oxide for mutagenic activity in 3 in vivo test systems. Mutat. Res., 117: 337-344.

HATFIELD, R. (1957) Biological oxidation of some organic compounds. Ind. Eng. Chem., 49: 192-196.

HELLMAN, T.M. & SMALL, F.H. (1974) Characterization of the odour properties of 101 petrochemicals using sensory method. J. Air Pollut. Contr. Assoc., 24: 979-982.

HEMMINKI, K. & FALCK, K. (1979) Correlation of mutagenicity and 4-(p-nitrobenzyl)-pyridine alkylation by epoxides. Toxicol. Lett., 4: 103-106.

HEMMINKI, K., PAASIVIRTA, J., KURKIRINNE, T., & VIRKKI, L. (1980) Alkylation products of DNA bases by simple epoxides. Chem.-biol. Interact., 30: 259-270.

HESLOT, H. (1962) Etude quantitative de réversions biochimiques induites chez la levure Schizosaccharomyces pombe par des radiations et des substances radiomimétiques. Abh. Dtsch. Akad. Wiss. Berlin, Kl. Med., 1: 193-228.

HEUSER, S.G. & SCUDAMORE, K.A. (1969) Determination of fumigant residues in cereals and other foodstuffs: A multi-detection scheme for gas chromatography of solvent extracts. J. Sci. Food Agric., 20: 566-572.

HIRASHIMA, T., OGUMA, T., HOSOGAI, Y., & FUJII, S. (1970) [Studies on gaseous antimicrobial agents. III. Determination of propylene oxide residue in food wrappings and containers.] J. Food Hyg. Soc. Jpn, 11: 161-163 (in Japanese).

HUSSAIN, S. & OSTERMAN-GOLKAR, S. (1984) Dose-response relationships for mutations induced in E. coli by some model compounds. Hereditas, 101: 57-68.

IARC (1976) Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anaesthetics, Lyons, International Agency for Research on Cancer, 293 pp (IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 11).

IARC (1985) Allyl compounds, aldehydes, epoxides, and peroxides, Lyons, International Agency for Research on Cancer (Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man, Vol. 36).

IRPTC (1984) Data profile on propylene oxide, Geneva, Switzerland, International Register on Potentially Toxic Chemicals, United Nations Environment Programme.

JACOBSON, K.H., HACKLEY, E.B., & FEINSILVER, L. (1956) The toxicity of inhaled ethylene oxide and propylene oxide vapours. Arch. ind. Health, 13: 237-244.

JENSEN, O. (1981) Contact allergy to propylene oxide and isopropyl alcohol in a skin desinfectant swab. Contact Dermatit., 7: 148-150.

KETEL, W.G. VAN (1979) Contact dermatitis from propylene oxide. Contact Dermatit., 5: 191-192.

KOLMARK, H.G. & GILES, N.H. (1955) Comparative studies of monoepoxides as inducers of reverse mutations in Neurospora. Genetics, 40: 890-902.

KOSKIKALLIO, J. & WHALLEY, E. (1959) Effect of pressure on the spontaneous and the base-catalysed hydrolyses of epoxides. Can. J. Chem., 37: 783-787.

KROST, K.J., PELLIZZARI, E.D., WALBURN, S.G., & HUBBARD, S.A. (1982) Collection and analysis of hazardous organic emissions. Anal. Chem., 54: 810-817.

LAWLEY, P.D. & JARMAN, M. (1972) Alylation by propylene oxide of deoxyribonucleic acid, adenine, guanosine, and deoxyguanylic acid. Biochem. J., 126: 893-900.

LYNCH, D.W., LEWIS, T.R., MOORMAN, W.J., BURG, J.R., GROTH, D.H., KHAN, A., ACKERMAN, L.J., & COCKRELL, B.Y. (1984a) Carcinogenic and toxicologic effects of inhaled ethylene oxide and propylene oxide in F344 rats. Toxicol. appl. Pharmacol., 76(1): 69-84.

LYNCH, D.W., LEWIS, T.R., MOORMAN, W.J., BURG, J.R., GULATI, D.K., KAUR, P., & SABHARWAL, P.S. (1984b) Sister-chromatid exchanges and chromosome aberrations in lymphocytes from monkeys exposed to ethylene oxide and propylene oxide by inhalation. Toxicol. appl. Pharmacol., 76(1): 85-95.

LYNCH, D.W., LEWIS, T.R., MOORMAN, W.J., LAL, J.B., BURG, J.R., GULATI, D.K., ZAVOS, P.M., & SABHARWAL, P.S. (1984c) Toxic and mutagenic effects of inhaled ethylene oxide and propylene oxide on spermatogenic functions in monkeys. Toxicologist, 3: 60.

MCLAUGHLIN, R.S. (1946) Chemical burns of the human cornea. Am. J. Ophthalmol., 29: 1355-1362.

MCMAHON, R.E., CLINE, J.C., & THOMPSON, C.Z. (1979) Assay of 855 test chemicals in ten tester strains using a new modification of the Ames test for bacterial mutagens. Cancer Res., 39: 682-693.

MESTRES, R. & BARROIS, C. (1964) Recherche et dosage de l'oxyde de propylène et du propylène-glycol dans les fruits par chromatographie gazeuse directe. Bull. Soc. Pharm. Montpellier, 24: 47-63.

MIGLIORE, L., ROSSI, A.M., & LOPRIENO, N. (1982) Mutagenic action of structurally-related alkene oxides on Schizosaccharomyces pombe: The influence, "in vitro", of mouse liver metabolizing system. Mutat. Res., 102: 425-437.

MISHMASH, E.H. & MELOAN, C.E. (1972) Indirect spectrophotometric determination of nanomale quantities of oxiranes. Anal. Chem., 44: 835-836.

NELIS, H.J.C.F. & SINSHEIMER, J.E. (1981) A sensitive fluorimetric procedure for the determination of aliphatic epoxides under physiological conditions. Anal. Biochem., 115: 151-157.

NIOSH (1977) Manual of analytical methods, 2nd ed., Cincinnati, Ohio, US Department of Health, Education and Welfare, National Institute for Occupational Safety and Health, Vol. 2, pp. S75-1 - S75-8.

OESCH, F. (1974) Purification and specificity of a human microsomal epoxide hydratase. Biochem. J., 139: 77-88.

OGUMA, T., HOSOGAI, Y., FUJII, S., & KAWASHIRO, I. (1968) [Gaseous antimicrobial agents. I. Determination of propylene oxide residues in foods.] J. Food Hyg. Soc. Jpn, 9: 395-398 (in Japanese).

OGUMA, T., HOSOGAI, Y., & FUJII, S. (1969) [Studies on gaseous antimicrobial agents. II. Determination of propylene oxide residue in fats and oils.] J. Food Hyg. Soc. Jpn, 10: 37-39 (in Japanese).

OSTERMAN-GOLKAR, S., EHRENBERG, L., SEGERBACK, D., & HALLSTROM, I. (1976) Evaluation of genetic risks of alkylating agents. II. Haemoglobin as a dose monitor. Mutat. Res., 34: 1-10.

OSTERMAN-GOLKAR, S., FARMER, P.B., SEGERBACK, D., BAILEY, E., CALLEMAN, C.J., SVENSSON, K., & EHRENBERG, L. (1983) Dosimetry of ethylene oxide in the rat by quantitation of alkylated histidine in haemoglobin. Teratog. Carcinog. Mutagen., 3: 395-405.

OSTERMAN-GOLKAR, S., BAILEY, E., FARMER, P.B., GORF, S.M., & LAMB, J.H. (1984) Monitoring exposure to propylene oxide through the determination of haemoglobin alkylation. Scand. J. Work environ. Health, 10: 99-102.

PERO, R.W., BRYNGELSSON, T., WIDEGREN, B., HOGSTEDT, B., & WELINDER, H. (1982) A reduced capacity for unscheduled DNA synthesis in lymphocytes from individuals exposed to propylene oxide and ethylene oxide. Mutat. Res., 104: 193-200.

PFEIFFER, E.H. & DUNKELBERG, H. (1980) Mutagenicity of ethylene oxide and propylene oxide and of the glycols and halohydrins formed from them during the fumigation of foodstuffs. Food Cosmet. Toxicol., 18: 115-118.

PHILLIPS, R.A., ZAHLER, S.A., & GARRO, A.J. (1980) Detection of mutagen-induced lesions in isolated DNA using a new Bacillus subtilis transformation-based assay. Mutat. Res., 74: 267-281.

RADDING, S.B., LUI, D.H., JOHNSON, H.L., & MILL, T. (1977) Review of the environmental fate of selected chemicals, Washington DC, US Environmental Protection Agency, Office of Toxic Substances (US EPA 560/5-77-003, PB 267121).

RAGELIS, E.P., FISHER, B.S., KLIMECK, B.A., & JOHNSON, C. (1968) Isolation and determination of chlorohydrins in foods fumigated with ethylene oxide or with propylene oxide. J. Assoc. Offic. Agric. Chem., 51: 709-715.

RANDERATH, K., REDDY, M.V., & GUPTA, R.C. (1981) ^{32}P-labelling test for DNA damage. Proc. Natl Acad. Sci., 78: 6126-6129.

REUZEL, P.G.J. & KUPER, C.F. (1983) Chronic (28-month) inhalation toxicity/carcinogenicity study of 1,2-propylene oxide in rats. Final Report, Zeist, The Netherland, TNO, Division of Nutrition and Food Research (Report No. V82.215/280853).

REUZEL, P.G.J. & KUPER, C.F. (1984) Chronic (28-month) inhalation toxicity/carcinogenicity study of 1,2-propylene oxide in rats, Zeist, The Netherland, TNO, Division of Nutrition and Food Research (Addendum to Report No. V82.215/280853).

ROSS, W.C.J. (1950) The reactions of certain epoxides in aqueous solutions. J. Chem. Soc., 2257-2271.

ROWE, V.K., HOLLINGSWORTH, R.L., OYEN, F., MCCOLLISTER, D.D., & SPENCER, H.C. (1956) Toxicity of propylene oxide determined on experimental animals. Arch. ind. Health, 13: 228-236.

RUDDICK, J.A. (1972) Toxicology, metabolism, and biochemistry of 1,2-propanediol. Toxicol. appl. Pharmacol., 21: 102-111.

RUSSELL, J.W. (1975) Analyses of air pollutants using sampling tubes and gas chromatography. Environ. Sci. Technol., 9: 1175-1178.

SCUDAMORE, K.A. & HEUSER, S.G. (1971) Ethylene oxide and its persistent reaction products in wheat flour and other commodities: Residues from fumigation or sterilization, and effects of processing. Pestic. Sci., 2: 80-91.

SINA, J.F., BEAN, C.L., DYSART, G.R., TAYLOR, V.I., & BRADLEY, M.O. (1983) Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat. Res., 113: 357-391.

SMYTH, H.F., SEATON, J., & FISHER, L. (1941) The single dose toxicity of some glycols and derivatives. J. ind. Hyg. Toxicol., 23: 259-268.

SNELLINGS, W.M., WEIL, C.S., & MARONPOT, R.R. (1984) A two-year inhalation study of the carcinogenic potential of ethylene oxide in Fischer 344 rats. Toxicol. appl. Pharmacol., 75: 105-117.

SPRINZ, H., MATZKE, H., & CARTER, J. (1982) Neuropathological evaluation of monkeys exposed to ethylene and propylene oxide, Kansas City, Missouri, Midwest Research Institute (Prepared for NIOSH) (PB 83-134817).

STEELE, L. & HADZIYEV, D. (1976) Sterilization of dehydrated potato granules with propylene oxide. Z. Lebensm. Unters.-Forsch., 162: 387-399.

STOCKER, W.G. & THIESS, A.M. (1979) Morbidity study on workers exposed to ethylene oxide/propylene oxide. In: The 7th Medichem Congress, Gera, 11-15 September, 1979.

STORCK, W.J. (1981) Output of big-volume chemicals fell in 1980. Chem. Eng. News, 59: 36-39.

SVENSSON, K. & OSTERMAN-GOLKAR, S. (1984) Kinetics of metabolism of propene and covalent binding to macromolecules in the mouse. Toxicol. appl. Pharmacol., 73: 363-372.

SWAN, J.D. (1954) Determination of epoxides with sodium sulfite. Anal. Chem., 26: 878-880.

TACHIZAWA, H., MACDONALD, T.L., & NEAL, R.A. (1982) Rat liver microsomal metabolism of propyl halides. Mol. Pharmacol., 22: 745-751.

THIESS, A.M., SCHWEGLER, H., FLEIG, I., & STOCKER, W.G. (1981a) Mutagenicity study of workers exposed to alkylene oxides (ethylene oxide/propylene oxide) and derivatives. J. occup. Med., 23: 343-347.

THIESS, A.M., FRENZEL-BEYME, R., LINK, R., & STOCKER, W.H. (1981b) Mortality study on employees exposed to alkylene oxides (ethylene oxide/propylene oxide) and their derivatives. In: Proceedings of the International Symposium on Prevention of Occupational Cancer, Helsinki, Finland, pp. 249-259.

US EPA (1981) Human exposure to atmospheric concentrations of selected chemicals, Research Triangle Park, North Carolina, US Environmental Protection Agency, Office of Air Quality Planning and Standards (US NTIS PB 84-102540, PB 83-265249).

US NTP (1984) Toxicology and carcinogenesis studies of propylene oxide in F344/N rats and B6C3F1 mice (inhalation studies), Research Triangle Park, North Carolina, National Toxicology Program (NTP 83-020) (NIH Publication No. 84-2523).

VOJNOVICH, C. & PFEIFER, V.F. (1967) Reducing the microbial population of flour during milling. Cereal Sci. Today, 12: 54-60.

VOOGD, C.E., STEL, J.J. VAN DE, & JACOBS, J.J.J.A.A. (1981) The mutagenic action of aliphatic epoxides. Mutat. Res., 89: 269-282.

WADE, D.R., AIRY, S.C., & SINSHEIMER, J.E. (1978) Mutagenicity of aliphatic epoxides. Mutat. Res., 58: 217-223.

WALLES, S.A. (1974) The influence of some alkylating agents on the structure of DNA in vitro. Chem.-biol. Interact., 9: 97-103.

WEBBER, D. (1984) Basic chemical output returns to growth. Top 50 chemical products. Chem. Eng. News, May 7: 8-10.

WEIL, C.S., CONDRA, N., HAUN, C., & STRIEGEL, J.A. (1963) Experimental carcinogenicity and acute toxicity of representative epoxides. Am. Ind. Hyg. Assoc. J., 24: 305-325.

WHO (1978) Environmental health problems associated with the manufacture and uses of synthetic organic chemicals, Geneva, World Health Organization (Report No. HCS/78.2).

WHO (1985) EHC 55: Ethylene oxide, Geneva, World Health Organization, 79 pp.

ZAMORA, P.O., BENSON, J.M., LI, A.P., & BROOKS, A.L. (1983) Evaluation of an exposure system using cells grown on collagen gels for detecting highly-volatile mutagens in the CHO/HGPRT mutation assay. Environ. Mutagen., 5: 795-801.