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Environmental Health Criteria 215

VINYL CHLORIDE

Please note that the layout and pagination of this pdf file and the printed EHC are not identical.
The corrigenda published by November 30, 2004 for this EHC are incorporated in this file

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World Health Organization
Geneva, 1999

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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CONTENTS

ENVIRONMENTAL HEALTH CRITERIA FOR
VINYL CHLORIDE

NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Case postale 356, 1219 Châtelaine, Geneva, Switzerland (telephone no. + 41 22 - 9799111, fax no. + 41 22 - 7973460, E-mail irptc@unep.ch).

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Environmental Health Criteria

PREAMBLE

Objectives

In 1973 the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(i)   to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;

(ii)   to identify new or potential pollutants;

(iii)   to identify gaps in knowledge concerning the health effects of pollutants;

(iv)   to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976, and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g., for genetic, neurotoxic, teratogenic and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly and so forth.

Since its inauguration the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of UNEP, ILO and WHO. In

this manner, with the strong support of the new partners, the importance of occupational health and environmental effects was fully recognized. The EHC monographs have become widely established, used and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents. As such, they include and review studies that are of direct relevance for the evaluation. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are used only when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and *in vitro* studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent

risk management decisions. They represent a thorough evaluation of risks and are not, in any sense, recommendations for regulation or standard setting. These latter are the exclusive purview of national and regional governments.

Content

The layout of EHC monographs for chemicals is outlined below.

- Summary — a review of the salient facts and the risk evaluation of the chemical
- Identity — physical and chemical properties, analytical methods
- Sources of exposure
- Environmental transport, distribution and transformation
- Environmental levels and human exposure
- Kinetics and metabolism in laboratory animals and humans
- Effects on laboratory mammals and *in vitro* test systems
- Effects on humans
- Effects on other organisms in the laboratory and field
- Evaluation of human health risks and effects on the environment
- Conclusions and recommendations for protection of human health and the environment
- Further research
- Previous evaluations by international bodies, e.g., IARC, JECFA, JMPR

Selection of chemicals

Since the inception of the EHC Programme, the IPCS has organized meetings of scientists to establish lists of priority chemicals for subsequent evaluation. Such meetings have been held in Ispra, Italy, 1980; Oxford, United Kingdom, 1984; Berlin, Germany, 1987; and North Carolina, USA, 1995. The selection of chemicals has been based on the following criteria: the existence of scientific evidence that the substance presents a hazard to human health and/or the environment; the possible use, persistence, accumulation or degradation of the substance shows that there may be significant human or environmental exposure; the size and nature of populations at risk (both human and other species) and risks for environment;

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international concern, i.e. the substance is of major interest to several countries; adequate data on the hazards are available.

If an EHC monograph is proposed for a chemical not on the priority list, the IPCS Secretariat consults with the Cooperating Organizations and all the Participating Institutions before embarking on the preparation of the monograph.

Procedures

The order of procedures that result in the publication of an EHC monograph is shown in the flow chart on p. xv. A designated staff member of IPCS, responsible for the scientific quality of the document, serves as Responsible Officer (RO). The IPCS Editor is responsible for layout and language. The first draft, prepared by consultants or, more usually, staff from an IPCS Participating Institution, is based initially on data provided from the International Register of Potentially Toxic Chemicals, and reference data bases such as Medline and Toxline.

The draft document, when received by the RO, may require an initial review by a small panel of experts to determine its scientific quality and objectivity. Once the RO finds the document acceptable as a first draft, it is distributed, in its unedited form, to well over 150 EHC contact points throughout the world who are asked to comment on its completeness and accuracy and, where necessary, provide additional material. The contact points, usually designated by governments, may be Participating Institutions, IPCS Focal Points, or individual scientists known for their particular expertise. Generally some four months are allowed before the comments are considered by the RO and author(s). A second draft incorporating comments received and approved by the Director, IPCS, is then distributed to Task Group members, who carry out the peer review, at least six weeks before their meeting.

The Task Group members serve as individual scientists, not as representatives of any organization, government or industry. Their function is to evaluate the accuracy, significance and relevance of the information in the document and to assess the health and environmental risks from exposure to the chemical. A summary and recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and by the need for a balanced geographical distribution.

EHC PREPARATION FLOW CHART

Commitment to draft EHC

Document preparation initiated

Possible meeting of a few experts to resolve controversial issues

Revision as necessary

Draft sent to IPCS Responsible Officer (RO)

Responsible Officer, Editor check for coherence of text and readability (not language editing)

First Draft

International circulation to contact points (150+)

Comments to IPCS (RO)

Review of comments, reference cross-check; preparation of Task Group (TG) draft

Editor

Task group meeting

Working group, if needed

Insertion of TG changes

Post-TG draft, detailed reference cross-checking

Editing

Graphics

Word-processing

French/Spanish translations of Summary

Camera-ready copy

Library for CIP data

Final editing

Approval by director, IPCS

WHO Publication Office

Printer → Proofs → Publication

→ Routine procedure

⇢ Optional procedure

The three cooperating organizations of the IPCS recognize the important role played by nongovernmental organizations. Representatives from relevant national and international associations may be invited to join the Task Group as observers. Although observers may provide a valuable contribution to the process, they can only speak at the invitation of the Chairperson. Observers do not participate in the final evaluation of the chemical; this is the sole responsibility of the Task Group members. When the Task Group considers it to be appropriate, it may meet *in camera.*

All individuals who as authors, consultants or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the RO if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a conflict of interest statement. Such a procedure ensures the transparency and probity of the process.

When the Task Group has completed its review and the RO is satisfied as to the scientific correctness and completeness of the document, it then goes for language editing, reference checking and preparation of camera-ready copy. After approval by the Director, IPCS, the monograph is submitted to the WHO Office of Publications for printing. At this time a copy of the final draft is sent to the Chairperson and Rapporteur of the Task Group to check for any errors.

It is accepted that the following criteria should initiate the updating of an EHC monograph: new data are available that would substantially change the evaluation; there is public concern for health or environmental effects of the agent because of greater exposure; an appreciable time period has elapsed since the last evaluation.

All Participating Institutions are informed, through the EHC progress report, of the authors and institutions proposed for the drafting of the documents. A comprehensive file of all comments received on drafts of each EHC monograph is maintained and is available on request. The Chairpersons of Task Groups are briefed before each meeting on their role and responsibility in ensuring that these rules are followed.

WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR VINYL CHLORIDE

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WHO TASK GROUP ON ENVIRONMENTAL HEALTH CRITERIA FOR VINYL CHLORIDE

A WHO Task Group on Environmental Health Criteria for Vinyl Chloride met at the Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany, from 25 to 29 January 1999. Professor H. Muhle welcomed the participants on behalf of the Institute and its Director, Professor U. Heinrich. Dr A. Aitio, IPCS, welcomed the participants on behalf of the Director, IPCS, and the three IPCS co-operating organisations (UNEP, ILO, and WHO). The Group reviewed and revised the draft and made an evaluation of the risks for human health and the environment from exposure to vinyl chloride.

The first and second drafts of this monograph were prepared, under the co-ordination of Dr I. Mangelsdorf, by the authors Dr J. Kielhorn, Dr C. Melber and Dr U. Wahnschaffe. In the preparation of the second draft, the comments received from the IPCS contact points were carefully considered.

Dr A. Aitio of the IPCS Central Unit was responsible for the scientific aspects of the monograph, and Dr P.G. Jenkins for the technical editing.

The efforts of all who helped in the preparation and finalisation of the monograph are gratefully acknowledged.

* * *

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ABBREVIATIONS

Epsilon A	1, N^6-ethenoadenine
Epsilon C	3, N^4-ethenocytosine
Epsilon dA	1, N^6-etheno-2'-deoxyadenosine
Epsilon dC	3, N^4-etheno-2'-deoxycytidine
Epsilon G	ethenoguanine
7-OEG	7-(2'-oxoethyl)guanine
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
ASL	angiosarcoma of the liver
BCF	bioconcentration factor
CA	chromosomal aberration
CAA	chloroacetaldehyde
CEO	chloroethylene oxide
CI	confidence interval (95% unless otherwise stated)
CNS	central nervous system
CYP2E1	cytochrome P-450 isozyme 2e1
ECD	electron capture detection
EDC	1,2-dichloroethane
FDA	Food and Drug Administration (USA)
FID	flame ionization detector
GC	gas chromatography
GST	glutathione S-transferase
HCC	hepatocellular carcinoma
HLA	human-leukocyte-associated antigen
HPLC	high performance liquid chromatography
HWD	hazardous waste dump
IR	infrared
LOAEL	lowest-observed-adverse-effect level

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MN	micronuclei
MOR	morbidity odds ratio
MS	mass spectrometry
MSW	municipal solid waste
NER	non-extractable residue
NOAEC	no-observed-adverse-effect concentration
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PCDD	polychlorinated dibenzodioxin
PCDF	polychlorinated dibenzofuran
PCE	tetrachloroethene (perchloroethene)
PID	photoionization detector
PVC	polyvinyl chloride
SCE	sister chromatid exchange
SIR	standardized incidence ratio
SLRL	sex-linked recessive lethal
SMR	standardized mortality ratio
TCE	trichloroethene
TEQ	toxic equivalent quantity
UV	ultraviolet
VC	vinyl chloride
VOC	volatile organic compound

1. SUMMARY

This monograph deals with vinyl chloride (VC) monomer itself and is not an evaluation of polyvinyl chloride (PVC), the polymer of VC. Exposures to VC in mixtures are not addressed.

1.1 Identity, physical and chemical properties, and analytical methods

Under ambient conditions, VC is a colourless, flammable gas with a slightly sweet odour. It has a high vapour pressure, a high value for Henry's Law constant and a relatively low water solubility. It is heavier than air and is soluble in almost all organic solvents. It is transported in liquid form under pressure.

At ambient temperatures in the absence of air, dry purified VC is highly stable and non-corrosive but above 450 °C, or in the presence of sodium or potassium hydroxide, partial decomposition can occur. Combustion of VC in air produces carbon dioxide and hydrogen chloride. With air and oxygen, very explosive peroxides can be formed, necessitating a continuous monitoring and limitation of the oxygen content, particularly in VC recovery plants. In the presence of water, hydrochloric acid is formed.

Polymerization reactions to PVC are technically the most important reactions from an industrial view, but addition reactions with other halogens at the double bond, e.g., to yield 1,1,2-trichloroethane or 1,1-dichloroethane, are also important.

The concentration of VC in air can be monitored by trapping it on adsorbents and, after liquid or thermal desorption, analysis by gas chromatography. In ambient air measurements, several adsorbents in series or refrigerated traps may be needed to increase the efficiency of trapping. Peak concentrations at workplaces can be measured with direct-reading instruments based on, for instance, FID or PID. In continuous monitoring, IR and GC/FID analysers combined with data logging and processing have been used. In analysis of VC in liquids and solids, direct injection, extraction and more increasingly head space or purge-and-trap techniques are applied. Also in these samples, VC is analysed by GC fitted to, for instance, FID or MS detectors.

1.2 Sources of human and environmental exposure

VC is not known to occur naturally although it has been found in landfill gas and groundwater as a degradation product of chlorinated hydrocarbons deposited as solvent wastes in landfills or in the environment of workplaces using such solvents. VC is also present in cigarette smoke.

VC is produced industrially by two main reactions: a) the hydrochlorination of acetylene; and b) thermal cracking (at about 500 /C) of 1,2-dichloroethane (EDC) produced by direct chlorination (ethylene and chlorine) or oxychlorination (ethylene, HCl and air/O_2) of ethylene in the "balanced process". The latter process is the most usual nowadays.

The world production of PVC (and therefore VC) in 1998 was about 27 million tonnes. PVC accounts for 20% of plastics material usage and is used in most industrial sectors. About 95% of the world production of VC is used for the production of PVC. The remainder goes into the production of chlorinated solvents, primarily 1,1,1-trichloroethane (10 000 tonnes/year).

Three main processes are used for the commercial production of PVC: suspension (providing 80% of world production), emulsion (12%) and mass or bulk (8%). Most of the case studies describing adverse effects of VC concern plants using the suspension (also called dispersion) process.

There have been reports of VC release through accidents in PVC plants or during transportation. VC recovery has been introduced in many countries to recover residual non-converted VC from polymerization and other sources of the process such as in off-gas and water effluents. Where special precautions are not taken, VC can be detected in PVC resins and products.

The level of residual VC in PVC has been regulated since the late 1970s in many countries. Since then, release of VC from the thermal degradation of PVC is either not detectable or is at very low levels.

Dioxins can be formed as contaminants in VC production. The levels of dioxins emitted into the environment are controversial.

1.3 Environmental transport, distribution and transformation

Owing to its high vapour pressure, VC released to the atmosphere is expected to exist almost entirely in the vapour phase. There are indications for wet deposition.

VC has a relatively low solubility in water and has a low adsorption capacity to particulate matter and sediment. Volatilization of VC is the most rapid process for removal of VC introduced into surface waters. Half-lives reported for volatilization from surface waters range from about 1 to 40 h.

Volatilization half-lives from soil were calculated to be 0.2–0.5 days. Estimated losses of VC (after one year under a 1 m soil cover) ranged from 0.1–45%, depending on soil type. Soil sorption coefficients estimated from physicochemical data indicate a low sorption potential and therefore a high mobility in soil. Another important distribution route is leaching through the soil into groundwater where VC may persist for years.

Laboratory experiments with aquatic organisms showed some bioaccumulation, but no biomagnification within the foodchain.

With few exceptions, VC is not easily degraded by unadapted microbial consortia under environmental conditions. Maximum unacclimated biodegradation half-lives of VC were estimated to be in the order of several months or years. However, special enrichment or pure (e.g., *Mycobacterium* sp.) cultures are capable of degrading VC under optimal culture conditions. The main degradation products were glycolic acid or carbon dioxide after aerobic conversion and ethane, ethene, methane or chloromethane after anaerobic transformation. Frequently, the degradation reaction of VC proceeded faster with aerobes than with anaerobes.

Reaction with photochemically produced OH radicals is the dominant atmospheric transformation process, resulting in calculated

tropospheric half-lives of 1 to 4 days. Several critical compounds, such as chloroacetaldehyde, formaldehyde and formyl chloride, are generated during experimental photolysis reactions.

Photolytic reactions as well as chemical hydrolysis are thought to be of minor importance in aqueous media. However, the presence of photosensitizers may enhance the transformation of VC.

There are indications for reactions of VC with chlorine or chloride used for water disinfection, thus leading to chloroacetaldehyde and other undesirable compounds. Another possibility for interaction is with salts, many of which have the ability to form complexes with VC, perhaps resulting in increased solubility.

Methods employed (with differing success) for removal of VC from contaminated waters include stripping, extraction, adsorption and oxidation. Some *in situ* bioremediation techniques (for groundwater or soil) couple evaporative and other methods with microbial treatment. VC in waste gases can be recycled, incinerated or microbially degraded. Most of the VC produced industrially is bound in PVC articles. Their incineration involves a risk of formation of PCDDs/PCDFs and other unwanted chlorinated organic compounds.

1.4 Environmental levels and human exposure

There is very little exposure of the general population to VC.

Atmospheric concentrations of VC in ambient air are low, usually less than 3 ：g/m^3. Exposure of the general population may be higher in situations where large amounts of VC are accidentally released to the environment, such as in a spill during transportation. However, such exposure is likely to be transient. Near VC/PVC industry and waste disposal sites, much higher concentrations (up to 8000 ：g/m^3 and 100 ：g/m^3, respectively) have been recorded.

Indoor air concentrations in houses adjacent to land fills reached maximal concentrations of 1000 ：g/m^3.

The main route of occupational exposure is via inhalation and occurs primarily in VC/PVC plants. Occupational exposures to VC

amounted to several thousands of mg/m^3 in the 1940s and 1950s, and were several hundreds of mg/m^3 in the 1960s and early 1970s. After the recognition of the carcinogenic hazards of VC, occupational exposure standards were set at approximately 13–26 mg/m^3 (5–10 ppm) in most countries in the 1970s. Compliance with these guidelines has considerably lowered workplace VC concentrations, but even in the 1990s higher concentrations have been reported and may still be encountered in some countries.

VC has occasionally been detected in surface waters, sediment and sewage sludges, with maxima of 570 μg/litre, 580 μg/kg, and 62 000 μg/litre, respectively. Soil samples near an abandoned chemical cleaning shop contained very high VC concentrations (up to 900 mg/kg). Maximal VC concentrations in groundwater or leachate from areas contaminated with chlorinated hydrocarbons amounted to 60 000 μg/litre (or more). High concentrations (up to 200 mg/litre) were detected in well water in the vicinity of a PVC plant 10 years after leakages.

The few data available show that VC can be present in tissues of small aquatic invertebrates and fish.

In the majority of drinking-water samples analysed, VC was not present at detectable concentrations. The maximum VC concentration reported in finished drinking-water was 10 μg/litre. There is a lack of recent data on VC concentrations in drinking-water, but these levels are expected to be below 10 μg/litre. If contaminated water is used as the source of drinking-water, higher exposures may occur. Some recent studies have identified VC in PVC-bottled drinking-water at levels below 1 μg/litre. The frequency of occurrence of VC in such water is expected to be higher than in tap water.

Packaging with certain PVC materials can result in VC contamination of foodstuff, pharmaceutical or cosmetic products, including liquors (up to 20 mg/kg), vegetable oils (up to 18 mg/kg), vinegars (up to 9.8 mg/kg) and mouthwashes (up to 7.9 mg/kg). Owing to the legislative action of many countries, a significant reduction in VC levels and/or in the number of positive samples has been achieved since the early 1970s.

Dietary exposure to VC from PVC packages used for food has been calculated by several agencies and, based upon estimated average intakes in the United Kingdom and USA, an exposure of < 0.0004 : g/kg per day was estimated for the late 1970s and early 1980s. An early study identified VC in tobacco smoke at the ng/cigarette range.

1.5 Kinetics and metabolism in laboratory animals and humans

VC is rapidly and well absorbed after inhalation or oral exposure. The primary route of exposure to VC is inhalation. In animal and human studies, under steady-state conditions, approximately 40% of inspired VC is absorbed after exposure by inhalation. Animal studies showed an absorption of more than 95% after oral exposure. Dermal absorption of VC in the gaseous state is not significant.

Data from oral and inhalation studies on rats indicate rapid and widespread distribution of VC. Rapid metabolism and excretion limits accumulation of VC in the body. Placental transfer of VC occurs rapidly in rats. No studies on distribution after dermal exposure have been reported.

The main route of metabolism of VC after inhalation or oral uptake involves oxidation by cytochrome P-450 (CYP2E1) to form chloroethylene oxide (CEO), a highly reactive, short-lived epoxide which rapidly rearranges to form chloroacetaldehyde (CAA). The primary detoxification reaction of these two reactive metabolites as well as chloroacetic acid, the dehydrogenation product of CAA, is conjugation with glutathione catalysed by glutathione *S*-transferase. The conjugation products are further modified to substituted cysteine derivatives (*S*-(2-hydroxyethyl)-cysteine, *N*-acetyl-*S*-(2-hydroxyethyl)cysteine, *S*-carboxymethyl cysteine and thiodiglycolic acid) and are excreted via urine. The metabolite carbon dioxide is exhaled in air.

CYP2E1 and glutathione *S*-transferase isoenzymes are known to have large inter-species and inter-individual variation in activity.

After inhalative or oral exposure to low doses, VC is metabolically eliminated and non-volatile metabolites are excreted mainly in the urine. Comparative investigations of VC uptake via

inhalation revealed a lower velocity of metabolic elimination in humans than in laboratory animals, on a body weight basis. However, when corrected on a body surface area basis, the metabolic clearance of VC in humans becomes comparable to that of other mammalian species. With increasing oral or inhalative exposure, the major route of excretion in animals is exhalation of unchanged VC, indicating saturation of metabolic pathways. Independently of applied dose, the excretion of metabolites via faeces is only a minor route. No studies were located that specifically investigated excretion via the bile.

CEO is thought to be the most important metabolite *in vivo*, concerning the mutagenic and carcinogenic effects of VC. CEO reacts with DNA to produce the major adduct 7-(2'-oxoethyl)guanine (7-OEG), and, at lower levels, the exocyclic etheno adducts, 1,N^6-ethenoadenine (, A), 3,N^4-ethenocytosine (, C) and N^2,3-etheno-guanine (, G). The etheno DNA adducts exhibit pro-mutagenic properties, in contrast to the major adduct 7-OEG. 7-OEG, , A, , C and , G have been measured in various tissues from rodents exposed to VC. Physiologically based toxicokinetic (PBTK) models have been developed to describe the relationship between target tissue dose and toxic end-points for VC.

1.6 Effects on laboratory mammals and *in vitro* test systems

VC appears to be of low acute toxicity when administered to various species by inhalation. The 2-h LC_{50} for rat, mouse, guinea-pig and rabbit were reported to be 390 000, 293 000, 595 000 and 295 000 mg/m^3, respectively. No data are available on acute toxicity after oral or dermal application. VC has a narcotic effect after acute inhalation administration. In rats, mice and hamsters, death was preceded by increased motor activity, ataxia and convulsions, followed by respiratory failure. In dogs, severe cardiac arrythmias occurred under narcosis after inhalative exposure to 260 000 mg/m^3. After acute inhalation exposure to VC in rats, pathological findings included congestion of the internal organs, particularly lung, liver and kidney, as well as pulmonary oedema.

No studies or relevant data are available for assessing effects of dermal exposure, skin irritation or sensitizing property of VC.

Short-term oral exposure to VC for 13 weeks in rats resulted in a no-observed-effect level (NOEL), based on increase in liver weight, of 30 mg/kg.

In various species, the main target organ for short-term (up to 6 months) inhalation exposure to VC was the liver. Increases in relative liver weights and hepatocellular changes were noted in rats at 26 mg/m^3 (the lowest dose level tested); at higher levels ($ 260 mg/m^3) more pronounced liver changes occurred in a dose-related manner. Other target organs were the kidney, lung and testis. Rats, mice and rabbits seem to be more sensitive than guinea-pigs and dogs.

Long-term exposure to VC by inhalation resulted in statistically significant increases in mortality in some strains of rats at a dose of as low as 260 mg/m³, in mice at 130 mg/m³ and in hamsters at 520 mg/m³ for various lengths of exposure. Rats exposed to 130 mg/m³ showed reduced body weight and increased relative spleen weight, hepatocellular degeneration and proliferation of cells lining the liver sinusoids. Exposure to higher levels produced degenerative alteration in the testis, tubular nephrosis and focal degeneration of the myocardium in rats. For rats and mice exposed via inhalation, the no-observed-adverse-effect level (NOAEL) concerning non-neoplastic effects is below 130 mg/m³.

Chronic feeding studies showed increased mortality, increased liver weights and morphological alteration of the liver.

After oral exposure, liver cell polymorphism (variation in size and shape of hepatocytes and their nuclei) could be seen in rats at levels as low as 1.3 mg/kg body weight. The NOAEL was 0.13 mg/kg body weight.

Long-term feeding studies in rats with VC in PVC granules yielded significantly increased tumour incidences of liver angiosarcoma (ASL) at 5.0 mg/kg body weight per day and neoplastic liver nodules (females) and hepatocellular carcinoma (HCC) (males) at 1.3 mg/kg body weight per day.

In inhalation studies with VC in Sprague-Dawley rats, a clear dose–response relationship was observed for ASL and, at high

concentrations, Zymbal gland carcinomas. No clear dose-dependency for hepatoma or extrahepatic angiosarcoma, nephroblastomas, neuroblastomas, or mammary malignant tumours was observed. In mice, the spectrum of tumours induced by long-term inhalation exposure is similar to that observed in rats but an increase in lung tumours was only observed in mice. In hamsters, an increased tumour incidence of ASL, mammary gland and acoustic duct tumours, melanomas, stomach and skin epithelial tumours was reported.

The mutagenic and genotoxic effects of VC have been detected in a number of *in vitro* test systems, predominantly after metabolic activation. VC is mutagenic in the Ames test in *S. typhimurium* strains TA100, TA1530 and TA1535 but not in TA98, TA1537 and TA1538, indicating mutations as a result of base-pair substitutions (transversion and transition) rather than frameshift mutations. This is in agreement with the finding that etheno-DNA adducts formed by the reactive metabolites CEO and CAA convert to actual mutations by base-pair substitutions.

Other gene mutation assays in bacteria, yeast cells and mammalian cells have revealed positive results exclusively in the presence of metabolic activation. Mutagenic effects were also reported in a human cell line containing cloned cytochrome P-450IIE1, which is capable of metabolizing VC. Gene mutation was also detected in plant (*Tradescantia*) cuttings exposed to VC. In gene conversion assays, positive results were reported with *Saccharomyces cerevisiae* in the presence of a metabolic activation system. VC exposure induced unscheduled DNA synthesis in rat hepatocytes and increased sister-chromatid exchange (SCE) in human lymphocytes after addition of exogenic activation system. No growth inhibition was detected in DNA repair-deficient bacteria without metabolic activation. Cell transformation assays revealed positive results both with and without metabolic activation.

VC exposure induced gene mutation and mitotic recombination in *Drosophila melanogaster* but not gene mutation in mammalian germ cells. VC showed clastogenic effects in rodents, increased SCE in hamsters and induced DNA breaks in mice. In host-mediated (rat) assays, VC induced gene conversion and forward mutations in yeast.

CEO and CAA were found to be mutagenic in different test systems. CEO is a potent mutagen, whereas CAA is highly toxic. CEO and CAA were found to be carcinogenic in mice, CEO being much more active than CAA.

Mutations of the *ras* and *p53* genes were analysed in liver tumours induced by VC in Sprague-Dawley rats: base-pair substitutions were found in the Ha-*ras* gene in hepatocellular carcinoma (HCC) and in the *p53* gene in ASL. These mutations are in agreement with the observed formation and persistence of etheno adducts in liver DNA, following exposure of rats to VC, and with the known pro-mutagenic properties of etheno adducts.

Studies into the mechanism of carcinogenicity of VC suggest that the reactive epoxide intermediate CEO interacts with DNA to form etheno adducts, which result in a base-pair substitution leading to neoplastic transformation.

1.7 Effects on humans

Concentrations of VC in the region of 2590 mg/m^3 (1000 ppm), which were not unusual prior to 1974, over periods ranging from 1 month to several years, have been reported to cause a specific pathological syndrome found in VC workers called the "vinyl chloride illness". Symptoms described were earache and headache, dizziness, unclear vision, fatigue and lack of appetite, nausea, sleeplessness, breathlessness, stomachache, pain in the liver/spleen area, pain and tingling sensation in the arms/legs, cold sensation at the extremities, loss of libido and weight loss. Clinical findings included scleroderma-like changes in the fingers with subsequent bony changes in the tips of the fingers described as acroosteolysis, peripheral circulatory changes identical with the classical picture of Raynaud's disease and enlargement of the liver and spleen with a specific histological appearance, and respiratory manifestations.

Studies in humans have not been adequate to confirm effects on the reproductive system. A few morbidity studies have reported elevated incidence of circulatory diseases among vinyl chloride workers. However, large cohort studies have found lower cardiovascular disease mortality.

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There is strong and consistent evidence from epidemiological studies that VC exposure causes the rare tumour, angiosarcoma of the liver. Brain tumours and hepatocellular carcinoma of the liver may also be associated with VC, although the evidence cannot be considered definitive. Other cancer sites reported to be in excess, but less consistently, include lung, lymphatic and haematopoietic tissue, and skin.

VC is mutagenic and clastogenic in humans. Frequencies of chromosomal aberrations (CA), micronuclei (MN) and SCE in the peripheral blood lymphocytes of workers exposed to high levels of VC have been shown to be raised compared to controls. Although in many studies the exposure concentrations and duration of exposure were only estimated, a dose–response relationship and a "normalization" of genotoxic effects with time after reduction of exposure can be seen.

Point mutations have been detected in *p53* and *ras* genes in tumours from highly exposed (before 1974) autoclave workers with liver angiosarcoma (ASL) and another VC worker with hepatocellular carcinoma.

Biological markers that have been investigated as indicators for VC exposure or VC-induced effects include a) excretion of VC metabolites (e.g., thiodiglycolic acid), b) genetic assays (e.g., chromosomal abnormalities or micronucleus assay), c) levels of enzymes (e.g., in liver function tests), d) serum oncoproteins (p21 and p53) and/or their antibodies as biomarkers of VC-induced effects.

Children living near landfill sites and other point sources may be at increased risk based on suggested evidence of early life sensitivity in animal studies. However, there is no direct evidence in humans.

In epidemiological studies, a clear dose–response is only evident for ASL alone or in combination with other liver tumours. Only one epidemiological study has sufficient data for quantitative dose–response estimation.

1.8 Effects on other organisms in the laboratory and field

There is a lack of standard toxicity data on the survival and reproduction of aquatic organisms exposed to VC. Care must be taken

when interpreting the data that are available, as most of it was generated from tests where the exposure concentration was not measured and therefore losses due to volatilization were not taken into account.

The lowest concentration of VC that caused an effect in microorganisms was 40 mg/litre. This was an EC_{50} value based upon inhibition of respiration in anaerobic microorganisms in a batch assay over 3.5 days.

The lowest concentration that caused an effect in higher organisms was 210 mg/litre (48-h LC_{50} for a freshwater fish); with a corresponding no-observed-adverse-effect concentration (NOAEC) of 128 mg/litre. Effects due to VC have been reported at lower concentrations in other species, but the ecological significance of these effects was not verified.

VC concentrations predicted to be non-hazardous to freshwater fish were calculated to range from 0.088 to 29 mg/litre.

There is a paucity of data concerning the effects of VC on terrestrial organisms.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, AND ANALYTICAL METHODS

This monograph deals with vinyl chloride (VC) monomer itself and is not an evaluation of polyvinyl chloride (PVC), the polymer of VC.

2.1 Identity

Chemical formula:	C_2H_3Cl
Chemical structure:	$H_2C=CHCl$
Relative molecular mass:	62.5
Common names:	Vinyl chloride
CAS chemical name:	Ethene, chloro-
IUPAC name:	Chloroethene
CAS Registry number:	75-01-4
EC Number:	602-023-007
EINECS Number:	2008310
Synonyms:	vinyl chloride monomer, monochloroethene; monochloroethylene; 1-chloroethylene, chloroethene, chloroethylene
Purity	99.9% (by weight); water: max. 120 mg/kg; HCl: max. 1 mg/kg (BUA, 1989) Up to the 1960s the purity was not so high (Lester et al., 1963)
Typical trace components	10–100 mg/kg range: chloromethane, chloroethane; 1–10 mg/kg range: ethyne (acetylene), 1,3-butadiene, butene, 1,2-dichloroethane, ethene, propadiene (allene), propene, 1-butyne-3-ene (vinyl acetylene) (BUA, 1989)

2.2 Physical and chemical properties

Some physical properties of VC are given in Table 1. Under ambient conditions, vinyl chloride is a colourless, flammable gas with a slightly sweet odour. It is heavier than air and has relatively low solubility. There are discrepancies in the literature with regard to Henry's Law constant (air-water partition coefficient, Hc). Whereas some authors give a value between 1 and 3 kPa.m^3/mol, other sources quote a value two orders higher. Large uncertainties in the absolute aqueous solubility in older studies probably contribute most to these discrepancies (Ashworth et al., 1988). It is an azeotrope with water: 0.1 parts water/100 parts vinyl chloride (Bönnighausen, 1986; Rossberg et al., 1986). VC is soluble in almost all organic solvents.

Since it is a gas that is heavier than air, VC can spread over the ground creating an exposure long distances away from the original source and can form explosive mixtures. The odour threshold value is very subjective (see Table 1) and is far above the present accepted occupational safety threshold values (see Annex 1).

VC is transported as a compressed liquid. As it does not tend to polymerize easily, liquid VC (in the absence of oxygen and water) can be stored and transported without polymerization inhibitors (Bönnighausen, 1986).

At ambient temperatures in the absence of air, dry purified VC is highly stable and non-corrosive. Above 450 °C, partial decomposition occurs yielding acetylene, hydrogen chloride and trace amounts of 2-chloro-1,3-butadiene (chloroprene) (Rossberg et al., 1986). This reaction also occurs by lower temperatures (at 30 °C and under) in the presence of sodium or potassium hydroxide (Bönnighausen, 1986).

Combustion of VC in air produces carbon dioxide and hydrogen chloride. Under oxygen deficient conditions, traces of phosgene may be formed (Rossberg et al., 1986). In chlorine-atom-initiated oxidation of VC, the vinyl chloride peroxide formed decomposes to formaldehyde, hydrogen chloride and carbon monoxide (Bauer & Sabel, 1975; Sanhueza et al., 1976).

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Table 1. Some physical and chemical properties of vinyl chloride

Melting point	−153.8 °C	Bönnighausen (1986); Dreher (1986)
Boiling point (at 101.3 kPa)	−13.4 °C	Bönnighausen (1986); Dreher (1986)
Flash point (open cup)	−78 °C	Bönnighausen (1986); Dreher (1986)
Autoignition temperature	472 °C	Bönnighausen (1986); Dreher (1986)
Critical temperature	156 °C	Bönnighausen (1986); Dreher (1986)
Critical pressure	5600 kPa	Bönnighausen (1986); Dreher (1986)
Explosion limits in air	3.8–29.3 vol% in air (20 °C); 4–22 vol%	Bönnighausen (1986) Dreher (1986)
Decomposition temperature	450 °C	Bönnighausen (1986)
Density (20 °C)	0.910 g/cm^3	Bönnighausen (1986)
Vapour pressure at −20 °C 0 °C 20 °C	78 kPa 165 kPa 333 kPa	Dreher (1986)
Solubility of VC in water; extrapolated from low pressure experiments over range 15–85 °C at 20 °C	0.95 wt% (9.5 g/litre) over temperature range 1.1 g/litre	DeLassus & Schmidt (1981) Euro Chlor (1999)
Solubility of water in 100 g VC	0.02 ml (−20 °C) 0.08 ml (+ 20 °C)	Bönnighausen (1986)
Henry's Law Constant (Hc) (kPa.m^3/mol)	1.96 at 17.5 °C 2.0–2.8 at 25 °C 18.8 at 20 °C	Gossett (1987) Ashworth et al. (1988) Euro Chlor (1999)
Solubility in organic solvents	soluble in most organic liquids and solvents; insoluble in lower polyalcohols	Dreher (1986) Bönnighausen (1986)

Table 1 (contd).

log *n*-octanol/water partition coefficient (log K_{ow})	1.58 (measured; 22 °C)	BUA (1989)
	1.36 (calculated)	BUA (1989)
	1.52	Gossett et al. (1983)
Odour threshold value	26–52 mg/m^3 by some, but by all at 2600 mg/m^3	Hori et al. (1972)
	650 mg/m^3	Baretta et al. (1969)
	10 700 mg/m^3	Patty (1963)

With air and oxygen, very explosive peroxides can be formed (Rossberg et al., 1986). There are reports of explosions in vinyl chloride plants (Terwiesch, 1982). In VC recovery plants there is a higher chance of explosion, which necessitates continuous monitoring and limitation of the oxygen content.

Polymerization reactions to form PVC are the most important reactions from an industrial view (see section 3.2.1.2).

$$nH_2C = CHCl \; 6 \; (- H_2C - CHCl -)_n; \quad) H_R = -71.2 \text{ kJ/mol}$$

The reaction is exothermic. Addition reactions with other halogens at the double bond, for instance, to yield 1,1,2-trichloroethane or 1,1-dichloroethane, are also important. Catalytic halogen exchange by hydrogen fluoride gives vinyl fluoride (Rossberg et al., 1986). In the presence of water, hydrochloric acid is formed which attacks most metals and alloys. This hydrolysis probably proceeds via a peroxide intermediate (Lederer, 1959).

Vinyl chlorine reacts with chlorine to form trichloroethane. 1,1-Dichloroethane is formed from the exothermal reaction of VC with hydrogen chloride in the presence of iron compounds.

2.3 Conversion factors

1 ppm   = 2.59 mg/m^3 at 20 °C and 101.3 kPa
1 mg/m^3 = 0.386 ppm

2.4 Analytical methods

2.4.1 General analytical methods and detection

Stringent regulations for the production, use and handling of carcinogenic VC have been made in several countries (see Annex 1) necessitating the usage of reliable methods to detect trace amounts of this compound in air, water and in PVC articles in such human contact applications as food packing, medical equipment and potable water transport.

VC in air has been monitored by trapping it on different adsorbents, e.g., activated charcoal, molecular sieve and carbotrap.

VC can be removed from adsorbents by liquid or thermal desorption and analysed by GC fitted with FID, PID or MS detection. In ambient air measurements, several adsorbents in sieves or refrigerated traps have been used to increase the efficiency of trapping. In continuous monitoring of workplace and ambient concentration, IR and GC/FID analysers can be used.

Direct injection, extraction and more increasingly head space or purge and trap techniques have been applied for analysis of liquids and solids. VC can be detected by GC fitted to, for instance, FID, PID, MS or Hall detectors.

A pre-concentration step and chemical derivatization may increase sensitivity.

An overview of analytical methods for detecting VC in various matrices is given in Table 2.

2.4.2 Sample preparation, extraction and analysis for different matrices

2.4.2.1 Air

Most methods are based on that of Hill et al. (1976a), using adsorption on activated charcoal, desorption with carbon disulfide and analysis by GC/FID. Kruschel et al. (1994) used a three-stage carbon molecular sieve adsorbent cartridge to collect a wide range of selected polar and non-polar VOCs. After purging with helium prior to

Table 2. Analytical methods[a]

Matrix	Sampling/preparation	Separation	Detector	Detection limit[b]	Comments	References
Air						
Expired air	collected in 50 ml pipettes; direct injection	GC (packed column)	FID	50 ppb (130 : g/m^3)		Baretta et al. (1969)
Expired air	multistage cryogenic trapping; thermal desorption	GC (packed & cap.)	FID; MS	low ppb	low reproducibility; long sampling time	Conkle et al. (1975)
Expired air	500 ml charcoal tubes	GC		0.3 mg/m^3		Krajewski & Dobecki (1978, 1980)
Expired air	1 litre canister; pressurized with neutral gas; cryogenic concentration	capGC	MS	n.g.	for collecting alveolar samples; e.g.,16 and 25 : g/m^3	Pleil & Lindstrom (1997)
Air in car interior	charcoal tube, CS$_2$ desorption	GC	FID	10 ppb (26 : g/m^3)		Going (1976); Hedley et al. (1976)
Ambient air	activated charcoal/CS$_2$	GC	FID	2.6 mg/m^3		Hill et al. (1976a)
Ambient air	silica gel at –78 °C, thermal desorption	GC	FID	2.6 mg/m^3		IARC (1978)

Table 2 (contd).

Ambient air	activated charcoal column; 24-h sampling	GC	n.g.	0.5 ppb $(1.3\ \mu g/m^3)$		Dimmick (1981)
Ambient air	sampling (1 to 10 litre) on carbon trap; thermal desorption	HRGC	MS FID	1 ng $(0.3\ \mu g/m^3)$	VOCs	Kruschel et al. (1994)
Ambient air	solid phase sample trap preconcentration	capGC	IMS	$2\ mg/m^3$	new method for field monitoring	Simpson et al. (1996)
Landfill gas	(20 litre) carbon molecular sieve; CS_2 desorption; conversion to 1,2,-dibromo derivative	capGC	ECD	$82\ ng/m^3$		Wittsiepe et al. (1996)
Tobacco smoke	charcoal tube, CS_2 extraction; conversion to 1,2,-dibromo derivative	GLC	ECD	15 pg per injection		Hoffmann et al. (1976)
Workplace air	CS_2 desorption	GC (packed column)	FID	$0.04\ \mu g$ (5 litre sample)	working range 0.4 to $40\ mg/m^3$	NIOSH (1994) (based on Hill et al., 1976a)
Workplace air	charcoal sorbent tube; extraction with nitro-methane	GC (packed column)	FID	$5\ mg/m^3$ ($3\ dm^3$ sample)		Kollar et al. (1988)

Table 2 (contd).

Matrix	Sampling/preparation	Separation	Detector	Detection limit[b]	Comments	References
Workplace air	carbon trap, thermal desorption	GC	FID	2.6 mg/m^3		Hung et al. (1996)
Workplace air	activated charcoal, CS$_2$ desorption	GC	FID	0.1 mg/m^3	working range 0.07–25 mg/m^3 for 30-litre samples	HSE (1987); ASTM (1993)
Workplace air	continuous sampling	process GC	FID	n.g.		Pau et al. (1988)
Workplace air	continuous sampling	pyrolysis	detection of HCl	1 mg/m^3		Nakano et al. (1996)
Water						
Water	purge & trap	GC	MC	n.g.	in PVC pipes	Dressman & McFarren (1978)
Water	purge & trap	GC	MS	0.05 : g/litre		Schlett & Pfeifer (1993)
Water	headspace	capGC	MS	1 : g/litre		Gryder-Boutet & Kennish (1988)
Water	purge & trap	capGC	PID-ELCD	n.g.	modification of US EPA Methods 601 & 602 for VOC	Driscoll et al. (1987)

Table 2 (contd).

Matrix	Sample preparation	Separation	Detection	Detection limit	Comments	Reference
Water	purge & trap	capGC	PID-ELCD	0.1 : g/litre	VOC	Ho (1989)
Water	purge & trap; CS_2 desorption; 1,2-dibromo derivatization	capGC	ECD	1.6 ng/litre		Wittsiepe et al. (1990, 1993)
Water		GC	PID and Hall detector	n.g.	VCM loss during laboratory holding time	Soule et al. (1996)
Water	purge & trap	GC	FID	n.g.	VOC	Lopez-Avila et al. (1987a)
Water	CS_2 desorption; conversion to 1,2,-dibromo derivative	capGC	ECD	1.6 ng/litre		Wittsiepe et al. (1990, 1996)
Bottled drinking-water	headspace with thermal desorption cold-trap injector (TCT)	GC	MS	10 ng/litre		Benfenati et al. (1991)
Water	solid phase micro-extraction	capGC	FID MS	n.g.		Shirey (1995)
Food, liquids, biological fluids and tissues						
Liquid drugs; cosmetics	headspace	GC	FID	0.1 ppb		Watson et al. (1979)
Food; liquids	headspace	GLC	confirmation with MS	10 ppb		Williams (1976a)

Table 2 (contd).

Matrix	Sampling/preparation	Separation	Detector	Detection limit[b]	Comments	References
Liquids	derivatization to 1-chloro-1,2-dibromoethane	GLC	ECD	15 : g/litre (vinegar); 50 : g/litre oil		Williams (1976b)
Food	direct injection	GC	FID	2–5 : g/kg	detection limit depends on medium	UK MAFF (1978)
Food	headspace	GC	FID	1 : g/kg		IARC (1978)
Oil		GC	FID	5 : g/litre		Rösli et al. (1975) based on Williams & Miles (1975)
Food	headspace	GC	n.g.	2–5 : g/kg		UK MAFF (1978)
Intravenous solutions	headspace	capGC	FID	1 : g/litre		Arbin et al. (1983)
Blood (rat)	headspace ethanol-water extraction	GC	FID	5 : g/litre		Zuccato et al. (1979)
Tissues (rat)	freezing, homogenization then as above	GC	FID	30 : g/kg		Zuccato et al. (1979)

Table 2 (contd).

Matrix	Preparation	Separation	Detection	Detection limit	Remarks	Reference
Urine	dry; dissolution in methanol; methylation with diazomethane	GC	MS	50 : g/litre	TDGA	Müller et al. (1979)
Urine	extraction and silylation	GC	FID	10 mg/litre	TDGA; standard: *o*-phthalic acid	Draminski & Trojanowska (1981)
Urine	conversion to dibutyl ester	GC	MS	< 0.5 : mol/litre	TDGA; standard: pimelic acid	Pettit (1986)
PVC						
PVC products	charcoal tube, CS_2 desorption	GC	FID	10 ppb (26 : g/m^3)		Going (1976)
PVC	headspace	packed column GC		5 ppb		ASTM (1985)
PVC	headspace	capGC	FID FID-PID		update suggestion for ASTM (1985)	Wright et al. (1992)
PVC	extraction/headspace	GC	FID		0.1 mg/kg	Puschmann (1975); IARC (1978)
PVC packaging of foods		HPLC		< 1 ppm	for temperatures simulating storage conditions (8 to 27 °C)	Kontominas et al. (1985)

Table 2 (contd).

Matrix	Sampling/preparation	Separation	Detector	Detection limit[b]	Comments	References
PVC	dynamic headspace with a sparging and focusing step before thermal desorption	GC	FID	low ppb		Poy et al. (1987)
PVC film or resin		GC	FID	2.2 ng (5 ppb (w/w))		Gilbert et al. (1975)
Packaging materials			MS	8.7 pg		
PVC bags	purge/trap (Tenax/charcoal)	GC	FID/ECD	0.3 ppb		Thomas & Ramstad (1992)

[a] **Abbreviations**: capGC = capillary gas chromatography; ECD = electron capture; ELCD = electrolytic conductivity detector; FID = flame ionization detector; GC = gas chromatography; GLC = gas-liquid chromatography; HRGL = high-resolution gas chromatography; IMS = ion mobility spectrometry; MC = microcoulometric titration detector; MS = mass spectrometry; PID = photoionization detector; SPME = solid-phase microextraction; TDGA = determination of the metabolite, thiodiglycolic acid; VOC = volatile organic chemical (a general method); n.g. = not given

[b] The % recovery was not given in most cases

analysis, levels of water and other interfering compounds were reduced sufficiently to allow cryogenic preconcentration and focusing of the sample onto the head of the analytical column. VC was detected at levels below the detection limit of former methods.

Landfill gas monitoring has been carried out by trapping VC on a molecular sieve, and samples have been analysed using, for instance, GC/MS (Bruckmann & Mülder, 1982) or GC/ECD with prior conversion to the 1,2-dibromo derivative (Wittsiepe et al., 1996).

2.4.2.2 Water

VC is first purged from the water and then collected for GC analysis by headspace/purge and trap. VC is highly volatile and has a low specific retention volume on Tenax-GC, the most commonly used trapping medium in purge/trap analysis. Combination traps such as Tenax/silica gel/charcoal (Ho, 1989) or Tenax/OV-1/silica (Lopez-Avila et al., 1987b) have been used. Another approach is to bypass the trap altogether by purging directly onto a cryocooled capillary column (Gryder-Boutet & Kennish, 1988; Pankow & Rosen, 1988; Cochran, 1988; Cochran & Henson, 1988), but here there are complications due to the need to remove water when stripping from an aqueous solution. A more recent adaptation of the headspace method uses solid-phase microextraction (SPME) in which a stationary phase, usually poly(dimethylsiloxane), coated on a fused-silica fibre is used to extract aqueous samples in completely filled sealed vials (Shirey, 1995).

It should be noted when measuring VC content in water or groundwater that samples should be analysed as soon as possible, as the VC content decreases with holding time (Soule et al., 1996).

2.4.2.3 PVC resins and PVC products

For the quantification of residual VC in PVC, a solid and a solution approach have been used. The former involves the equilibration of a solid polymer sample at 90 °C in a sealed system, followed by headspace analysis with single or multiple extraction (Berens et al., 1975; Kolb, 1982). The solution approach involves the equilibration of a 10% solution of PVC in dimethylacetamide in a sealed system, followed by analysis of the headspace gas (Puschmann, 1975). A automatic dynamic headspace method involving a sparging

and a focusing step before desorption into the GC column has been developed to increase the sensitivity of the solution approach method (Poy et al., 1987).

2.4.2.4 Food, liquid drug and cosmetic products

For monitoring VC in foods in contact with PVC packaging, headspace GC is the usual method. Before the levels of VC allowed in PVC was regulated in the 1970s (see Annex I), many of the VC levels observed were high enough to be determined by direct injection methods. Limits of detection are given as 2, 5 and 5 : g/kg for aqueous, ethanolic, and oleaginous medium respectively using headspace-GC-FID (UK MAFF, 1978). Williams (1976a,b) reported a gas-liquid chromatographic method using subsequent GC-MS confirmation, and a further GC/ECD method requiring derivatization to 1-chloro-1,2-dibromoethane for determination of VC content in liquid foods.

Methods for VC levels in liquid drug and cosmetic preparations were described by Watson et al. (1979). A weighed aliquot of the commercial product in a tightly septum-sealed vial with accurately known headspace volume is heated to 50 °C for 30 min. A portion of the warm headspace gas is then injected into a GC equipped with FID and a styrene-divinylbenzene porous polymer column.

2.4.2.5 Biological samples

There are few data on VC analysis in biological tissues. The only report available was on rat blood and tissues (Zuccato et al., 1979).

2.4.2.6 Human monitoring

Methods for measuring VC concentrations in exhaled air (breath) have been described (see Table 2) but, although useful for studying metabolism, they are not well suited for biological monitoring due to the short half times in the body and the saturable metabolism of VC.

Metabolites of vinyl chloride have been identified in the urine of rats (Müller et al., 1976; Green & Hathway, 1977) and humans (Müller et al., 1979) using GC-MS. As there is a strong correlation between VC exposure in humans and increased excretion of thiodiglycolic acid (Müller et al. 1978), this metabolite has been using

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for monitoring purposes. It is, however, not specific for VC as certain drugs and other C_2 compounds also have thiodiglycolic acid as a urinary metabolite (Müller et al., 1979). Since thiodiglycolic acid is also detected in unexposed subjects (Müller et al., 1979; van Sittert & de Jong, 1985) and even premature babies (Pettit, 1986), this approach can only be used to demonstrate high levels of exposure. A discussion of biological markers for VC exposures and VC-induced liver cancer is presented in section 8.5.

Thiodiglycolic acid has been determined by dissolving the dried urine residue in methanol, methylating with diazomethane and analysing with GC-MS (Müller et al., 1979), analysing the metabolite as its dibutyl ester by GC-MS using selected ion monitoring (Pettit, 1986), and by using GC/FID (Draminski & Trojanowska, 1981). Care must be taken with methods which analyse for VC metabolites, as these metabolites are not specific to VC.

A specific and sensitive new method has been reported for the quantification of the VC metabolite *N*-acetyl-*S*-(2-hydroxyethyl) cysteine by exchange solid-phase extraction and isotope dilution HPLC-tandem mass spectrometry (Barr & Ashley, 1998). This method may prove useful for monitoring occupational VC exposure, as the detection limit of 0.68 : g/litre is low enough to detect this metabolite even in people with no overt exposure to VC, ethylene oxide or ethylene dibromide.

2.4.2.7 Workplace air monitoring

Before the 1960s, when it was established that VC was a carcinogenic substance, halogen detectors and explosimeters were used, non-specific for VC, with detection limits of 518–1295 mg/m^3 (200-500 ppm). Gradually more sophisticated techniques became available for detection of low ppm levels of VC, such as IR analysers, FID, PID (ECETOC, 1988) and more recently mass spectrometry. In order to check for leaks or for control measurements during cleaning and repair work, detector tubes or direct-reading instruments with FID or PID can be used, although they are not specific for VC and regular calibration is necessary (Depret & Bindelle, 1998).

Continuous analyses based on, for instance, IR, GC/FID or HCl detection have been developed (IARC, 1978; Pau et al., 1988; Nakano et al., 1996). Analysers can be equipped for computerized data logging and processing. The detection limit of an IR analyser depends on, for instance, path length and is about 1.3 mg/m^3 (IARC, 1978). The analyser detecting HCl from VC pyrolyzed in a quartz tube was reported to have a detection limit of 1 mg/m^3 when the sampling time was 40 seconds (Nakano et al., 1996).

Breathing zone concentrations can be measured by sampling VC with portable pumps or diffusion on activated charcoal (Nelms et al., 1977; Heger et al., 1981; ASTM, 1993; NIOSH, 1994; Du et al., 1996). By using thermosorption tubes (carbotrap 110-400), detection limits can be decreased and the use of carbon disulfide in desorption avoided (Hung et al., 1996).

Passive monitors for occupational personal monitoring of exposure to VC are commercially available.

3. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

3.1 Natural occurrence

VC is not known to occur naturally.

3.2 Anthropogenic sources

Anthropogenic sources of VC include the intentional manufacture of the compound for further processing, primarily to PVC, and unintentional formation of VC in, for instance, sanitary landfills, as a degradation product of chlorinated hydrocarbons such as those used as solvents, and the subsequent presence of VC in emitted gases and groundwater. VC is also found in tobacco smoke.

3.2.1 Production levels and processes

VC was first synthesized by Regnault in 1835. It was not until the 1930s that techniques were devised to polymerize VC into stable forms of PVC.

VC production methods were altered in 1974 in many countries after the confirmation that VC was a human carcinogen. Manufacturers developed closed production methods to reduce exposure of the workforce.

Annual total world production of VC, which is approximately equal to PVC production, was about 17 million tonnes in 1985 and over 26 million tonnes in 1995 (see Table 3). More than half the world's capacity (64%) in 1985 was concentrated in Western Europe and the USA. Since that time many new VC/PVC plants have been opened or are under construction in SE Asia, Eastern Europe, the Indian subcontinent and developing and oil-producing countries. Thus there has been a geographical shift of VC/PVC production.

The leading producers of PVC and therefore also of VC are the USA, Japan, Germany, France and SE Asian countries such as

Table 3. World PVC (and therefore VC) production/capacity 1980–1998

Region	Production/capacity in 1000 tonnes/year				
	1980[a]	1985[a]	1990[a]	1995[b]	1998[c]
World capacity	16 000	17 000	20 700	26 400	~27 000
World production	11 750	14 200	18 300		
North America total	3200	3390	4700	6070	
Suspension and mass	2810	2990			
Vinyl acetate copolymer	200	210			
Emulsion	190	190			
Western Europe total	3900	4330	4800	5750	~ 5600
Suspension and mass	33 350	3700			
Vinyl acetate copolymer	130	130			
Emulsion	420	500			
Eastern Europe	925	1100	1200	2700[d]	
Former Soviet Union	370	700	760		
China	150	400	790		
Japan	1400	1550	2070	8200[e]	
SE Asia	330	600	900		
South America	400	540	780		
Rest of the world	1075	1590	2300	3680	

[a] Allsopp & Vianello (1992)
[b] Rehm & Werner (1996)
[c] Although exact figures are not available, an increase in world production was seen in 1998 but no great increase in Western Europe (personal communication, European Council of Vinyl Manufacturers, 1999)
[d] Including former Soviet Republics
[e] Total Asia

Taiwan and China (CHEM-FACTS, 1992). The capacity has only increased moderately in the USA and Western Europe in recent years. Significant increases in production have been reported for Japan and Taiwan. All the countries of Eastern Europe have PVC plants and have exported PVC to Western European countries. The PVC capacity and imports and exports for each country are given in CHEM-FACTS (1992).

VC is produced in Western Europe by 14 companies. The plants are in Belgium (3 plants), France (3 plants), Germany (8 plants), Italy (4 plants), the Netherlands (1 plant), Spain (2 plants), Sweden (2 plants), United Kingdom (1 plant) (Euro Chlor, 1999).

The manufacture of VC/PVC is one of the largest consumers of chlorine.

3.2.1.1 Production of VC

VC is produced industrially by two main reactions, the first is hydrochlorination of acetylene, which proceeds via the following reaction:

$$C_2H_2 + HCl \; \mathbf{6} \; CH_2=CHCl$$
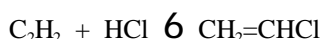
This route was used in the past when acetylene, produced via calcium carbide from coal, was one of the important basic feedstocks for the chemical industry (Rossberg et al., 1986). Today all USA and most Western European manufacturers use the "balanced process" described below. However, many Eastern European countries such as Poland and the countries of the former Soviet Union still use acetylene to manufacture VC because of relatively cheap raw materials such as calcium carbide and natural gas. Mercury has been used as a catalyst, although a new catalyst has now been developed in Russia, based on platinum metal salts instead of mercury, which has increased yields with acetylene conversion from 95 to 99% (Randall, 1994).

The second major production process involves thermal cracking [reaction iii] (at about 500 °C) of 1,2-dichloroethane (EDC), produced by direct chlorination [reaction i] of ethylene or oxychlorination [reaction ii] of ethylene in the "balanced process".

[i] $\qquad CH_2=CH_2 + Cl_2 \; \mathbf{6} \; Cl\,CH_2–CH_2\,Cl$

[ii] $\qquad CH_2=CH_2 + 2\,HCl + 5\,O_2 \; \mathbf{6} \; Cl\,CH_2–CH_2\,Cl + H_2O$

[iii] $\qquad Cl\,CH_2–CH_2\,Cl \; \mathbf{6} \; CH_2=CHCl + HCl$
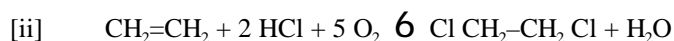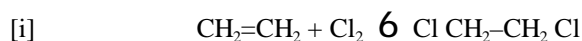
After the cracking (pyrolysis), HCl and unconverted EDC are separated from VC by two steps of distillation and recycled. The VC

is stored either under pressure at ambient temperature or refrigerated at approximately atmospheric pressure (European Council of Vinyl Manufacturers, 1994). More than 90% of the VC produced today is based on this route (Rossberg et al., 1986; Allsopp & Vianello, 1992).

Other methods of industrial production include:

a) VC from crack gases, where unpurified acetylene and ethylene are chlorinated together, acetylene being first chlorinated to 1,2-dichloroethane.

b) VC from ethane, which is readily available in some countries. The major drawback is that ethane must first be functionalized by substitution reactions giving rise to a variety of side chain reactions and therefore the reaction must be kinetically controlled to obtain maximal VC yield.

3.2.1.2 Production of PVC from VC

Many PVC plants are fully integrated beginning with ethylene and chlorine (or sodium chloride).

VC is a gas at ambient temperatures but is handled as a compressed volatile liquid in all polymerization operations. PVC polymerization reactors are thick-walled jacketed steel vessels with a pressure rating of 1725 kPa. The polymerization of VC is strongly exothermic. The explosive limits of VC in air are 4–22 vol%, and the plant must be designed and operated with this in mind, particularly when handling unreacted VC in the recovery system (Allsopp & Vianello, 1992).

Three main processes are used for the commercial production of PVC: suspension (providing 80% of world production), emulsion (12%) and mass or bulk (8%). In Western Europe, the proportion of PVC produced by the different processes is: 80% suspension; 13% mass; 5% emulsion and 2% copolymers (Wrede, 1995).

In the suspension (also called dispersion) process, polymerization takes place at 40–70 °C (depending on the type of PVC being produced) in a reactor (autoclave) of 25–150 m^3 capacity fitted with

a jacket and/or condenser for heat removal, as the reaction is strongly exothermic. Precautions have to be taken in order to avoid explosive mixtures with air. Liquid VC under its autogenous vapour pressure is dispersed in water by vigorous stirring to form droplets of average diameter 30–40 : m. The polymerization takes place within these droplets and is started by addition of initiators dissolved in the monomer. Stabilizers are added to prevent the drops rejoining and to prevent the already polymerized PVC particles from agglomerating. The reaction conditions can be exactly controlled and the properties of the product, such as relative molecular mass, can be controlled exactly. Once polymerization has ended, the autoclave charge is emptied into degassing tanks, and the non-polymerized VC is degassed, compressed and stored for reuse (ECETOC, 1988; Allsopp & Vianello, 1992).

During the polymerization process, the PVC is dispersed in the aqueous phase and it cannot be prevented that a film of PVC forms on the inside wall of the reactor. This film interferes with the transfer of heat between the reactor and contents, and the process has to be interrupted periodically to allow the reactor to be cleaned. The autoclave, after being emptied, is opened, rinsed and washed either with solvents or more usually by means of automatic high-pressure jets (ECETOC, 1988). The latest development in this area is the use of proprietary build-up suppressants, which are applied before every PVC batch. After each batch, low pressure rinse with water can remove loose polymers and the batch cycle is ready to restart. The reactor needs then to be opened for a thorough cleaning only after 500 or more batches (Randall, 1994).

Before awareness of the toxicity of VC, it was the autoclave cleaning personnel who were primarily highly exposed to the compound. In the past autoclaves were cleaned manually; the inside had to be scraped with a spatula, or sometimes hammer and chisel to remove the encrusted polymer adhering to the walls of the vessel and mixing devices. Lumps of polymer often released monomer when broken, resulting in high concentrations of VC in the autoclave. Before about 1970, it was usual to check that the level was below 1036 mg/m^3 (400 ppm), i.e. two orders of magnitude below the lower explosion limit of VC. Occupational exposure limits are now 18 mg/m^3 (7 ppm) or less (see Annex I). Further details of workplaces with a former high exposure to VC are given in section 5.3 and Jones (1981).

Once polymerization has ended, the polymerization batch is transferred to the stripping unit and then to the slurry tank. The slurry is a suspension of PVC in water that has to be permanently stirred; it is then dewatered in a centrifuge decanter and dried. The resulting dried powder is either stored in silos or bagged. PVC is then further processed into ready-to-use resins (Depret & Bindelle, 1998).

3.2.1.3 PVC products

PVC is a polymer of VC with 700–1500 monomeric units. It is relatively inexpensive and is used in a wide range of applications. PVC is a generic name. Each producer makes a range of PVC polymers, which vary in morphology and in molecular mass according to the intended use. PVC resins are rarely used alone but can be mixed with heat stabilizers, e.g., lead, zinc and tin compounds (Allsopp & Vianello, 1992), lubricants, plasticizers (e.g., diethylhexyl phthalate) fillers and other additives, all of which can influence its physical and mechanical properties (Williamson & Kavanagh, 1987; Allsopp & Vianello, 1992). Such additives may constitute up to 60% of the total weight in some finished PVC plastics (Froneberg et al., 1982). These plastics are formed into a multitude of consumer products by extrusion, thermoprocessing and rotational moulding, and into rigid or flexible film by extrusion or calendering.

PVC accounts for 20% of plastic material usage and is used in most industrial sectors (ECETOC, 1988; European Council of Vinyl Manufacturers, 1994).

C **Packaging**
  C bottles (produced by blow-moulding) for containing liquid foods, beverages, cooking oils, vinegar, etc.
  C rigid film (calendered or extruded) which is converted into tubes and shaped containers by subsequent vacuum or pressure-forming for packaging of various foodstuffs
  C flexible film (made by blowing or calendering) for wrapping solid foods such as cheese, meat, vegetables, fresh fruit, etc.
  C coatings in metal cans

C **Building** - floor coverings, wall coverings, windows, roller shutters, piping; 58% of the water supply network and 80% of the

waste water disposal systems in Europe use pipes and fittings made from PVC.

C **Electrical appliances** - wires and cables insulation

C **Medical care** - equipment such as blood bags and gloves; pharmaceutical and cosmetic packaging. Worldwide, more than 25% of all plastic-based medical devices used in hospitals are made from PVC (Hansen, 1991)

C **Agriculture** - piping; drainage; tubing in dairy industry

C **Automobiles** - car dash boards and lateral trimming

C **Toys**

At present, the largest use of PVC is in the building sector (Rehm & Werner, 1996).

3.2.2 Emissions from VC/PVC plants

3.2.2.1 Sources of emission during the production of VC

Process waste, by-products and unreacted material from a balanced process and from a PVC plant include (Randall, 1994): a) light/heavy ends from EDC purification (from direct chlorination and oxychlorination reactors); b) heavy ends from VC purification (from pyrolysis reactor); c) pyrolysis coke/tars (from thermal reactions in the pyrolysis reactor); d) spent catalyst (from direct chlorination, oxychlorination); e) recovery of unreacted VC (from PVC reactor); f) offspec batches (from PVC reactor); g) aqueous streams (from EDC washing, vent scrubbing, oxychlorination water; from centrifuge, VC stripping, slurry tanks); h) vent gases (from distillation columns, flash drums, reactor vents, storage tanks, vessel openings; from VC recovery systems, dryer stacks, centrifuge vent, blending, storage facilities); i) spills and leaks (sampling, pumps, flanges, pipes, loading/unloading, valves; bag filling, agitator seals); and j) equipment cleaning (tanks, towers, heat exchangers, piping; PVC reactor, product dryer, recovery system).

a)   *Strategies for minimizing emissions*

During the sixties, some control of exposure levels was introduced resulting in an important decrease of estimated ambient levels of VC.

In the 1970s, efforts were focused on controlling emissions at the most significant emission points: reactors, filters and storage tanks. Elementary modifications of equipment, room and local ventilation by fans, provisional operation procedures, etc., enabled the reduction of exposure levels in working areas.

Technical developments have achieved further reductions:

C   removal of residual VC from the PVC suspension by stripping between polymerization and drying with a flow of steam or in closed-loop systems;

C   appropriate collection of residual vents to thermal oxidizers or other abatement systems;

C   reduction of all sources of fugitive emission by maintenance and upgraded equipment;

C   high pressure internal cleaning of the autoclaves to remove PVC crusts;

C   intensive removal of VC before opening or a closed process design.

Appropriate working procedures, personnel awareness and high standard equipment, associated with good maintenance practices, are the recommended ways to reduce fugitive emission to very low levels (Depret & Bindelle, 1998).

b)   *Disposal of by-products*

The main waste streams of EDC/VC production process in Europe are light ends (gases: VC, EDC, HCl, ethylene, dioxins; aqueous effluents: EDC, copper, dioxins) and heavy ends (viscous tars). According to the PVC Information Council the total amount produced is approximately 0.03 tonnes of by-products per tonne of VC produced (European Council of Vinyl Manufacturers, 1994). The

fractions are either used as feedstocks for other processes or combusted under controlled conditions (> 900 °C) or by catalytic oxidation to produce CO_2, CO, HCl and water which can be recycled (see above). Exit gases should be treated using HCl absorbers and gas scrubbers. Spent catalyst, metal sludges and coke from EDC cracking should be disposed of in controlled hazardous waste dumps (HWD) or incinerated under controlled conditions. Sludges from effluent purification should be either combusted under controlled conditions or deposited in HWD (European Council of Vinyl Manufacturers, 1994).

3.2.2.2 Emission of VC and dioxins from VC/PVC plants during production

a) *VC*

An estimated 550 tonnes of VC was released into air, 451 kg to water and 1554 kg to soil from manufacturing and processing facilities in the USA in 1992, although this was not an exhaustive list (ATSDR, 1997). From a VC capacity of 6 200 000 tonnes, an average emission of 80 g/tonne can be calculated (Depret & Bindelle, 1998).

Euro Chlor (1999) reported emissions of VC from suspension PVC plants in Europe to be 448 tonnes/year, 22 tonnes/year being released in waste water. An estimated emission value of 300 tonnes VC/year was provided by German producers (BUA, 1989), i.e., about 55 g VC/tonne PVC. Total VC emissions in England and Wales were reported to be 3800 tonnes in 1993 and 18 990 tonnes in 1994 (HMIP, 1996).

An estimated 200 000 tonnes of VC was released into the worldwide atmosphere during 1982 (based on a worldwide PVC production of 17 million tonnes), i.e., 12 kg/tonne of PVC produced (Hartmans et al., 1985). In 1974, a VC emission of 0.5 kg/tonne PVC was estimated (Kopetz et al., 1986).

b) *Dioxins*

PCDDs/PCDFs, some of which are classified as human carcinogens (IARC, 1997), are formed during EDC/VC production. Concentrations in VC distillation residues (PU4043) (probably "heavy ends") for two production factories were 3192 and 5602 ng ITEQ

(international toxic equivalent)/kg, which was estimated to be 12 to 30 g of dioxin/year at a production level of 200 000 tonnes VC/year in heavy ends (Stringer et al., 1995). However, the VC/PVC industry argues that, although dioxins may be found in production wastes, these are incinerated and are not ultimately emitted to the environment (Fairley, 1997), at least in those countries where waste streams are regulated (not all countries possess such high standards of waste incineration). Some companies do not incinerate their waste products but dispose of them in other ways, e.g., deep-well injection (Stringer et al., 1995).

Wastewater from VC production can also be contaminated with PCDDs/PCDFs, in particular if they contain suspended solids. Installation of filtration devices should lower solid levels and subsequently PCDD/PCDF emissions (Stringer et al., 1995). Using such filtration devices, PCDD/PCDF concentrations in wastewater from EDC/VC/PVC facilities in the USA ranged from not detectable to 6.7 pg/litre TEQ (Carroll et al., 1996).

Annual global emission of dioxins into the environment from EDC/VC manufacture has been estimated to be 0.002–0.09 kg TEQ by the European PVC industry but 1.8 kg by Greenpeace (Miller, 1993).

Virgin suspension PVC resin from 11 major production sites in Europe was found not to contain any process-generated PCDDs/PCDFs at concentrations above the limits of quantification (2 ppt) (Wagenaar et al., 1998).

3.2.3 Accidental releases of VC

3.2.3.1 PVC plant and transport accidents

An explosion occurred at a VC recovery plant in 1978 in Germany, which was set off by vinyl chloride peroxides (Terwiesch, 1982; see also section 2.2).

A freight train with 12 tank cars of VC was derailed in McGregor, Manitoba, Canada in March, 1980 under near-blizzard conditions and –20 °C and two of the tanks released VC (Charlton et al., 1983). One car lost 47 500 litres in the first hour and the other car

lost 23 100 litres at an initial rate of 1400 litres/hour, decreasing to 45 litres/hour after 31 h. In the first 15 min, 5680 litres of VC vapourized by free surface evaporation; thereafter only 2.5% of the discharging liquid evaporated rapidly. The remaining liquid in the snow bank was assumed to have evaporated at a rate of 15% per hour, leaving about 900 litres of VC in the snow bank after 36 h. Although there was an explosion hazard, no fire occurred.

Two incidences, in 1988 and 1996, occurred in Germany involving accidental release of VC due to derailment of trains transporting the liquid substance (Neuhoff, 1988; Anon, 1996). Both accidents were followed by explosion and fire. Derailment of a goods train occurred 1 km from Schönebeck (near Magdeburg in Germany) and the subsequent explosion and fire produced a 600- to 800-m black column of smoke. In all, 1044 tonnes of VC were involved of which 261 tonnes burnt and 350 tonnes could be reclaimed after the fire; 153 tonnes of HCl were released. Median measurements of the numerous air samples taken at the place of accident or surroundings did not exceed the German technical guidance level of 5 vol ppm, although these were not taken until 14 h after the fire. Maximum concentrations of VC measured were 78 mg/m^3 (30 ppm) near the train and 26 mg/m^3 (10 ppm) at a distance of 200 m from the centre of the fire (Hahn et al., 1998). Levels in nearby industrial sewage pipes were up to 1250 ppm (Anon, 1996). A cytogenic analysis was carried out on some of the general population exposed to VC from this accident (Hüttner & Nikolova, 1998; see section 8.1 and Table 42).

3.2.3.2 *Leakage and discharge from VC/PVC plants*

Leakage from a waste liquor basin of a VC/PVC plant in Finland caused high concentrations of VC and dichloroethene in groundwater in 1974. Concentrations of up to 484 mg/litre of the chlorocarbons were measured in groundwater in the mid-1980s (Nystén, 1988).

It should be noted that in the 1960s and before, when the toxicity of VC was not known, large amounts of PVC production sludges containing VC were dumped onto landfills (and possibly still are in countries where there are no adequate restrictions).

3.2.4 VC residues in virgin PVC resin and products

3.2.4.1 VC residues in different PVC samples

VC is not soluble in PVC nor is it absorbed or adsorbed in the resin particle. It is entrapped and can escape to the ambient air (Wheeler, 1981). PVC in a bulk-container loses its residual monomer at a rate of 25 to 50% per month. Heating tends to accelerate this step, but when the residual monomer has disappeared PVC is not a significant source of VC.

Since the 1970s when VC was confirmed as a human carcinogen, it has been mandatory in many countries to "degas" PVC after polymerization (see section 3.3.1) and before further processing. There are limit values for VC content in PVC (see Annex I). For example, in 1974 raw PVC usually contained more than 1000 ppm of residual VC. This was subsequently reduced to 10 ppm by regulation (German Environmental Office, 1978). In a survey of 45 samples of raw PVC from various countries carried out in 1976–1977, over a third had VC residues of > 1 ppm, but a third had residues of over 50 ppm, with 4 samples over 200 ppm. The samples with the highest residue level came from Hungary, Rumania, Italy and the USA (German Environmental Office, 1978).

3.2.4.2 VC residues in PVC products

In a survey of PVC products carried out in 1976–1977, the following indoor articles had a VC content of > 0.05 ppm: bathroom tiles, piping, plastic bottle for table oil, and kitchen film. The highest concentrations were found in music records, those bought recently having a VC content of up to 210 ppm and one record 10 years old having a content of 970 ppm. In record shops and other rooms containing many records, this could have been an important source of VC. In contrast, the VC content of toys, kitchen utensils, food wrappings, wallpaper and car interiors was < 0.05 ppm (German Environmental Office, 1978).

Whereas in 1974 the typical level of residual VC in PVC bottles was 50 mg/kg, introduction of improved manufacturing practices at the polymer resin processing stage reduced this to 3 mg/kg by 1975. In a 1978 survey, 22 out of 24 PVC bottles contained VC at less than 0.4 mg/kg (UK MAFF, 1978).

In a more recent survey, VC residues in various PVC samples were given as follows: rigid water bottle (850 ppb); thin plasticized food film (3 ppb); monopolymer powder (10 ppb); copolymer film (15 ppb) (Poy et al., 1987). PVC film is still used widely for food packaging. For example, in Denmark, in 1990, 129/239 samples of cling-film used for cheese wrapping were of PVC (Svensson, 1994).

Residual VC could not be detected (< 0.1 ppm) in two PVC products from Thailand (Smerasta et al., 1991) or in PVC and products from it in Poland (Stareczek, 1988). PVC medical devices are regulated in the USA and have to meet certain requirements (a maximum of 5 ppb residual monomer for flexible compounds and a 10 ppb ceiling for rigid compounds (Rakus et al., 1991)).

Levels of VC found in food and pharmaceutical articles are given in section 5.1.4. Annex I gives current regulations for VC content in various PVC products.

3.2.4.3 VC formation as a result of heating PVC

a) *Thermal degradation of PVC*

PVC is thermally stable below 225 °C. Between 225 °C and its ignition temperature of 475 °C, thermal degradation results in the release of about 50 compounds (Boettner et al. 1969). PVC does not degrade back to VC. Thermal degradation of two types of bulk PVC samples at 148–232 °C resulted in the release of long-chain aliphatic alcohols, toluene, benzene, various chlorinated species, and a major peak of HCl. The main components released at 260 °C–315 °C were aromatic hydrocarbons such as benzene, phenol and adipates, along with various aliphatic alcohols, alkenes, anhydrides, some of them chlorinated, and carbon monoxide (Froneberg et al., 1982). When 1 kg of PVC is heated to 300 °C, it releases about 13 g HCl and 5 g CO.

b) *Release of VC from heating PVC*

Various PVC resins from different producers were tested for VC evolution over the 130 to 500 °C range using a heating rate of 10 °C/min. A consistently low level of VC, amounting to 15–30 ppm (based on resin), was found in the volatile decomposition products

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from all of the samples tested, regardless of resin type or manufacturing source (USA) (Wakeman & Johnson, 1978). A 100-mg sample was programmed for heating from 200 to 450 °C at 3 °C/min; this resulted in the formation of a total of 23.2 ppm VC, the major portion being generated in the 275–350 °C region. Dehydro-chlorination occurred most rapidly between 250 and 275 °C. During this period only 2.3 ppm of VC was formed. The VC evolved by heating PVC is the VC monomer entrapped in the PVC resin.

At temperatures required for thermoforming PVC for food packaging applications (90–120 °C for a few seconds), no detectable VC was formed in up to 1 h of exposure at 130 °C (detection limit of analysis in air - 1 ppb). Temperatures for calendering and extrusion operations are 175–210 °C. Maximum VC levels determined at 210 °C were 0.5 ppm (resin basis) after 5 min and 1.2 ppm after 30 min (Wakeman & Johnson, 1978).

In more recent studies into VC formation during the thermal welding of plasticized PVC sheeting (about 225 °C), in normal field situations such as piping in sewers, VC concentrations were usually not above the detection limit of 0.05 ppm. Only where there was poor ventilation were higher levels detected (0.2 ppm VC; 1.0–3.5 ppm HCl) (Williamson & Kavanagh, 1987).

3.2.5 Other sources of VC

3.2.5.1 VC as a degradation product of chlorinated hydrocarbons

VC as a gas, in leachate and groundwater (see Table 4), has been found in landfills and surroundings where there were no VC/PVC production facilities in the vicinity. It was found that VC can be formed, under anaerobic conditions, from the reductive halogenation of the more highly chlorinated chloroethenes: tetrachloroethylene (PCE), trichloroethene (TCE), and the dichloroethene isomers (*cis*-1,2-DCE, *trans*-1,2-DCE, and 1,1-DCE) (Parsons et al., 1984; Vogel & McCarty, 1985; McCarty, 1996, 1997, see Fig. 1). PCE and TCE are widely used as industrial solvents in particular for degreasing and cleaning metal parts and electronic components, and in dry cleaning. Production levels for 1984 were 260 and 200 thousand tonnes for PCE and TCE, respectively (Wolf et al., 1987). Careless handling, storage and disposal, as well as the high chemical stability of these
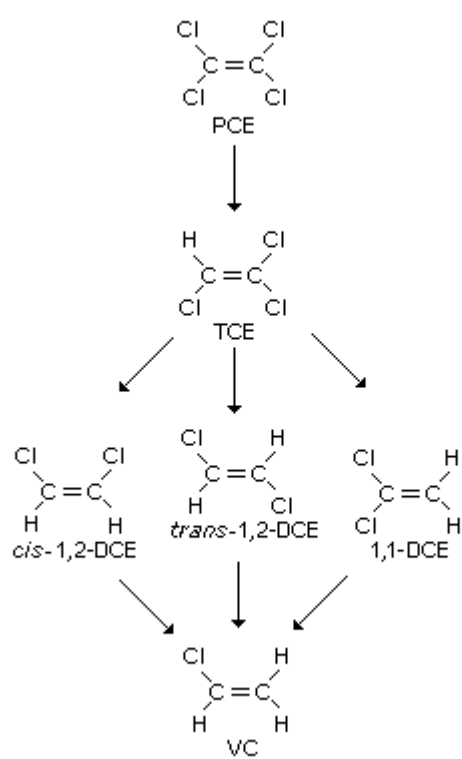
Fig. 1. Pathway for anaerobic microbial degradation of chlorinated
ethenes to form vinyl chloride
(PCE = perchloroethene, TCE = trichloroethene, DCE = dichloroethene)

Table 4. Vinyl chloride found in landfill/waste disposal sites as a gas, in leachate and in groundwater
formed probably from degradation of higher chloroethenes

Sample	Place (year) of sampling	Value[a]	Concentrations	Reference
Landfill gas	2 landfills USA	max	230 mg/m^3	Lipsky & Jacot (1985)
		average	34 mg/m^3	
Landfill gas	landfill, UK	max	11 mg/m^3	Ward et al. (1996)
	plume, 100 m from boundary due to subsurface migration (1991)		40 mg/m^3	
Landfill gas	landfill, Braunschweig, Germany	mean	9 mg/m^3	Henning & Richter (1985)
Gas effluents	garbage dump, Berlin, Germany		0.27 mg/m^3	Höfler et al. (1986)
Gas	Germany,	average		Janson (1989)
	industrial waste disposal site		41 mg/m^3	
	municipal waste disposal site		10 mg/m^3	
Gas	Germany, waste disposal site	range	0.03–0.3 mg/m^3	Bruckmann & Mülder (1982)
Landfill gas	UK, 7 waste disposal sites	range	< 0.1–87 mg/m^3	Allen et al. (1997)
Soil air	Germany, solvent waste sites	3 max out of 200	128 mg/m^3, 47 mg/m^3, 5 mg/m^3	Köster (1989)

Table 4 (contd).

Leachate	MSW, Wisconsin, USA (1982)	range	61 : g/litre	Sabel & Clark (1984)
Leachate	USA sites established before 1980 (6 chosen sites)	range	8–61 : g/litre	Chilton & Chilton (1992)
Leachate or groundwater plume	industrial landfill municipal landfill	range	140–32 500, 20–61 000 : g/litre	Brown & Donnelly (1988)
Groundwater, Wells	Germany, contaminated water	range range	< 5–460 : g/litre 15–1000 : g/litre	Brauch et al. (1987)
Groundwater	Germany, solvent waste site	3 max samples/200	1000 : g/litre, 500 : g/litre, 200 : g/litre	Köster (1989)
Groundwater	Germany	max	120 : g/litre	Milde et al. (1988)
Groundwater	Santa Clara Valley, USA (near plants manufacturing electronic equipment which use significant amounts of chlorinated solvents)	range	50–500 : g/litre	Wolf et al. (1987)
Groundwater	Germany: 136 samples from down-gradient wells of 100 waste disposal sites	max mean	12 000 : g/litre 1694 : g/litre	Dieter & Kerndorff (1993)
Groundwater	sand aquifer near industrial site, Michigan, USA. Concentration increased with depth consistent with methane	max	> 5 : g/litre at 10 m; 56 400 : g/litre at 23 m	Semprini et al. (1995)
Outwash aquifer	Gloucester landfill, Canada (1988)	range	< 1–40 : g/litre	Lesage et al. (1990)

[a]   This column indicates whether the concentration is a maximum (max), average or range value

compounds, have made them, and consequently VC, some of the most frequently encountered groundwater contaminants (Arneth et al., 1988). Although VC may be further degraded to less chlorinated and non-chlorinated ethenes, and possibly finally to carbon dioxide and ethane, this proceeds only at a slow rate under highly reducing conditions (Freedman & Gossett, 1989; DiStefano et al., 1991; De Bruin et al., 1992; see also section 4.2). As a consequence, VC can be detected in landfill sites in and surrounding areas through spreading. Reports from several countries show high levels of VC contamination of soil and groundwater, aquifers and wells (see Table 4 and section 5.1).

There have recently been several field studies in PCE/TCE-contaminated landfill sites and aquifers (Major et al., 1991, 1995; Fiorenza et al., 1994; Lee et al., 1995, see Table 5). These have shown that under anaerobic conditions, PCE and TCE can be intrinsically biodegraded to ethene by indigenous methanogenic, acetogenic and sulfate-reducing bacteria. Furthermore, under aerobic conditions there is a potential for direct or co-metabolic oxidation of DCE and VC. Therefore, an efficient bioremediation of chlorinated ethene-contaminated aquifers may occur in contaminant plumes characterized by upgradient anaerobic and downgradient aerobic zones, such as where anaerobic, chlorinated ethene plumes discharge to aerobic surface water bodies. However, this depends on the ability of the stream-bed microbial community to degrade efficiently and completely DCE and VC over a range of contaminant concentrations (Cox et al., 1995; Bradley & Chapelle, 1998a). It should be noted that this bioremediation occurs under specific conditions. The biodegradation studies listed in chapter 4 give conflicting results.

Each landfill site has individual conditions (e.g., presence of other solvents such as acetone and methanol), so that the degradation rates cannot be directly compared. The most extensively studied site of intrinsic chlorinated solvent biodegradation is the St Joseph (Michigan, USA) Superfund site where groundwater concentrations of TCE as high as 100 mg/litre have been found, with extensive transformation to *cis*-DCE, VC and ethene. Conversion of TCE to ethene was most complete where methane production was highest and where removal of nitrate and sulfate by reduction was most complete (McCarty, 1996; Weaver et al., 1996). At another site in the USA (Dover Air Force Base), half-lives of 1 to 2 years have been estimated

Table 5. Some examples of formation of VC through biodegradation of tetrachloroethene in landfill sites (concentrations in mg/litre unless stated otherwise)[a]

Site	Sample	PCE	TCE	*cis*-DCE	VC	Ethene	Reference
Chemical transfer factory facility, North Toronto, Canada	groundwater downgradient well	4.4 n.d.	1.7 none	5.8 76	0.22 9.7	0.01 0.42	Major et al. (1991)
Carpet backing manufacturing plant, Ontario, Canada	groundwater downgradient from lagoon	n.d. n.d.		56 4.5	4.2 5.2	0.076 low	Fiorenza et al. (1994)
Refuse landfills (average of 8)		7.15 (ppmv)	5.09 (ppmv)	not measured	5.6 (ppmv)		McCarty & Reinhard (1993)
Landfill	groundwater well	0.54 3.4 15	2.6 14 270	2.2 44 140	2.7 54 48	33 43 14	Lee et al. (1995)
Heavily polluted site (solvent distributor) in Netherlands	groundwater	20	70	20	2		Middeldorp et al. (1998)

[a]   PCE = tetrachloroethene; TCE = trichloroethene; DCE = dichloroethene; n.d. = not detected

for each stage in the reaction chain (e.g., DCE to VC; VC to ethene) (Ellis et al., 1996). The degradability of chlorinated aliphatic compounds was studied under methanogenic conditions in batch reactors with leachate from eight landfill sites in Denmark. PCE and TCE were found to be degraded in only three of the eight leachates, with significantly different conversion rates. In one leachate, complete conversion of chlorinated ethenes, including conversion of VC, was observed within 40 days, while another leachate showed only 50% conversion of PCE (Kromann et al., 1998).

No known microorganism can aerobically destroy PCE. Laboratory studies have shown that some anaerobic bacteria (e.g., *Dehalobacter restrictus*) use chlorinated solvents for respiration (halorespiration), breaking them down in the process to form *cis*-dichloroethene, although restricted diet conditions are necessary (Sharma & McCarty, 1996). Recently, a coccoid bacterium has been isolated (provisionally named *Dehalococcoides ethenogenes* strain 195) which, together with extracts from mixed microbial cultures, can dechlorinate PCE, removing further chlorine atoms to form vinyl chloride and finally ethene (Maymó-Gatell et al., 1997).

Escape of landfill gas from the disposal site can take place via the surface (emission) or into the ambient soil (migration). VC is emitted from the landfill surface into the ambient air (Wittsiepe et al., 1996). Awareness of this problem has encouraged the development of *in situ* bioremediation of chlorinated solvents and VC using anaerobic or aerobic co-metabolic processes (Dolan & McCarty, 1995b; Jain & Criddle, 1995; Semprini, 1995; see section 4.2).

The estimated emission of vinyl chloride from landfill sites in the USA is 60–33 000 tonnes/annum (Lahl et al., 1991).

3.2.5.2 VC formation from tobacco

VC was identified in the smoke of all 13 cigarettes tested (1.3–16 ng/cigarette) and in both small cigars tested (14–27 ng/cigar). The level correlates directly with the chloride content of the tobacco. Filter tips with charcoal reduce selectively the VC content of cigarette smoke (Hoffmann et al., 1976).

3.3 Uses

About 95% of the world production of VC is used for the production of PVC. The remainder is used for the production of chlorinated solvents, primarily 1,1,1-trichloroethane (10 000 tonnes per year; European Council of Vinyl Manufacturers, 1994), via the more toxic 1,1,2-trichloroethane and 1,1-dichloroethane.

VC was previously used as a refrigerant (Danziger, 1960) and as a propellant in aerosol sprays for a variety of products, such as pesticides, drugs and cosmetics (Wolf et al., 1987). These uses have been banned since 1974 in the USA and in other countries.

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION AND TRANSFORMATION

4.1 Transport and distribution between media

Depending on the sources, VC can enter the environment via air, water or soil. The most critical matrices are probably air and groundwater. Euro Chlor (1999) calculated the partitioning of VC into environmental compartments, based upon the Mackay Level 1 model, to be 99.99% air, 0.01% water, < 0.01% soil and < 0.01% sediment.

4.1.1 Air

Owing to its high vapour pressure (saturation vapour pressure P_0 \$ 10^{-4} mmHg; see also section 2), VC released to the atmosphere is expected, based on calculations of Eisenreich et al. (1981), to exist almost entirely in the vapour phase. The atmospheric life-time of VC is limited by its reaction with photochemically produced OH radicals (see section 4.2.2).

VC is volatilized to the atmosphere from area sources such as landfill sites. Models have been developed to predict such short-range dispersion. These models were validated by VC concentrations ranging from < 5 to 31 : g/m^3 (< 2 to 12 ppb) measured in the vicinity of a landfill in Los Angeles 3 years after it last received any waste containing VC (Chitgopekar et al., 1990).

No data are available on wet deposition.

In order to model distribution processes, liquid : air partition coefficients have been determined (Gargas et al., 1989). Coefficients of 0.43 and of 24.4 were obtained for 0.9% saline : air and for olive oil : air, respectively.

4.1.2 Water and sediments

VC has a relatively low solubility in water (see section 2), and the solubility can be increased by the presence of salts (see section 4.2.3).

Experimental data on adsorption to particulate matter in the water column or to sediment are not available. A partition constant (unitless) of 8.2 for a sediment-water system was calculated (from a K_{ow} value of 17) by Mabey et al. (1982), indicating a low adsorption capacity. A high input of VC into water may lead to low-level long-term storage in the associated sediment (Hill et al., 1976b).

Volatilization of VC acts as a significant transport mechanism. It is considered to be the most rapid route for removal of VC from surface water, but to be an unlikely pathway for disappearance from groundwater that is not directly exposed to air (Smith & Dragun, 1984). Volatilization parameters such as vapour pressure and Henry's Law constants indicate that VC is highly volatile. Another factor, the reaeration rate ratio (rate constant for loss of VC from aqueous solution divided by the rate constant for oxygen uptake by the same solution), was reported to be 0.675 at 25 °C (theoretical calculation by Mabey et al., 1982) and approximately 2 (experimental measurement by Hill et al., 1976b). The results of measurements or calculations of volatilization half-lives of VC from water bodies are given in Table 6; they range from < 1 h to 5 h (measured in models for disturbed or quiescent water) and from 2.5 to 43 h (calculated for natural water bodies). In groundwater, however, VC may remain for months or years (ATSDR, 1990).

More or less complex models have been developed to describe the stability of VC in aquatic ecosystems (Hill et al., 1976b; Miller, 1992).

4.1.3 Soil and sewage sludge

Owing to its high vapour pressure, VC can be expected to volatilize rapidly, especially from dry soil surfaces. No experimental data are available. However, volatilization of VC from soil can be predicted based upon its physicochemical properties. The amount of VC volatilized from a soil depth of 1 m in 1 year was reported to range from 16 to 45% in a sandy soil and 0.1 to 0.7% in a clay soil. These calculations were based upon a Henry's Law constant of 0.44 and a degradation half-life of between 30 and 180 days (Jury et al., 1992).

It has been observed at landfill sites that subsurface migration of VC is a significant transport mechanism (Hodgson et al., 1992; Little

Table 6. Half-lives reported for volatilization of VC from water

Source	Method	Conditions	Half-life	Reference
Dilute aqueous solution (200 ml) stored in an open container	experimental (laboratory)	22–25 °C, rapid continuous stirring continuous stirring (200 rpm) discontinuous stirring (5% of time) quiescent, no stirring	25.8 min 26–27.6 min ~ 80–90 min 290 min	Dilling et al. (1975); Dilling (1977); Callahan et al. (1979)
Flowing channel	experimental (field)	water input: 35 litre/second flow velocity: # 0.50 m/second depth: 30 cm	0.9 h	Scherb (1978)
Stream	calculation	based on H_c = 243 kPa.m^3/mol depth: 1 m flow velocity: 1 m/second wind current: 3 m/second	2.5 h	Lyman et al. (1990)
	calculation	based on reaeration rate ratio of 2; assumed oxygen reaeration rates[a]:		US EPA (1985a)
Pond		0.008 h^{-1}	43.3 h	
River		0.04 h^{-1}	8.7 h	
Lake		0.01 h^{-1}	34.7 h	

[a]   According to Tsivoglou (1967); Lyman et al. (1990)

et al., 1992; Ward et al., 1996). Quantitative experimental data on the potential of VC for gaseous subsurface migration (see section 5.1.1) were not found.

Because of its solubility in water, VC can be leached through the soil to groundwater. Additionally, the high solubility of VC in many organic solvents may increase its mobility at special locations, e.g., landfills or waste disposal sites. Standard experimental studies on soil sorption of VC are lacking. The soil adsorption coefficients of VC were estimated from its water solubility, octanol/water partition coefficient and from the molecular topology and quantitative structure-activity relationship analysis method according to equations given by Chiou et al. (1979), Kenaga & Goring (1980), Lyman et al. (1982, 1990) and Sabljic (1984). The K_{oc} values obtained ranged from 14 to 240, indicating a low adsorption tendency and therefore a high mobility of VC introduced into soil (US EPA , 1985a; Stephens et al., 1986; ATSDR, 1997).

A field study performed to determine non-extractable (bound) residues (NER) of highly volatile chlorinated hydrocarbons gave a low value of 2.4% for VC, as measured in a lysimeter after one growth period in the upper (10 cm) soil layer (Klein et al., 1989).

VC was assumed not to appear frequently in sewage sludge due to its low adsorption potential (log K_{ow} < 2.0) and its high volatilization tendency (Wild & Jones, 1992).

4.1.4 Biota

VC has been identified in environmental samples of fish tissue (see section 5.1.5) and in several species of aquatic laboratory animals (molluscs, crustaceans, insects and vertebrates) and algae experimentally exposed to VC-containing water (see section 4.3). Reports on the presence of VC in terrestrial plants and animals have not been found in the literature.

Further experimental data, e.g., in what way and to what extent VC is capable of entering the biota, are lacking. However, a few estimations have been made on the basis of the physicochemical properties of VC. They refer to uptake of VC by terrestrial plants and

animals. Plant uptake was considered to be unlikely (Ryan et al., 1988; Shimp et al., 1993) because, at an assumed half-life of < 10 days (Ryan et al., 1988), VC should be lost from the system rather than be taken up by the plant. Another study (Wild & Jones, 1992) screened organic contaminants for possible transfers into plants and animals by summarizing approach data. Within the three categories used (high, moderate, low potential) VC was classified in the following way:

C   retention by root surface: low;
C   uptake and translocation: moderate;
C   foliar uptake: high;
C   transfer to animal tissues by soil ingestion: low;
C   transfer to animal tissues by foliage ingestion: moderate.

4.2 Transformation

4.2.1 Microbial degradation

There have been many studies on the biodegradation of VC under various simulated environmental conditions and these are listed in Tables 8 to 10. The biodegradation studies have given contradictory results, with no evidence of degradation under some aerobic conditions such as surface water (Hill et al., 1976b) and sewage (Helfgott et al., 1977) and under anaerobic conditions such as groundwater (Barrio-Lage et al., 1990). Unacclimated biodegradation half-lives of VC were generally estimated to be of the order of several months or years (Howard et al., 1991). However, other studies reported complete degradation in 3 months in simulated aerobic groundwater (Davis & Carpenter, 1990). Where degradation is reported care must be taken to ensure that the loss of VC is due to degradation and not from other losses such as volatilization from the test system. Phelps et al. (1991b) reported that > 99% of VC was lost from a bioactive reactor compared to 60% from the control reactor.

Significant microbial degradation of VC under aerobic and anaerobic conditions has been detected in studies using enrichment or pure cultures isolated mostly from sites contaminated with different organic chemicals (Tables 8 to 10). Vinyl chloride cannot be used by most microorganisms as sole carbon source, but it can be degraded/metabolized in the presence of propane, methanol,

3-chloropropanol, propylene, isopropene and glucose. However, in some cases VC can even serve as sole substrate, as is seen with *Mycobacterium* sp. (Table 9). The main degradation products include glycolic acid or CO_2 after aerobic conversion (Tables 7 to 9) and ethane, ethene, methane or chloromethane after anaerobic transformation (Table 10). Anaerobic mineralization of VC to CO_2 has been demonstrated (Table 10) and may occur under special conditions (Bradley & Chapelle, 1998b).

A complete mass balance was given by degradation studies with radiolabelled VC, for example, in aerobic resting cell suspensions of *Rhodococcus* sp. A starting concentration of 1 mg [1,2-^{14}C] VC produced more than 66% $^{14}CO_2$ and 20% ^{14}C aqueous phase products, and 10% was incorporated into the biomass (Malachowsky et al., 1994). Aerobic cultures of *Mycobacterium aurum* growing on a special filter material were reported to mineralize VC quantitatively according to the following equation:

$$VC + microorganisms\ \mathbf{6}\ biomass + HCl + CO_2 + H_2O\ (Meier,\ 1994).$$
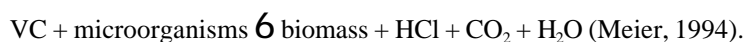
The underlying reaction mechanisms for the aerobic and anaerobic degradation of VC have been postulated to be oxidative and reductive dehalogenations, respectively, involving a variety of pathways (Vogel et al., 1987; Barrio-Lage et al., 1990; Ensley, 1991; Castro et al., 1992a; Leisinger, 1992; Castro, 1993; Meier, 1994; Hartmans, 1995; Jain & Criddle, 1995).

Frequently, the degradation reaction of VC proceeds more readily with aerobes than with anaerobes (Tables 7 to 10). The reverse occurs (Freedman & Gossett, 1989; Semprini et al., 1995) with PCE, an important precursor of VC in the environment (see chapter 3). Thus, two-stage treatment systems consisting of anaerobic (first stage) and aerobic (second stage) cultures have been proposed to achieve the complete degradation of a range of alkenes having different degrees of chlorination (Leisinger, 1992; Murray & Richardson, 1993; Nelson & Jewell, 1993). Recently, a chlorobenzoate-enriched biofilm reactor using *Desulfomonile tiedjei* DCB-1 was developed which degraded PCE under anaerobic conditions without any detectable VC remaining (Fathepure & Tiedje, 1994).

Table 7. Aerobic degradation of vinyl chloride by mixed microbial consortia from different sites

Inoculum	Test design/conditions[a]	Measured parameter	Initial concentration	Duration	Efficiency of degradation	Reference
Surface water samples	room temperature	VC	20 ml/2.9 ml	41 h	no degradation	Hill et al. (1976b)
Mixed consortium from natural aquatic systems	21 °C; + / - nutrients	VC	20–120 mg/litre	several weeks	no degradaion	Hill et al. (1976b)
Mixed consortium from domestic sewage	20 °C + nutrients	oxygen demand		25 days	no degradation	Helfgott et al. (1977)
Mixed consortium from activated municipal sewage sludge	25 °C; + nutrients	$^{14}CO_2$	0.05 mg/litre	5 days	21.5% degradation	Freitag et al. (1982, 1985)
Naturally occurring consortium from groundwater	simulated aquifers: soil-water microcosms (prepared with sub-surface soil and groundwater (20 °C)	$^{14}CO_2$, VC	1 mg/kg soil-water	108 days	> 99% degradation 65% mineralization (CO_2)	Davis & Carpenter (1990)
			0.1 mg/kg soil-water	109 days	50% mineralization (CO_2)	

Table 7 (contd).

Inoculum	Test design/ conditions[a]	Measured parameter	Initial concentration	Duration	Efficiency of degradation	Reference
Consortium indigenous to anaerobic aquifer systems (contaminated with CHs)	aquifer sediment microcosms	$^{14}CO_2$, VC	17 : mol/litre	84 h	22–39% mineralization (CO_2)	Bradley & Chapelle (1996)
Consortium indigenous to creek sediment (contaminated with DCE)	creek bed sediment microcosms	$^{14}CO_2$, VC	0.2–57 : mol/litre	24 h	6.2–58% mineralization (CO_2)	Bradley & Chapelle (1998a)
Consortium from aquifer material (from a VC-contaminated site)	soil microcosms	VC	5.3 mg/litre	95 h	little change in VC concentration	Dolan & McCarty (1995a)

[a]   CH = chlorinated hydrocarbons; DCE = dichloroethene

Table 8. Elimination of vinyl chloride in aerobic tests with mixed microbial consortia utilizing special substrates[a]

Inoculum	Additional substrate	Test	Efficiency of degradation	Remarks	Reference
Mixed methanotrophs	methane	laboratory studies	removal of up to 100% within 4 h–30 days	inhibition by methane and 1,1-DCE possible; toxic effects of VC and VC products possible	Fogel et al. (1986, 1987); Strandberg et al. (1989); Uchiyama et al. (1989); Nelson & Jewell (1993); Dolan & McCarty (1995a); Chang & Alvarez-Cohen (1996)
	methane	field study (groundwater)	about 95% in-situ transformation i.c. = 0.03 mg/litre	inhibition by methane possible	Semprini et al. (1990, 1991)
Mixed microbial consortia	propane	laboratory study	> 99% loss after 30 days i.c. = 4–20 mg/litre	> 60% loss in control	Phelps et al. (1991b); Lackey et al. (1994)
	methane plus propane	laboratory study	82 to > 99% loss after 10–21 days; i.c. = 1–20 mg/litre		Phelps et al. (1991b); Lackey et al. (1994)
Mixed methanotrophs	methane plus formate	laboratory study	2.3 : mol VC per mg of cells during 26 h i.c. = 14.8 mg/litre	relative TCs from highest to lowest: *trans*-DCE; *cis*-DCE; VC; TCE; 1.1-DCE	Dolan & McCarty (1995a)
Mixed consortia	methane	laboratory study	removal of up to > 99% within 15 days i.c. = 0.55 mg/litre		Deipser (1998)

[a]   i.c.= Initial concentration; DCE = dichloroethene; TCE = trichloroethene; TC = transformation capacity

Table 9. Survey on isolated bacterial cultures capable of degrading vinyl chloride under aerobic conditions

Inoculum	Additional substrate	Major degradation product[a]	Remarks	Reference
Mixed culture consisting of *Rhodococcus rhodochrous* and 2 bacteria of the order Actinomycetales	n. sp.	CO_2 (> 67%)		Malachowsky et al. (1991)
Bacterium of the order Actinomycetales	propane, glucose or acetate	CO_2 (> 67%)		Phelps et al. (1991a)
Alcaligenes denitrificans ssp. *Xylosoxidans*	isoprene	n. sp.		Ewers et al. (1990)
Methylosinus trichosporium OB3b	methane	n. sp.	inactivation possible	Tsien et al. (1989); Chang & Alvarez-Cohen (1996)
	methane	glycolic acid (44%; determined at 68% conversion)		Castro et al. (1992a)
Mycobacterium sp. ; *M. aurum*	no	CO_2; initially: chloro-oxirane (epoxide)	VC as primary substrate; inhibition possible	Hartmans et al. (1985, 1992); Hartmans & DeBont (1992); Meier (1994)

Table 9 (contd).

Inoculum	Additional substrate	Major degradation product[a]	Remarks	Reference
Mycobacterium aurum L1	no	CO_2, HCl	maximum growth rates at 1 mmol VC/litre	Hauschild et al. (1994)
Mycobacterium vaccae (JOB 5)	propane	n. sp.		Wackett et al. (1989)
Nitrosomonas europaea	ammonia	n. sp.		Vannelli et al. (1990)
Pseudomonas sp.	3-chloro-propanol	glycolic acid (71%; determined at 25% conversion)		Castro et al. (1992b)
Rhodococcus sp.	propane	CO_2 (> 66%)		Malachowsky et al. (1994)
Rhodococcus erythropolis	isoprene	n. sp.		Ewers et al. (1990)
Xanthobacter (strain Py 2)	propylene	n. sp.		Ensign et al. (1992)

[a]   The degradation efficiency is given in parentheses; n. sp. = not specified

Table 10. Survey on anaerobic microbial degradation of vinyl chloride[a]

Inoculum	Test design/ Conditions	Major degradation products	Efficiency of degradation	Remarks	Reference
Mixed methanogenic consortium (from PCE-, TCE-, VC-contaminated groundwater)	liquid cultures (20 °C) groundwater with sterile sand	n. sp.	i.c. = 400 : g/litre approx. 50% (100%) after 4 (11) weeks		Brauch et al. (1987)
	without sterile sand		approx. 20% (55%) after 4 (11) weeks		
Mixed consortium (from TCE-contaminated water)	incubation of groundwater plus waste water (9 : 1) (21 °C)	n.sp.	94% within 16 days i.c. = 18 : g/litre		Nerger & Mergler-Völkl (1988)
Mixed consortium (from compost)	digesters filled with mature sieved compost from private households	n.sp.	low degradation (0.2 mg/m^3 compost/h)		Deipser (1998)
Mixed consortium (from natural sites)	soil-groundwater microcosms (25 °C)	(< 1% CO_2)	no degradation in 5 months i.c. = 2 mg/litre		Barrio-Lage et al. (1990)

Table 10 (contd).

Inoculum	Test design/ Conditions	Major degradation products	Efficiency of degradation	Remarks	Reference
Mixed consortium (from natural sites)	flow-through column packed with soil, a. s.: mixture of phenol, citrate, ammonium dihydrogenphosphate, methanol and methane	methane plus ethene (82%), CO_2 (7%)	89% degradation (in 9–15 days)	traces of chloromethane	Barrio-Lage et al. (1990)
Consortium indigenous to anaerobic aquifer systems (contaminated with CHs)	aquifer sediment micro-cosms, anaerobic con-ditions plus Fe(III) as Fe-EDTA	CO_2	15–34% mineralization in 84 h (versus 3–5% without Fe-EDTA amendment) i.c. = 17 : mol/litre		Bradley & Chapelle (1996)
Mixed methanogenic or methanol-enriched consortia	varying conditions 15–30 °C	chloroethane or ethene (plus ethane)	slow degradation		Baek et al. (1990); Carter & Jewell (1993); Skeen et al. (1995)

Table 10 (contd).

Enriched PCE- and TCE-degrading consortia	batch cultures (35 °C)	ethene	partial to nearly complete degradation	inhibition by PCE possible	Freedman & Gossett (1989); DiStefano et al. (1991); Tandoi et al. (1994)
Mixed anaerobic consortia from river sediment and wastewater sludge	fixed-bed column[b] 24 °C a.s.: lactate	ethene plus ethane	almost complete conversion of PCE (95–98%) via VC		De Bruin et al. (1992)
Methanobacterium thermoautotrophicum	resting cell suspensions (60 °C)		no degradation i.c. = 10^{-3} mol/litre		Castro et al. (1994)
"*Dehalococcoides ethenogenes* strain 195"[c] + mixed microbial consortia	anaerobic H_2-PCE[b] enrichment culture	ethene	90% conversion of PCE via VC	decay in rate of VC conversion	Maymó-Gatell et al. (1995, 1997)

[a] a.s. = additional substrate; i.c. = initial concentration; n.sp. = not specified; CH = chlorinated hydrocarbons; PCE = tetrachloroethene; TCE = trichloroethene

[b] starting material PCE

[c] preliminary name

There have been many efforts to use the VC-degrading capacities of microorganisms in practical applications such as the purification of waste gases (Meier, 1994) or of municipal waste waters (Narayanan et al., 1995) and the remediation of landfill leachates (Lesage et al., 1993), groundwaters (McCarty, 1993; Holliger, 1995) and contaminated soils (Schulz-Berendt, 1993). Possible limitations arise from physical (temperature, accessibility of substrate), chemical (pH, redox state, concentration of VC and other contaminants, presence of additional secondary substrates, salinity) and biological (presence of predators, competition phenomena, adsorption of microbes to surfaces) factors (Van der Meer et al., 1992).

4.2.2 Abiotic degradation

4.2.2.1 Photodegradation

Studies on the photodegradation of VC are summarized in Table 11. They include direct and indirect photolysis.

VC in the vapour phase or in water does not absorb wavelengths above 220 nm or 218 nm, respectively (Hill et al., 1976b). However, solar radiation reaching the troposphere lacks wavelengths below about 290 nm due to the stratospheric ozone shield. So, direct photolysis of VC is expected to be insignificant under environmental conditions, because there is no overlap between the absorption spectrum of VC and the sunlight radiation spectrum (Callahan et al., 1979). Consistently, no photodegradation was observed with pure VC in the gas phase or in water at wavelengths above 220 nm. After irradiation at 185 nm, VC was photolysed (Table 11).

In the environment, indirect photolysis occurs and includes reactions of VC in the presence of photosensitizers and those (Table 12) with photochemically produced reactive particles.

A variety of photolytic products was formed after irradiation of VC under several experimental conditions (Table 11). Some intermediates, e.g., chloroacetaldehyde, were of considerable photochemical stability. Therefore, the photooxidation is unsuitable as a means of removing VC from waste gases (Gürtler et al., 1994). On the other hand, treatment of water contaminated with VC and

Table 11. Survey on vinyl chloride photolysis studies

Medium	Irradiation (Duration)	Photolytic degradation	Photolytic products[a]	Reference
VC in a high-vacuum system	medium pressure arc	yes	primary products: radicals (C_2H_3, Cl); C_2H_2, HCl	Fujimoto et al. (1970)
VC in air	sunlight (outdoors)	yes (half-life = 11 weeks ± 50%)	n.sp.	Pearson & McConnell (1975)
	xenon arc (> 290 nm)	yes	CO (90%); HCl	
VC in air	high pressure mercury lamp	yes (> 99% within 15 min)	chloroacetaldehyde, HCl, CO_2	Kagiya et al. (1975)
	outdoors	yes (55% within 2 days)		
VC in air (dry)	> 230 nm (4 h)	yes	chloroacetaldehyde (primary product), HCl, CO, formyl chloride	Müller & Korte (1977)
VC in air	< 400 nm (45 min)	yes	CO_2, CO, H_2O, HCl, HCOOH, C_2H_2	Woldbaek & Klaboe (1978)
	sunshine (3–45 h)	very slow		
VC (adsorbed on silica gel)	> 290 nm (n.sp.)	yes (15.3% of applied amount)	n.sp.	Freitag et al. (1985)

Table 11 (contd).

Medium	Irradiation (Duration)	Photolytic degradation	Photolytic products[a]	Reference
VC in an oxygen atmosphere[b]	185 nm (up to 50 min)	yes (quantum yield: 2–3)	formyl chloride, monochloro-acetaldehyde, acetylene, CO, CO_2, monochloroacetyl chloride, HCl[c], formic acid[c]	Gürtler et al. (1994)
	254 nm (up to 6 h)	no		
VC in air	xenon lamp	yes (initial k: 0.09 second^{-1})	n.sp.	Haag et al. (1996)
VC in air plus nitrogen oxides	UV (> 290 nm) (up to 22 h)	yes (half-life = 1–7 h, + NO half-life = 18 h, – NO)	formic acid, HCl, CO, formal-dehyde, ozone, (other minor products)	Cox et al. (1974); Dilling et al. (1976); Gay et al. (1976); Carassiti et al. (1977)
	xenon lamp (0–120 min)	yes	formaldehyde, Hcl	Kanno et al. (1977)
	< 400 nm (25 min)	yes (increase in reaction rate as compared to NO_2/NO being absent)	at low NO_2 conc.: the same products as observed in air (see above); at high NO_2 conc.: additionally nitrosyl chloride, N_2O	Woldbaek & Klaboe (1978)

Table 11 (contd).

VC in air plus 1,1-DCE	xenon lamp	yes (initial k: 0.15 second^{-1})	n.sp.	Haag et al. (1996)
VC in pure water (10 mg/litre)	> 300 nm (90 h)	no		Hill et al. (1976b)
VC in natural water samples (10 mg/litre)	> 300 nm (20 h)	no		
VC in water plus photosensitizers	> 300 nm	yes (rapid)	various products	
VC in PVC plant effluent	> 300 nm sunlight (25 h)	yes (half-life = 40 h) very little	n.sp.	

[a]   n.sp. = not specified; DCE = dichloroethene
[b]   direct photolysis
[c]   in the presence of water vapour

Table 12. Rate constants and half-lives for gas-phase reactions of vinyl chloride with OH radicals and other reactive particles

VC reaction with [a]	Rate constant (in units of cm^3/molecule-sec) [b]	Temperature (°C) [c]	Assumed atmospheric concentration of the reactive particle [c]	Calculated half-life [c,d]	Reference
с OH	5.6×10^{-12} (measured)	27	1×10^6 molecules/cm^3	1.4 days	Cox et al. (1974); US EPA (1985a)
с OH	4.5×10^{-12} (measured)	23 (296 K)	1×10^6 molecules/cm^3	1.8 days	Howard (1976); US EPA (1985a)
с OH	6.60×10^{-12} 5.01×10^{-12} 3.95×10^{-12} (measured)	26 (299 K) 85 (358 K) 149 (423K)	n.sp.	n.sp.	Perry et al. (1977)
с OH	6.60×10^{-12} (Perry et al., 1977)	26	1×10^6 molecules/cm^3	1.2 days	US EPA (1985a)
с OH	6.60×10^{-12} (Perry et al., 1977)	room temperature (298 ± 2 K)	1×10^6 molecules/cm^3 (12-h daytime average, Crutzen, 1982)	(3.5 days)	Atkinson et al. (1979, 1987); Atkinson (1985)
с OH	6.60×10^{-12} (measured) 5.3×10^{-12} (calculated)	room temperature	n.sp.	n.sp.	Atkinson (1987)

Table 12 (contd).

⦵ OH	6.60×10^{-12} (Perry et al., 1977)	25 ± 2 (298 ± 2 K)	5×10^5 molecules/cm^3	(approx 3 days)	Tuazon et al. (1988)
⦵ OH	6.60×10^{-12} (Perry et al., 1977)	26	5×10^5 molecules/cm^3 (Crutzen, 1982)	2.2–2.7 days	BUA (1989)
⦵ OH	6.8×10^{-12} (Becker et al., 1984)	27 (300 K)	5×10^5 molecules/cm^3 (Crutzen, 1982)	approx 2.4 days	BUA (1989)
⦵ OH	6.60×10^{-12} (Perry et al., 1977)	26	8×10^5 molecules/cm^3	1.5 days	Howard (1989)
⦵ OH	4.0×10^{-12} cm^3/mol-sec (measured)	26 (299 K)	n.sp.	n.sp.	Kirchner et al. (1990)
⦵ OH	10.6×10^{-12} (calculated)	n.sp.	n.sp.	n.sp.	Klamt (1993)
⦵ OH	n.sp.	n.sp.	1×10^6 molecules/cm^3 (24-h average)	(42 h)	Pitts (1993)
⦵ OH	6.60×10^{-12} (Perry et al., 1977)	n.sp.	6.5×10^5 molecules/cm^3 (estimated global mean; Tie et al., 1992)	(2.7 days)	Helmig et al. (1996)

Table 12 (contd).

VC reaction with [a]	Rate constant (in units of cm^3/molecule-sec)[b]	Temperature (°C) [c]	Assumed atmospheric concentration of the reactive particle [c]	Calculated half-life [c,d]	Reference
⋅ OH	6.60×10^{-12} (Perry et al., 1977)	26	7.5×10^5 molecules/cm^3 (24-h average, BUA, 1993)	1.6 days	Palm (1997) personal communication
⋅ NO₃	2.3×10^{-16} (measured)	room temperature (298 ± 2 K)	2.4×10^9 molecules/cm^3 (12-h nighttime average, Platt et al., 1984)	(42 days)	Atkinson et al. (1987)
⋅ NO₃	1.4×10^{-16} (measured)	23 (296 ± 1 K)	n.sp.	n.sp.	Andersson & Ljungström (1989)
Cl	12.7×10^{-11} (measured)	25 (298 ± 2 K)	n.sp.	n.sp.	Atkinson & Aschmann (1987); Grosjean & Williams (1992)
O₃	1.9×10^{-19}	25	n.sp.	n.sp.	Gay et al. (1976); Singh et al. (1984)
O₃	2.0×10^{-18}	n.sp.	n.sp.	4 days	Hendry & Kenley (1979); ECETOC (1983)
O₃	$2.45 \ (\pm 0.45) \times 10^{-19}$	room temperature (~ 25)	n.sp.	n.sp.	Zhang et al. (1983)

Table 12 (contd).

O_3	2.5×10^{-19} (Zhang et al., 1983)	25	7×10^{11} molecules/cm^3 (Singh et al., 1978)	(66 days)	Atkinson & Carter (1984); Atkinson et al. (1987)
O_3	2.45×10^{-19} (Zhang et al., 1983)	25	1×10^{12} molecules/cm^3	33 days	US EPA (1985a)
O_3	1.2×10^6 cm^3/mole-sec	27	1.6×10^{12} molecules/cm^3	4.2 days	Lyman et al. (1982, 1990); US EPA (1985a)
O_3	1.7×10^{-19}	22	7×10^{11} molecules/cm^3	67 days	Klöpffer et al. (1988)
O_3	2.5×10^{-19} (calculated according to AOP)	n.sp.	n.sp.	n.sp.	Meylan & Howard (1993)
	19×10^{-19} (calculated according to FAP)	n.sp.	n.sp.	n.sp.	
O (^{3}P)	8.6×10^{-13}	25	2.5×10^4 molecules/cm^3	373 days	Sanhueza & Heicklen (1975); US EPA (1985a)
O (^{3}P)	5.98×10^{-13}	25	2.5×10^4 molecules/cm^3	532 days	Atkinson & Pitts (1977); US EPA (1985a)

[a]   O(^{3}P) = oxygen atom
[b]   AOP = Atmospheric Oxidation Program (currently used by US EPA); FAP = Fate of Atmospheric Pollutants (part of US EPA's Graphical Exposure Modeling system, GEMS)
[c]   n.sp. = not specified
[d]   Values in parentheses reported as 'lifetime'

other halogenated organic compounds by means of UV-enhanced oxidation (UV/ozone or UV/hydrogen peroxide) was reported to be successful (Zeff & Barich, 1992).

The atmospheric fate of VC depends on its reaction with reactive particles such as free OH and NO_3 radicals, Cl atoms, ozone and singlet oxygen. As can be seen from Table 12, the reaction with OH radicals is the dominant transformation process, showing calculated tropospheric half-lives of 1-2 days or more. Factors influencing indirectly (via OH radical concentration) the lifetime of VC are the degree of air pollution and solar radiation, leading to spatial, diurnal and seasonal variations (e.g., Hesstvedt et al., 1976). Reaction products include formaldehyde (HCHO) and formyl chloride (HCOCl), the latter being a stable potential toxicant (Tuazon et al., 1988; Pitts, 1993).

Rate constants for the photodegradation of VC in aqueous solutions have been reported to range from 6.99×10^9 mol^{-1} $second^{-1}$ (Grosjean & Williams, 1992) to 7.1×10^9 mol^{-1} $second^{-1}$ (Klöpffer et al., 1985). Mabey et al. (1982) reported that photolysis of VC was not an environmentally relevant process. They reported oxidation rate constants of $< 10^8$ $mol^{-1}h^{-1}$ and 3 $mol^{-1}h^{-1}$ for reactions with singlet oxygen ($^1O_2$) and peroxy radicals (RO_2), respectively. On the basis of an average OH radical concentration of 10^{-17} mol in natural water, the k_{OH} rate constant resulted in a half-life of approximately 110 days (US EPA, 1985a). Both of the other reactions appeared to be negligible.

4.2.2.2 Hydrolysis

Observations on chemical hydrolysis of VC derive from experiments with effluent water from a VC plant (pH = 4.3–9.4; 50 °C; 57 h; Callahan et al., 1979), water of different pH values (85 °C; 27 h; Hill et al., 1976b; Mabey et al., 1982), water saturated with O_2 (85 °C; 12 h; Hill et al., 1976b), water plus ethanol (120 °C; Rappoport & Gal, 1969) and two natural water samples (pH = 6.1/4.2 for river/swamp water, both at room temperature and at 85 °C; 41 h; Hill et al., 1976b). In all cases, no or only slow hydrolysis occurred. The hydrolytic half-life was estimated to be < 10 years at 25 °C (Hill et al., 1976b). Hydrolysis experiments under strongly alkaline, high temperature (and therefore environmentally irrelevant) conditions resulted in a polymerization of VC (Jeffers & Wolfe, 1996).

4.2.3 Other interactions

Under experimental conditions, VC and chlorine in water form chloroacetaldehyde, chloroacetic acid and other unidentified compounds (Ando & Sayato, 1984).

Many salts have the ability to form complexes with VC, thus possibly leading to an increase in its solubility (Callahan et al., 1979).

4.3 Bioaccumulation

Owing to its high vapour pressure and low octanol/water partition coefficient, VC is expected to have little tendency for bioaccumulation (BUA, 1989). Theoretical calculations resulted in bioconcentration factors (BCFs) of 2.8 (based on a log K_{ow} of approximately 0.9) and around 7 (based on a water solubility of 2763 mg/litre) in aquatic organisms (US EPA, 1985a). A BCF of 5.7 (based on log K_{ow} = 1.23) was calculated by Mabey et al. (1982) for aquatic microorganisms.

Experiments performed with ^{14}C-VC (initial concentration: 250 : g/litre) in a closed laboratory model aquatic ecosystem gave the following results: after 3 days at 26.7 °C 34% of the ^{14}C was found in the water and 65% in the air. The organisms from different trophic levels contained ^{14}C residues (in VC equivalents, : g/kg) of 1307 (alga, *Oedogonium cardiacum*), 621 (waterflea, *Daphnia magna*), 123 (snail, *Physa sp.*), 1196 (mosquito larva, *Culex pipiens quinquefasciatus*) and 312 (fish, *Gambusia affinis*) (Lu et al., 1977). These values led to BCFs ranging from 3 to 31 when compared to the VC water concentration of 42 : g/litre, indicating some bioaccumulation, but no biomagnification within the food chain.

Another study determined BCFs for green algae (*Chlorella fusca*) after a 24-h exposure to 0.05 mg VC/litre and for fish (golden ide, *Leuciscus idus melanotus*) exposed to a constant average concentration of 0.05 mg VC/litre over 3 days. BCFs of 40 and < 10, respectively, were found (Freitag et al., 1985).

After 5 days of incubation of 0.05 mg VC/litre in activated sewage sludge, an accumulation factor of 1100 (based on the distribution of VC between sludge, dry weight and water) was observed (Freitag et al., 1985).

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4.4 Ultimate fate following use

4.4.1 Waste disposal

Several methods have been employed for removal of VC from waste water: stripping with air, steam or inert gas (Nathan, 1978; Cocciarini & Campaña, 1992; Hwang et al., 1992), extraction (Nathan, 1978) or adsorption onto activated charcoal or adsorbent resin (Nathan, 1978; Dummer & Schmidhammer, 1983, 1984).

Like VC waste gases produced during other processes (see chapter 3), the recovered VC can be recycled or incinerated (US EPA, 1982; BUA, 1989). Special biological filters have been developed for degrading VC in waste emissions (Meier, 1994, 1996; see also section 4.2.1).

Incineration leading to the total destruction of VC requires temperatures ranging from 450 °C to 1600 °C and residence times of seconds for gases and liquids, or hours for solids (HSDB, 1995).

Photochemical oxidations (Topudurti, 1992; Zeff & Barich, 1992; Berman & Dong, 1994; see also section 4.2.2) are further methods of VC elimination. UV-enhanced oxidation (oxidants used: ozone, hydrogen peroxide) was applied for purification of polluted waters, (e.g., waste, leachate, groundwater) (Zeff & Barich, 1992). Treatment with sodium dichromate in concentrated sulfuric acid was recommended for the destruction of small quantities of VC, for instance, from experimental laboratories (HSDB, 1995).

Chlorinated volatile organic compounds (VOCs) can be removed from drinking-water/groundwater by treatment with activated charcoal (Schippert, 1987), air stripping (after water is pumped to the surface) (Boyden et al., 1992) or by air sparging (applied *in situ*) (Pankow et al., 1993). Recently, on-site and *in situ* bioremediation techniques, which couple evaporative or other methods with microbial treatment, have been developed for restoration of groundwater systems (Roberts et al., 1989; Portier et al., 1992, 1993; Fredrickson et al., 1993; McCarty, 1993; Lackey et al., 1994) or soils (Schulz-Berendt, 1993) contaminated with VC and other VOCs.

4.4.2 Fate of VC processed to PVC

Most of the VC produced is used for the manufacture of PVC (see section 3) and will therefore be connected with the fate of PVC. PVC and articles made from it can be disposed of in landfills, incineration or feedstock recycling. While rigid PVC is an extremely persistent material, flexible PVC may be less recalcitrant to disintegration (Harris & Sarvadi, 1994). At incineration, PVC plastics do not depolymerize to form VC (Harris & Sarvadi, 1994), but produce volatile aliphatic hydrocarbons and volatile chlorinated organic compounds (Nishikawa et al., 1992; see also section 3.2.4). There is evidence for formation of PCDFs/PCDDs (Theisen et al., 1989, 1991; IPCS, 1989).

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental levels

There is very little exposure of the general population to VC.

Concentrations of VC in ambient air are low, usually less than 3 : g/m^3. Exposure of the general population may be higher in situations where large amounts of VC are accidentally released to the environment, such as a spill during transportation. However, such exposure is likely to be transient. Near VC/PVC industry and waste disposal sites, relatively much higher concentrations, up to 8000 : g/m^3 and 100 : g/m^3, respectively, have been observed. VC has only rarely been detected in surface waters, sediment or sewage sludges. Maximal VC concentrations in groundwater or leachate from areas contaminated with chlorinated hydrocarbons amount to 60 000 : g/litre.

5.1.1 Air

5.1.1.1 Outdoor air

Atmospheric air levels of VC in rural/remote and suburban/urban areas range from not detectable to 24 : g/m^3 (Table 13). Higher values were recorded in industrial areas, with maxima in the vicinity of VC/PVC producing or processing plants, even at distances of 5 km. Peak concentrations were as high as 86 mg/m^3 (33 ppm) and 17 mg/m^3 (7 ppm), measured, respectively, in 1974 in the USA and 1983 in China (Table 13). In many countries, VC concentrations near plants have decreased with time due to regulatory measures (Table 13).

In more recent years attention has been paid to the occurrence of VC near waste disposal sites, where levels of up to 0.18 mg/m^3 (70 ppb) have been detected (Table 13). This is much less than the significant amounts of VC found in undiluted landfill gas (see section 3). Bruckmann & Mülder (1982) assumed that gas discharges of landfills are diluted by a factor of 10^4 when entering the atmosphere.

VC emissions of < 0.5 : g/m^3 (remote from VC plants) or of a few : g/m^3 (near VC plants) in Germany and the Netherlands were

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Table 13. Vinyl chloride measured in ambient (atmospheric) air[a]

Country; site and year of sampling	Value[b]	Concentrations ($\mu g/m^3$)	Reference
Rural/remote areas Canada: pine forest near Barrie, Ontario year n. sp.	single	0.1	Kruschel et al. (1994)
Germany: Westerland, Schwarzwald, Lüneburger Heide, Bayer Wald; prior to 1977	mean values	6.6–24	Bauer (1981)
Germany: Taunus; 1975	mean value (n = 4)	0.1	Dulson (1978)
USA: rural Northwest USA (Pullman, Washington); 1974–1975	(n = n. sp.)	n.d. (< 0.013)	Grimsrud & Rasmussen (1975)
USA: over ocean Sandy Hook, NJ (3 miles offshore); 1974	(n = n. sp.)	n.d. (< 26)	Lillian et al. (1975)
Suburban/urban areas Canada: urban (22) and rural (1) sites; 1989–1990	mean[c] (n = 1370; 4% > detection)	0.06	Dann & Wang (1992)
Germany: Berlin (3 sites); 1977	range (n=78) means	n.d. (n.sp.) – 3.5 0.3–0.4	Dulson (1978); Lahmann (1980)
Germany: Frankfurt/M. (city); 1974	n = 1	2.6	Bergert & Betz (1976)
Germany: Frankfurt/M. (suburban); 1975	mean (n = 16)	21.1	Arendt et al. (1977)
Germany: Merkenich (North-Rhine Westfalia); 1980	annual mean	3.6	German Expert Group on the Environment (1988)

Table 13 (contd).

Country; site and year of sampling	Value[b]	Concentrations (: g/m^3)	Reference
Germany: Cologne (3 stations); 1979–1986	means (n = n.sp.)	0.5–15.3	Anon (1981); BUA (1989)
Germany: several sites; year n. sp.	mean values	0.2–11	Bouscaren et al. (1987)
Germany: Hamburg (12 sites in the city); 1986–1987	annual means (n = 300)	2.4–9.0 (including 1-butene)	Bruckmann et al. (1988)
USA: New Jersey (3 urban sites: Newark, Elizabeth, Camden); 1981–1982	geom. mean (3/113)[d] and (0/105)[d]	1981: 0 1982: 0 (detection limit: 0.013)	Harkov et al. (1983, 1984)
USA (eastern): urban sites; 1989	daily mean (n=397; 2% > detection)	0.62	Dann & Wang (1992)
Industrial sites			
Canada: Shawinigan (vicinity of VC poly-merization plant); year n. sp.	range	n.d. – 117	Thériault et al. (1983)
China: dormitories for workers (50, 100 and 1000 m from a VC polymerization plant)	n = 16×3 (4 h/day for 4 days at 3 stations)		Zhao et al. (1994)
1983	maxima daily means	17 400 / 5900 / 1500 4810 / 1080 / 580	
1984	maxima daily means	7800 / 2500 / 1400 4080 / 720 / 500	
1986	maxima daily means	6600 / 2000 / 1100 3120 / 820 / 520	
1988	maxima daily means	12 700 / 1000 / 300 4430 / 320 / 200	
1989	maxima daily means	3100 / 700 / 300 760 / 220 / 170	

Table 13 (contd).

Country; site and year of sampling	Value[b]	Concentrations ($\mu g/m^3$)	Reference
Finland: 1.2 km from a PVC plant			Kinnunen (1996)
1993	range of monthly means	0.1–1.3	
1994	range of monthly means	0.1–0.8	
1995	range of monthly means	< 0.1–0.1	
	range of single measurements (n . 4000)	0.1–11	
1996	range of monthly means	0.1–0.4	Kinnunen (1997)
	range of single measurements (n . 7000)	0.1–13	
Germany: n.sp.; prior to 1980	maximum	252	Bouscaren et al. (1987)
Germany: Ruhrgebiet West; year n. sp.	99th percentile	69	BUA (1989)
Germany: 1978–1982	max. (n = n.sp.)	113	Bauer (1981)
Germany: Marl (80 m and 500 m above chemical plant);1970	mean (n = 24) mean (n = 9)	213 108	Rohrschneider et al. (1971)
Germany: Frankfurt/M. (industrial area); year n.sp.	n.sp.	4.5	Atri (1985)
Netherlands: > 600 m from VC plant; 1976–1977	maximum mean	ca. 600 210	Besemer et al. (1984)
0–500 m distant 500 m distant; 1978	range (n = 200) range (n = 100) mean	< 21–504 13–55 18	
Netherlands: VC/PVC plants; 1980	range (n = n.sp.)	7.8–181	Guicherit & Schulting (1985)

Table 13 (contd).

Country; site and year of sampling	Value[b]	Concentrations ($\mu g/m^3$)	Reference
UK: 5 VC plants; 1984 (April–July)	overall means daily means (ranges related to the 5 plants, total n = 440)	< 13–228 23–218	Turner et al. (1984)
Plant VI (7 stations, 0–4.8 km distant)	max. (n = 28);	20 202 (0 km), 880 (0.8 km)	
Plant IX (15 stations, 0.8–5 km distant)	means (n = 180); maximum	311–1373 8806 (5 km)	
USA: 1974–1975; VC plant (Narco) (4 stations, < 250 – > 1000 m distant)	(n = 708) means geom. means maximum	3.4–262 0–28 27 045 (< 250 m)	US EPA (1975); Dimmick (1981)
PVC plant (Aberdeen) (4 stations, < 250 – > 1000 m distant)	(n = 438) means geom. means maximum	11.6–958 3.7–372 23 430 (300 m)	
PVC plant (Louisville) (4 stations, < 250 – > 1000 m distant)	(n = 712) means geom. means maximum	11.4–101 5–30 814 (250–400 m)	
USA: residential areas near chemical plants (n = 15); 1974	range (n = 30)	n.d. – 104	US EPA (1975)
USA: Houston, Texas; 1974	range (n = 18.)	8–3238	Gordon & Meeks (1977)
USA: residential areas in the vicinity of VC/PVC plants; prior to 1975	max. (n = n.sp.) mean (n = n.sp.)	> 2560 44	Fishbein (1979)
USA: vicinity of VC/PVC plants (Texas, 7 stations); 1977	max.	34	McMurry & Tarr (1978)

Table 13 (contd).

Country; site and year of sampling	Value[b]	Concentrations ($\mu g/m^3$)	Reference
Areas in the vicinity of waste sites			
Belgium: Mellery; prior to 1990	no details	19	Lakhanisky et al. (1993)
Germany: surroundings of a hazardous waste site; about 1988	no details	< 3	Pudill (1993)
Germany: 2 landfills near Bochum; 1990–1991	range (n = 16)	< 0.082–0.65	Wittsiepe et al. (1996)
USA: West Covina, California; 1981–1984	range (24-h av; n = 32) max	26–104 130	Camarena & Coy (1984)
USA: West Covina, California; 1984 site A (200 m distant from landfill) site B (20 m distant from landfill)	24-h averages 5-day average 24-h averages 5-day average	13–31 (n = 5 days) 23 5.7–18 10.4 (n = 5 days)	Baker & MacKay (1985)
USA: southern California, 1981 after 1981	max. range (6 stations)	18 5–18	Stephens et al. (1986)
USA: California; prior to 1990	max.	30	Little et al. (1992)
USA: New York (2 sites) 1982	range	n.d. (5.4) – 16	Lipsky & Jacot (1985)
Miscellaneous			
USA: all outdoor site types; prior to 1988	mean (n = 574)	8.5	Shah & Singh (1988)

[a] n.d. = not detected (detection limit in parentheses, if specified); n.sp. = not specified

[b] This column indicates whether the concentration is a maximum (max), average or range value

[c] Values below detection set to 0.5 method detection limit (0.1 $\mu g/m^3$)

[d] Values in parentheses = no. detected / no. sampled

derived from a computer model (Besemer et al., 1984; WHO, 1987; LAI, 1992). Ambient air concentrations in three geographical areas of the USA were computed to range from trace to about 3 : g/m^3 (Pellizzari et al., 1979).

5.1.1.2 Indoor air

Indoor air concentrations of VC in houses near landfills in the USA reached concentrations of up to 1 mg/m^3 air (Little et al., 1992: 2 landfills, maxima of 0.13 and 0.3 mg/m^3; Stephens et al., 1986: 1 landfill, maximum of 1 mg/m^3), thus exceeding the maximum outdoor levels reported in Table 13 for areas adjacent to landfills. Moreover, the Californian monitoring programme, collecting a total of 500 air samples at two outdoor and four indoor sites downwind of a landfill, revealed that the 120 samples containing the most VC ($ 0.025 mg/m^3; 10 ppb) were taken inside homes (Little et al., 1992). It is assumed that in addition to atmospheric transport, subsurface migration of VC accounts for the elevated indoor air levels of VC (Wood & Porter, 1987; Hodgson et al., 1992; Little et al., 1992).

A room being painted with a red latex paint based on a terpolymer of vinyl chloride, vinyl acetate and ethylene showed VC levels of 75 and 10 : g/m^3 (29 and 4 ppb), respectively, during and some time (less than one day) after painting (Going, 1976).

In the early 1970s it was investigated whether VC was present in car interiors as a result of volatization from PVC. Measurements of VC concentrations in the interior of seven different new 1975 automobiles gave positive results for two of them. Levels of 1036 to 3108 : g/m^3 (0.4 to 1.2 ppm) were detected (detection limit: 130 : g/m^3; 0.05 ppm) (Hedley et al., 1976). Another study (Going, 1976) did not find VC in the interior ambient air of 16 new and used cars and 4 mobile homes (detection limit: 26 : g/m^3; 10 ppb). It should be noted that since this time the levels of VC in PVC resins have been drastically reduced (see section 3.2.4).

5.1.2 Water and sediment

Owing to its high volatility, VC has rarely been detected in surface waters. The concentrations measured generally do not exceed 10 : g/litre, with a maximum of 570 : g/litre from contaminated sites (Table 14).

Table 14. Vinyl chloride concentrations measured in surface water[a]

Country, source	Year of sampling	Value[b]	Concentrations (: g/litre)	Remarks	Reference
Germany					
River Rhine	(prior to) 1978	typical conc. (n = many)	1		Anna & Alberti (1978)
River Rhine	1982		< 0.2		Malle (1984)
River Rhine	1990	range (n = 78)	< 0.01–0.031		Wittsiepe (1990)
Tributaries of Rhine (Northrhine-Westfalia)	(prior to) 1978	typical conc. (n = many)	< 1–5		Anna & Alberti (1978)
Surface water from unspecified sites in former FRG	n.sp.	range (n = n.sp.)	< 0.0004–0.4	$ 150 samples	Wittsiepe et al. (1990)
River Main	1990	range (n = 22)	< 0.004–0.008		Wittsiepe (1990)
River Lippe	1989	range (n = 54)	0.12–0.4	receiving wastewater from VC/PVC plants	Wittsiepe (1990)
River Ruhr (plus artificial lake)	1990	range (n = 60)	< 0.0004–0.005 (lake: up to 0.06)		Wittsiepe (1990)

Table 14 (contd).

Country, source	Year of sampling	Value[b]	Concentrations (μg/litre)	Remarks	Reference
Germany (contd).					
River Wupper	1989	range (n = 36)	up to 0.069		Wittsiepe (1990)
River Saale	1990	range (n = 4)	up to 69	receiving wastewater from an industrial area of the former GDR	Wittsiepe (1990)
Japan					
Rivers in Osaka	1995	range (n = 28)	up to 1.2	(3/28)[c]	Yamamoto et al. (1997)
USA					
Delaware River	1976–1977	(n = 11)	n. d.		Sheldon & Hites (1978)
Surface water from different sites in New Jersey	1977–1979	maximum (n = 606) median	566 0	(21/606)[c]	Page (1981)
Surface water from 9 states	n.sp.	maximum (n = n.sp.)	9.8		Burmaster (1982); Dyksen & Hess (1982)

Table 14 (contd).

USA (contd).					
Final effluent from a waste- water treatment plant in Los Angeles	1980–1981	mean (n = 5)	6.2		Gossett et al. (1983)
Surface waters	prior to 1984	median (n = 1048)	< 5	(63/1048)[c]	Staples et al. (1985)
Indian River Lagoon (near water discharge of VC), several stations	n.sp.	(n = n.sp.)	n.d. (< 1.0)		Wang et al. (1985)
Surface water near 3 landfills in Florida	1985–1990	(n = n.sp.)	n.d.		Hallbourg et al. (1992)
Surface water at a landfill in Florida (Orange County)	1989–1990 1992–1993	range (n = 5)	0.23 n.d.		Chen & Zoltek (1995)

[a] n.d = not detected (detection limit in parentheses, if specified); n.sp. = not specified; GDR = German Democratic Republic
[b] This column indicates whether the concentration is a maximum (max), average or range value
[c] Values in parentheses = no. detected / no. sampled

Much higher levels of up to 56 000 ：g/litre have been found in groundwater samples from contaminated sites (Table 15).

The levels in drinking-water supplies ranged from not detected to 2 ：g/litre in samples collected in 100 German cities in 1977. In a state-wide USA study performed in 1981–1982, random samples (taken from randomly selected water systems) had concentration ranges of n.d. to 1.1 ：g/litre, and non-random samples (taken from systems that were likely to be contaminated with VOCs) varied from n.d. to 8 ：g/litre. Prior to 1980 single maximum values of up to 380 ：g/litre were reported from the USA (Table 16).

One reason for the occurrence of VC in drinking-water may be that residual VC can migrate from PVC pipes used in some water distribution systems into the water flowing through them. This has been found out by field (Dressman & McFarren, 1978) and experimental (Banzer, 1979; Nakamura & Mimura, 1979; Ando & Sayato, 1984) studies. The extent of leaching depended on the VC concentration in the pipe material. In the field study the highest VC concentrations (1.4 ：g/litre) consistently occurred in water from new pipes, whereas the lowest level (0.03 ：g/litre) was found in the oldest (9 years of age) distribution system. VC concentrations in landfill leachate samples amounted to up to 61 mg/litre (Table 17). A gross analysis of water (no specification) available for the USA and based on 5553 observations reported maximum and median concentrations of VC as high as 202.6 mg/litre and 107 ：g/litre, respectively (US EPA, 1985a).

No VC was detected in urban stormwater run-off from 15 cities in the USA (n = 86) during a monitoring project concerning priority pollutants (Cole et al., 1984).

Generally, a time trend cannot be derived from the water analysis data available.

Most sediment samples contain very low VC concentrations, even at rather contaminated sites. Sediment was monitored for VC during 1981–1982 in Florida (USA) at several stations (n = 8) of the Indian River Lagoon and a conveying canal. Although the latter received discharged water having VC concentrations of 34–135 ：g/litre, no VC was detected in the sediment samples (3 from each station,

collected monthly over a year), the detection limit being 2 ng/g (Wang et al., 1985). The same was true for surface water (Table 14) and oyster (section 5.1.5) samples from this site. Sediment samples (n = 2) taken near the discharge zone of a wastewater treatment plant in Los Angeles County (California, USA) contained < 0.5 : g VC/kg dry weight. The corresponding water concentration of VC was 6.2 : g/litre (Gossett et al., 1983). A survey of 343 sediment samples from the USA gave a median VC concentration of < 0.5 : g/kg dry weight (Staples et al., 1985). However, higher VC concentrations were also reported. According to US EPA (1985a), VC was detected in sediment samples (no further details given) in the USA at levels ranging from 0–580 : g/kg (n = 649; median = 23 : g/kg).

5.1.3 Soil and sewage sludge

5.1.3.1 Soil

Subsurface soil samples near the waste pit of an abandoned chemical cleaning shop in southern Finland showed VC concentrations as high as 900 mg/kg (Salkinoja-Salonen et al., 1995). After an accidental spillage of VC into snow in 1980, VC levels as high as 500 mg/kg were measured in the soil at up to 2 m depth (Charlton et al., 1983).

5.1.3.2 Sewage sludge

VC has been detected in municipal sewage sludges in the USA. The concentrations ranged from 3 to 110 mg/kg dry weight (corresponding to 145 to 3292 : g/litre), being detected in 3 of 13 samples, with a median concentration of 5.7 mg/kg dry weight (corresponding to 250 : g/litre) (Naylor & Loehr, 1982). Another study reported a mean concentration of 35.4 mg/kg dry weight for 6 of 44 samples (Fricke et al., 1985). A range of 8–62 000 : g/litre was found in 35 of 435 raw sludge samples (Burns & Roe, 1982).

5.1.4 Food, feed and other products

VC is not a general contaminant of foodstuff and pharmaceutical or cosmetic products, but it can be detected after contact of these products with PVC packaging materials. The use of PVC as packaging material for food, drink and drugs began in the early sixties

Table 15. Vinyl chloride concentrations measured in groundwater[a]

Country; source of groundwater	Year of sampling	Value[b]	Concentrations (μg/litre)	Remarks	Reference
Canada					
from a VC spill site	1980	maximum; 10 weeks after the spill	10 000 < 20		Charlton et al. (1983)
beneath a landfill near Ottawa	1988	range (n = 37)	< 1–40	(5/37)[c]	Lesage et al. (1990)
Finland					
from village wells (contaminated by leakage of a waste liquor basin of VC/PVC industry - detected in 1974)	mid-1980	range	5–200 mg/litre (including DCE)		Nystén (1988); Salkinoja-Salonen et al. (1995)
Germany					
from different sites (4 sites)		mean values	n.d. (< 5) – 460		Brauch et al. (1987)
from different wells of a large surface contamination (5 wells)		mean values	15–1040		
from a catchment area of a water-works (TCE / PCE-contaminated)		range (n = 30)	< 1–120		Milde et al. (1988); Nerger & Mergler-Völkl (1988)
contaminated by waste disposal sites (92 sites)	until 1988	range (n = 113) mean median	< 1–12 000 2700 475	(14/113)[c]	Schleyer et al. (1988)

Table 15 (contd).

from a site contaminated with chlorinated hydrocarbons	n.sp.	(n = 3)		corresponding air pockets in soil	Köster (1989)
			1000	128 000 : g/m^3	
			500	47 000 : g/m^3	
			200	5000 : g/m^3	
from a site contaminated with chlorinated hydrocarbons (in Berlin)	ca. 1989	max. (n = 5)	110		Leschber et al. (1990)
from a contaminated site (in Braunschweig)	n.sp.	range (n = 3)	710–1670		Kästner (1991)
of a catchment area of a waterworks	1989	(n = n.sp.)	up to 0.130		Wittsiepe et al. (1990)
Contaminated by accidental spillage of TCE and PCE	1989	(n = n.sp.)	up to 3		
Contaminated by waste disposal sites (~ 100 sites)	n.sp.	mean (n = 136) max.	1693 12 000	18% positive	Dieter & Kerndorff (1993)
USA					
from different sites in New Jersey	1977–1979	max. (n = 1060)	9.5	(4/1060)[c]	Page (1981)
from 9 states		max.	380	7% positive	Dyksen & Hess (1982)
monitoring wells near industrial waste sites in Connecticut	n.sp.	max.	635	present in 3 out of 9 wells	Stuart (1983)

Table 15 (contd).

Country; source of groundwater	Year of sampling	Value[b]	Concentrations (: g/litre)	Remarks	Reference
USA (contd).					
from Nassau County, Long Island	1980	range (n = >100)	1.6–2.5		Connor (1984)
from Miami, Florida	n.sp.	mean (n = 3)	6.8		Parsons et al. (1984)
from a TCE spill site in Vero Beach, Florida	n.sp.	mean (n = 3)	82		Parsons et al. (1984)
monitoring wells near MSW landfills in Minnesota		n.sp.	present (in 5/20 sites), but not quantified		Sabel & Clark (1984)
near 3 plants manufacturing electronics equipment (Santa Clara Valley)	n.sp.	range (n = 3)	50–500	chlorinated solvents stored in underground tanks	White Paper (1984) cited in Wolf et al. (1987)
near solvent recovery facilities Connecticut Wisconsin	1980 1983	range (n = 4)	n.d. (< 10) – 2700 n.d. (< 10) – 210		Cline & Viste (1985)
from a residential area in Long Island, New York (several wells)	1983	maximum	2800	contamination from dry-cleaning shop	Andreoli (1985)
near a landfill in New Jersey	(about 1981)	max. (n = ~ 100)	692		Shechter (1985)

Table 15 (contd).

Description	Year	Type[b]	Concentration	Remarks	Reference
monitoring wells around hazardous waste landfill in S. California	1985	max.	2600	seasonal, spatial and analytical variations	Stephens et al. (1986)
monitoring wells near an airforce base in Ohio	1990	range (n = 64)	n.d. (1–2) – 12	(5/64)[c]	EMO (1992)
near 3 landfills in Florida (10 locations)	1985–1990	mean values	< 0.22–26.5		Hallbourg et al. (1992)
monitoring wells at a landfill in central Florida (Orange County)	1989–1990 1992–1993	range (n = 3)	n.d. – 0.23 4.8–48.4	increase of VC with time, decrease in total VOC	Chen & Zoltek (1995)
from an industrial site; recycling operations (1940–1987); California		(n = n.sp.)	51–146		Topudurti (1992)
near a former waste disposal facility in Wisconsin: on-property off-property		(n = n.sp.) max. max.	77 5		US EPA (1992)
Contaminated by TCE > 10 years before (17 sites)	1991	maxima minima	< 5–56 400 < 5–321		Semprini et al. (1995)
near Plattburg, New York (2 locations)	n.sp.	(n = 2)	8 and 384		Bradley & Chapelle (1996)

[a]   n.d. = not detected (detection limit in parentheses, if specified); n.sp. = not specified; TCE = trichloroethene; PCE = tetrachloroethene; VOC = volatile organic compounds; max. = maximum; MSW = municipal solid waste
[b]   This column indicates whether the concentration is a maximum (max), average or range value
[c]   Values in parentheses = no. detected / no. sampled

Table 16. Vinyl chloride measured in drinking-water supplies[a]

Country; source	Year of sampling	Value[b]	Concentration (: g/litre)	Remarks	Reference
Germany					
drinking-water supplies of 100 cities	1977	range	n.d. – 1.7		Bauer (1981)
drinking-water (no details)	n.sp.	(n = n.sp.)	ca. 1.6 ng/litre		Wittsiepe et al. (1993)
USA					
finished drinking-water	(prior to) 1975	max. (n = n.sp.)	10		Fishbein (1979)
water supplies from Florida and Philadelphia	(prior to) 1975	max. (n = n.sp.)	5.6 & 0.27		
raw drinking-water (13 cities)	1975–1979	2 positives	2.2 & 9.4	(2/13)[c]	CEQ (1981)
finished drinking-water (25 cities)		1 positive	9.4	(1/25)[c]	
drinking-water wells (state New York)	(prior to) 1980	max. (n = n.sp.)	50		CEQ (1981); Burmaster (1982); Craun (1984)

Table 16 (contd).

drinking-water of 113 cities	(prior to) 1981	range mean	0.05–0.18 0.052		Kraybill (1983)
drinking-water supplies (166)	1977–1981	range of positives	trace – 380	(82/1288)[c]	Cotruvo et al. (1986)
finished water supplies (using groundwater sources) from 51 states in the USA	1981–1982	max.: random samples: (n = 466) non-random samples: (n = 479)	1.1 8.4	(1/466)[c] (6/479)[c]	Westrick et al. (1984)
private wells in Nebraska (n = 63)	1982	max.	4.5	(1/63)[c]	Goodenkauf & Atkinson (1986)

[a]   n.d. = not detected (detection limit in parentheses, if specified); n.sp. = not specified
[b]   This column indicates whether the concentration is a maximum (max), average or range value
[c]   Values in parentheses = no. detected / no. sampled

Table 17. Vinyl chloride concentrations measured in leachate[a]

Country; source	Year of sampling	Value[b]	Concentrations (: g/litre)	Remarks	Reference
Canada					
MSW landfill leachate from	1988	n.sp.	14		Lesage et al. (1993)
Guelph (Ontario)	1989	n.sp.	23		
USA					
landfill leachates from Minnesota	n.sp.	(n = 6)	not quantified	present in 1/6 samples	Sabel & Clark (1984)
landfill leachates from Wisconsin	prior to 1982	max. (n = 4)	61	(1/4)[c]	
landfill leachates (municipal and industrial)	prior to 1985	range (n = 5)	n.d. (< 10) – 120		Cline & Viste (1985)
landfill leachates:	prior to 1988	range (n = n.sp.)		total number of landfills: 58	Brown & Donnelly (1988)
municipal			20–61 000		
industrial			140–32 500		
MSW leachates (several states in the USA)	(prior to) 1988	range (n = n.sp.) median	8–61 40	(6/?)[c]	Chilton & Chilton (1992)

[a] n.d. = not detected (detection limit in parentheses, if specified); n.sp. = not specified; MSW = municipal solid waste
[b] This column indicates whether the concentration is a maximum (max), average or range value
[c] Values in parentheses = no. detected / no. sampled

(chapter 3), whereas legislative action for safeguarding consumers from exposure to VC did not begin until the early seventies (starting with a ban on the use of PVC containers for packaging alcoholic beverages in the USA; Anon, 1973). Current EC and US FDA regulations on the level of VC in PVC materials intended to come into contact with foodstuffs are listed in Annex 1.

VC concentrations measured in PVC-packed food and drink of several countries are compiled in Table 18. A maximum value of 20 mg/kg was found in liquors. Other positive samples included vegetable oils (up to 18 mg/kg), vinegars (up to 9.8 mg/kg), margarines (up to 0.25 mg/kg), fruit drinks (> 0.2 mg/kg) and bottled water (< 0.6 : g/litre).

Retail surveys of foods showed a significant reduction in VC levels and/or in the number of positive samples since 1974 (UK MAFF, 1978, 1984; van Lierop, 1979; Codex Committee, 1984).

The latest data were from the 1990s (Table 18) and refer to bottled drinking-water. In addition to small amounts of VC, there were also indications for the presence of possible reaction products of VC with chlorine (Fayad et al., 1997).

Pharmaceutical and cosmetic products were less frequently monitored. The highest concentration, amounting to 7.9 mg/kg, was detected in mouthwashes (Table 19).

Reports on analyses of animal feed were not available.

The potential for leaching of residual VC from PVC packaging into the contents has been demonstrated by a variety of product analyses (Tables 18 and 19) and by experimental studies using food or food simulants (Daniels & Proctor, 1975; Hocking, 1975; Tester, 1976; Diachenko et al., 1977; Pfab & Mücke, 1977; UK MAFF, 1978; Chan et al., 1978; vom Bruck et al., 1979; van Lierop, 1979; Benfenati et al., 1991; Thomas & Ramstad, 1992). Altogether, the results indicated that the amount of VC migrating into food or solvent was proportional to the VC concentration in the PVC packaging, to storage time and to increasing temperature.

Table 18. Levels of vinyl chloride in food and drink packaged, stored or transported in PVC articles

Country	Year[a]	Product	No.[a,b]	Concentrations[c] (μg/kg)	Reference
Canada	n.sp.	alcoholic beverages	22	< 25–1600	Williams & Miles (1975)
		vinegars	28	n.d. (10) – 8400	
		peanut oil	10	300–3300	
Canada	n.sp.	alcoholic beverages	10	n.d. (10) – 2100	Williams (1976a)
		vinegars	10	300–7800	
		vinegars	9	14–9800	Williams (1976b)
		sherry	3	500–2400	
		peanut oil	3	3800–18 000	
Canada	n.sp.	oil	5	80–2100	Page & O'Grady (1977)
		vinegars	5	10–5700	
Canada	1981–1982	vinegars	n.sp.	27–43	Codex Committee (1984)
		other foods	n.sp.	< 10	
Italy	n.sp.	drinking-water (PVC-bottled)	10	0.013–0.083	Benfenati et al. (1991)
Netherlands	1975	oil samples	8	> 50	Van Lierop (1979)
		salad dressing	1	250	
		margarine	4	60–250	
		ready-made salads	n.sp. (whole batch)	> 50	
		wine	n.sp.	760	

Table 18 (contd).

Netherlands	1976	margarine fish biscuit	1 1 3	60 90 20–130	Van Lierop (1979)
	1977	peanut butter (very small individually wrapped portions)	1	4100	Van Lierop (1979)
	1978	various foods: soya oil vinegar salmon salad	67 (3 +) 1 1 1	n.d. (0.1) – 2 0.3 0.6 2	Van Lierop (1979)
Norway	1975	butter/margarine salad juices vinegar mustard	16 14 8 27 5	n.d. (2) 2–15 6–25 6–2790 9–14	Ehtesham-Ud Din et al. (1977)
Saudi Arabia	n.sp.	drinking-water (PVC-bottled)	9 × 48[d]	< 0.6	Fayad et al. (1997)
Sweden	1974	edible fats	127	n.d. (2) – 127	Fuchs et al. (1975)
Sweden	1975–1976	various foods (edible fats and oils, ketchup, vinegar, lime juice, fruit syrup)	104	n.d. (2) – 600 (mostly: < 10)	Albanus et al. (1979)

Table 18 (contd).

Country	Year[a]	Product	No.[a,b]	Concentrations[c] (: g/kg)	Reference
Switzerland	1973–1975	edible oils	41	n.d. (5) – 1750	Rösli et al. (1975)
United Kingdom	n.sp.	spirits	n.sp.	0–250	Davies & Perry (1975)
United Kingdom	1974	fruit drinks	25	10 – > 200	UK MAFF (1978)
	1977		13	< 10	
	1974	cooking oil	23	10 – > 200	
	1977		7	< 2	
	1975	butter, soft margarine	51	< 2 – 200	
	1977		9	< 2	
USA	1971	vegetable oil	1	7000	Breder et al. (1975)
	1974		3	700	
USA	1973	spirits	n.sp.	up to 20 000	Anon (1973); US FDA (1973)
USA	1973–1975	alcoholic beverages	n.sp.	11 000–25 000	Codex Committee (1984)

[a]   n.sp. = not specified
[b]   + = number of samples positive
[c]   n.d. = not detected (detection limit in parentheses, if specified)
[d]   9 brands (locally produced and imported)

Table 19. Vinyl chloride detected in pharmaceutical and cosmetic products packaged in PVC materials

Product	No.[a]	Concentration[b] (: g/kg or : g/litre)	Reference
Blood coagulant solutions	30	n.d. (15)	Breder et al. (1975)
Mouthwashes	11	n.d. (20–30) – 7900	
Several capsules, tablets and mouthwashes	11	n.d. (10–30)	Watson et al. (1977)
Large volume parenterals	5	n.d. (0.1) – < 1	Watson et al. (1979)
Mouthwashes	5	7–120	
Shampoos	4	9–17	
Body oils	4	n.d. (0.1) – 41	
Intravenous solutions	n.sp. (many)	n.d. (1)	Arbin et al. (1983)
Cefmetazole sodium (Zefazone® sterile powder)	4	n.d. (0.3) – <1	Thomas & Ramstad (1992)

[a] n.sp. = not specified
[b] n.d. = not detected (detection limit in parentheses, if specified)

Until 1974 the use of VC as a propellant in aerosol sprays was allowed in the USA (chapter 3). Realistic application of such aerosol products (hairspray, deodorant, insecticide, disinfectant, furniture polish or window cleaner) resulted in high (ppm range) indoor air concentrations of VC (Gay et al., 1975).

There have been no reports on VC levels found in food, pharmaceutical or cosmetic products in recent years. This may be due to regulatory measures for PVC packaging in several countries (see Annex 1).

5.1.5 *Terrestrial and aquatic organisms*

Oysters (*Crassostrea virginica)* from the Indian River Lagoon in Florida (USA) contained no detectable levels of VC (detection limit: 0.4 ng/g). The samples were collected weekly (1981) and monthly (1982) at three sites (Wang et al., 1985). VC was also not detected in the corresponding water and sediment samples (section 5.1.2).

Another study (Gossett et al., 1983) did find low concentrations of VC (< 0.3 : g/kg wet weight) in a sample of small invertebrates from just above the bottom sediments (n = 1), in a muscle sample of shrimp (n = 1) and in liver samples of several fish species (n = 4). The animals were collected in 1981 in final effluent waters from a wastewater treatment plant in Los Angeles County (Palos Verdes, California, USA) that had VC concentrations of 6.2 : g/litre (section 5.1.2).

Data on fish tissue (no further details given) available from the US EPA STORET database were reported by US EPA (1985a). VC levels ranged from 0–250 mg/kg (n = 530; median: 6 mg/kg).

5.2 General population exposure

Exposure of the general population to VC is possible by several routes. They include inhalation of air polluted with VC (section 5.1.1), mainly in the vicinity of VC/PVC plants or waste disposal sites, intake of contaminated drinking-water (sections 5.1.2 and 5.1.4), ingestion of food, beverages and medicines packed in PVC (section 5.1.4), and absorption through skin from PVC-wrapped cosmetics (section 5.1.4).

Normally, the general population is exposed to only small amounts of VC, if at all. However, the exposure varies according to the countries' regulatory measures, the occurrence of accidents or the spread of precursor substances.

5.2.1 *Estimations*

Estimations of the respiratory intake of VC reported for the USA ranged from 0 to 48.3 mg per person per day, based on exposure values of 0 to 2.1 mg/m^3 and assuming that 23 m^3 of air are inhaled per day (US EPA, 1985b). According to Seiber (1996) over 100 000 Californians, particularly those living near landfills, may be exposed to VC levels of 2.59 : g/m^3 (1 ppb) or more.

A European study (Besemer et al., 1984) evaluating the exposure of the Dutch population to VC in ambient air assumed an average exposure of about 0.2 : g/m³, which resulted in a calculated daily intake of 4 : g VC per person. Small fractions of the population were concluded to be exposed to higher average levels: 0.01% (> 8.5 millions) to > 5 : g/m³, 0.04% to 4–5 : g/m³, and 0.05% to 3–4 : g/m³. The corresponding estimated daily intakes of VC were > 100 : g, 80 : g and 60 : g, respectively.

Intake via drinking-water from public water supplies in the USA was estimated to exceed 1 : g/litre for 0.9% of the population, 5 : g/litre for 0.3% and 10 : g/litre for 0.1% of the population. These would result in daily VC intakes (assuming a 70-kg man and 2 litres of water/day) of $ 2, 10, and 20 : g/day. Maximal values were estimated to be approximately 120 : g/day (US EPA, 1985b).

Another study (Benfenati et al., 1991) estimated the daily intake of VC from PVC-bottled drinking-water bought in Italian supermarkets. Based on the analytical results (Table 18) and assuming a consumption of 2 litres of water per person per day and a storage time of 2 months for the PVC bottles, the authors calculated that the oral intake could exceed 100 ng VC per person per day.

Evaluation of the results of food surveillance programmes from the United Kingdom led to a calculated maximum likely VC intake of 1.3 : g/day per person in 1974, of 0.1 : g/day per person in 1976, and less than 0.02 : g/day per person by 1978 (UK MAFF, 1978, 1984). These calculations were based on the typical daily consumption of fruit drink, cooking oil and soft margarine.

Evaluating and summing up possible maximum user intakes of VC from PVC-bottled liquor, wine and oil, and food packaged in PVC materials, the US FDA calculated a maximum lifetime-averaged exposure of 25 ng/person per day (US FDA, 1986). An earlier review reported an estimated dietary intake of VC of 40 ng/day per person in the USA (Codex Committee, 1984).

The intake by food and drinking-water in the Netherlands was estimated (without specifying details) to be about 0.1 : g/day per person or less (Besemer et al., 1984). Estimates (no details given) of

the average human intake for Switzerland were reported to be 3 ng/kg body weight per day (Lutz & Schlatter, 1993).

5.2.2 Monitoring data of human tissues or fluids

Monitoring human tissues or fluids as an indirect measure of exposure to VC has not frequently been applied. As with workers in the plastics industry (section 5.3), the urine of premature babies was found to contain large amounts of thiodiglycolic acid (thiodiacetic acid), a metabolite of VC (chapter 6), but the relationship to possible VC exposure was questionable (Pettit, 1986).

5.3 Occupational exposure

The main route of occupational exposure to VC is via inhalation (Sittig, 1985), while dermal absorption is considered to be negligible (ECETOC, 1988).

Industrial environments associated with VC exposure include VC production plants, VC polymerization (PVC production) plants and PVC processing factories. Estimates of numbers of workers exposed to VC were, for example, in the USA (1981–1983) in the range of 80 000 (ATSDR, 1997) or in Sweden (1975–1980) more than 5000 (Holm et al., 1982). Since, at the onset of VC/PVC production in the USA and Western Europe, VC was not recognized as a toxic compound, no precautions against contact were provided for nor was regular workplace monitoring performed. Therefore, only sporadic measurements or retrospective estimates (Table 20) of exposures are available for the period prior to 1975. Published data from various countries on VC contamination of workplace air throughout the early and later periods are compiled in Table 21 and 22. Highest exposures occurred in the VC/PVC production plants, with peak concentrations of several thousand ppm whereas much lower exposure levels were measured in processing plants. Owing to standard-setting and legislative regulations by national authorities and technical improvements, levels dropped markedly to values of a few ppm in many countries. Official exposure limits can serve as an additional indication of approximate VC concentrations occurring in plants in many countries. These limits have declined gradually (IARC, 1979). Generally, standards require that exposures do not exceed 13 to

26 mg/m^3 (5 to 10 ppm) (Torkelson, 1994; Rippen, 1995; ACGIH, 1999).

Table 20. Retrospective estimates of daily occupational
exposures to vinyl chloride prior to 1975[a]

Country	Period	VC exposure (mg/m^3)	Reference
Germany	"first years"	> 2600	Szadkowski & Lehnert
	prior to 1971	1300	(1982)
	1971	260	
	1974	5.2–7.8	
Norway	1950–1954	5200	Hansteen et al. (1978);
	1955–1959	2600	Heldaas et al. (1984)
	1960–1967	1300	
	1968–1972	260	
	1973–1974	207	
Sweden	1945–1954	1300	Holm et al. (1982)
	1955–1964	780	
	1965–1969	520	
	1970–1974	130	
United Kingdom	1945–1955	2600	Barnes (1976);
	1955–1960	1040–1300	Anderson et al. (1980);
	1960–1970	780–1040	Purchase et al. (1987)
	mid 1973	390	
	1975	13	
	1940–1955	1300–2070	Jones et al. (1988)
	1956–1974	390–1300	
USA	1945–1955	2600	Wu et al. (1989)
	1955–1970	780–1300	
	1970–1974	260–520	
	1975	< 2.6–13	

[a]   Exposure levels during autoclave cleaning may have been as high as
    7800 mg/m^3 (Barnes, 1976)

However, even in the 1990s the standards were not always realized in all countries (Table 21).

Table 21. Levels of vinyl chloride reported for workplace air samples in VC/PVC production plants

Country	Workplace	Year[c]	Concentrations reported (mg/m^3)[c]	Reference
China	PVC production plant	n.sp.	30–210	Bao et al. (1982)
Croatia	plastics industry	n.sp.	mean = 13 5200 (occasional peak)	Fucic et al. (1990a)
Croatia	VC/PVC plant	1949–1987	mean = 543 up to 1300 (occasional peak)	Hozo et al. (1996, 1997)
Former Czechoslovakia	n.sp.	n.sp.	2–41	Hrivnak et al. (1990)
Egypt	VC/PVC plant	n.sp.	0.05–18 (8-h TWA)	Rashad et al. (1994)
Finland	PVC production plant, breathing zone concentrations (TWA)	1981–1985 1986–1989 1993	n.d. range 1.6 < 0.3–57 1.6 < 0.3–46 0.3 < 0.3–26	Viinanen (1993)
France	PVC production plant	1977–1978	2.3–7.3 (range of monthly means)	Haguenoer et al. (1979)
Germany	PVC production department	1974	< 65–181	Fleig & Thiess (1974)

Table 21 (contd).

	PVC production plant	1977	1.3–91	German Environ-mental Office (1978)
	PVC production plant	1979	12 (12-h TWA; stationary); 15.5 (12-h TWA; personal)	Heger et al. (1981)
Germany	24 plants	1981–1984	3% of 33 samples: > 5 (90 percentile: < 1); (shift means)	Coenen (1986); BIA (1996)
	46 plants	1989–1992	all of 117 samples: < 5 (90 percentile: < 0.1); (shift means)	
Italy	VC/PVC plants	1950–1985	< 13– $ 1300	Pirastu et al. (1991)
The Netherlands	PVC plant	1976–1977	2.6–26 (8-h TWA)	De Jong et al. (1988)
Norway	PVC plant	1974	65	Hansteen et al. (1978)
Poland	VC/PVC plant (several departments)	1974	(30–600)[a]	Studniarek et al. (1989)
		1975	(30–270)[a]	
		1976	(15–60)[a]	
		1977	(6–150)[a]	
		1978	(1–30)[a]	
		1979	(1–15)[a]	
		1981	(0.1–36)[a]	
		1982	(0.1–12)[a]	
	(autoclave cleaners)	1974	(990)[a]	
		1982	(9–180)[a]	

Table 21 (contd).

Country	Workplace	Year[c]	Concentrations reported (mg/m^3)[c]	Reference
Poland (contd).	breathing zone of VC synthesis mechanic	1986 1987 1988 1989 1990	21.3 66.9 43.7 0.7 0.2	Dobecki & Romaniwicz (1993)
Romania	PVC production plant	1965–1967	112–554	Anghelescu et al. (1969)
Russia	VC/PVC plant 16 probes (whole plant) under the reactor in compressor room	1990–1993 1990–1993 1990–1993	1–9 (range of annual means) up to 200 (range of annual means) up to 400 (range of annual mean)	Gáliková et al. (1994)
Singapore	PVC production plant	1976 after 1983	2.6–54 (15.3)[a] up to 26 (short-term) (3.9)[a]	Ho et al. (1991)
Sweden	PVC production plant PVC production plant	1974–1981 1974–1980	0.26–114 (8-h TWA) 0.26–5.7 (6-h TWA)	Holm et al. (1982)

Table 21 (contd).

Taiwan	PVC plants (n = 5): 15 different operation units (e.g. outside reaction tank)[b]	n.sp.	range (n=114): n.d. (0.13) – 1009 range (n=4): 6–1009 (mean: 296; median: 86)	Du et al. (1996)
	15 different job titles (e.g. tank supplier)[b]		range of TWA (n=85): n.d. – 3680 range (n=9): 5.7–3680 (mean: 660; median: 23.7)	
United Kingdom	PVC production plant (full-time autoclave cleaner)	"early days"	7800	Barnes (1976)
USA	PVC plant	1950–1959 1960–1963	up to 10 400; 13–2140 (8-h TWA) up to 1300; 13–620 (8-h TWA)	Ott et al. (1975)
	PVC plant	n.sp.	up to 650 (weekly TWA)	Baretta et al. (1969)
USA	VC/PVC plants	1973	up to 390 (TWA); peaks 2600–10 400	Rowe (1975)
Former USSR	VC/PVC plants	early 1950s	100–800	Smulevich et al. (1988)
	PVC producing plant		50–800 (occasionally 87 300)	Filatova & Gronsberg (1957)
Former Yugoslavia	PVC production plant	1974	> 195	Orusev et al. (1976)

[a]   Concentrations in parentheses designate geometric means
[b]   Showing highest mean VC concentration
[c]   n.sp.= not specified; TWA = time-weighted average; n.d. = not detected

Table 22. Levels of vinyl chloride reported for workplace air samples in PVC processing plants

Country	Workplace	Year	Concentrations reported (mg/m³)	Reference
China	PVC processing plant	n.sp.	$ 30	Bao et al. (1982)
Germany	PVC processing department	1974	< 2.6–67	Fleig & Thiess (1974)
Germany	polymer extrusion (17 plants)	1989–1992	all of 33 samples: < 8 (90 percentile: < 0.15) (shift means)	BIA (1996)
Sweden	PVC processing plant	1974	< 0.26–0.8	Holm et al. (1982)
Sweden	PVC processing plant	prior to 1975	>13 – $ 26 (8-h TWA)	Lundberg et al. (1993)
Russia	PVC processing plant (rubber footwear plant)	prior to 1990	0.007–1.26	Solionova et al. (1992)
Russia	PVC processing plant (synthetic leather plant)	prior to 1966	< 113.6	Bol'shakov (1969)
UnitedKingdom	PVC processing plants (cable factories)	n.sp.	0.4–0.9	Murdoch & Hammond (1977)
USA	automotive assembly plant(s)	1970s	0.13–7.8 (2 personal samples)	Nelson et al. (1993)

Whereas in industrialized countries factories that could not satisfy the rigorous regulations of the early 1970s to reduce VC emissions were forced to close down, in the countries of eastern Europe and developing countries this was not possible for socioeconomic reasons and large plants with old-fashioned technologies continued to function (Hozo et al., 1996).

Autoclave cleaners in Croatia were exposed to extremely high concentrations of VC (between 1295 and 3885 mg/m^3; 500 and 1500 ppm). A retrospective investigation of exposure to VC has been conducted with 37 autoclave workers (emptying and cleaning) in Split, Croatia, who were exposed to VC in a suspension polymerization plant. The investigation covered the period from 1969 to 1987, when the factory was closed because of its VC emissions. At the beginning, measurements were done by simple means (Draeger's tubes) and later, from 1980 on, by infra-red spectroscopy. The 37 workers were exposed to average VC concentrations of 1412 mg/m^3 (543 ppm) (Hozo et al., 1996; Hozo, 1998).

6. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

6.1 Absorption

Animal and human studies have shown that VC is readily and rapidly absorbed. The primary route of exposure to VC is inhalation. However, the net uptake after exposure by inhalation is only 30–40% of inspired VC. This is due to the fact that VC is taken up rapidly until it reaches a blood concentration in equilibrium with that based upon inspired concentration and the blood-to-air partition coefficient. Uptake then decreases to an amount sufficient to replace that metabolized. The importance of metabolism was shown by Bolt et al. (1977) who showed that uptake of VC ceased once equilibrium was reached.

While uptake by the oral route is near 100%, any VC not metabolized during first pass through the liver will be expired. Thus, the net dose may be less than the uptake, especially at high doses resulting in saturation of metabolizing enzymes.

6.1.1 Oral exposure

In a study reported by Watanabe & Gehring (1976) and Watanabe et al. (1976a), male rats received a single dose by gavage of 0.05, 1.0, 20 or 100 mg/kg body weight and ^{14}C-labelled VC and the excreted radioactivity was determined for 72 h. As only 2.4, 2.2, 1.0 and 0.5%, respectively, of the administered radioactivity (Table 23) was recovered in the faeces (total recovery 91, 89, 81 and 82%, respectively), it can be assumed that there is nearly complete absorption of VC in the gastrointestinal tract. Likewise, oral administration of 0.25 or 450 mg/kg body weight ^{14}C-VC to male rats resulted in excretion of only 4.6 or 0.7%, respectively (Table 23), of the applied radioactivity via faeces 0–72 h after application (Green & Hathway, 1975).

Similar results were obtained by Feron et al. (1981), who fed rats with different amounts of VC monomer in PVC powder via the diet. The average amount of VC detected in faeces was 8, 10 and 17% for

Table 23. Excretion of radioactivity in rats (in % of applied dose) 72 h after a single oral dose of VC[a]

Dose in mg/kg body weight	VC in exhaled air	CO_2 in exhaled air	Urine	Faeces	Carcass and tissues	Total recovery	Reference
0.05	1.4	9.0	68.3	2.4	10.1	91.2	Watanabe et al. (1976a)
0.25	3.7	13.5	75.1	4.6	n.g.	n.g.	Green & Hathway (1975)
1.0	2.1	13.3	59.3	2.2	11.1	88.8	Watanabe et al. (1976a)
20	41.6	4.8	22.6	1.0	11.0	81.0	Watanabe & Gehring (1976)
100	66.6	2.5	10.8	0.5	1.8	82.3	Watanabe et al. (1976a)
450	91.9	0.7	5.4	0.7	n.g.	n.g.	Green & Hathway (1975)

[a] n.g. = not given

oral intakes of 2.3, 7.0 and 21.2 mg/kg body weight per day, respectively. Since the VC excreted in the faeces was considered by the authors to be still enclosed in PVC granules and was not bioavailable, it was concluded that the available VC was nearly completely absorbed in the gastrointestinal tract.

Studies conducted by Withey (1976) have shown the rapid absorption of VC from the gastrointestinal tract in male rats after a single gavage application of 44 to 92 mg/kg body weight in aqueous solution. Highest blood levels were always measured within 10 min after administration. After an oral dose of 10 mg VC/kg body weight, peak levels in brain, liver, kidney and lung were measured 5 min after dosing, indicating rapid absorption from gastrointestinal tract (Zuccato et al., 1979).

6.1.2 Inhalation exposure

Bolt et al. (1977) blocked the metabolism of VC in male rats by i.p. injection of 6-nitro-1,2,3-benzothiadiazole (50 mg/kg body weight), a compound that inhibits most microsomal monooxygenases. The rats were exposed to approximately 1.2 mg/m^3 ^{14}C-labelled VC in a closed system 30 min after the injection. VC was taken up by the animals until equilibrium was reached between VC in the atmosphere and in the organism after 15 min, suggesting a rapid uptake of VC. Similarly, equilibrium blood levels were observed by Withey (1976) in male rats 30 min after the start of exposure to 18 200 mg VC/m^3 (head only).

Bolt et al. (1976) measured the decline of ^{14}C-VC in a closed system due to uptake by 3 male rats using an initial concentration of 130 mg/m^3. The radioactivity in the air of the exposure system decreased with a half-life of 1.13 h. Calculation of the clearance of VC revealed an absorption of inspired VC of about 40%. These results are in accordance with the data of Hefner et al. (1975a), who reported in kinetic studies on male rats a similar decline at the same exposure concentration.

Krajewski et al. (1980) measured the retention of VC in the lungs of five human male volunteers exposed for 6 h to 7.5, 15, 30 or 60 mg/m^3 through a gas mask. The percentage of retention (mean

42%) was independent of the VC concentration and reached the highest level of 46% in the first 15 min of exposure.

Buchter et al. (1978) reported toxicokinetic experiments on themselves. In an open system, about 3–5 min after the start of inhalation of 6.5 mg VC/m^3 in the exposure atmosphere, an equilibrium was reached between VC inspired and VC expired; 26% (person A) and 28% (person B) of the VC inspired were removed by the body, probably by absorption and subsequent metabolism. Metabolism started within the first minutes of exposure, suggesting fast absorption of VC.

Breath samples were measured of volunteers who had showered in VC-contaminated well water (Pleil & Lindstrom, 1997). For a brief 10-min shower exposure of 25 ： g/m^3 (inhalation) and 4 ： g/litre (dermal contact in water), 0.9 ： g absorbed dose of VC and a blood concentration of 0.01 ： g/litre was calculated.

6.1.3 Dermal exposure

Hefner et al. (1975b) exposed the whole body (excluding the head) of male rhesus monkeys to 2080 (2.5 h) or 18 200 mg/m^3 (2.0 h) ^{14}C-labelled VC. Very little VC was absorbed through the skin. Although minuscule, the quantity absorbed appeared concentration-dependent. The major portion of the VC absorbed was eliminated by the lungs. The authors argued that no significant percutaneous absorption would be expected under occupational exposure conditions.

6.2 Distribution and retention

Data from inhalation and oral studies on rats indicate rapid and widespread distribution of VC. Rapid distribution of VC was also reported in humans after inhalation exposure. Rapid metabolism and excretion limit accumulation of VC in the body. Data on distribution after oral exposure showed similar results. No studies are available concerning distribution after dermal exposure. Under conditions of blocked VC metabolism, VC has been found to accumulate in adipose tissue.

6.2.1 Oral exposure

Green & Hathway (1975) investigated the distribution in the tissues of young rats 0.25, 2 and 4 h after oral administration of 30 mg/kg body weight [^{14}C]-VC using whole-animal autoradiography. At 15 min after gavage, most radioactivity was detected in the liver, followed by the gut (no data about the stomach), and there were small amounts in the lung and kidney. After 2 h, label was observed in the liver, kidney, small intestine, stomach, skin, para-auricular region (probably Zymbal glands), and there were small amounts in lung and heart. A similar distribution was determined after 4 h, with additional label in the thymus, salivary gland and Harders gland, but no radioactivity in the stomach lumen.

The distribution of VC and VC metabolites remaining in the body (11.1% of recovered radioactivity) 72 h after a single oral administration via gavage of 1 mg/kg body weight ^{14}C-VC was described as follows (expressed as % of administered radioactivity per gram tissue): liver 0.182, skin 0.076, carcass 0.046, plasma 0.053, muscle 0.031, lung 0.061, fat 0.045 (no data about amount in the kidney). A similar distribution pattern was observed using doses of 0.05 or 100 mg/kg body weight (Watanabe et al., 1976a).

6.2.2 Inhalation exposure

Whole body autoradiograms of male rats showed radioactivity in the liver, bile duct, digestive lumen and kidneys when animals were exposed for 5 min to 52 g/m^3 ^{14}C-labelled VC and sacrificed 10 min after the end of the exposure period. Animals sacrificed 2–3 h after the exposure period showed a wider distribution of radioactivity, with most of the labelled substances being observed in the liver, urinary system, digestive lumen, lacrimal glands, skin and thymus (Duprat et al., 1977).

Buchter et al. (1977) pretreated male rats i.p. with 50 mg/kg body weight 6-nitro-1,2,3-benzothiadiazole (to block VC metabolism) and exposed the rats in a closed system for 5 h to VC concentrations of between 65 and 26 000 mg/m^3. Authors observed an equilibrium between ^{14}C-labelled VC in the gas phase and the exposed organism. The distribution of VC was independent of the exposure concentration. The following distribution of VC (labelled and unlabelled) in different organs (expressed as mol VC in 1 g tissue per

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mol VC in 1 ml air) was reported immediately after the exposure period: blood 0.65, liver 0.62, spleen 0.59, kidney 0.59, muscle 0.68 and adipose tissue 8.3. These results indicated that unmetabolized VC is accumulated in adipose tissue due to its lipophilicity. In contrast, without blockage of VC metabolism, most radioactivity was detected in kidney and liver (5 h, 260 mg/m^3).

In similar studies Bolt et al. (1976) measured radioactivity (representing mostly VC metabolites) in different organs immediately after exposure of male rats to ^{14}C-VC (initial concentration 130 mg/m^3) for 5 h. Highest levels were detected in the kidney (2.13%; expressed as % of incorporated VC per g tissue) and liver (1.86%), followed by spleen (0.73%), muscle (0.32%), adipose tissue (0.22%) and brain (0.17%).

Distribution pattern changed with longer post-exposure observation periods. Watanabe et al. (1976b) reported the following percentages of ^{14}C activity (mostly VC metabolites) in rats per gram tissue 72 h after inhalation exposure to 26 or 2600 mg/m^3 ^{14}C-labelled VC, respectively, for 6 h: liver (0.139; 0.145), kidney (0.079; 0.057), skin (0.072; 0.115); carcass (0.048; 0.049), plasma (0.051; not detected), muscle (0.052; 0.038), lung (0.065; 0.046), fat (0.026; not detected). There was no significant difference between low and high dose. 72 h after the exposure period most of radioactivity had been excreted; 13.8% (low dose), 14.5% (high dose) of total recovered radioactivity remained in carcass and tissues (Table 25). A similar distribution pattern were presented by Watanabe et al. (1978b) using the same experimental design but rats exposed once or repeatedly to 13 000 mg/m^3. Furthermore, the authors detected no significant difference between single and repeated exposure.

Ungváry et al. (1978) presented evidence for the permeability of the placenta to VC. After exposure of pregnant rats to 5500, 18 000 or 33 000 mg VC/m^3 for 2.5 h on day 18 of gestation, VC was detected in fetal (13, 23 and 31 : g/ml, respectively) and maternal blood (19, 32 and 49 : g/ml), as well as in amniotic fluid (4, 5 and 14 : g/ml).

Toxicokinetic experiments on humans (self-experiments) were reported by Buchter et al. (1978). Using an open system with a concentration of 6.5 mg VC/m^3 inspired air, the concentration in the

expired air reached a constant concentration after about 5 min exposure in subject A and 7 min in subject B, indicating the end of the distribution phase.

6.2.3 *Partition coefficients* in vitro

In vitro studies using the vial equilibration method (3 h incubation, blood and tissue homogenates from male Sprague-Dawley rats) revealed the following VC partition coefficients for male rats: blood/air 2.4; fat/blood 10.0; muscle/blood 0.4; liver/blood 0.7; and kidney/blood 0.7 (Barton et al., 1995). In similar experiments tissue/air partition coefficients were obtained for different rodent species (Gargas et al., 1989; Clement International Corporation, 1990; Table 24). These data suggested that the concentration of VC in adipose tissue is higher than in other tissues. Furthermore, in all species in which both sexes were tested, partition coefficients for fat/air were greater in females than in males (Table 24).

6.3 Metabolic transformation

The main route of metabolism of VC in the liver into non-volatile compounds after inhalative or oral uptake involves 3 steps: a) the oxidation by cytochrome P-450 to form chloroethylene oxide (CEO, also known as 2-chlorooxirane), a highly reactive, short-lived epoxide that rapidly rearranges to form chloroacetaldehyde (CAA); b) the detoxification of these two reactive metabolites as well as chloroacetic acid, the dehydrogenation product of CAA, through conjugation with glutathione catalysed by glutathione *S*-transferase; c) the modification of the conjugation products to substituted cysteine derivatives, which are excreted via urine. The main metabolic pathways are shown in Fig. 2. At high dose levels the metabolism of VC is saturable.

The first step in VC metabolism requires microsomal mixed-function oxidases (cytochrome P-450 enzymes) together with oxygen and NADPH as cofactors. This was confirmed by studies *in vitro* (Barbin et al., 1975; Guengerich et al., 1979) and *in vivo* (Reynolds et al., 1975a,b; Guengerich & Watanabe, 1979; Bartsch et al., 1979; Guengerich et al., 1981). The major catalyst of the oxidation is CYP2E1 in humans. This has been demonstrated by *in vitro* systems using purified human CYP2E1 or by inhibition of catalytic activity in

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Table 24. Tissue/air VC partition coefficients for rodent tissues[a]

Species; strain	Sex	Blood/ air	Liver/ air	Muscle/ air	Fat/ air
Rat; F344	male	1.60	1.99	2.06	11.8
	female	1.55	2.05	2.39	21.1
Rat; CDBR	male	1.79	3.0	2.18	14.6
	female	2.12	1.66	1.28	19.2
Rat; Wistar	male	2.10	2.69	2.72	10.2
	female	1.62	1.48	1.06	22.3
Mouse; B6C3F$_1$	male	2.83	n.g.	n.g.	n.g.
	female	2.56	n.g.	n.g.	n.g.
Mouse; CD-1	male	2.27	n.g.	n.g.	n.g.
	female	2.37	n.g.	n.g.	n.g.
Hamster; Syrian golden	male	2.74	3.38	2.56	14.3
	female	2.21	1.31	1.96	21.1

[a] Data from Clement International Corporation (1990); vial equilibration method (Gargas et al., 1989), blood or tissue homogenates incubated for 1–4 h until equilibrium was achieved, as indicated by two consecutive time points without significant difference; n.g. = not given

Table 25. Percentage of ^{14}C activity eliminated during 72 h following inhalation exposure to [^{14}C]-vinyl chloride for 6 h in male rats[a]

Exposure groups (number of animals)	26 mg/m^3 (4)	2600 mg/m^3 (4)	13 000 mg/m^3 (2)
Expired as unchanged VC	1.6	12.3	54.5
Expired as CO_2	12.1	12.3	8.0
Urine	68.0	56.3	27.1
Faeces	4.4	4.2	3.2
Carcass and tissues	13.8	14.5	7.3

[a] Expressed as percentage of the total ^{14}C activity recovered (similar experimental design; Watanabe & Gehring, 1976; Watanabe et al., 1976b, 1978b)

ClHC=CH₂
Vinyl chloride

CYP2E1
mixed-function oxidase

DNA adducts

Protein
adducts

H₂C—CH
Cl
2-chloroethylene oxide

H₂O   HCl
epoxide hydrolase

HO—CH₂—CHO
glycolaldehyde

ClH₂C—C
O
H
2-chloroacetaldehyde

rearrangement

glutathione

glutathione

G—S—CH₂—CHO
S-formylmethyl glutathione

*aldehyde
dehydrogenase*

ClH₂C—C
O
OH
2-chloroacetic acid[a]

cys-S—CH₂—CHO
S-formylmethyl cysteine[a]

glutathione

G—S—CH₂—COOH
S-carboxymethyl glutathione

cys-S—CH₂—CH₂OH
S-(2-hydroxyethyl)-cysteine

cys-S—CH₂—COOH
S-carboxymethyl cysteine[a]

N-Ac-cys-S—CH₂—CH₂OH
N-acetyl-S-(2-hydroxyethyl)-cysteine[a]

NH₃

(transamination)

CO₂

(oxidative decarboxylation)

major pathway
minor pathway

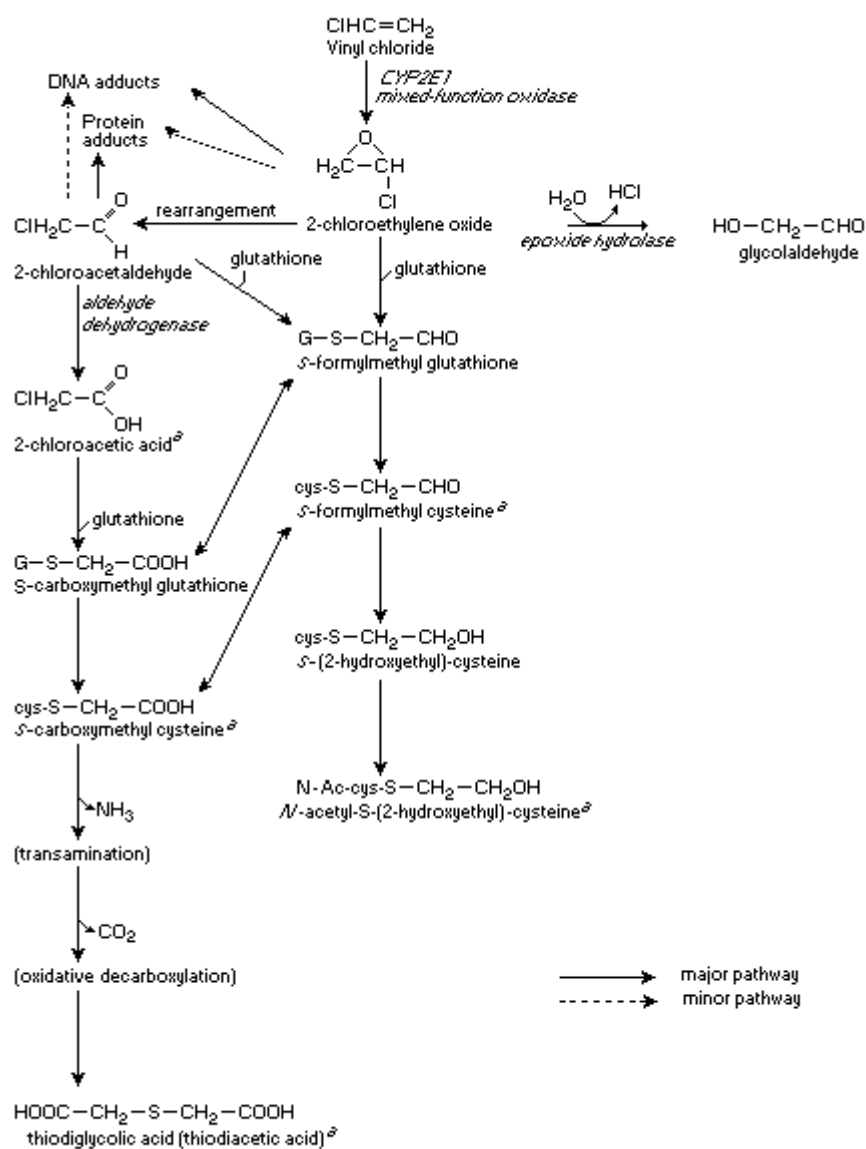HOOC—CH₂—S—CH₂—COOH
thiodiglycolic acid (thiodiacetic acid)[a]

Fig 2. Proposed metabolic pathways for vinyl chloride (Plugge & Safe, 1977;
Guengerich et al., 1979; Bolt et al., 1980; adapted from ATSDR, 1997).
[a]   Detected in urine

human liver microsomes with rabbit anti-human CYP2E1. In liver microsomes from *uninduced* rats, VC is activated solely by CYP2E1, at concentrations ranging from 1 to 10^6 ppm in the gas phase, according to Michaelis-Menten kinetics (El Ghissassi et al., 1998). The following kinetic constants were determined:

K_m = 7.42 ± 0.37 : mol/litre;

V_{max} = 4674 ± 46 nmol.mg protein $^{-1}$ min^{-1}.

Comparison of the V_{max} obtained in this study to the V_{max} determined *in vivo* in rats (Gehring et al., 1978; Filser & Bolt, 1979) shows that virtually all the metabolic activation of VC *in vivo* occurs in the liver.

Applying the pharmacokinetic model developed by Andersen et al. (1987) to describe the metabolism of inhaled gases and vapours, the uptake of VC by rats *in vivo*, as determined by Gehring et al. (1978) and by Filser & Bolt (1979), could be accurately predicted.

Using S9 extracts from human liver samples, Sabadie et al. (1980) observed a great interindividual variability in the capacity to activate VC into mutagenic metabolites. This is in agreement with the observation of Guengerich et al. (1991) who found that levels of CYP2E1 varied considerably among individual humans. Sabadie et al. (1980) noted that the average activity of human samples is similar to that of rat samples.

Chloroethylene oxide (CEO) has a half-life of only 1.6 min at pH 7.4 and 37 °C (Malaveille et al., 1975). It can spontaneously rearrange to CAA (Barbin et al., 1975) or hydrolyse to glycolaldehyde (Guengerich et al., 1979; Guengerich, 1992). The latter reaction can also be catalysed by epoxide hydrolase (Fig. 2).

Evidence for the detoxification of reactive VC metabolites through conjugation with hepatic glutathione catalysed by glutathione *S*-transferase (GST) has been shown by measuring the decrease of the hepatic non-protein sulfhydryl content (primarily glutathione) and the excretion of thiodiglycolic acid via urine in rats after inhalative exposure to high levels (> 260 mg/m^3) of VC (Watanabe & Gehring, 1976; Watanabe et al., 1976c, 1978a; Jedrychowski et al., 1984).

The conjugation products *S*-carboxymethyl glutathione and *S*-formylmethyl glutathione are excreted in the urine of animals as

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substituted cysteine derivatives [*N*-acetyl-*S*-(2-hydroxyethyl)cysteine, *S*-carboxymethyl cysteine and thiodiglycolic acid] and the metabolite CO_2 in exhaled air (Green & Hathway, 1975, 1977; Watanabe et al., 1976a,b; Müller et al., 1976; Bolt et al., 1980). Thiodiglycolic acid has been detected in the urine of workers occupationally exposed to 0.36–18.2 mg/m^3 (Müller et al., 1978).

An alternative pathway has been suggested from inhibition studies of VC metabolism with ethanol (Hefner et al., 1975c). Pretreatment of rats with ethanol (5 ml/kg body weight) significantly reduced the depression of the concentration of non-protein sulfhydryl in the liver caused by exposure to 2780 mg VC/m^3 for 105 min. This inhibition was less pronounced in rats exposed to # 260 mg/m^3. It is postulated that at low concentrations, a sequential oxidation to 2-chloroethanol, 2-chloroacetaldehyde and 2-chloroacetic acid, involving alcohol dehydrogenase, takes place. It is speculated that ethanol inhibits specific P-450 enzymes. However, this hypothesis has not been substantiated by further experimental data and this pathway has not been recognized as a direct pathway in recent physiologically based pharmacokinetic (PBPK) models and risk assessments based on them (sections 6.6 and 10).

VC exposure does not result in enzyme induction but, on the contrary, causes destruction of the cytochrome P-450 protein responsible for its biotransformation (Pessayre et al., 1979; Du et al., 1982). The impaired rate of oxidative metabolism associated with P-450 destruction may partly explain the phenomenon of saturation of the VC metabolism already at relatively low dosage levels and on the other hand explain the tolerance to liver damage in experimental animals subjected to continuous intermittent exposure to high VC concentrations (73 000 mg/m^3, 7 h/day, 5 days/week for 6 weeks).

Enzymes metabolizing VC were shown to be saturated in rats at a concentration of 650 mg/m^3 (rats exposed in a closed system; Bolt et al., 1977; Filser & Bolt, 1979). In rhesus monkeys saturation of metabolic elimination of VC was observed at atmospheric concentrations greater than 520 mg/m^3 (closed system; Buchter et al., 1980). Saturation of metabolism occurred in rats at a single oral dose of 20 mg/kg body weight by gavage (Watanabe & Gehring, 1976; Table 23). Saturation conditions were not reached in humans at an inhalation exposure to 60 mg/m^3 for 6 h (Krajewski et al., 1980).

In closed systems, after the initial absorption of VC until equilibrium between atmosphere and organism, the continued absorption is attributed to metabolism (Bolt et al., 1977). Rats exposed to VC concentrations that did not exceed the above-mentioned threshold of saturation metabolized VC in accordance with first-order kinetics with a half-time of 86 min. At concentrations above saturation, the elimination followed zero-order kinetics (Hefner et al., 1975a,c; Filser & Bolt, 1979).

Although VC is primarily metabolized in the hepatocyte (Ottenwälder & Bolt, 1980), the primary target cell for carcinogenicity in the liver is the sinusoidal cell, as can be seen from the incidence of ASL in both animals and humans. Non-parenchymal cells have only 12% of the activity of hepatocytes in transforming VC into reactive, alkylating metabolites (Ottenwälder & Bolt, 1980). VC does not induce DNA damage in isolated non-parenchymal liver cells, as measured by an alkaline comet assay (Kuchenmeister et al., 1996), whereas it does in isolated hepatocytes. However, the majority of the DNA adduct studies have been conducted or related to the hepatocyte. It can be postulated that the majority of reactive metabolites can leave the intact hepatocyte to produce tumours in the sinusoidal cells (Laib & Bolt, 1980). The greater susceptibility of the sinusoidal cells to the carcinogenic effects of VC may also result from the inability of the sinusoidal cells to repair one or more of the DNA adducts produced by VC as efficiently as the hepatocyte.

6.4 Elimination and excretion

After low doses, VC is metabolically eliminated and non-volatile metabolites excreted mainly in the urine. At doses that saturate the metabolism, the major route of excretion is exhalation of unchanged VC. Independent of applied dose, the excretion of metabolites via faeces is only a minor route. The metabolic clearance of VC is slower in humans than in experimental animals, on a body weight basis. However, it is comparable in several mammalian species, including humans, when calculated on a body surface area basis.

6.4.1 Oral exposure

Male rats were gavaged with different doses of ^{14}C-labelled VC, and the radioactivity excreted was determined during the following

72 h (Green & Hathway, 1975; Watanabe & Gehring, 1976; Watanabe et al., 1976a). Results are presented in Table 23. With low doses radioactivity was mainly excreted as conjugated metabolites via the urine or exhaled as ^{14}C-labelled CO_2 (section 6.3), but with doses of 20 mg/kg body weight or more the main elimination route was exhalation of unchanged VC (Table 23), suggesting saturated metabolism. A minor route of excretion at all doses tested is via the faeces.

Measuring the elimination of radioactivity in the urine as a function of time revealed biphasic elimination at dose levels up to 100 mg/kg body weight with a half-life of approximately 4.6 h in the initial rapid phase (first-order kinetics) (Watanabe et al., 1976a).

At low doses (1 mg/kg body weight) pulmonary elimination (as CO_2) during the first 4 h was monophasic with a half-life of 58 min, but with a dose of 100 mg/kg body weight elimination of mainly unchanged VC was biphasic with an initial rapid phase (half-life 14.4 min) followed by a slow phase (half-life 41 min) (Watanabe et al., 1976a).

Most of the radioactivity excreted via urine or exhaled as the metabolite CO_2 was eliminated during the first 24 h after gavaging of 0.25 or 450 mg/kg body weight, whereas elimination of unchanged VC via the lung was complete within 3–4 h (Green & Hathway, 1975).

Pretreatment of rats with unlabelled VC (up to 300 mg/kg body weight per day orally for 60 days) had no effect on the rate of elimination of a single oral dose of ^{14}C-VC (oral application on day 1 and 60) (Green & Hathway, 1975), suggesting that VC did not induce its metabolism.

6.4.2 Inhalation exposure

Metabolic elimination of VC has been investigated in different species, measuring the decline of VC in the gas phase of a closed system into which VC was initially injected (Buchter et al., 1978; Filser & Bolt, 1979; Buchter et al., 1980). Using VC concentrations that did not exceed the saturation threshold (section 6.3), the following first-order metabolic clearance rates for VC (expressed in

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litre/h per kg body weight; initial concentration in mg/m^3 in parentheses) were determined: rat 11.0 (< 650), mouse 25.6 (130), gerbil 12.48 (130), rabbit 2.74 (130), rhesus monkey 3.55 (< 520), humans 2.08 (26). Because the metabolism of VC is perfusion-limited (Filser & Bolt, 1979), comparison of clearance rates should be made on a body surface area basis rather than a body weight basis. In this case, these six mammalian species exhibit similar clearance rates. With exposure concentrations above the "saturation point" ($> 650 \, mg/m^3$), the maximum velocity of metabolic elimination in rats was 110 : mol/h per kg body weight (Filser & Bolt, 1979) or 3.6 mg/h per kg body weight (Barton et al., 1995).

Elimination and excretion of ^{14}C in rats within 72 h after a 6-h exposure to 26, 2600 or 13 000 mg/m^3 ^{14}C-labelled VC is shown in Table 25 (similar experimental design; Watanabe et al., 1976b, 1978b; Watanabe & Gehring, 1976). The amount of expired VC increased with the exposure concentration, whereas the relative urinary excretion of metabolites decreased, indicating a saturation of metabolism. Minor decreases were seen in the proportion excreted via the faeces or expired as CO_2.

Measuring the time course of expiration in these experiments, the pattern of pulmonary elimination of unchanged VC was similar at all exposure concentrations, following first-order kinetics with half-lives of 20.4, 22.4 (Watanabe et al., 1976b) and 30 min (Watanabe et al., 1978b), respectively. After a 6-h exposure to 26 and 2600 mg/m^3, elimination of the ^{14}C-label via urine as a function of time revealed a biphasic excretion of radioactivity with estimated half-lives for the first (rapid) phase of 4.6 and 4.1 h (Watanabe et al., 1976b). Because of extremely variable excretion curves in the second phase, no attempts were made to estimate the half-lives of the slow phase, which accounted for less than 3% of the radioactivity excreted in the urine. Similar results were presented by Bolt et al. (1976). Rats exposed for 5 h to 130 mg/m^3 ^{14}C-VC excreted 70% of incorporated radioactivity during the first 24 h after exposure in urine and less than 3% in the following 3 days.

The rate of elimination of a single inhalative exposure to ^{14}C-VC is not influenced by prior repeated exposure to the same concentration (13 000 mg/m^3) of unlabelled VC 6 h/day, 5 days/week for 7 weeks (Watanabe et al., 1978b).

In human volunteers, the mean concentration of VC in the expired air up to 30 min after a 6-h exposure to 7.5–60 mg/m^3 reached no more than 5% of the inhaled concentration (Krajewski et al., 1980).

When male volunteers were exposed to 130 (n=6), 650 (n=4) or 1300 mg/m^3 (n=4) for 7.5 h, the VC concentration in expired air was 2.6, 23 or 52 mg/m^3, respectively, 1 h after exposure (Baretta et al., 1969).

6.5 Reaction with body components

6.5.1 Formation of DNA adducts

In vitro, both CEO and CAA can form etheno adducts with nucleic acid bases (Fig. 3; Bolt, 1986; Bartsch et al., 1994; Barbin, 1998), but the former exhibits greater reactivity (Guengerich, 1992). In addition, 7-OEG has been characterized as a major reaction product of CEO with guanine (Scherer et al., 1981), whereas CAA does not yield this adduct (Oesch & Doerjer, 1982). 1,N^6-Ethenoadenosine and 3,N^4-ethenocytidine were characterized as reaction products of VC with ribonucleosides in the presence of a microsomal activation system (Barbin et al., 1975; Laib & Bolt, 1978). Analysis of DNA incubated *in vitro* with rat liver microsomes, an NADPH-regenerating system and [^{14}C]-VC revealed the formation of 7-OEG, the major DNA adduct, and of 1,N^6-etheno-2N-deoxyadenosine (, dA) and 3,N^4-etheno-2N-deoxycytidine (, dC) (Laib et al., 1981). More recently, Müller et al. (1997) quantified six adducts in DNA treated with CEO, including 7-OEG, the four ethenobases and 5,6,7,9-tetrahydro-7-hydroxy-9-oxoimidazo[1,2-"]purine. The reactivity of CAA towards double-stranded B-DNA is very low (Guengerich, 1992). CAA reacts with unpaired A and C bases to yield , A and , C, respectively. Treatment of DNA with CAA has also been reported to result in the formation of N^2,3-, G and 1,N^2-, G moieties (Oesch & Doerjer, 1982; Kusmierek & Singer, 1992; Guengerich, 1992).

The formation of , dC and tentatively of , dA in liver DNA from rats exposed to VC in their drinking-water for 2 years was reported by Green & Hathway (1978). In subsequent studies, , A and , C were found in the nucleotides in hydrolysates of rat liver RNA and 7-OEG but not , A or , C in DNA after exposure to [^{14}C]-VC (Laib & Bolt,
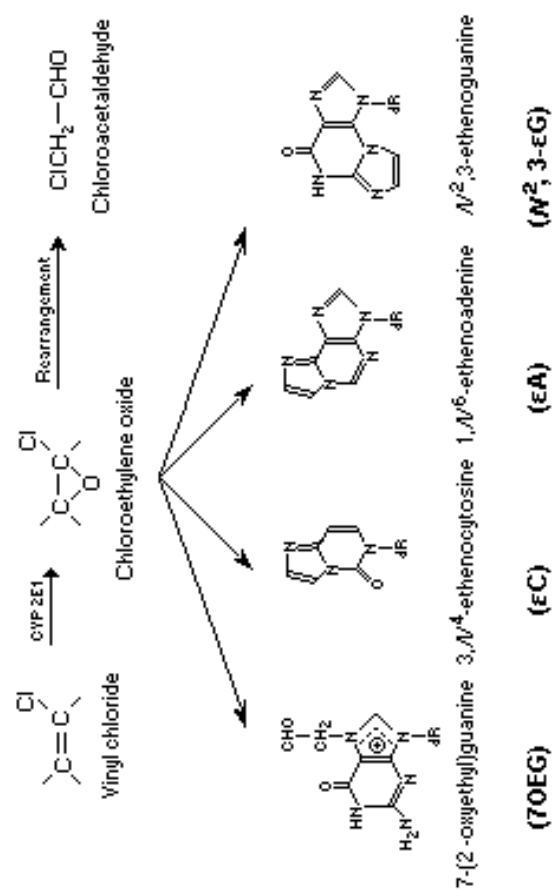
Fig 3. Vinyl chloride reactive metabolites and nucleic acid adducts formed from them *in vivo* (adapted from Ciroussel et al., 1009)

1977, 1978; Laib et al., 1981). Similar results were found in mice (Osterman-Golkar et al., 1977). More recent studies, using analytical methods (HPLC and fluorescence spectrophotometry, monoclonal antibodies and negative-ion chemical ionization with mass spectrometry using electrophore labelling; Fedtke et al., 1989, 1990a; Eberle et al., 1989) or experimental designs with greater sensitivity (young rats, short delay between exposure and analysis), have led to conclusive demonstration of , dA and , dC as DNA adducts in different rat organs after inhalation exposure to VC (Table 26). The concentration of DNA adducts was 3- to 8-fold higher in the liver than in the lung and kidney, reflecting the higher capacity of the liver for metabolic activation of VC (Fedtke et al., 1990b; Swenberg et al., 1992). Both etheno bases (, C and , A) accumulated in rat liver DNA during intermittent exposure to VC (1300 mg/m^3). Only , C accumulated in rat lung and kidney, , A appearing to accumulate principally in the target organ, the liver (Guichard et al., 1996). Subsequently, analysis of further tissues showed increased levels of , A in the testis, but not in the brain and spleen of rats exposed intermittently for 8 weeks; levels of , C increased in the testis and spleen but not in the brain (Barbin, in press).

The rate of reaction of CAA with nucleic bases is slower than with CEO (Zajdela et al., 1980). In *in vitro* studies, CEO but not CAA was shown to be the main entity giving rise to etheno adducts (Guengerich, 1992). Furthermore, as discussed in section 7.8, CEO but not CAA show similar toxicity/mutagenic profiles to VC in a metabolically competent human B-lymphoblastoid line (Chiang et al., 1997). These findings seem to corroborate the original suggestion that it is CEO rather than CAA that is the main source of etheno adducts (Van Duuren, 1975; Guengerich et al., 1981; Gwinner et al., 1983).

In pre-weanling rats exposed to VC, 7-OEG had a half-life of ~62 h, while the etheno adducts are highly persistent with a half-life for , G of ~30 days (Swenberg et al., 1992). Studies on the persistence of , A and , C in the liver of adult rats have shown that there is no significant decrease in adduct levels 2 months after termination of VC exposure (Guichard et al., 1996). This is in contrast with the known repair of etheno adducts *in vitro* (Dosanjh et al., 1994). The rat and human 3-methyladenine DNA glycosylases can excise , A from DNA (Saparbaev et al., 1995). , C can be released by the human mismatch-specific thymine-DNA glycosylase (Saparbaev & Laval, 1998).

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DNA adduct formation seems to be age-dependent; about 5- to 6-fold more DNA adducts were determined in young animals compared to adults (Laib et al., 1989). Similar results were presented by Fedtke et al. (1990b) who exposed adult and 10-day-old Sprague-Dawley rats (Table 26). Ciroussel et al. (1990) exposed 7-day-old and 13-week-old rats (strain BD IV) for 2 weeks to VC and detected 6 times more DNA adducts in the liver of young rats compared to adults (Table 26).

It should be noted that background levels of etheno bases have been found in various tissues in unexposed rodents (Guichard et al., 1996; Fernando et al., 1996; Barbin, in press) and humans (Nair et al., 1995, 1997). Lipid peroxidation products have been shown to react with nucleic acid bases yielding etheno adducts (El Ghissassi et al., 1995a; Chung et al., 1996; Bartsch et al., 1997). The role of lipid peroxidation products in the endogenous formation of background levels of etheno bases is further supported by the finding of elevated levels of ,dA and ,dC in the liver from Long Evans Cinnamon rats (Nair et al., 1996) and from patients with Wilson's disease or with primary haemochromatosis (Nair et al., 1998).

Etheno adducts are also formed via substituted oxiranes formed from other vinyl monomers, e.g., vinyl bromide (Bolt, 1994) and vinyl and ethyl carbamate (urethane) (Park et al., 1993).

6.5.2 Alkylation of proteins

Bolt et al. (1980) studied covalent binding of radiolabel to proteins in rats exposed to ^{14}C-labelled VC. The target of alkylation is the free sulfhydryl group of proteins. The liver always showed the highest binding rate. The fraction of VC that was irreversibly bound to proteins was independent of the VC dose applied, indicating no threshold effect even at low doses. *In vivo* studies on rats (Guengerich & Watanabe, 1979) have shown that the amount of total VC metabolites bound in the liver to proteins is twice that bound to DNA, RNA and lipids. Osterman-Golkar et al. (1977) reported the alkylation of cysteine (*S*-(2-hydroxyethyl)cysteine) and histidine ((*N*-1-and *N*-3) hydroxyethylhistidine) of the globin precipitate of haemoglobin and small amounts of the alkylated histidines in proteins from testis in mice exposed to 1,2-^{14}C-vinyl chloride.

Table 26. Detection of DNA adducts *in vivo* after VC inhalation in rats[a]

Strain; sex; age	Treatment; post-exposure survival time	Investigated organs	Alkylated bases in DNA (max. concentration in pmol/: mol unmodified base in specified organs)	Comments	References
BD IV; male & female; 7 days	1300 mg/m^3, 7 h/day, 7 days/week for 2 weeks; none	liver, lung, brain, kidney	, dA (0.131, 0.105, 0.06, b.d.l.); , dC (0.492, 0.246, 0.216, b.d.l.)	higher sensitivity of young rats compared with adults (see section 7.7.4)	Ciroussel et al. (1990)
BD IV; male; 13 weeks	1300 mg/m^3, 7 h/day, 7 days/week for 2 weeks; none	liver	, dA (0.019); , dC (0.080)		Ciroussel et al. (1990)
S.-D.; male & female; 10 days	1560 mg/m^3, 4 h/day for 5 days; 0, 3, 7, 14 days	liver, lung, kidney, brain, spleen	7-OEG (162, 20, 29, <10, <10); N^2,3-, G (1.81, 0.21, 0.31, <0.12, <0.12); measured immediately a.e.	higher sensitivity of young rats compared with adults (see section 7.7.4) concerning liver adducts	Fedtke et al. (1990b)
S.-D.; female; adult	1560 mg/m^3, 4 h/day for 5 days; 0, 3, 7, 14 days	liver, lung, kidney	7-OEG (43, 20, n.g.); N^2,3-, G (0.47, 0.27, <0.12); measured immediately a.e.	DNA adduct formation max. at the end of exposure; most DNA adducts in the liver	Fedtke et al. (1990b)
S.-D.; male & female; 11 days	5200 mg/m^3, 7 h/day on days 1–9 and 24 h on day 10; none	liver, lung	, dA (0.05, 0.13) , dC (0.16, 0.33)	more DNA adducts in the lung than in the liver	Eberle et al. (1989)

Table 26 (contd).

S.-D.; male & female; 10 days	1560 mg/m^3, 4 h/day for 5 days; 0, 3, 7, 14 days	liver, lung, kidney	7-OEG (162, 20, 29); N^2,3-, G (1.81, 0.21, 0.31); , dC (0.98, 0.30, 0.29); , dA (0.21, 0.065, 0.04); measured immediately a.e.	DNA adduct formation max. at the end of exposure; most DNA adducts in the liver	Swenberg et al. (1992)
S.-D.; male; 6 weeks	1300 mg/m^3, 4 h/day, 5 days/week for 1, 2, 4, 8 weeks; none	liver, lung, kidney, lymphocytes	, dA (liver: background 0.0004, a.e. up to 0.045; background lung and kidney up to 0.033, no increase a.e.); , dC (liver: background 0.0007, a.e. up to 0.08; kidney: background 0.086, a.e. up to 0.16; lung: background 0.072, a.e. up to 0.38)	exposure-time-dependent increase of adducts in liver (ca. 100-fold); no (lymphocytes) or slight increase (ca. 2-fold in kidney, ca. 5-fold in lung) of adducts in other organs but higher background levels	Guichard et al. (1996)
	8 weeks	brain, testis, spleen	, dA (increase in testis, not in brain or spleen) , dC (increase in testis and spleen, but not in brain)		Barbin (in press)

[a]   a.e. = after exposure; b.d.l. = below detection limit; n.g. = not given; S.-D. = Sprague-Dawley; , dA = 1,N^6-ethenodeoxyadenosine; , dC = 3,N^4-ethenodeoxycytidine; 7-OEG = 7-(2-oxoethyl)guanine; , G = ethenoguanine

In vitro studies have shown that incubation of rat liver microsomes with ^{14}C-labelled VC results in NADPH-dependent microsomal uptake and covalent binding to microsomal proteins (Kappus et al., 1975, 1976; Baker & Ronnenberg, 1993). It has been suggested that VC metabolites might be involved in the destruction of the haem moiety of cytochrome P-450 in the liver (Guengerich & Strickland, 1977).

6.6 Modelling of pharmacokinetic data for vinyl chloride

There has been progress in recent years in the development of physiologically based toxicokinetic (PBTK) models describing the toxicokinetics of chemicals. These theoretical models permit predictions of the dose of active metabolites reaching target tissues in different species, including humans, and, therefore, have improved the toxicokinetic extrapolation in cancer risk assessments. PBTK models have also been used as a tool to examine the behaviour of VC in mammalian systems. The description of PBTK models for VC is presented in Annex 2.

7. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

7.1 Acute toxicity

VC appears to be of low acute toxicity when administered to various species by inhalation. A summary of acute toxicity is given in Table 27. No data are available on acute toxicity after dermal application.

VC has a narcotic effect (see also section 7.6) after inhalative administration of high doses. In rats, mice and hamsters, death was preceded by increased motor activity, twitching of extremities, tremor, ataxia, tonic-clonic convulsions and accelerated respiration (Patty et al., 1930; Mastromatteo et al., 1960; Prodan et al., 1975). In dogs, severe cardiac arrhythmias occurred under narcosis after inhalative exposure to 260 000 mg VC/m^3 (Oster et al., 1947). Similar results were reported by Carr et al. (1949). Pneumonitis was more frequent in experimental mice than in controls 8 and 18 months after a single 1-h exposure to 1000, 3000, 13 000 or 130 000 mg/m^3 (Hehir et al., 1981).

After acute inhalative exposure to VC, pathological findings in the rat included congestion of the internal organs, particularly lung, liver and kidney as well as pulmonary oedema (Patty et al., 1930; Mastromatteo et al., 1960; Lester et al., 1963; Prodan et al., 1975).

Exposure to VC (3900 mg/m^3) for 24 h did not cause pathological changes in male and female rats or female New Zealand rabbits. In mice, exposure to the same concentration for 4 and 8 h resulted in circulatory changes, while longer exposure (12 and 24 h) caused vasomotor paralysis followed by characteristic shock with subsequent alterations in the liver and lungs (Tátrai & Ungváry, 1981).

7.2 Short-term toxicity

7.2.1 Oral exposure

Groups of 15 male and 15 female weanling Wistar rats were gavaged with VC dissolved in soya-bean oil (0, 30, 100 and 300 mg/kg body weight, once daily, 6 days/week for 13 weeks). The

Table 27. Toxicity of VC after acute inhalation exposure[a]

Species	Duration of exposure	Parameter	Value in g/m^3	References
Rat	2 h	LC_{50} LC_{100}	390 525	Prodan et al. (1975)
Rat	30 min	LC_{100}	780	Mastromatteo et al. (1960)
Rat	1 h	ataxia, hyperventilation	130	Hehir et al. (1981)
Mouse	2 h	LC_{50} LC_{100}	293 375	Prodan et al. (1975)
Mouse	30 min	LC_{100}	780	Mastromatteo et al. (1960)
Guinea-pig	2 h	LC_{50} LC_{100}	595 700	Prodan et al. (1975)
Guinea-pig	30 min	death, threshold dose	780	Mastromatteo et al. (1960)
Guinea-pig	2–6 h	deep narcosis, no death	260	Patty et al. (1930)
Guinea-pig	18–55 min	death, threshold dose	390-650	Patty et al. (1930)
Guinea-pig	90 min	narcosis, threshold dose	65–130	Patty et al. (1930)
Rabbit	2 h	LC_{50} LC_{100}	295 700	Prodan et al. (1975)

[a] Cited studies not conducted according to present-day standards

treatment caused no noticeable changes in appearance or behaviour, body weight gain or food intake. The total number of white blood cells and the sugar content of the blood were slightly decreased by the intermediate and high dose levels. The activities of serum ASAT and ALAT and of urinary ASAT were decreased in males given the top dose. There were no other significant changes in the haematological or biochemical indices and no treatment-related alterations were observed in the microscopic constituents of the urine. The relative

weight of the liver in males and females showed a tendency to increase with increasing doses of VC but the difference from the controls was statistically significant only at the highest dose level. The NOEL was given as 30 mg/kg body weight (Feron et al., 1975). In contrast, in another study, all male and female Wistar rats (presumably a total of 15 rats) receiving once daily 300 mg VC/kg body weight in peroxide-free corn oil by gavage died within 60 days of treatment (Knight & Gibbons, 1987).

7.2.2 Inhalation exposure

A summary of the non-neoplastic effects of VC after short-term inhalation is presented in Table 28. Information on carcinogenic effects after short-term inhalation are presented in section 7.7 and Table 30.

In various species, the main target of VC toxicity is the liver. A dose-related significant increase in relative liver weight was found in male rats at exposure levels of 26, 260 and 7800 mg/m^3 (Bi et al., 1985). Degenerative effects on liver parenchyma were reported in rabbits at a dose level of 520 mg/m^3 (Torkelson et al., 1961), in rats at 1300 mg/m^3 (Torkelson et al., 1961; Wisniewska-Knypl et al., 1980), and in mice at 2600 mg/m^3 (Lee et al., 1977). Bi et al. (1985) reported a decreased relative testis weight in rats at exposure levels of 260 and 7800 mg/m^3; however, the effect was not dose-related. These authors also reported a higher incidence and severity of damage to the testicular seminiferous tubules at all dose levels tested (26, 260 and 7000 mg/m^3), the differences with the controls being statistically significant only at the two highest dose levels. However, the severity of the testicular damage was clearly dose-related (correlation coefficient 0.993; $P < 0.01$) suggesting an adverse effect of VC on the testes already at 26 mg/m^3. Effects on relative liver weight were detected in rats at 26 mg/m^3 (Bi et al., 1985) (see also Table 28 and section 7.5.1). Effects on the kidney (Lee et al., 1977; Feron et al., 1979a,b; Himeno et al., 1983) and the lung (Suzuki, 1980) were observed in rats and/or mice at higher doses (Table 28). For mice a LOEL of 130 mg/m^3 was given (decreased survival; Hong et al., 1981). Rats, mice and rabbits seem to be more sensitive than guinea-pigs and dogs (Torkelson et al., 1961; Hong et al., 1981).

Table 28. Toxicity of vinyl chloride in animals after short-term inhalation exposures – non-neoplastic effects[a]

Species, strain; number of animals per dose per exposure period	Doses in mg/m³	Exposure duration; frequency; post-exposure observation period	Significant effects	References
Rat, Wistar; 8 (3 mo) or 30 (6 mo) m rats	0, 26, 260, 7800	3 or 6 mo; 6 d/week, 6 h/d; none	26 mg/m³: relative spleen and heart weight ↑ (6 mo); incidence of testicular seminiferous tubule damage ↑* (exposure period not specified) ≥ 26 mg/m³: relative liver weight ↑ (6 mo) 260 mg/m³: relative heart weight ↑ (3 mo) ≥ 260 mg/m³: relative testis weight ↓ (6 mo); incidence of testicular tubule damage ↑ 7800 mg/m³: relative kidney and spleen weight ↑ (3 mo)	Bi et al. (1985)
Rat; n.g.; at high dose 10 f & 10 m (control 5 f & 5 m); other groups 20–24 m & 24 f	0, 130, 260, 520, 1300	4.5 (high dose) or 6 mo; 5 d/week, 7 h/d; none	130 mg/m³: NOEL (body and organ weight, survival, haematology, clinical chemistry, urine analysis, histopathology) 260 mg/m³: relative liver weight ↑ (m+f) 1300 mg/m³: granular degeneration in centrilobular liver parenchyma #; liver weight ↑ (m)	Torkelson et al. (1961)
Rat, Wistar; 8–10 m	0, 130, 1300, 52 000	1, 3, 6 mo; 5 d/week, 5 h/d; none	130 mg/m³: slight changes such as proliferation of hepatocellular SER (3–6 mo)# ≥ 1300 mg/m³: liver weight ↑ (1–6 mo), ultrastructural hepatocellular changes (swollen mitochondria, lipid droplets ↑) after 3 and 6 mo #	Wisniewska-Knypl et al. (1980)

Table 28 (contd).

Rat, Sprague-Dawley; 110–128 rats per sex	0, 2465	24.5 weeks; 7 h/d, 5 d/week; up to 19 weeks	2465 mg/m^3: mortality ↑# (m+f), haematology and clinical chemistry :	Groth et al. (1981)
Rat, Wistar; 10 f & 10 m	0, 13 000	4, 13, 26 weeks; 5 d/week, 7 h/d; none	13 000 mg/m^3, ≥ 4 weeks: body weight ↓, blood clotting time ↓ ≥ 13 weeks: liver function (BSB-retention test) ↓; liver and kidney weight ↑ (m+f)	Feron et al. (1979a,b)
			26 weeks: spleen weight ↑ (m+f); clear cell foci and basophilic foci in the liver ↑ (m+f)#	Feron & Kroes (1979)
Rat, Sherman; 12–15 rats/sex	0, 52 000	92 d; 5 d/week, 8 h/d; none	52 000 mg/m^3: relative liver weight ↑ and spleen weight ↓ (m+f); white blood cell counts ↓; swelling of hepatocytes with vacuolization, compression of sinusoids #	Lester et al. (1963)
Mouse, CD-1; 8–28 mice/sex	0, 130, 650, 2600	1, 3, 6 mo; 5 d/week, 6 h/d; 12 mo	≥ 130 mg/m^3: survival after 6 mo exposure ↓ # (low dose: m, 1/8 versus 22/28 in control; f, 0/8 versus 23/28; tumour incidences no differences)	Hong et al. (1981)
Mouse, CD-1; 36 mice/sex	0, 2600	3-9 exposures; 5 d/week, 6 h/d; none	2600 mg/m^3: early deaths (2 m + 1 f)*; pathological changes in dead animals: acute toxic hepatitis (congestion, diffused necrosis), tubular necrosis in renal cortex	Lee et al. (1977)

Table 28 (contd).

Species, strain; number of animals per dose per exposure period	Doses in mg/m^3	Exposure duration; frequency; post-exposure observation period	Significant effects	References
Mouse, n.g.; 5 m (1 mo) or 14 m (6 mo)	6500 (no control)	1 or 6 mo; 5 d/week, 5 h/d; none	6500 mg/m^3: hyperplastic nodules and dilatated sinusoids in liver parenchyma after 6 mo exposure #	Schaffner (1979)
Mouse, CD-1; 3–16 m	0, 6500, 15 600	5–6 mo; 5 d/week, 5 h/d; 2–37 d	$ 6500 mg/m^3: proliferation and hypertrophy of bronchiolar cells, hypersecretion of bronchial and bronchiolar epithelium, hyperplasia of alveolar epithelium, bronchiolar inflammation # (only pulmonary effects recorded; effects not dose related)	Suzuki (1980)
Mouse, CD-1; 10 m	13 000 (no control)	10 weeks; 5 d/week, 4 h/d; none	13 000 mg/m^3: focal lung hyperplasia, proliferation of sinusoidal cells of the liver, proliferative effects in renal glomeruli, giant cells in testis #	Himeno et al. (1983)
Mouse, ICR; n.g.	a) 0, 13 000, 26 000; b) 78 to 104	a) 5 to 6 d, b) 62 d; a) 4 h/d, b) continuously; none	basophilic stippled erythrocytes 8 (#) in a) and b), effect not dose related	Kudo et al. (1990)

Table 28 (contd).

Hamster, golden Syrian; 56 f	0, 520	6 mo; 5 d/week, 6 h/d; life span	520 mg/m^3: survival $\downarrow$	Drew et al. (1983)
Guinea-pig, n.g.; 10–12 m & 8–12 f	0, 130, 260, 520	6 mo; 5 d/week, 7 h/d; none	520 mg/m^3: NOEL (body and organ weight, survival, clinical chemistry, histopathology)	Torkelson et al. (1961)
Rabbit, n.g.; 3 rabbits/sex	0, 130, 260, 520	6 mo; 5 d/week, 7 h/d; none	260 mg/m^3: NOEL (body and organ weight, survival, clinical chemistry, histopathology)	Torkelson et al. (1961)
			520 mg/m^3: degeneration of centrilobular liver parenchyma (m+f) with periportal cellular infiltration (f) #	
Dog; n.g.; 1 dog/sex	0, 130, 260, 520	6 mo; 5 d/week, 7 h/d; none	130–520 mg/m^3: no effects recorded (body and organ weight, survival, haematology, clinical chemistry, urine analysis, histopathology) #	Torkelson et al. (1961)

[a]   d = day; mo = month, m = male; f = female; n.g. = not given; * = increase not significant; # = no data about significance; $\uparrow$ = increased; $\downarrow$ = decreased; ∶ = no change

7.2.3 Dermal exposure

No studies were available on short-term dermal exposure.

7.3 Long-term toxicity – effects other than tumours

7.3.1 Oral exposure

Studies on effects induced by long-term oral application of VC in rats are presented in detail in Table 29. Studies on other species are not available.

Long-term feeding studies in male and female rats showed increased mortality in males at doses $ 5.0 mg/kg body weight per day (Feron et al., 1981) and in females at doses of $ 1.3 mg/kg body weight per day (Feron et al., 1981; Til et al., 1983, 1991). At 14.1 mg/kg body weight per day, blood clotting time was decreased and "-fetoprotein levels in blood serum were increased (Feron et al., 1981). Skin fibrosis was observed at 30 mg/kg body weight per day administered by gavage (Knight & Gibbons, 1987).

As for short-term exposure, the primary target organ of VC in rats after long-term oral exposure is the liver. Female rats appeared to be more sensitive than males to the hepatotoxicity of VC (section 7.7.4). Increased relative liver weights were found at 14.1 mg/kg body weight per day after feeding periods of 6 or 12 months (Feron et al., 1981). Morphological alterations of the liver included extensive hepatocellular necrosis at doses $ 5 mg/kg body weight per day, foci of haematopoiesis at 14.1 mg/kg body weight per day, and cysts and liver cell polymorphism (variation in size and shape of hepatocytes and their nuclei) at doses $ 1.3 mg/kg body weight per day (Feron et al., 1981; Til et al., 1983, 1991). Foci of hepatocellular alteration (clear cell, mixed cell, eosinophilic and basophilic foci) were common findings. Clear cell, mixed cell and eosinophilic foci occurred at doses $ 1.3 mg/kg body weight per day and basophilic foci at doses $ 0.014 mg/kg body weight per day (Til et al., 1983, 1991).

7.3.2 Inhalation exposure

A summary of non-neoplastic and neoplastic effects after long-term intermittent inhalation of VC is presented in Table 32 with

details of exposure regime (see also section 7.7). Long-term exposure to VC by inhalation resulted in increased mortality in rats exposed to a dose of 260 mg/m^3 for 12, 18 and 24 months, in mice exposed to 130 mg/m^3 for 6, 12 and 18 months and in hamsters exposed to 520 mg/m^3 for 6, 12 and 18 months (Drew et al., 1983). Maltoni et al. (1984) reported increased mortality in rats (BT15) and hamsters (BT8) at lower dose levels (2.6 and 130 mg/m^3, respectively), but no statistical evaluation was performed. Rats exposed to 130 mg/m^3 showed reduced body weight and increased relative spleen weight (Sokal et al., 1980; see below). At this dose morphological alterations were reported in rat liver, such as hepatocellular lipid accumulation and mitochondrial swellings (Wisniewska-Knypl et al., 1980) as well as proliferation of cells lining the liver sinusoids (Sokal et al., 1980). Exposure to higher doses revealed degenerative alteration in the testis (1300 mg/m^3; Sokal et al., 1980) and tubular nephrosis and focal degeneration of the myocardium (13 000 mg/m^3; Feron & Kroes, 1979) in rats.

Male Wistar rats (42–80 per group) exposed to 0, 130, 1300 and 52 000 mg VC/m^3, 5 days/week, 5 h daily, for 10 months, showed significantly reduced body weight in all treatment groups; general condition and behaviour were not altered. Relative organ weights of spleen and heart (except at the mid dose) were significantly elevated at $ 130 mg/m^3, as well as liver and kidney weights at mid- and high-dose levels and testis weights at the high-dose level. X-ray analysis did not show any skeletal alterations. Histopathology revealed statistically significantly increased incidences of nuclear polymorphism (nuclei of variable size and irregular shape) of hepatocytes and proliferation of reticuloendothelial cells lining liver sinusoids at the two highest dose levels. Fatty degeneration of hepatocytes was found at all exposure levels. Ultrastructural changes in hepatocytes seen at all exposure levels, but not in controls, included swollen and giant mitochondria with broken cristae, proliferation and dilatation of smooth endoplasmic reticulum, nuclear membrane invaginations, areas of cytoplasmic degradation and increased numbers of small lipid droplets (Sokal et al., 1980; Wisniewska-Knypl et al., 1980). In addition, Sokal et al. (1980) reported necrotic foci of the spermatogenic epithelium and disorders of spermatogenesis accompanied by large multinuclear syncytial cells in the testis predominantly at 1300 mg/m^3. Haematology, urine analysis and clinical chemistry did not reveal differences of toxicological significance.

Thus NOEL for rats or mice concerning non-neoplastic effects could not be derived, since effects were observed at the lowest levels studied (130 mg/m^3).

7.4 Skin and eye irritation; sensitization

No relevant data on skin irritation were identified. No studies were available on sensitizing effects of VC in animals. Erythema and second-degree burns were reported in a worker after accidental exposure to liquid VC (see section 8.3.2.1). Dryness of eyes and nose was reported by volunteers exposed to 1300 mg/m^3 (see section 8.2).

7.5 Reproductive toxicity, embryotoxicity and teratogenicity

7.5.1 Male reproductive toxicity

Inhalation studies on rats showed some evidence of reduced fertility and morphological alterations of the testis. It should be noted that none of the studies cited were conducted according to current guidelines (OECD, 1983a,b).

In dominant lethal studies on mice no reduction in fertility was observed (Anderson et al., 1976; Table 35). However, reduced fertility was noted in male CD rats (12 per group) mated once on week 11 of exposure (0, 130, 650 or 2600 mg/m^3; 6 h/day, 5 days per week). VC treatment decreased dose-dependently the ratio of pregnant to mated females; this was significant at mid- and high-dose level (Short et al., 1977; see also section 7.8.2).

Bi et al. (1985; for details see Table 28 and section 7.2.2) observed decreased relative testis weight at 260 mg/m^3 and morphological alterations in the testis of rats even at the lowest dose of 26 mg/m^3. Morphological alterations in the testis of rats were also reported by Sokal et al. (1980, see section 7.3.2).

VC was administered to adult female CD rats at 0, 24, 260 and 2860 mg/m^3, 6 h/day, 5 days/week for at least 10 weeks prior to mating until day 4 of lactation (94 + days) in a two-generation study. Alterations in reproductive performance and fertility were not

detected at any dose level tested. Centrilobular hypertrophy in the liver and increased relative liver weights, however, were noted at all dose levels tested in a dose-related manner (Shah, 1998).

7.5.2 Embryotoxicity and teratogenicity

Although the available studies did not follow guideline standards, the information leads to the conclusion that there is embryotoxicity or fetal toxicity, including increased numbers of resorptions, decreased numbers of live fetuses and delayed development at dose levels producing maternal toxicity. VC treatment did not induce gross malformations. There is evidence for the permeability of the placenta to VC (Ungváry et al., 1978; see section 6.2.2).

John et al. (1977, 1981) investigated mice, rats and rabbits for teratogenic effects of inhaled VC. In all three species a similar experimental design was used. Pregnant CF-1 mice were exposed 7 h/day to 0, 130 or 1300 mg VC/m^3 on day 6–15 of gestation. For both concentrations tested, concurrent control groups were sham-exposed. Animals were observed daily and maternal body weight recorded at several intervals (no further data). The mice were sacrificed on day 18 of gestation. After determination of external anomalies, one-third of each litter (19–26 litters per group) was examined for soft tissue anomalies and the other mice for skeletal anomalies. Exposure to 1300 mg/m^3 led to deaths (5 of 29 bred females, $P < 0.05$), reduced maternal body weight gain ($P < 0.05$) and food consumption ($P < 0.05$). No maternal toxicity was apparent in females exposed to 130 mg/m^3. The number of live fetuses per litter and fetal body weight were significantly decreased and the number of resorptions significantly increased at 1300 mg/m^3, but these values were within the range observed for the second concurrent control group or for historical controls. No soft tissue or external anomalies were detected. Significantly increased incidences of three skeletal variants (delayed skull and sternebrae ossification, unfused sternebrae) in the high-dose group were indicative of delayed skeletal development. No developmental toxicity was observed at 130 mg/m^3.

Sprague-Dawley rats were exposed to 0, 1300 or 6500 mg/m^3 on gestation day 6–15 and dams were sacrificed on day 21 of gestation. Low-dose exposure resulted in reduced maternal weight gain

($P < 0.05$). At the high-dose level further maternal effects like reduced food consumption and increased liver weight were observed ($P < 0.05$), and one out of 17 pregnant rats died (no further information). Examination of 16–31 litters per group revealed significantly decreased fetal weight in the low-dose but not in the high-dose group. Significantly increased incidences in dilated ureter were observed at 6500 mg/m^3.

Rabbits were exposed on gestation day 6-18 to 0, 1300 or 6500 mg/m^3 and sacrificed on gestation day 29. Except for reduced food consumption in the low-dose group and 1 death in 7 bred females of the high-dose group, no further evidence of maternal toxicity was observed. In the high-dose group only 5 litters were examined, but in other groups 11–19 litters. Compared to the concurrent control, litter size was significantly reduced in the low-dose group (but not at 6500 mg/m^3). However, there was an increase in litter size in this treatment group compared to controls concurrent to the high-dose group. The incidence of delayed ossification of the sternebrae was increased at 1300 mg/m^3, but not in the high-dose group (John et al., 1977, 1981).

Ungváry et al. (1978) exposed pregnant CFY rats continuously to 0 or 4000 mg VC/m^3 during the first, second or last third of pregnancy (gestation day 0–8, 7–13 or 13–20). Dams were sacrificed on gestation day 20 and living, dead or resorbed fetuses were recorded. Placenta and fetuses were weighed and fetuses macroscopically investigated. One half of each litter was examined for soft tissue anomalies including histopathology of organs with abnormalities and the other half was processed for investigation of the skeletal system. Maternal weight gain was significantly reduced in pregnant rats exposed during the last third of pregnancy. Increased relative liver weight was observed in dams exposed during the first or second third, but histopathology revealed no pathological changes in the liver of any VC-treated rat. No further signs of maternal toxicity were reported. Examination of 13 to 28 litters per group revealed increased fetal loss in per cent of total implantation sites after exposure during gestation day 0–8 compared with the concurrent control. However, this value was not significant compared with other control groups (e.g., control exposed gestation day 13–20) of the same study. None of the soft tissue or skeletal anomalies were attributed to VC treatment.

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Exposure of 40 pregnant white Wistar rats to VC (mean level of 6.15 mg/m^3 during whole gestation) resulted in elevated embryonic mortality, lowered fetal weight, and induction of external and internal anomalies in the development of the fetus (Mirkova et al., 1978).

7.6 Special studies

7.6.1 Neurotoxicity

Profound narcosis was reported in guinea-pigs exposed to 65 000 mg VC/m^3 for 90 min (Patty et al., 1930). Ataxia was observed at this dose level after 5 min of exposure. The anaesthetic action of VC was also observed in dogs (Oster et al., 1947) and mice (Peoples & Leake, 1933). Mastromatteo et al. (1960) reported deep narcosis in rats and mice exposed to 260 000 mg/m^3 for 30 min. The narcotic effect was preceded by increased motor activity after 5 min of exposure, twitching of extremities (after 10 min), ataxia (after 15 min) and tremor (after 15 min). Rats exposed to 130 000 mg/m^3 for 60 min showed ataxia preceded by hyperactivity but no narcotic effect (Hehir et al., 1981).

Neuropathological alterations were observed in rats exposed to 78 000 mg/m^3 (4 h/day, 5 days/week) for 12 months (Viola, 1970; Viola et al., 1971). During the exposure period, the rats were slightly soporific. Histopathology revealed diffuse degeneration in the gray and white matter of the brain and at the level of the white matter zones of reactive gliosis. In the cerebellum, atrophy of the granular layer and degeneration of Purkinje cells were most prominent. In addition, peripheral nerve bundles were often surrounded and invaded by fibrotic processes.

Reports on neurotoxicity in humans occupationally exposed to VC are given in section 8.3.2.3.

7.6.2 Immunotoxicity

Sharma & Gehring (1979) investigated mitogen-stimulated transformation in splenic lymphocytes isolated from mice exposed to 26, 260 or 2600 mg/m^3 for 2, 4 or 8 weeks (6 h/day, 5 days/week). The treatment produced no effects on body or organ weight, except

increased spleen weight in high-dose groups, no effects on haematological parameters and no pathological alterations at necropsy. VC exposure caused stimulation of spontaneous lymphocyte transformation in lymphocyte cultures prepared from mice exposed for 2 weeks to the high dose and from mice exposed for 4 weeks at all dose levels, but this was not dose-dependent. The response of lymphocytes to phytomitogens was increased at 2600 mg/m^3 after exposure for 2 weeks and at all dose levels after exposure for 4 or 8 weeks, with more pronounced effects at the mid-dose level. Stimulation of lymphocyte transformation was not observed in lymphocytes from unexposed mice cultured in the presence of VC, indicating that metabolites of VC formed *in vivo* may be responsible for this effect.

Exposure of mice to 26 mg/m^3 for 6 months (Bi et al., 1985; Table 28) or rats to 130 mg/m^3 for 10 months (Sokal et al., 1980; section 7.3.2) induced increased relative spleen weight, whereas much higher doses (52 000 mg/m^3 for 92 days) produced decreased spleen weight and reduced white blood cell counts (Lester et al., 1963; see Table 28).

Reports on immunological and lymphoreticular effects in humans occupationally exposed to VC are given in section 8.3.2.

7.6.3 Cardiovascular effects

Viola (1970) demonstrated thickening of the walls of small arterial vessels (in some vessels blockage of lumen) due to endothelial fibrosis and proliferation of endothelial cells in rats exposed to 78 000 mg/m^3 (4 h/day, 5 days/week) for 12 months. Exposure of rats to 13 000 mg/m^3 for 12 months (Feron & Kroes, 1979; see Table 32) resulted in thickened walls of arteries and focal degenerations of the myocardia.

Oster et al. (1947) observed cardiac arrhythmias (e.g., ventricular extrasystoles and fibrillation, auriculoventricular block) in dogs at a dose level of 260 000 mg/m^3.

Bi et al. (1985) reported increased relative heart weight in rats exposed for 6 months to 26 mg/m^3 or for 3 months to 260 mg/m^3 (Table 28).

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Impaired peripheral circulation as well as other cardiovascular effects in occupational exposed humans are described in section 8.3.2.

7.6.4 Hepatotoxicity

Data on hepatotoxicity are presented in sections 7.2 and 7.3.

7.7 Carcinogenicity

VC causes a wide spectrum of tumours in animals and this spectrum is similar in a number of different species (see Table 33). For example in rats, the following tumours have been described after VC inhalation exposure: liver and other angiosarcomas, other liver tumours, mammary gland carcinoma, nephroblastoma, neuroblastoma, stomach tumours and Zymbal gland tumours. The lowest dose at which an increase in tumour incidences was observed when rats were exposed by inhalation was 130 mg/m^3 for liver angiosarcoma (ASL) and 13 mg/m^3 for mammary tumours. There is evidence that animals are more susceptible to tumour induction early in life. There is also evidence that liver tumours are induced in female rats at lower doses than in males.

VC is also carcinogenic in animals after oral application. The spectrum of tumours is similar to that observed after inhalation exposure. The lowest observed dose producing a carcinogenic effect (ASL) in rats was 1.3 mg/kg body weight per day.

7.7.1 Oral exposure

Details of studies on the carcinogenicity of VC in rats after oral administration are tabulated in Table 29. There are three gavage studies: two studies with 52 or 59 weeks gavage and a 32- or 18-week follow-up and a 2-year lifetime gavage study with small numbers of animals and high mortality at high doses (Maltoni et al., 1981 [BT11 and BT27] and Knight & Gibbons, 1987). The two feeding studies used PVC powder containing VC incorporated into the diet; the numbers of animals were large, and the administration comprised the whole lifetime of the animals (Feron et al., 1981; Til et al., 1983, 1991).

Table 29. Long-term toxicity/carcinogenicity of vinyl chloride in experimental animals after oral administration[a]

Species; strain; initial number of animals per dose; vehicle	Dose; route of exposure; exposure period; frequency of treatment; post-exposure observation period	1) Effects other than tumours (dose in mg/kg bw/d); 2) number of animals for histopathological evaluation of neoplastic effects; 3) type of tumour: number of animals with this tumour/dose group (unless otherwise given)	Reference
Rat; Wistar; 60–80 rats/sex; PVC powder (vehicle) con-taining VC incorporated into the diet	0, 1.7, 5.0, 14.1 mg/kg bw./d, bioavailable [d] (oral intake 0, 1.8, 5.6, 17.0 mg/kg bw/day); oral feed; lifespan study, terminated at week 135 (m) and 144 (f); diet provided 4 h/d; none	**1)** $\geq$ 1.7 mg/kg: haematology, biochemistry, urine analyis, organ function, body weight and food consumption ↔; mortality ↑* (f); liver clear cell foci (f+m), basophilic foci (f), eosinophilic foci (m+f) ↑*; liver-cell polymorphism ↑* (m); liver cysts ↑* (f); $\geq$ 5.0 mg/kg: general condition ↓ (m+f, at mo 18); mortality ↑* (f+m); liver basophilic foci ↑* (m); extensive liver necrosis ↑* (f); 14.1 mg/kg: extensive liver necrosis and liver cysts ↑* (m); focal haematopoiesis in liver ↑* (m); liver weight ↑* (f+m at mo 6, f at mo 12, interim sacrifice); blood clotting time at mo 6 and alpha-fetoprotein at mo 12 ↓* (f+m); **2)** 55, 58, 56, 59 m and 57, 58, 59, 57 f; **3)** ASL in m: 0, 0, 6*, 27* and in f: 0, 0, 2, 9*; neoplastic liver nodules in m: 0, 1, 7*, 23* and in f : 2, 26*, 39*, 44*; hepatocellular carcinoma in m: 0, 1, 2, 8* and in f: 0, 4, 19*, 29*; lung angiosarcoma in m: 0, 0, 4*, 19* and in f: 0, 0, 1, 5*	Feron et al. (1981) [e]

Table 29 (contd).

Rat; Wistar; 100 rats/sex except high dose (50 per sex); PVC powder (vehicle) containing VC incorporated into the diet	0, 0.014, 0.13, 1.3 mg/kg bw./d, bioavailable [d] (oral intake 0, 0.018, 0.17, 1.7 mg/kg bw./day); oral feed; lifespan study, terminated at week 149 (m) and 150 (f); diet provided 4 h/d; none	**1)** $ 0.014 mg/kg: bw. and food consumption ↔ (m+f); liver basophilic foci ↓* (f); 1.3 mg/kg: mortality ↓* (f; at week 149); liver glutathione level at week 40 or 80 ↔ (satellite groups); liver clear cell (m+f), basophilic (m), eosinophilic (f), and mixed cell foci (f) ↓*; liver cysts ↓* (f); moderate to severe liver-cell polymorphism ↓* (m+f); **2)** 99, 99, 99, 49 m and 98, 100, 96, 49 f; **3)** ASL in m: 0, 0, 0, 1 and 0, 0, 0, 2 in f; neoplastic liver nodules in m 0, 0, 0, 3 and 0, 1, 1, 10* in f; hepatocellular carcinoma in m 0, 0, 0, 3* and 1, 0, 1, 3 in f	Til et al. (1983, 1991) [f]
Rat; Sprague-Dawley; 40 rats/sex; pure virgin olive oil	0, 3.33, 16.6, 50 mg/kg bw./d; gavage; 52 weeks; once daily, 4–5 d/week; up to 84 weeks [c]	**1)** $ 16.6 mg/kg: survival ↑# (m); 3.33 & 50: bw ↑# (m); **2)** 40 f and 40 m per group; **3)** ASL in m: 0, 0, 4, 8* and in f: 0, 0, 6*, 9*; Zymbal gland carcinoma in m: 0, 0, 1, 1 and in f: 1, 0, 1, 0; extrahepatic angiosarcoma in m: 0 in all groups and in f: 0, 2, 0, 2; nephroblastoma in m: 0, 0, 2, 1 and in f: 0, 0, 1, 1;	Maltoni et al. (1981, 1984) [BT 11] [b]
Rat; Sprague-Dawley; 75 rats/sex; pure virgin olive oil	0, 0.03, 0.3, 1.0 mg/kg bw./d; gavage; 59 weeks; once daily, 4–5 d/week; up to 77 weeks [c]	**1)** $ 0.03 mg/kg: survival and bw ↔ #; **2)** 75, 75, 73, 75 m and 75, 75, 73, 75 f; **3)** ASL in m: 0, 0, 0, 1 and in f: 0, 0, 1, 2; Zymbal gland carcinoma in m: 0, 0, 0, 2 and in f: 1, 0, 0, 3; extrahepatic angiosarcoma in m: 0 in all groups and in f: 0, 0, 0, 1; nephroblastoma 0 in all groups	Maltoni et al. (1981, 1984) [BT 27] [b]

Table 29 (contd).

Species; strain; initial number of animals per dose; vehicle	Dose; route of exposure; exposure period; frequency of treatment; post-exposure observation period	1) Effects other than tumours (dose in mg/kg bw/d); 2) number of animals for histopathological evaluation of neoplastic effects; 3) type of tumour: number of animals with this tumour/dose group (unless otherwise given)	Reference
Rat; Wistar; 10–20 rats/sex; peroxide-free corn oil	0, 3, 30, 300 mg/kg bw./d; gavage; 95–125 weeks; once daily; none	1) 3 mg/kg: bw ：, rat skin composition ：, mortality 1/16 (control n.g.) 30 mg/kg: bw ：, mortality 5/15; biochemical parameters for skin fibrosis 8* 300 mg/kg: mortality 15/15 within first 60 days of treatment; 2) 20, 16, 15, 10; 3) Liver tumors (predominantly angiosarcomas): 0, 1, 11, 10 #	Knight & Gibbons (1987)

[a] In all studies vehicle-treated controls; analysis of VC concentration in vehicle in all studies except Knight & Gibbons (1987); bw. = body weight; d = day; f = females; m = males; mo = months; n.g. = not given; * = effect significant at $P # 0.05$; # = no statistical evaluation; ： = unchanged; 9 = decreased; 8 = increased
[b] Study number in experiments done by Maltoni and coworkers
[c] Animals were kept until spontaneous death or sacrificed at the end of given post exposure observation period
[d] Bioavailability studied in an ancillary study
[e] Study comparable to OECD guidelines 451 with acceptable restrictions (OECD, 1981a,b)
[f] Study comparable to OECD guidelines 453 (OECD, 1981a,b)

A statistically significant increase in the incidence of ASL was seen in Sprague-Dawley rats at a dose level of 16.6 mg VC/kg body weight per day (gavage; study BT 11), and some similar tumours were also observed at dose levels of 0.3 and 1.0 mg/kg body weight per day (Maltoni et al., 1981). Hepatic angiosarcomas were also observed in gavage studies in Wistar rats (Knight & Gibbons, 1987). This tumour type is very rare in untreated rats (4 in several thousand rats of the colony used by Maltoni et al., 1981). Because of short dosage and follow-up in the first study, and small number of animals due to early mortality in the third, these studies probably did not reflect the total carcinogenic potential of VC.

The results of the two feeding studies carried out by another working group (Feron et al., 1981; Til et al., 1983, 1991) confirmed the findings presented by Maltoni et al. (1981) concerning ASL (induction at 1.3 mg/kg body weight per day, significant at 5.0 mg VC/kg body weight per day). Furthermore these feeding studies presented evidence for significantly increased tumour incidences of neoplastic liver nodules (females) and of hepatocellular carcinoma (HCC) (males) at 1.3 mg/kg body weight per day (Til et al., 1991).

7.7.2 Inhalation exposure

After the first reports of the carcinogenicity of VC in rats (Viola, 1970; Viola et al., 1971), Maltoni and coworkers intensively investigated the effects of inhalation exposure to VC in different laboratory animals[a]. Study results were published in Maltoni et al. (1974), Maltoni & Lefemine (1975) and Maltoni et al. (1979), and the final report in Maltoni et al. (1981, 1984). Detailed information on these inhalation studies as well as pertinent studies from other working groups is tabulated in Table 30 (short-term studies) and Table 32 (long-term studies). A summary of tumour types induced by long-term inhalation exposure to vinyl chloride in different species is given in Table 33. Further studies on inhalative carcinogenicity of VC not discussed in this section, but leading to similar results to the studies tabulated below, were performed on rats (short-term: Hong et al., 1981;

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[a] Studies performed at Beautivoglio (BT) Laboratories; studies numerated BT1–BT27

Table 30. Short-term inhalation studies on carcinogenicity of vinyl chloride in experimental animals[a]

Species; strain; age at start of experiment; initial number of animals per dose per exposure period; type of control;	Doses in mg/m^3; exposure period; frequency of treatment; post-exposure observation period	1) Number of animals for histopathological evaluation; 2) type of tumour: number of animals with this tumour/dose group (unless otherwise given); other observations	References
Rat; Sprague-Dawley; 11 weeks; 120 (control 240) f & m; untreated control	0, 15 600, 26 000; 5 weeks; 4 h/d, 5 d/week; 149 weeks[c]	1) 227, 120, 118; 2) (#) ASL: 0, 0, 1; extrahepatic angiosarcoma: 0, 0, 0; Zymbal gland carcinoma: 0, 9, 9; hepatoma: 0, 0, 1; nephroblastoma: 0, 1, 0; neuroblastoma: 0, 1, 0	Maltoni et al. (1981) [BT 10][b]
Rat; Sprague-Dawley; 11 weeks; 120 (control 240) f & m; untreated control	0, 15 600, 26 000; 25 weeks; 1 h/d, 4 d/week; 129 weeks[c]	1) 227, 118, 119; 2) (#) ASL: 0, 3, 1; extrahepatic angiosarcoma: 0, 2, 0; Zymbal gland carcinoma: 0, 5, 9	Maltoni et al. (1981) [BT 10][b]
Rat; Sprague-Dawley; 1-day-old; see number of animals for evaluation; no control;	15 600, 26 000; 5 weeks; 4 h/d, 5 d/week; 119[c]	1) 18 m and 24 f at low dose, 24 m and 20 f at high dose; 2) ASL in m: 5, 6 and in f:12, 9; extrahepatic angiosarcoma in m: 5, 6 and in f: 12, 9; hepatoma in m: 9, 13 and in f: 11, 7	Maltoni et al. (1981) [BT 14][b]

Table 30 (contd).

Rat; Sprague-Dawley; 6, 18, 32, or 52 weeks; 110–128 rats/sex per age group; treated control	0 or 2465; 24.5 weeks; 7 h/d, 5 d/week; scheduled sacrifice at 3, 6 and 9 months, termination at week 43	**1)** 84–128 rats per sex per age group; **2)** angiosarcomas (mostly in liver) in the 4 age groups in exposed m: 1.2, 2.2, 7.4, 18% and in exposed f: 2.3, 7.2, 28, 13%; only 1 subcutaneous angio-sarcoma (m) in all control groups (739 mice) #; older adults more susceptible to angiosarcoma-inducing effect	Groth et al. (1981)
Rat; Wistar or Sprague-Dawley; 3 days; 2–27 rats per sex per strain; treated control	0, 6.5, 13, 26, 52, 104, 208; 3 weeks; 8 h/d, 5 d/week; 10 weeks	**1)** 2–27 rats of each sex per dose per strain; **2)** dose dependent increase in ATPase-deficient liver foci (preneoplastic lesion), presumably significant at $ 52 mg/m^3 (m Sprague-Dawley rats at $ 104 mg/m^3); f more susceptable than m in both strains	Laib et al. (1985a)
Rat; Wistar; age-dependency studied early in life, see **2)**; 4-10 rats per sex; treated control	0 or 5200; 5–83 days, see **2)**; 8 h/d, 7 d/week; rats sacrificed at the age of 4 months	**1)** 2–10 rats of each sex per dose per exposure period; **2)** age dependent increase in ATPase-deficient liver foci (preneoplastic lesion) studied, rats exposed a) during gestation or at postnatal day 1–5 (b), 1–11 (c), 1–17 (d), 1–47 (e), 1–83 (f), 7–28 (g), or 21–49 (h); no effect in a & b, foci area steeply increased in c and d but not further enhanced in e and f, foci area not lowered in g but only a few foci in h	Laib et al. (1985b)
Mouse; CD1; 5–6 weeks; 30–60 m; treated control	0, 2.6, 26, 260, 780, 1560; 4 weeks; 6 h/d, 5 d/week; 0, 12, 40 weeks	**1)** see **2)**; **2)** pulmonary tumour incidences (#):week 0 post-exposure: no tumour week 12: 0/18, 0/10, 0/9, 0/6, 6/9, 8/9 week 40: 0/17, 1/9, 3/9, 6/9, 5/7, 6/7; study focused on lung tumours (no details on other tumours); tumours derived from type II alveolar cells	Suzuki (1983)

Table 30 (contd).

Species; strain; age at start of experiment; initial number of animals per dose per exposure period; type of control;	Doses in mg/m³; exposure period; frequency of treatment; post-exposure observation period	1) Number of animals for histopathological evaluation; 2) type of tumour: number of animals with this tumour/dose group (unless otherwise given); other observations	References
Mouse; CD-1; 2 months; 8–28 mice/sex; treated control	0, 130, 650, 2600; 1, 3, 6 months; 6 h/d, 5 d/week; 12 months	**1)** 60, 40, 44, 38 m and 60, 40, 40, 38 f for cumulative effects; **2)** cumulative (f+m); ASL: 1, 2, 13*, 18*; extrahepatic angiosarcoma 0, 2, 6*, 2; bronchioloalveolar tumor 16, 18, 52*, 50*; cumulative (f): metastatic lung adenocarcinoma 0, 4*, 2, 6*; mammary carcinoma 4, 10*, 13*, 6; tumours at different organ sites in f and m increased in proportion to dose or duration of exposure at higher dose levels	Hong et al. (1981)

[a]   d = day; f = females; m = males; n.g. = not given; # = no statistical evaluation; * = significant at $P \# 0.05$
[b]   Study number in experiments done by Maltoni and coworkers
[c]   Animals were kept until spontaneous death or sacrificed at the end of given post-exposure observation period

long-term: Viola et al., 1971; Maltoni et al., 1974; Lee et al., 1977; Maltoni et al., 1981, 1983, 1984; Bi et al., 1985; Maltoni & Cotti, 1988; Froment et al., 1994) and mice (short-term: Suzuki, 1978, 1981; Schaffner, 1979; Hehir et al., 1981; Himeno et al., 1983; Adkins et al., 1986; long-term: Keplinger et al., 1975; Lee et al., 1977; Holmberg et al., 1979; Drew et al., 1983).

7.7.2.1 Short-term exposure

Several carcinogenicity studies have been performed where animals were exposed by inhalation for rather short periods (up to 6 months) and kept for different post-exposure periods up to lifetime (Table 30). The tumour spectrum in rats and mice is very similar to that observed in long-term inhalation studies (compare with Table 32). Hehir et al. (1981) presented evidence that even one single high dose ($ 13 000 mg/m^3) resulted in a dose-related increase of pulmonary tumours in mice. This effect was also demonstrated by repeated administration to mice at lower dose levels with exposure periods varying between 1 and 6 months (Hong et al., 1981; Suzuki, 1983). Incidences of ASL, extrahepatic angiosarcoma and mammary gland carcinoma were elevated in mice with increasing exposure periods at doses of 130 or 650 mg/m^3 (Hong et al., 1981). Also in rats, angiosarcomas, predominantly in the liver, were induced by VC inhalation for 25 weeks (15 600 mg/m^3, 1 h/day, Maltoni et al., 1981; 2465 mg/m^3, 7 h/day, Groth et al., 1981). Short-term exposure led to increased incidences of carcinoma of the Zymbal gland, a sebaceous gland of the ear canal in rats, at high doses ($ 15 600 mg/m^3; Maltoni et al., 1981, BT10).

Short-term exposure studies on the effect of age on susceptibility to tumour induction are discussed in section 7.7.3.

7.7.2.2 Long-term exposure

a) *Rats*

Although differences in experimental design, notably in the duration of follow-up, and the low overall frequency of tumours tend to confuse the picture, a dose-response relationship could be observed in studies BT1, BT2, BT9 and BT15 on Sprague-Dawley rats for ASL (Table 31, Fig. 4 and chapter 10) and Zymbal gland carcinomas,

Table 31. Incidence of angiosarcomas of the liver (ASL) and mammary tumours observed in Sprague-Dawley rats[a]

Exposure (ppm)	Concentration (mg/m³)	ASL (males)	ASL (females)	ASL (males + females)	Mammary adeno-carcinomas
0	0	0/173	0/239	0/412	12/239
1	2.6	0/58	0/60	0/118	12/60
5	13	0/59	0/60	0/119	22/60
10	26	0/59	1/60	1/119	11/60
25	65	1/60	4/60	5/120	15/60
50	130	2/174	13/180	15/354	61/180
100	260	0/60	1/60	1/120	3/60
150	390	1/60	5/60	6/120	6/60
200	520	7/60	5/60	12/120	5/60
250	650	1/29	2/30	3/59	2/30
500	1300	0/30	6/30	6/60	1/30
2500	6500	6/30	7/30	13/60	2/30
6000	15 600	3/29	10/30	13/59	0/30
10 000					3/30

[a]   The data are combined from the experiments BT1, BT2, BT9 and BT15 conducted by Maltoni et al. (1984). Control animals from several experiments are combined in the 0 ppm group. Animals were exposed 4 h/day, 5 days/week for 52 weeks; the follow-up was until the death of the animals or until week 83 (BT1), 90 (BT2), 90 (BT9) or 95 (BT15). Tumours were scored at the time of death. Adapted from Reitz et al. (1996)

while it was less clear for nephroblastomas, neuroblastomas and mammary malignant tumours.

Lee et al. (1978) and Drew et al. (1983) reported similar findings on the incidence of ASL. Female rats seem to be more susceptible to ASL tumours than males (Lee et al., 1978; Maltoni et al., 1981). ASL was detected at 26 mg/m³ and the incidence was statistically significant at 130 mg/m³, which was at a lower level than other
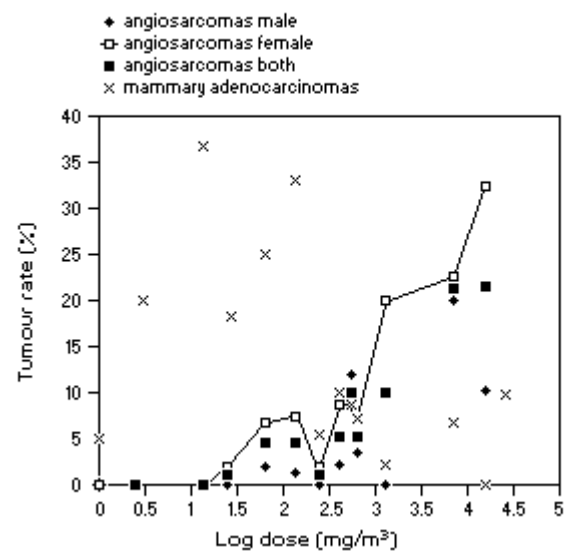
Fig. 4. Dose-response relationship for inhalation exposure of rats to vinyl chloride and hepatic angiosarcoma and mammary adenocarcinoma (from Maltoni et al., 1981, 1984; Table 31)

tumour types with the exception of mammary gland tumours (13 mg/m^3; see Table 33) (Maltoni et al., 1981). VC exposure also caused angiosarcomas at extrahepatic sites (Maltoni et al., 1981, BT14 see Table 30; Lee et al., 1978; Drew et al., 1983).

Increased incidences of other tumour types than those reported by Maltoni et al. (1981) in Sprague-Dawley rats were shown by Drew et al. (1983) in Fischer-344 rats (neoplastic liver nodules and hepatocellular carcinoma) and by Feron & Kroes (1979) in Wistar rats (tumour of the nasal cavity). These were single dose experiments.

Drew et al. (1983; see Table 32) studied the effect of exposure duration (6, 12, 18 or 24 months) on tumour incidences and demonstrated that longer exposure periods, and thus greater cumulative exposures, led to an increase in tumorigenic responses concerning liver angiosarcoma, angiosarcoma at all sites, and hepatocellular carcinoma in female F-344 rats. This exposure duration-related effect was not observed in mice and hamsters, except angiosarcoma at all sites in hamsters.

The lowest reported dose (13 mg/m^3) to cause a statistically significant increase in tumour incidences was demonstrated for mammary adenocarcinoma in female rats (Maltoni et al. 1981; BT15). Although this tumour type is common in untreated rats and no clear dose-response relationship was shown (probably due to reduced survival in the high-dose groups, Maltoni et al., 1984; BT1, BT2, BT9, BT15), the increase in tumour rate was considered by the Task Group to be of toxicological relevance, since the incidence was increased compared to concurrent and historical controls of the same colony (Maltoni et al., 1981, 1984) and similar results on mammary gland tumours were presented in further studies on rats (Drew et al., 1983) and other species (Lee et al., 1978; Maltoni et al., 1981, 1984; Drew et al., 1983) (see also Table 33; Fig. 4).

b) *Mice*

In mice, the spectrum of tumours induced by long-term inhalation exposure is similar to that observed in rats, but an increase in lung tumours was only observed in mice (Lee et al., 1978; Maltoni et al., 1981; Drew et al., 1983, see also Table 32). At a dose level of 130 mg/m^3, incidences in angiosarcoma (liver, extrahepatic or all sites

Table 32. Inhalation studies on the long-term toxicity/carcinogenicity of vinyl chloride in experimental animals[a]

Species; strain; age at start of experiment; initial number of animals per dose per exposure period; type of control;	Doses in mg/m³; exposure period; frequency of treatment; post-exposure observation period	1) Effects other than tumours (dose in mg/m³); 2) number of animals for histopathological evaluation of neoplastic effects; 3) type of tumour: number of animals with this tumour/dose group (unless otherwise given)	Reference
Rat; Sprague-Dawley; 13 weeks; 30 rats/sex; untreated control	0, 130, 650, 1300, 6500, 15 600, 26 000; 52 weeks; 4 h/d, 5 d/week; 83 weeks [c]	1) $ 650: survival ♀# (f, in m at $ 1300); $ 15 600: body weight ♀# (m, in f at 26 000); 2) 29-30 m and 29-30 f per group; 3) ASL in m: 0, 0, 1, 0, 6*, 3, 3 and in f : 0, 1, 2, 6*, 7*, 10*, 4; Zymbal gland carcinoma in m: 0, 0, 0, 3, 1, 3, 10* and in f: 0, 0, 0, 1, 1, 4, 6*; hepatoma in f: 0, 0, 0, 5, 2, 1, 0; nephroblastoma in m: 0, 0, 1, 2, 5*, 4, 3 and in f: 0, 1, 4*, 4*, 1, 1, 2; neuroblastoma in m: 0, 0, 0, 0, 2, 2, 2 and in f: 0, 0, 0, 0, 2, 1, 5*; mammary adenocarcinoma in f: 0, 2, 2, 1, 2, 0, 3	Maltoni et al. (1981, 1984) [BT1][b]
Rat; Sprague-Dawley; 13 weeks; 60 rats/sex, control 85 m and 100 f; untreated control	0, 260, 390, 520; 52 weeks; 4 h/d, 5 d/week; 91 weeks [c]	1) $ 130: survival ♀# (m, in f at 520); 2) 59–60 rats per treatment group, control 65 m and 100 f; 3) ASL in m: 0, 0, 1, 7* and in f: 0, 1, 5*, 5*; mammary adenocarcinoma in f: 1, 3, 6*, 5; nephroblastoma in m: 0, 8*, 8*, 5* and in f: 0, 2, 3, 2	Maltoni et al. (1981, 1984) [BT2][b]

Table 32 (contd).

Species; strain; age at start of experiment; initial number of animals per dose per exposure period; type of control;	Doses in mg/m^3; exposure period; frequency of treatment; post-exposure observation period	1) Effects other than tumours (dose in mg/m^3); 2) number of animals for histopathological evaluation of neoplastic effects; 3) type of tumour: number of animals with this tumour/dose group (unless otherwise given)	Reference
Rat; Sprague-Dawley; 13 weeks; 150 rats per sex, control 50 m and 50 f; untreated control	0, 130; 52 weeks; 4 h/d, 5 d/week; 90 weeks [c]	1) survival ♀# (f); 2) 144 m and 150 f, control 48 m and 50 f; 3) ASL in m: 0, 2 and in f: 0, 12*; mammary adenocarcinoma in f: 5, 59*; no significant effects on incidences of other tumour types	Maltoni et al. (1981, 1984) [BT9][b]
Rat; Sprague-Dawley; 13 weeks; 60 rats/sex; untreated control	0, 2.6, 13, 26, 65; 52 weeks; 4 h/d, 5 d/week; 95 weeks [c]	1) $ 2.6 survival ♀# (m+f); 2) 58–60 m and 60 f per group; 3) ASL in m: 0, 0, 0, 0, 1 and in f: 0, 0, 0, 1, 4; mammary adenocarcinoma in f: 6, 12, 22*, 21*, 15*; nephroblastoma in m: 0, 0, 0, 0, 1; hepatoma in f: 0, 0, 0, 0, 1	Maltoni et al. (1981, 1984) [BT15][b]
Rat; Spague-Dawley; 13 weeks (pregnant rats) or gestation day 12 (embryos); see number of animals for for evaluation; untreated control	0, 6500; life time (up to 69 weeks); 4 h/d, 5 d/week for 7 weeks, than 7 h/d, 5 d/week; none	1) survival & body weight ♀# 2) 60, 54 dams, progeny 158, 63 m and 149, 64 f 3) tumour incidences in % (#): ASL[d] : 0, 50.0 in dams and 0, 56.2 in m and 0, 73.0 in f progeny; hepatocellular carcinoma: 0, 9.2 in dams, 0.6, 42.2 in m and 0, 60.3 in f progeny mammary carcinoma: 7.4, 7.4 in dams, 5.4, 4.7 in f progeny; neuroblastoma[d]: 0, 59.2 in dams, 0, 48.4 in m and 0, 42.8 in f progeny	Maltoni & Cotti (1988)

Table 32 (contd).

Rat; Fischer-344; 8–9 weeks, 2nd experiment: 2, 8, 14, 20 mo (6 mo exposure) or 2, 8, 14 mo (12 mo exposure); n.g. (only f, see number of rats for evaluation); n.g.	0 or 260; 6, 12, 18, 24 mo, 2nd experiment 6 or 12 mo exposure at different age; 6 h/d, 5 d/week; life span	**1)** survival ♀* (exposure periods > 6 mo); **2)** 112 (control), 76, 55, 55, 55 per exposure period; 2nd experiment 6 mo exposure: 112 (control), 76, 52, 51, 53 per age group; 2nd experiment 12 mo exposure: 112 (control), 55, 54, 49 per age group; **3)** ASL: 1, 4*, 11*, 13*, 19*; angiosarcoma all sites: 2, 4, 12*, 15*, 24*; mammary fibroadenoma: 24, 28*, 28*, 24*, 26*; mammary adenocarcinoma: 5, 6, 11*, 9*, 5*; neoplastic liver nodules: 4, 15*, 20*, 7*, 6*; hepatocellular carcinoma: 1, 3, 4*, 8*, 9*; 2nd experiment 6 mo exposure: ASL: 1, 4*, 2, 0, 0; angiosarcoma all sites: 2, 4, 2, 0, 0; mammary fibroadenoma: 24, 28*, 23*, 17, 20; mammary adenocarci-noma: 5, 6, 2, 3, 2; neoplastic liver nodules: 4, 15*, 10*, 2, 4; hepatocellular carcinoma: 1, 3, 6*, 0, 1; 2nd experiment 12 mo exposure: ASL: 1, 11*, 5*, 2; angiosarcoma all sites: 2, 12*, 5*, 2; mammary fibroadenoma: 24, 28*, 16*, 15; mammary adenocarcinoma: 5, 11*, 4, 0; neoplastic liver nodules: 4, 20*, 4, 4; hepatocellular carcinoma: 1, 4*, 1, 0;	Drew et al. (1983)
Rat; Wistar; 11 weeks; control 40 m, other groups 30 m; untreated control	0, 130, 650, 1300, 6500, 15 600, 26 000; 52 weeks; 4 h/d, 5 d/week; 113 weeks [c]	**1)** $ 130: survival & body weight ♀# **2)** 38, 28, 28, 27, 25, 26, 27; **3)** (#):ASL: 0, 0, 1, 3, 3, 3, 8; hepatoma: 0, 0, 0, 0, 1, 2, 0; nephroblastoma: 0, 1, 0, 2, 0, 2, 1; neuroblastoma: 0, 0, 0, 0, 1, 1, 3; Zymbal gland carcinoma: 0, 0, 0, 0, 0, 2, 2	Maltoni et al. (1981, 1984) [BT17][b]

Table 32 (contd).

Species; strain; age at start of experiment; initial number of animals per dose per exposure period; type of control;	Doses in mg/m^3; exposure period; frequency of treatment; post-exposure observation period	1) Effects other than tumours (dose in mg/m^3); 2) number of animals for histopathological evaluation of neoplastic effects; 3) type of tumour: number of animals with this tumour/dose group (unless otherwise given)	Reference
Rat; Wistar; newly weaned; 62 rats/sex; treated control	0 or 13 000; 52 weeks, 10 rats per dose per sex sacrificed at week 4, 13, 26 (see section 7.2); 7 h/d, 5 d/week; none	1) mortality 8# (9 m and 10 f still alive at week 52); body weights 9* (f+m); blood clotting time 9#; liver function 9# (BSB-retention test); relative liver, kidney and spleen weight 8*; degree of tubular nephrosis 8# (f+m); focal degeneration of myocardium and thickened walls of arteries # (f+m); haematopoietic activity in the spleen 8# (f+m); distended liver sinusoids # (f+m); 2) 62 m and 62 f per group; 3) cumulative tumours (#):ASL: 0, 3 in m and 0, 6 in f ; Zymbal gland tumour: 0, 7 in m and 0, 4 in f; tumour of nasal cavity: 0, 10 in m and 0, 10 in f;	Feron et al. (1979a,b) Feron & Kroes (1979)
Rat; CD; 2 mo; 36 rats/sex; treated control	0, 130, 650, 2600; 12 mo, 4 rats/dose per sex terminated at month 1, 2, 3, 6, 9; 6 h/d, 5 d/week; none	1) $ 650: survival 9# (m+f); 2) 35, 36, 36, 34 m and 35, 36, 34, 36 f; 3) tumours combined for all exposure periods: ASL: 0, 0, 2, 6 in m and 0, 0, 10*, 15* in f; lung angiosarcoma: 0, 0, 0, 4 in m and 0, 0, 3, 9* in f; other tumours not related to VC treatment	Lee et al. (1978)

Table 32 (contd).

Rat [no further data provided]	0, 14, 25, 266, 3690; 52 weeks; 4.5 h/d, 5 d/week	**1)** no data **2)** 70, 50, 39, 43, 51 m **3)** ASL: 0, 0, 7.7, 9.3, 11.8%; other angiosarcomas: 0, 1.0, 2.5, 0, 3.9% other liver tumours: 2.8, 2.0, 2.6, 11.6, 13.7% haemoblastoma: 4.3, 14.0, 15.4, 34.9, 2.0% other tumours: 21.5, 28.1, 15.4, 9.3, 23.5%	Kurlyandski et al. (1981)
Mouse; Swiss; 11 weeks; 30 mice per sex, control 80 m and 70 f; untreated control	0, 130, 650, 1300, 6500, 15 600, 26 000; 30 weeks; 4 h/d, 5 d/week; 51 weeks [c]	**1)** $ 130: survival 9# (m+f); $ 1300: body weight 9# (m, in f at $ 650); **2)** 80, 30, 30, 30, 29, 30, 26 m and 70, 30, 30, 30, 30, 30, 30 f; **3)** combined (f+m) tumours (#): ASL: 0, 1, 18, 14, 16, 13, 10; liver angioma: 0, 1, 11, 5, 5, 7, 6; extrahepatic angiosarcoma: 1, 1, 3, 7, 8, 1, 1; lung tumour: 15, 6, 41, 50, 40, 47, 46; mammary carcinoma in f : 1, 13, 12, 9, 10, 9, 14	Maltoni et al. (1981, 1984) [BT4][b]
Mouse; Swiss CD-1; 8–9 weeks, 2nd experiment: 2, 8, 14 mo (6 or 12 mo exposure); n.g. (only f, see number of mice for evaluation); n.g.	0 or 130; 6, 12, 18 mo, 2nd experiment 6 or 12 mo exposure at different age; 6 h/d, 5 d/week; lifespan	**1)** survival 9* (all exposure periods); **2)** 71 (control), 67, 47, 45 per exposure period; 2nd experiment 6 mo exposure: 71 (control), 67, 49, 53 per age group; 2nd experiment 12 mo exposure: 71 (control), 47, 46, 50 per age group; **3)** angiosarcoma (all sites): 1, 29*, 30*, 20*; mammary gland carcinoma: 2, 33*, 22*, 22*; lung carcinoma: 9, 18*, 15*, 11*; 2nd experiment 6 mo exposure: angiosarcoma (all sites): 1, 29*, 11*, 5; mammary gland carcinoma: 2, 33*, 13*, 2; lung carcinoma: 9, 18*, 13*, 7; 2nd experiment 12 mo exposure: angiosarcoma (all sites): 1, 30*, 17*, 3; mammary gland carcinoma: 2, 22*, 8*, 0; lung carcinoma: 9, 15*, 9*, 3;	Drew et al. (1983)

Table 32 (contd).

Species; strain; age at start of experiment; initial number of animals per dose per exposure period; type of control;	Doses in mg/m³; exposure period; frequency of treatment; post-exposure observation period	1) Effects other than tumours (dose in mg/m³); 2) number of animals for histopathological evaluation of neoplastic effects; 3) type of tumour: number of animals with this tumour/dose group (unless otherwise given)	Reference
Mouse; CD-1; 2 mo; total 36 mice/sex; treated control	0, 130, 650, 2600; 1, 2, 3, 6, 9, and 12 mo (4 mice per group per sex per exposure period); 6 h/d, 5d/week; none	**1)** $ 650: survival 9# (tumour development), all mice in high-dose group and females in mid-dose group died or were terminated at mo 10–12; **2)** 26, 29, 29, 33 m and 36, 34, 34, 36 f; **3)** tumours combined for all exposure periods: bronchioloalveolar adenoma (#):1, 8, 10, 22 in m and 0, 4, 12, 26 in f; ASL: 0, 3, 7*, 13* in m and 0, 0, 16*, 13* in f; extrahepatic angiosarcoma: 0, 5*, 2, 0 in m and 0, 1, 3, 9* in f; mammary tumours(#): 0, 9, 3, 13 in f; incidences exposure time-dependent	Lee et al. (1978)
Hamster; Syrian golden; 11 weeks; 30 m, 60 m in control; untreated control	0, 130, 650, 1300, 6500, 15 600, 26 000; 30 weeks; 4 h/d, 5 d/week; 79 weeks [c]	**1)** $ 130: survival 9#; **2)** see initial number of hamsters; **3)** (#): ASL: 0, 0, 0, 2, 0, 1, 0; acoustic duct tumour: 0, 0, 0, 3, 1, 2, 1; melanoma: 0, 1, 1, 0, 0, 1, 2, 1; forestomach tumour: 3, 3, 4, 9, 17, 10, 10; skin epithelial tumour: 3, 9, 3, 7, 3, 1, 7;	Maltoni et al. (1981, 1984) [BT8][b]

Table 32 (contd).

Hamster; Syrian golden; 8–9 weeks, 2nd experiment: 2, 8, 14, 20 mo (6 mo exposure) or 2, 8, 14 mo (12 mo exposure); n.g. (only f, see number of hamster for evaluation); n.g.	0 or 520; 6, 12, 18 mo, 2nd experiment 6 or 12 mo exposure at different age; 6 h/d, 5 d/week; life span	**1)** survival $\mathcal{Q}$* (all exposure periods); **2)** see tumour incidences; **3)** tumour incidences in control and at different exposure periods: angiosarcoma (all sites): 0/143 (control), 13/88*, 4/52*, 2/103; mammary carcinoma: 0/143, 28/87*, 31/52*, 47/102*; stomach adenoma: 5/138, 23/88*, 3/50*, 20/101*; skin carcinoma: 0/133, 2/80; 9/48*, 3/90; 2nd experiment 6 mo exposure: angiosarcoma (all sites): 0/143 (control), 13/88*, 3/53*, 0/50, 0/52; mammary carcinoma: 0/143, 28/87*, 2/52*, 0/50, 1/52; stomach adenoma: 5/138, 23/88*, 15/53*, 6/49*, 0/52; skin carcinoma: 0/133, 2/80; 0/49, 0/46, 0/50; 2nd experiment 12 mo exposure: angiosarcoma (all sites): 0/143 (control), 4/52*, 1/44, 0/43; mammary carcinoma: 0/143, 31/52*, 6/44*, 0/42; stomach adenoma: 5/138, 3/50*, 10/44*, 3/41; skin carcinoma: 0/133, 2/80; 0/38, 0/30;	Drew et al. (1983)
Rabbit; n.g.; n.g.; 40 exposed to VC, 20 controls (no data about sex); treated control	0, 26 000; 15 mo; 4 h/d, 5 d/week; n.g.	**1)** n.g.; **2)** see tumour incidences; **3)** tumour incidences: skin acanthoma: 0/20 (control), 12/40*; lung adenocarcinoma 0/20, 6/40	Caputo et al. (1974)

[a] * = significant at *P* # 0.05; #: no statistical evaluation; f = females; m = males; mo = months; n.g. = not given
[b] Study number in experiments done by Maltoni and coworkers
[c] Animals were kept until spontaneous death or sacrificed at the end of given post exposure observation period
[d] Presumably significant in all exposed groups

Table 33. Summary of tumour types induced by long-term inhalation exposure to vinyl chloride
Lowest reported dose that significantly increased tumour incidences by tumour type (dose in mg/m^3)

Species	Liver angio-sarcoma	Angio-sarcoma (other sites)	Other liver tumours	Lung carcinoma	Mammary gland carcinoma	Nephro-blastoma	Skin tumour	Neuro-blastoma	Stomach tumour	Zymbal gland tumour
Rat	130 in f [c] 520 in m [c]	extrahepatic 260 in f [b,d] lung 2600 in f [e]	neoplastic nodules 260 in f [b,d] hepato-cellular carcinoma 260 in f [d]		13 in f [h]	260 in m [b,g] 650 in f [g]		6500 in f [b,k]	fore-stomach papilloma 78 000 in f + m [i]	26 000 in f + m [f]
Mouse	650 in f + m [e]	130 in m [b,e] all sites 130 in f [b,d]		130 in f [b,d]	130 in f [b,d]					

Table 33 (contd).

Species	Liver angio-sarcoma	Angio-sarcoma (other sites)	Other liver tumours	Lung carcinoma	Mammary gland carcinoma	Nephro-blastoma	Skin tumour	Neuro-blastoma	Stomach tumour	Zymbal gland tumour
Rabbit							acanthoma 26 000, n.d. about sex [b,j]			
Hamster		all sites 520 in f [b,d]			520 in f [b,d]		carcinoma 520 in f [b,d]		adenoma 520 in f [b,d]	

[a] Exposure in all studies 4–7 h/day, 5 days/week, exposure period at least 6 months
     f = females; m = males; n.d. = no data
[b] The lowest dose tested with the study design described in the cited study

[c] Maltoni et al. (1981; BT9)	[f] Maltoni et al. (1981; BT1)	[i] Maltoni et al. (1981; BT6)
[d] Drew et al. (1983)	[g] Maltoni et al. (1981; BT1, BT2)	[j] Caputo et al. (1974)
[e] Lee et al. (1978)	[h] Maltoni et al. (1981; BT15)	[k] Maltoni & Cotti (1988)

combined), lung carcinoma, and mammary gland carcinoma showed a statistically significant increase (Lee et al., 1978; Drew et al., 1983). Doses lower than 130 mg/m^3 were not investigated, but at the dose levels investigated, the angiosarcoma frequencies were higher in mice than in rats (Lee et al., 1978). No clear-cut relationship with time of exposure (6–18 months) and incidence of ASL was observed; this could, however, have been due to decreased survival and shorter follow-up after longer exposure time (Drew et al., 1983).

c)   *Other species*

Limited data are available on other species. In experiment BT8 with male Syrian golden hamsters, low frequencies of ASL, acoustic duct tumours and melanomas were observed. In addition, an increased incidence in forestomach and skin epithelial tumours was reported, but these tumours were also observed in controls, there was no dose-response relationship and a statistical evaluation was not presented (Maltoni et al., 1981).

Female hamsters were exposed to a single dose for different exposure periods (Drew et al., 1983). Angiosarcomas (all sites), skin tumours and increased incidences in mammary gland carcinoma and stomach adenomas (glandular portion of the stomach) were reported (Drew et al., 1983).

In a study reported only as an abstract, Caputo et al. (1974) reported increased incidences in skin acanthoma and lung adenocarcinoma in rabbits exposed to VC.

7.7.3 The effect of age on susceptibility to tumour induction

Recently there has been some concern about early-life sensitivity to vinyl chloride (Hiatt et al., 1994; Cogliano et al., 1996). However, there is contradictory evidence (Drew et al., 1983 versus Groth et al., 1981) concerning the effects of age on ASL induction in rats, but final conclusions on increased susceptibility in 6- to 8-weeks-old animals could not be drawn from these data. The discrepancy in results with rats is probably due to differences in strain and/or experimental design. However, there is evidence from other studies that there is possibly a higher sensitivity to liver tumour induction in different rat strains in the first weeks of life, a life-phase much earlier than that

studied by Drew et al. (1983). Studies on DNA adduct formation support these results.

F-344 rats, hamsters and mice (Swiss and B6C3F$_1$) of different age at the beginning of the exposure period (2, 8, 14 or 20 (not mice) months old) were exposed to VC using the same experimental design and same exposure period (Drew et al., 1983; see Table 32 for details).

For ASL in rats, angiosarcoma at all sites and mammary carcinoma in all three species, neoplastic nodules in rats and lung carcinoma in Swiss mice, the tumour response was highest in young animals (2-month-old) exposed for 6 or 12 months. The validity of the demonstrated age-related effects is limited in this study because only statistical evaluation in comparison to control or to all other groups, but not related to each other exposure group, was performed. In addition, exposure later in life automatically shortens the period of follow-up, and thus tends to lead to an apparent elevated sensitivity at young age.

The effect of age on the susceptibility to induction of ASL in Sprague-Dawley rats was also studied by Groth et al. (1981; see Table 30 for details). Rats aged 6, 18, 32 or 52 weeks were exposed to VC at the same dose level and exposure period. In contrast to Drew et al. (1983), the results of this study demonstrated that the older the rats were at the start of the exposure period, the greater was the tumour incidence. The maximum incidence was observed in male rats 52 weeks old at first exposure and in females 32 weeks old at first exposure (significantly increased compared to 6- or 18-week-old females). For males the effect of age was statistically significant.

Exposure of 1-day-old rats of the same strain to high VC concentrations for 5 weeks (BT14, see Table 30) revealed a remarkably higher incidence of ASL, extrahepatic angiosarcoma and hepatoma compared with 11-week-old rats exposed within the same experimental design (BT10; Maltoni et al., 1981; see Table 30). However, these experiments were not concurrent, and the tumour response in different series from this laboratory has been variable (Tables 31, 32).

Maltoni & Cotti (1988) exposed 13-weeks-old pregnant Sprague-Dawley rats and their progeny from the 12th day of gestation to VC

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(Table 32). Although no statistical evaluation was performed it seems that there was no significant difference between the dams and the progeny concerning incidences in ASL, mammary carcinoma, and neuroblastoma. The incidence of hepatocellular carcinoma, however, was 9% in dams and 42% in male and 60% in female progeny. In this study the duration of exposure (and also of latency) was up to 69 weeks for the progeny, but 56 weeks for the dams.

Laib et al. (1985a; see Table 30) presented evidence for dose-related increased induction of ATPase-deficient liver foci in Wistar and Sprague-Dawley rats, discussed as preneoplastic hepatocellular lesions, after a 3-week exposure to low concentrations ($ 52 mg/m^3). The increased induction of these foci was restricted to a well-defined period of highest sensitivity beginning with rapid liver growth in 7- to 21-day-old rats. No induction of these foci was reported in adult rats exposed to 5200 mg/m^3 for 70 days after partial hepatectomy (no further details) (Laib et al., 1985b).

Comparative investigations on the alkylation of liver DNA in young and adult Wistar rats exposed under the same exposure conditions confirmed the age-related sensitivity of rats to VC (section 6.5.1 and Table 26.)

7.7.4 The effect of gender on susceptibility to tumour induction

There is evidence that female rats of various strains are more susceptible to liver tumour induction than males. Maltoni et al. (1981, 1984) reported in all studies on Sprague-Dawley rats (BT1, BT2, BT9, BT15; see Table 32) a higher incidence of ASL in female rats compared with males after long-term inhalation. Similar results were presented by Feron et al. (1979a,b) on Wistar rats, Lee et al. (1978) on CD rats (Table 32) and Groth et al. (1981, Table 30) on Sprague-Dawley rats. In inhalation experiments with pregnant Sprague-Dawley rats, the investigators observed a higher incidence of ASL and hepatocellular carcinoma in the female progeny than in the males (Maltoni & Cotti, 1988; Table 32).

After long-term oral administration of VC (Table 29), incidences of ASL (BT11, Sprague-Dawley rats; Maltoni et al., 1981), neoplastic liver nodules and hepatocellular carcinoma (Wistar rats; Feron et al.,

1981 (not ASL) and Til et al., 1991) were higher in females than in males. Interestingly, preneoplastic alterations in the liver, like increased basophilic foci (Til et al., 1991; Table 29) or ATPase-deficient foci (Laib et al., 1985a; Table 30), were observed in female rats at lower doses than in males.

Although statistical analysis of sex differences was not performed, in rats there is a tendency towards a higher susceptibility to VC-induced ASL in female animals. Data on species other than rats are not sufficient for an assessment of sex differences (Table 30, 32).

7.7.5 *Carcinogenicity of metabolites*

CAA was reported to induce hepatocellular tumours in $B6C3F_1$ mice when administered orally in drinking-water (Daniel et al., 1992). CEO caused local tumours after repeated subcutaneous injection and skin tumours in mice in classical initiation-promotion experiments (CEO used as an initiator and 12-O-*n*-tetradecanoylphorbol-13-acetate as a promoter), whereas CAA did not under comparable conditions (Zajdela et al., 1980).

7.8 Genotoxicity

Genotoxicity studies on VC *in vitro* and *in vivo* in laboratory animals are given in sections 7.8.1 and 7.8.2, respectively. Genotoxicity studies on the metabolites of VC are described in section 7.8.3, and the mutagenic/promutagenic properties of DNA adducts formed by the reactive VC metabolites CEO and CAA are discussed in section 7.8.4. Data on gene mutation and cytogenetic damage in humans exposed to VC are given in section 8.4. A summary on the genotoxicity of VC *in vitro* and *in vivo*, including human data, is presented in Table 36.

7.8.1 In vitro *studies*

Relevant studies on the genotoxicity of VC *in vitro* are presented in Table 34. Genotoxic activity of VC has been detected in several *in vitro* test systems, predominantly after metabolic activation.

Table 34. Genotoxicity of vinyl chloride *in vitro*[a]

Test type	Test organism; species strain	Exposure conditions; comments	Results with MA	Results without MA	Reference
Ames test	Bact.; *Salmonella typhimurium* TA1535 TA1536 TA1537 TA1538	20% VC in atmosphere; up to 90 min	 + - - -	 - - - -	Rannug et al. (1974)
Ames test	Bact.; *S. typhimurium* TA1530 TA1535 TA1538 G-46	0.2, 2, 20% VC in atmosphere; 1.5–48 h; dose- and time-dependent effect	 + + - -	n.g.	Bartsch et al. (1975)
Ames test	Bact.; *S. typhimurium* TA98 TA100 TA1535 TA1538	20% VC in atmosphere; 3, 6, 9 h; time-dependent effect	 - + + -	 - + + -	McCann et al. (1975)
Ames test	Bact.; *S. typhimurium* TA1530	1) 2–20% VC in atmosphere; 16 h; dose-dependent effect	 +	 +	De Meester et al. (1980)

Table 34 (contd).

Assay	Test system	Conditions	−S9	+S9	Reference
Ames test	Bact.; *S. typhimurium* TA98	0.1–10% VC in atmosphere; 18 h; dose-dependent effect	−	−	Shimada et al. (1985)
	TA100		+	+	
	TA1535		+	+	
	TA1537		−	−	
	TA1538		−	−	
Ames test	Bact.; *S. typhimurium* TA100	VC in DMSO added to soft agar and bacteria	n.g.	−	Laumbach et al. (1977)
Ames test	Bact.; *S. typhimurium*	83 mM VC in liquid suspension; 30 min		n.g.	Bartsch et al. (1975)
	TA1530		−		
	TA1535		−		
	G-46		−		
Gene mutation assay	Bact.; *Escherichia coli* K12	10.6 mM VC in medium; 2 h	+	−	Greim et al. (1975)
Forward mutation assay	Yeast cells; *Schizosaccharomyces pombe* P1	16, 32, 48 mM VC in medium; 1 h; dose-dependent effect	+	−	Loprieno et al. (1977)
Forward mutation assay	Yeast cells; *S. pombe* SP.198	16 or 48 mM VC in medium; 5–240 min; time-dependent effect	+	−	Loprieno et al. (1976)

Table 34 (contd).

Test type	Test organism; species strain	Exposure conditions; comments	Results with MA	Results without MA	Reference
Reverse mutation assay	Yeast cells; *Saccharomyces cerevisiae* XV185-14C	incubated with 0.275 or 0.55% VC in DMSO; 4–48 h	n.g.	-	Shahin (1976)
Forward mutation assay	Fungi; *Neurospora crassa* Ema 5297	VC solution in ethanol for 3–4 h or 25, 50% VC in atmosphere for 3.5 or 24 h	-	-	Drozdowicz & Huang (1977)
Gene mutation/ deletion assay	Plant; *Tradescantia spec.* clone 4430	plant cutings exposed to VC in atmosphere; 6 h; positive at $ 195 mg/m^3	n.g.	+	Van't Hof & Schairer (1982)
Cell gene mutation assay	mammalian cells; Chinese hamster V79	5, 10, 20, 30% VC in atmosphere; 5 h; dose-dependent effect	+	-	Drevon & Kuroki (1979)
HGPRT gene mutation assay	human cells; B-lymphoblastoid line	25–400 : M VC in medium for 24 h; cells with metabolizing system	+	n.g.	Weisman (1992)
Gene con- version assay	yeast cells; *S. cerevisiae* D4	48 mM VC in incubation medium; 180–360 min	+	-	Loprieno et al. (1976)

Table 34 (contd).

Assay	Test system	Conditions	Result without MA	Result with MA	Reference
Gene con-version assay	yeast cells; *S. cerevisiae* D5	incubation in 0.275 or 0.55% VC in DMSO; 4–48 h	n.g.	-	Shahin (1976)
Gene con-version assay	yeast cells; *S. cerevisiae* D7RAD	2.5% VC in atmosphere for 1 h	+	-	Eckardt et al. (1981)
Cell transfor-mation assay	mammalian cells; BHK C1 13	10, 20, 30, 40, 50% VC in atmosphere; no data about exposure period	+	n.g.	Styles (1980)
Cell transfor-mation assay	mammalian cells; BALB/c-3T3 C1 1-13	18, 180, 1315, 2662 mg/m^3 VC in atmosphere; 24 h; dose-dependent effect	n.g.	+	Tu et al. (1985)
Rec-assay (DNA repair)	Bact.; *B. subtilis* 168M or MC-1	initial 22 mM; 24 h	n.g.	-	Elmore et al. (1976)
Unscheduled DNA synthesis	mammalian cells; rat hepatocytes	5.0, 7.5 or 10% VC in atmosphere; 18 h; dose-dependent effects	+	n.g.	Shimada et al. (1985)
SCE assay	human cells; stimulated lymphocytes	10, 25, 50, 75, 100% VC in atmosphere; 3 h; dose-dependent effect	+	-	Anderson et al. (1981)

[a]   Bact. = bacteria; DMSO = dimethylsulfoxide; MA = metabolic activation; n.g. = not given; SCE = sister-chromatid exchange; + = positive; - = negative

VC is mutagenic in the Ames test in the presence of metabolic activation in *Salmonella typhimurium* strains TA100, TA1530 and TA1535 but not in TA98, TA1537 and TA1538 (Rannug et al., 1974; Bartsch et al., 1975; McCann et al., 1975; De Meester et al., 1980; Shimada et al., 1985) indicating that the mutations are the result of base-pair substitutions (transversion and transition) rather than frameshift mutations. This is in agreement with the finding that etheno-DNA adducts formed by the reactive metabolites CEO and CAA (see section 6.5.1) are converted to actual mutations by base-pair substitutions (see section 7.11.2 and 8.4). Barbin et al. (1997) examined p53 mutations in VC-induced rat liver tumours and detected in 12 samples (11 ASL, 1 HCC) only one deletion but 12 base-pair substitutions (transversion and transition).

In some studies, VC has been shown to also exert mutagenic activity in *S. typhimurium* without addition of S9-mix (McCann et al., 1975; De Meester et al., 1980; Shimada et al., 1985), but the mutagenic effect was enhanced by addition of a metabolic activation system (De Meester et al., 1980; Shimada et al., 1985; Victorin & Ståhlberg, 1988). This increase was more pronounced when liver extracts were derived from animals pretreated with an enzyme inducer (Aroclor 1254) (De Meester et al., 1980). The reason for the mutagenic activity in the Ames test in the absence of S9-mix has been suggested to be a result of non-enzymic breakdown of VC or an internal bacterial metabolism (Bartsch et al., 1976; Shimada et al., 1985), but the origin of the direct mutagenic effect remains unclear.

Positive results in the Ames test were also observed with metabolic activation by extracts prepared from human liver biopsies (Bartsch et al., 1975). Mutagenicity of VC was dependent on concentration (Bartsch et al., 1975; De Meester et al., 1980; Shimada et al., 1985) and exposure duration (Bartsch et al., 1975; McCann et al., 1975). VC was mutagenic when plates were exposed to a VC atmosphere in a closed (Bartsch et al., 1975 and Table 34) or in a dynamic flow-through system (Victorin & Ståhlberg, 1988). No mutagenic effect was observed when VC was dissolved in aqueous solution with (Bartsch et al., 1975) or without (Rannug et al., 1974; Laumbach et al., 1977) metabolic activation, probably due to rapid loss of VC in aqueous solution by evaporation (Bartsch et al., 1975).

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Other gene mutation assays in bacteria (Greim et al., 1975), yeast cells (Loprieno et al., 1976, 1977) and mammalian cells (Drevon & Kuroki, 1979) revealed positive results exclusively in the presence of metabolic activation. Mutagenic effects were also reported in a human cell line containing cloned cytochrome P450IIE1, which is capable of metabolizing VC (Weisman, 1992). Gene mutation was also detected in plant cuttings (*Tradescantia*) exposed to VC (Van't Hof & Schairer, 1982). No mutagenicity was observed in *Neurospora crassa* with or without addition of exogenic activation system (Drozdowicz & Huang, 1977) but the validity of this study is limited by contradictory documentation.

In gene conversion assays, positive results were reported with *Saccharomyces cerevisiae* in the presence of a metabolic activation system (Loprieno et al., 1976; Eckardt et al., 1981). No mutagenic effects were observed without metabolic activation (Shahin, 1976).

VC exposure induced unscheduled DNA synthesis in rat hepatocytes (Shimada et al., 1985) and increased sister-chromatid exchange in human lymphocytes after addition of an exogenic activation system (Anderson et al., 1981). No growth inhibition was detected in DNA repair-deficient bacteria without metabolic activation (Elmore et al., 1976).

Cell transformation assays revealed positive results with (Styles, 1980) or without (Tu et al., 1985) metabolic activation.

7.8.2 In vivo *studies*

Key studies on the genotoxicity of VC *in vivo* are documented in Table 35. VC exposure induced gene mutation and mitotic recombination in *Drosophila melanogaster* but not gene mutation in mammalian germ cells. VC showed *in vivo* clastogenic effects, increased sister chromatid exchanges and induced DNA breaks. VC induced also gene conversion and forward mutations in host-mediated assays.

Mutagenic activity of VC was reported in the mitotic recombination assay (Vogel & Nivard, 1993) and the sex-linked recessive lethal (SLRL) assay (Magnusson & Ramel, 1976; Verburgt

Table 35. Genotoxicity of vinyl chloride *in vivo*[a]

Species/Strain/Sex	Test type	Test conditions; comments	Results	References
Gene mutation				
Mouse/CD-1/m	dominant lethal assay	20 mice/group exposed to 0, 7800, 26 000 or 78 000 mg/m^3 for 6 h/d for 5 d before 8 wk mating; survival 100, 90, 95 and 45%	-	Anderson et al. (1976, 1977)
Rat/CD/m	dominant lethal assay	12 mice/group exposed to 0, 130, 650, or 2600 mg/m^3 for 6 h/d, 5 d/wk; one mating during week 11 of exposure; no mortality	-	Short et al. (1977)
Mouse/CD-1/m	dominant lethal assay	a) 13 m exposed to 26 000 mg/m^3 for 4 h/d for 5 d (11 controls) before 7 wk mating; b) 20 m exposed 4 h/d, 5 d/wk to 13 000 mg/m^3 for 10 wk before 3 wk mating	-	Himeno et al. (1983)
Mouse/C57BL/f	mouse spot test	44 pregnant mice exposed to 12 000 mg/m^3 for 5 h on gestation day 10 (51 controls)	-	Peter & Ungváry (1980)
Mouse/Swiss/n.d.	host-mediated forward mutation assay	4–6 mice exposed orally to 700 mg/kg bw. in olive oil; yeast cells (S. pombe SP.198) inoculated in peritoneum for 3, 6 or 12 h	+	Loprieno et al. (1976)

Table 35 (contd).

D. melanogaster/ Berlin K/m	dominant lethal assay	m exposed to 0 or 78 000 mg/m^3 for 2 d; total number of eggs per group at least 6950; increase not significant; no differences in hatchability (> 80%)	-	Verburgt & Vogel (1977)
D. melanogaster/ Karsnäs/m	Drosophila SLRL test	a) m exposed to 0, 1, 10, 20% VC in air for 3 h (at least 491 chromo-somes tested); b) m exposed to 0, 1, or 10% VC for 3 h after pretreatment with 1% phenobarbiturate solution for 24 h; a) positive at $ 1% VC; no dose dependency; pretreatment in b) increased mutagenicity	+	Magnusson & Ramel (1978)
D. melanogaster/ Berlin K/m	Drosophila SLRL test	50 m/group exposed continuously a) to 0, 78, 520, 2210, 26 000, 78 000, 130 000 mg/m^3 for 2 d or b) to 0, 78, 2210 mg/m^3 for 17 d; a) positive at $ 2210 mg/m^3, no clear dose response; b) positive at $ 78 mg/m^3	+	Verburgt & Vogel (1977)
Mitotic recombination				
D. melanogaster/ LS/f + m	mitotic recombination assay	eye mosaic assay; 48- to 72-h-old larvae exposed to 5200 mg/m^3 for 17 h; light spots of at least 500 eyes scored in adult f (control 250 eyes scored); survival not reduced	+	Vogel & Nivard (1993)

Table 35 (contd).

Species/Strain/Sex	Test type	Test conditions; comments	Results	References
Chromosomal abnormalities				
Rat/Wistar/m	cytogenetic assay	24 m/group exposed to 3900 mg/m^3 for a) 5 d (6 h/d) or b) 3 mo (6 h/d, 5 d/wk); bone marrow sampled 24 h after exposure period; increased number of cells with any abnormality, significant in a)	+	Anderson & Richardson (1981)
Hamster/Chinese/ f+ m	cytogenetic assay	2 m + 2 f per group exposed to 2.5% for 6, 12, or 24 h; 5 m + 5 f exposed to 5% VC for 24 h; bone marrow samples prepared 26 h after start of exposure; control 7 m + 7 f; increased aberrations at $ 6 h (gaps excluded), effect dose related	+	Basler & Röhrborn (1980)
Mouse/CBA/m	micronucleus assay	3 m exposed to 0 or 5% VC for 4 h; bone marrow examined 30 h after exposure	+	Jenssen & Ramel (1980)
Mouse CFLP	micronucleus assay	0, 260, 860 or 2600 mg/m^3 for 2 × 4 h	+	Rodics et al. (1981)
Mouse/ C57Bl/6J/f + m	micronucleus assay	10 f and 10 m exposed to 0 or 130 000 mg/m^3 for 6 h; bone marrow examined 24 or 48 h after exposure	+	Richardson et al. (1983)

Table 35 (contd).

D. melanogaster/ Berlin K/m	sex chromosome loss	m exposed to 0 or 78 000 mg/m^3 for 2 d and chromosomes analysed in progeny (at least 6725 m + f per group)	-	Verburgt & Vogel (1977)
D. melanogaster/ ring-X/m	sex chromosome loss	m exposed to 0 or 126 000 mg/m^3 for 48 h; chromosome loss determined in F$_1$ (at least n = 428; 3 broods)	+	Ballering et al. (1996)
Other effects				
Rat/Wistar/m	host mediated gene conversion assay	20–30 rats exposed to 0 or 1% VC for 24 h, starting 1 h after yeast cell (*S. cerevisiae* D7RAD) injection (i.v.)	+	Eckardt et al. (1981)
Mouse/NMRI/f	alkaline elution assay in liver DNA	3–5 f per group; exposure to 1300 mg/m^3 for 39, 60, 117, 234 h (6 h/d, 5 d/ wk) and sacrificed a) 2 h or b) 18 h (exposed for 36, 114, 231 h) after exposure period; concurrent control sacrificed after 36 or 231 h; positive in a) at 39 h, in b) at 114 h	+	Walles & Holmberg (1984)
Hamster/Chinese f + m	SCE assay	2 m + 2 f per group exposed to 1.25 or 2.5% VC for 6, 12, or 24 h; bone marrow samples prepared 26 h after start of exposure; control 4 m + 4 f; dose- and time-dependent effect	+	Basler & Röhrborn (1980)

[a] d = day; f = females; m = males; mo = months; n.d. = no data; SCE = sister-chromatid exchange; SLRL = sex-linked recessive lethals; wk = weeks; + = positive; - = negative

& Vogel, 1977; Magnusson & Ramel, 1978) on *D. melanogaster*. The lowest effective concentration in the SLRL assay was 2210 mg/m^3 with a 2-day exposure period and 78 mg/m^3 after 17 days of exposure (Verburgt & Vogel, 1977). In the same study, negative results were observed at higher exposure concentrations with a 2-day exposure period in assays on *D. melanogaster* for dominant lethals, translocations (not tabulated) and sex chromosome loss. These results were discussed by the authors as a consequence of a saturation effect observed in the SLRL test (Verburgt & Vogel, 1977). However, sex chromosome loss was observed in studies by Ballering et al. (1996) in *D. melanogaster* exposed to higher concentrations.

No mutagenic activity was detected in the dominant lethal assay with mice (Anderson et al., 1976; Himeno et al., 1983) and rats (Short et al., 1977). No mutagenicity was reported in the mouse spot test (Peter & Ungváry, 1980). Chromosomal aberrations in rats (Anderson & Richardson, 1981) and hamsters (Basler & Röhrborn, 1980) were reported and mouse bone marrow micronucleus tests (Jenssen & Ramel, 1980; Richardson et al., 1983) gave positive results.

VC exposure (260, 650 and 1300 mg/m^3) induced single-strand breaks dose-dependently in the liver DNA of NMRI mice (Walles & Holmberg, 1984; Walles et al., 1988). Increased frequencies of sister-chromatid exchange and chromosome aberrations were observed in the bone marrow of Chinese hamsters after exposure to 1.25, 2.5 or 5% (v/v) for 24 h (Basler & Röhrborn, 1980).

7.8.3 Genotoxicity of VC metabolites

Metabolic activation of VC is necessary to form the genotoxic metabolites. The metabolites themselves are genotoxic in the absence of metabolic activation (see also section 6.3). The VC metabolites, chloroethylene oxide (chloro-oxirane), chloroacetaldehyde, and chloroacetic acid were investigated for genotoxicity. *In vitro* studies discussed in this section were performed without metabolic activation unless otherwise stated. Information on the mechanism of mutagenesis is presented in section 6.5 and 7.11.2.

Chloroethylene oxide (CEO) was found to be the most effective VC metabolite regarding forward mutation and gene conversion in

yeast (Loprieno et al., 1977), gene mutation in mammalian cells (Huberman et al., 1975) and reverse mutation in bacteria (Malaveille et al., 1975; Rannug et al., 1976; Hussain & Osterman-Golkar, 1976). The mutational specificity of CEO was investigated in *Escherichia coli*, using *trpA* mutant strains. In this system, CEO induced all types of base-pair substitutions (except one, which was not tested) (Barbin et al., 1985b). GC **6** AT transitions were the most frequent, followed by AT **6** TA transversions. This metabolite inhibited growth in DNA repair-deficient bacteria (Elmore et al., 1976; Laumbach et al., 1977).

CAA was 450 times less mutagenic than CEO in the Ames test but more active than the concurrent positive control ethylene oxide (Rannug et al., 1976). Positive results were reported with CAA in gene mutation assays in bacteria (Malaveille et al., 1975; Bartsch et al., 1975; McCann et al., 1975; Hussain & Osterman-Golkar, 1976; Elmore et al., 1976; Laumbach et al., 1977; Perrard, 1985), yeast cells (Loprieno et al., 1977), mammalian cells (Huberman et al., 1975), in a human lymphoblast cell line (Sanchez & Recio, 1991) and in human cells using shuttle vectors (Matsuda et al., 1995).

With chloroacetic acid no enhancement of the mutation frequency could be detected in bacteria (Bartsch et al., 1975; Malaveille et al., 1975; Rannug et al., 1976) or mammalian cells (Huberman et al., 1975).

Evidence for mutagenic activity of photoreaction products formed from VC was presented by Victorin & Ståhlberg (1991). Mixtures of VC (up to 260 mg/m^3) and nitrogen dioxide (but not VC alone) were mutagenic in *S. typhimurium* TA100 after 40 min UV irradiation of the gas mixture before exposure of bacteria.

CEO but not CAA showed a similar toxicity/mutagenic profile to VC in the *hprt* locus in a metabolically competent human B-lymphoblastoid cell line (Chiang et al., 1997; see also section 8.4.2).

7.8.4 *Other toxic effects of VC metabolites*

In the above studies on the genotoxic effects of CAA (see section 7.8.3), this compound appeared to be highly cytotoxic in various cellular systems. CAA has also a high acute toxicity in animals, with

a LD_{50} value of 0.15 mmol/kg body weight. Kandala et al. (1990) showed *in vitro* the concentration-dependant reversible inhibition of DNA synthesis by CAA in rat and mouse cells without a reduction in thymidine uptake or formation of nucleotides. In isolated rat hepatocytes, CAA stimulates lipid peroxidation (Sood & O'Brien, 1993).

7.8.5 Mutagenic and promutagenic properties of DNA adducts formed by VC metabolites

The major DNA adduct of VC, 7-($2N$-oxoethyl)guanine (7-OEG), lacks miscoding properties (Barbin et al., 1985a). In contrast, $1,N^6$-ethenoadenine (, A), $3,N^4$-ethenocytosine (, C) and $N^2,3$-ethenoguanine (, G) showed miscoding properties (Singer, 1996; see Table 37). The promutagenic properties of the etheno adducts involve mainly base-pair substitution mutations (Grollman & Shibutani, 1994). Site-specific mutagenesis studies in *E. coli* and in mammalian cell lines have shown that both , G and , C can induce G:C 6 A:T transitions; , C can also lead to C:G 6 A:T transversions (Cheng et al., 1991; Moriya et al., 1994). , A can induce misincorporation of G, C, or A during replication, thus inducing the base-pair substitutions A:T 6 C:G, A:T 6 G:C or A:T 6 TA (Basu et al., 1993; Pandya & Moriya, 1996).

7.8.6 Mutations in VC-induced tumours

Barbin et al. (1997) examined the presence of *p53* gene mutations (the function of the *p53* gene is described in section 8.4.2) in ASL and HCC tumours induced by VC in Sprague-Dawley rats. Mutations were found in 11/25 ASL and 1/8 HCC. A twelve-base deletion was found in one tumour; all others were base-pair substitutions. Nine of the point mutations were observed at A:T base pairs and of three G:C 6 A:T transitions (Table 43).

Mutations of the *p53* gene were also found in tumours from vinyl chloride-exposed autoclave workers with liver angiosarcoma (ASL) and hepatocellular carcinoma (HCC) (Hollstein et al., 1994; Boivin et al., 1997; see also section 8.4 and Table 43). To date (1998) 11 out of 15 (73%) ASL from VC-exposed workers have been shown immunohistochemically to have mutant p53 protein. Furthermore, a statistically significant trend for mutant p53 protein has been found in the serum of VC-exposed workers (Smith et al., 1998). In contrary

Table 36. Summary of genotoxic effects induced by exposure to vinyl chloride *in vitro* and *in vivo*[a]

In vitro											*In vivo*											
Bacteria		Yeast		Plants	Mammalian			Human			Insects			Mammalia					Humans[c]			
GM	DD	GM	GC	GM	GM	DD	CT	GM	SCE		GM	AN	MR	GM	CA	MN	DD	SCE	GM	CA	MN	SCE
+	-[b]	+	+	+	+	+	+	+	+		+	-	+	-	+	+	+	+	+	+	+	+

[a] AN = aneuploidy; CA = chromosomal aberration; CT = cell transformation; GM = gene mutation; GC = gene conversion; DD = DNA damage; MN = micronuclei; MR = mitotic recombination; SCE = sister-chromatid exchange

[b] Single study, only tested without metabolic activation

[c] These results are described in Table 42 (section 8.4.1)

Table 37. Evidence for base-pair substitutions caused by etheno-DNA adducts

Ethenobase	Base incorporated opposite adduct [a]	Base-pair substitution		System used for study	Reference
1,N^6-ethenoadenine (ε A)	C	AT → GC transition	*in vivo*	bacteriophage M13-Nhei in *E. coli*	Basu et al. (1993)
	A	AT → TA	*in vivo*	single-strand vector shuttle in *E. coli* or simian kidney (COS) cells;	Pandya & Moriya (1996)
	C	AT → CG transversions			
3,N^4-ethenocytosine (ε C)	A	CG → TA transition	*in vivo*	single-strand vector shuttle in *E. coli* or simian kidney (COS) cells;	Moriya et al. (1994)
	T	CG → AT transversion	*in vitro*	*E. coli* DNA polymerase I system	Zhang et al. (1995)
			in vivo	M13AB28 in SOS-(UV)-induced *E. coli*	Jacobsen & Humayun (1990)
			in vivo	M13 *glyU* phage transfection of *E. coli* tester strain	Borys et al. (1994)
			in vitro	*E. coli* DNA polymerase I system	Simha et al. (1991); Palejwala et al. (1991)

Table 37 (contd).

Ethenobase	Base incorporated opposite adduct [a]	Base-pair substitution		System used for study	Reference
N^2,3-ethenoguanine (, G)	T	GC 6 AT transition	*in vivo*	*E. coli* DNA synthesis by M13G*1 assay	Cheng et al. (1991)
			in vitro	*E. coli* DNA polymerase I (Klenow fragment); exonuclease-free Klenow; *Drosophila melanogaster* polymerase '' -primer compex; human immunodeficient virus-I reverse transcriptase (HIV-RT)	Singer et al. (1991)
			in vitro	*E. coli* DNA-dependent RNA polymerase	Mroczkowska & Kusmierek (1991)
1,N^2-ethenoguanine	A G	GC 6 TA GC 6 CG transversions	*in vitro*	*E. coli* DNA polymerase I (exonuclease-free Klenow)	Langouet et al. (1997)

[a]   A = adenine;   C = cytosine;   G = guanine;   T = thymine

to studies in humans, no mutations were found in codons 12, 13 and 61 of the Ki-*ras* gene in rat liver tumours induced by VC, but mutations were found involving codon 61 of the Ha-*ras* proto-oncogene (Froment et al., 1994; Boivin-Angèle et al., in press) (see Table 44 and section 8.4.2).

Connexin genes have been shown to restore normal cell growth when transfected into certain tumorigenic cells and thus are considered to form a family of tumour suppressor genes. Mutations of the *connexin 37 (Cx37)* gene in rat liver tumours (22 hepaticangiosarcomas and 3 hepatocellular carcinomas) induced by VC were analysed by PCR-single-strand conformation polymorphism analysis and DNA sequencing. The results suggested that *Cx37*-mediated gap junctional intercellular communication may be disturbed in most of these angiosarcomas but mutation of the *Cx37* gene is rare (Saito et al., 1997).

7.9 Factors modifying toxicity

Concurrent administration of ethanol (5% in drinking-water until termination at month 30) and VC (1560 mg/m^3, inhalation 4 h/day, 5 days/week for 1 year) to male Sprague-Dawley rats (80 rats per group for histopathological evaluation) resulted in increased incidences of ASL from 23% after exposure to VC alone to 50% in rats exposed to VC and ethanol versus 0% in ethanol-treated rats and 0% in concurrent controls. Ethanol had an additive effect on the incidence of hepatocellular carcinoma (VC 43%, VC-ethanol 60%, ethanol 10%, control 1.3%) and lymphosarcoma (VC 7.5%, VC-ethanol 14%, ethanol 5%, control 2.5%) (Radike et al., 1981). This effect may be due to the interaction of ethanol with VC metabolism.

Induction of certain enzymes of the mixed-function oxidase system by pretreatment with phenobarbital (Jaeger et al., 1974, 1977; Reynolds et al., 1975a,b,c) or the mixture of polychlorinated biphenyls (Arochlor 1254) (Reynolds et al., 1975a,b; Conolly et al., 1978) enhanced acute hepatotoxicity in rats as measured by increased activity of hepatic enzymes and/or focal hepatic necrosis. Administration of SKF-525A, an inhibitor of the mixed-function oxidase system, 30 min prior to VC exposure in phenobarbital-pretreated rats, inhibited the enhancing effect of phenobarbital on VC hepatotoxicity (Jaeger et al., 1977). Application of cysteine, a rate-

limiting precursor in hepatic glutathione (detoxification of reactive chemicals), via drinking-water prior to VC exposure protected Arochlor 1254-pretreated rats against acute VC hepatotoxicity (Conolly & Jaeger, 1979).

7.10 Mechanisms of toxicity - mode of action

7.10.1 *Mechanisms of VC disease*

Based on evidence of immunological abnormalities, such as hyperimmunoglobinaemia and circulating immune complexes in workers with "vinyl chloride disease" (section 8.3), Ward et al. (1976) have proposed a possible mechanism for the vascular changes associated with this disease. Reactive VC metabolite(s) bind(s) to a protein, resulting in a structurally abnormal protein. This protein would react as an antigen and initiate an immune response with B-cell proliferation and hyperimmunoglobinaemia. Circulating immune complexes formed by interaction of this antigen and antibodies would precipitate in the extremities of exposed humans in response to the cold and activate the complement sequence. The cryoprecipitates and reactions secondary to the complement activation are proposed to produce vascular occlusion and fibrinogen/fibrin conversion. The mechanism is supported by findings of IgG deposition with associated complement C3 and fibrin in histological lesions (Grainger et al., 1980). The resulting vascular insufficiency would explain the observed clinical, radiological and histological findings in skin, skeletal and soft tissues, and lungs (section 8.3) in workers occupationally exposed to high concentrations of VC (Ward et al., 1976). No further studies were identified that would directly confirm this mechanism, and the degree to which it has been accepted is not clear. The available evidence does not seem sufficient to suggest an autoimmune disease as a pathogenetic mechanism. Further studies will be needed to establish the true significance of the possibly transient immunological abnormalities in VC-induced disorders.

7.10.2 *Mechanism of carcinogenesis*

There is a large body of data showing that VC acts as a genotoxic carcinogen. After metabolic activation to CEO by CYP2E1, VC exerts various genotoxic effects (including gene mutations and

chromosomal aberrations) in different organisms, including bacteria, yeasts, mammalian cells in culture, Drosophila, rodents and humans (Table 36). Among the mutagenic events induced by VC, base-pair substitutions appear, so far, to be the most frequent. VC in the presence of an activation system has a transforming activity on mammalian (rodent) cells in culture (see Table 34).

Studies *in vitro* have demonstrated that metabolically activated VC and its electrophilic metabolites CEO and CAA can alkylate nucleic acid bases. 7-OEG, the major DNA adduct formed by VC and CEO does not exhibit promutagenic properties. In contrast, four minor adducts, , A, , C, N^2,3-, G and 1,N^2-, G, show promutagenic properties, inducing mainly base-pair substitution mutations and a low level of frameshift mutations.

7-OEG and three etheno adducts (, A, , C, N^2,3-, G) have been detected in DNA from rats and mice exposed to VC. Highly variable background levels of , A and , C were found in all the tissues examined. Following exposure of rats to VC, significantly elevated levels of , A and , C were measured in most tissues, except the brain; there was also no significant increase of , A levels in the kidney and spleen.

The liver is one of the primary targets for VC-induced carcinogenesis in rats and humans. It is also, by far, the major tissue involved in VC activation in rats. Following exposure of rats to VC, the distribution of etheno adduct levels (induced by the exposure) is rather homogeneous within the organism. , C was shown to accumulate as a function of length of exposure in at least three organs (liver, kidney and lung). In contrast, , A accumulated in the liver but not in the kidney and lung. In addition, adduct levels (, A, , C) did not decrease in the liver, for at least two months following the end of exposure. Etheno adducts are formed as endogenous background levels in various tissues in humans; no data are available on etheno adduct levels in humans exposed to VC.

Mutations have been found in liver tumours associated with exposure to VC. In human ASL, the Ki-ras gene is activated through a GC 6 AT mutation at base 2 of codon 13. Mutations, all AT 6 TA transversions, have been described in the *p53* gene in three human

ASL. The Ki-ras gene activation is not found in rat ASL. However, 44% of rat ASL were found to contain a mutated *p53* gene: most mutations were base-pair substitutions, involving mainly A:T base pairs. The data suggest the existence of hot spots for mutations in the *p53* gene, and one mutation found in two rat ASL was equivalent to the same mutation characterized in one human ASL associated with VC exposure. The Ha-ras gene is activated in rat HCC induced by VC, through an AT 6 TA transversion in codon 61.

The mutation spectra observed in liver tumours (ASL and/or HCC) associated with VC exposure in humans and rats are clearly distinct from those observed in sporadic liver tumours or in hepatic tumours associated with other exposures. In rats, the substitution mutations found at A:T base pairs in the *ras* and *p53* genes are consistent with the promutagenic properties of ₂A and with the accumulation and persistence of this lesion in hepatic DNA.

Altogether, available data suggest that etheno adducts could be involved in the initiation of hepatocarcinogenesis by VC. However, they cannot explain the observed tissue- and cell-specificity.

More studies on the formation and repair of etheno adducts at the cellular level (cell specificity), as well as at the molecular (gene and DNA sequence) level, are warranted. Carcinogenesis is a multi-step process and, obviously, there is a need for quantitative evaluation of other critical biological end-points, such as effects of VC on apoptosis, cell proliferation or intercellular communication *in vivo*.

8. EFFECTS ON HUMANS

Only reports on effects for humans of exposure to VC have been considered here and not reports where exposure has been to a number of chemicals, e.g., at landfills, in factories manufacturing a number of chemicals or in the PVC processing industry.

8.1 General population exposure

After an accident in Schönebeck, Germany in June 1996, involving the derailment of a train carrying VC and subsequent fire, 325 persons were documented as having acute symptoms but these correlated with exposure to the pyrolytic products (e.g., HCl) and not to VC itself. But a study on 29 persons exposed as a result of this accident showed a significant increase in chromosomal aberrations compared to an unexposed control group (Hüttner & Nikolova, 1998; see also Table 42 and section 3.2.3).

A case has been reported of epithelioid haemangioendothelioma involving liver, bone and lungs in a man living for over 8 years several hundred metres from a toxic waste dump next to a chemical plant producing VC (Shin et al., 1991).

There have been several reports on the possible increased prevalence of congenital malformations in populations exposed to emissions from polymerization facilities (Edmonds et al., 1975, 1978; Infante, 1976; Thériault et al., 1983; Rosenman et al., 1989) but none of these studies showed a statistically significant correlation between developmental toxicity and proximity to the facility (Clemmesen, 1982; Hemminki & Vineis, 1985). A number of studies (e.g., Goldberg et al., 1995; Dolk et al., 1998) examined risk for cancer and for adverse reproductive outcome in relation to proximity to landfills. Although VC is one of the potential emissions from the landfills, these studies do not directly address the population exposure to VC and were not further considered.

In England and Wales, from 1975–1987 data, there were no confirmed non-occupationally exposed cases of ASL (Elliott & Kleinschmidt, 1997). In the USA, five non-occupational cases were reported living within 1.6 km of a VC plant (Brady et al., 1977).

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8.2 Controlled human studies

Three men and three women were exposed twice daily with a 6-h interval for three successive days to 0, 0.4, 0.8, 1.2, 1.6 or 2.0% VC. The NOEL was between 0.8 and 1.2%. Above this, dizziness, nausea, dulling of vision and auditory cues were reported (Lester et al., 1963).

Thirteen male volunteers were exposed to 130, 650 and 1300 mg/m^3 for 7.5 h and subjective and neurological responses were measured before the subject entered the chamber, 15 min after entrance and at 1-h intervals thereafter; 24-h post-exposure urine and blood samples were taken and tested. No significant adverse effects were noted with the exception of some dryness of eyes and nose at 1300 mg/m^3. The exposure had no noticeable effect on neurological responses nor did it produce significant changes in the results of mental, coordination or manual dexterity tests conducted during the exposure period. All clinical laboratory studies performed in the post-exposure period were normal and not significantly different from pre-exposure values (Baretta et al., 1969).

8.3 Occupational exposure

8.3.1 Overview

VC was first produced commercially in the late 1920s. Various effects caused by exposure to VC were reported: cardiac arrhythmia in experimental animals (Oster et al., 1947); hepatic abnormalities in VC workers (Tribukh et al., 1949; Filatova et al., 1958), acroosteolysis, Raynaud-type-phenomenon and sclerodermoid skin lesions (Lelbach & Marsteller, 1981). But it was not until it was found that VC could cause cancer in animals (Viola et al., 1971; Maltoni et al., 1974) and humans (Creech & Johnson, 1974) that levels of VC in the workplace were drastically reduced. Some VC workers, in particular autoclave cleaners, were estimated to have been exposed to as much as 2600 mg/m^3 (1000 ppm) in the 1950s or earlier, reducing to a tenth of this level by the mid-1970s (Table 20). After 1975 levels were usually 2.6–13 mg/m^3 (1–5 ppm) in many countries, but in some countries where production plants were not modernized, workers were or are exposed to high levels of VC (Fucic et al., 1990a; Gáliková et al., 1994; Hozo et al., 1996, 1997; see also Table 21).

It should be noted that the non-neoplastic and neoplastic effects described in the following sections are due in most cases to the high exposure of workers to VC before 1974. No cases of ASL (section 8.3.1) have been reported to the International Register of Cases among (West) European workers first exposed after 1972 (Storm & Rozman, 1997). This is not the case for Eastern European countries where the old regulation of 194 mg/m^3 (75 ppm) in the working environment was valid until recently (Hozo et al., 1997).

8.3.2 Non-neoplastic effects

8.3.2.1 Acute toxicity

In acute VC intoxication, the symptoms described include vertigo, nausea and headache. At higher concentrations, VC exerts narcotic effects and at one time was considered as a possible anaesthetic (Patty et al., 1930; Peoples & Leake, 1933; Oster et al., 1947).

VC caused almost immediate death of VC polymerization workers in two incidents of accidental poisoning. No values were given but the strong smell and the narcotic effects of VC were reported (Danziger, 1960).

Concentrations of VC of the order of 26 000 mg/m^3 (1%) in the air induce unconsciousness and cardiac arrhythmia. Exposure of two workers to 2.5% VC for 3 min caused dizziness, disorientation and a burning sensation in the soles of the feet. There was complete recovery except for a slight headache lasting 30 min (Danziger, 1960).

A man whose hands were accidentally sprayed with VC developed erythema and some second-degree burns which healed without complication (Harris, 1953). A patient complaining of eye burns from VC recovered 48 h after the eye was rinsed for 15 min with saline (McLaughlin, 1946).

8.3.2.2 Effects of short- and long-term exposure

Concentrations of VC in the region of 2590 mg/m^3 (1000 ppm), which were not unusual prior to 1974, over periods ranging from 1 month to several years, have been reported to cause a specific pathological syndrome found in VC workers called the "vinyl chloride

illness". Symptoms described were earache and headache, dizziness, unclear vision, fatigue and lack of appetite, nausea, sleeplessness, breathlessness, stomachache, pain in the liver/spleen area, pain and tingling sensation in the arms/legs, cold sensation at the extremities, loss of libido and weight loss (Thiess & Versen, 1974). Clinical findings included scleroderma-like changes in the fingers with subsequent bony changes in the tips of the fingers described as acroosteolysis, peripheral circulatory changes similar to Raynaud's disease, and enlargement of the liver and spleen with a specific histological appearance, and respiratory manifestations (Lange et al., 1974; Suciu et al., 1975; Veltmann et al., 1975; Lelbach & Marsteller, 1981).

8.3.2.3 *Organ effects*

a) *Skin and skeletal tissues*

Occupational acroosteolysis has largely affected the most highly exposed workers involved in scraping the insides of autoclaves in the PVC production process (Harris & Adams, 1967; section 3). It is a rare bone disease resulting in de-calcification of the terminal phalanges of the hands and other extremities (Cordier et al., 1966; Wilson et al., 1967; Markowitz et al., 1972). In these cases, acroosteolysis was often preceded by soreness and tenderness, numbness, pallor and cyanosis of the extremities especially the hands, a Raynaud-type phenomenon caused by reversible constriction of the arterioles. Sclerodermoid-like changes appear in the skin of the hands and forearms and osteolytic and sclerotic lesions of the bones, particularly the extremities and sacroiliac joints (Lange et al., 1974). Most of the abnormalities disappeared and bones showed signs of healing a year or two after the men had stopped work (Harris & Adams, 1967). A chronothermodynamic study of Raynaud's phenomenon secondary to past exposure to VC showed that, although reduced, the symptoms were still present after 8 years (Fontana et al., 1996).

A review of five studies from four countries involving 725 workers at risk from VC exposure showed that 3% developed acroosteolysis; 10% Raynaud-type phenomenon and 6% sclerodermoid skin lesions (Lelbach & Marsteller, 1981). Genetic susceptibility has been suggested as a possible reason that not all

workers who had been in contact with VC developed symptoms (Black et al., 1983, 1986). The scleroderma-like syndrome induced by VC exposure appears to be different from that of other (systemic) scleroderma (Ostlere et al., 1992). It has a shorter incubation period (1 month to 3 years compared to 4 to 44 years) (Ishikawa et al., 1995) and there are immunological differences (section 8.3.2.3f).

b) *Hepatic effects*

Exposure to VC is associated with hepatomegaly and/or splenomegaly and with various histological lesions in the liver (Lange et al., 1974; Ho et al., 1991). In one carefully described study, advanced portal hypertension with histological findings of non-cirrhotic fibrosis was diagnosed in 17 of 180 VC polymerization workers (Lelbach & Marsteller, 1981).

Focal hepatocellular hyperplasia and focal mixed hyperplasia (hyperplasia of sinusoidal cells along with hyperplasia of hepatocytes) are early histological alterations indicative of VC exposure (Tamburro et al., 1984). The precursor stage of ASL is characterized by subcapsular fibrosis, progressive portal fibrosis and a borderline increase of intralobular connective tissue, all associated with focal stimulation and proliferation of sinusoidal lining cells and hepatocytes. Transition to angiosarcoma is preceded by focal dilatation of sinusoids with enlarged dedifferentiated lining cells often containing peg-like hyperchromatic polymorphic nuclei (Popper & Thomas, 1975; Gedigk et al., 1975).

There is a great similarity between the histological sequences in the liver of rodents exposed by inhalation to VC (chapter 7; Spit et al., 1981) and the lesions observed in VC-exposed workers (Popper et al., 1981).

Twenty of the 39 "liver disease deaths" reported in an Italian study of highly exposed PVC workers were due to liver cirrhosis, the remainder being due to miscellaneous liver disorders. A statistical evaluation was not possible (Pirastu et al., 1990). In another study, two of 21 heavily exposed VC workers died from sequelae to noncirrhotic portal fibrosis and portal hypertension (Lelbach, 1996). In the USA and European cohort studies of VC-exposed workers

(study descriptions are given in section 8.3.3), deaths from chronic non-malignant diseases of the liver had a low SMRs of 62 and 88; in the European study this was significantly less than expected (Wong et al., 1991; Simonato et al., 1991).

c)   *Cardiovascular effects*

Some old studies reported statistically non-significant increased mortality due to cardiovascular diseases among workers exposed to VC (Ebihara, 1982; Greiser et al., 1982).

Laplanche et al. (1992) report an elevated incidence of circulatory system diseases other than Raynaud's disease (RR 1.4, 95% CI 1.0–1.8) in a 7-year follow-up of a cohort of 1100 VC workers. The increased risk was mainly due to hypertension and "other circulatory disorders". Likewise, another study with a 5-year follow-up on the incidence of arterial hypertension (AH) and coronary heart disease (CHD) in 105 VC and PVC workers exposed to VC at between 4 and 1036 mg/m^3 showed that exposed workers had significantly higher blood pressure than controls. The estimated relative risk (RR) for AH in exposed workers was twice as high as in the controls, while there was no significant difference regarding CHD. There was an exposure-response relationship between the intensity of exposure and the incidence of AH (Kotseva, 1996).

In contrast, both the large cohort studies reported a statistically significant deficit in the mortality from cardiovascular diseases, with SMRs of 87 and 81. In the USA study, the mortality was even lower for the subcategory of arteriosclerotic heart disease (SMR 74.5, 95% CI 81.6–89.2 (Simonato et al., 1991; Wong et al., 1991). In the Canadian study (Thériault & Allard, 1981), there was a statistically non-significant 20% deficit in cardiovascular mortality, based on 25 exposed cases.

d)   *Respiratory effects*

Adverse respiratory effects reported in older case studies included increased incidence of emphysema (Suciu et al., 1975), decreased respiratory volume and vital capacity, respiratory insufficiency (Suciu et al., 1975), decreased respiratory oxygen and carbon dioxide transfer

(Lloyd et al., 1984), pulmonary fibrosis of the linear type (Suciu et al., 1975), abnormal chest X-rays (Lilis et al., 1975) and dyspnoea (Walker, 1976). This is probably due in part to confounding by smoking and presence of PVC-resin dust, which is known to cause respiratory lesions (Mastrangelo et al., 1979; Lilis, 1981).

Both large cohorts (Wong et al., 1991; Simonato et al., 1991) found a deficit in the mortality from non-malignant respiratory diseases (SMR 81.6, and 77, respectively). Despite overall deficit in mortality from respiratory diseases, Wong et al. (1991) found an excess of emphysema/chronic obstructive pulmonary disease (COPD) mortality, which, however, was highest among workers with a duration of exposure less than 10 years.

e) *Neurotoxicity*

In patients with chronic occupational exposure, neurological disturbances include sensory-motor polyneuropathy (Perticoni et al., 1986; Podoll et al., 1990), trigeminal sensory neuropathy, slight pyramidal signs and cerebellar and extrapyramidal motor disorders (Langauer-Lewowicka et al., 1983). Psychiatric disturbances included neurasthenic or depressive syndromes (Penin et al., 1975). Sleeplessness (Gnesina et al., 1978; Gnesina & Pshenitsina, 1980; Langauer-Lewowicka et al., 1983; Gnesina & Teklina, 1984) and loss of sexual functions (see below) were frequently encountered. Pathological EEG alterations were found in a high proportion of patients (Penin et al., 1975; Stýblová et al., 1981).

f) *Immunotoxicity*

The major immunological abnormalities reported in VC disease patients include hyperimmunoglobulinaemia with a polyclonal increase in IgG, cryoglobulinaemia, cryofibrinogenaemia, and *in vivo* activation of complement (Ward et al., 1976). Immunofluorescent examinations of skin and lung biopsies have demonstrated the deposition of IgG with associated complements C3 and fibrin in relation to the histological lesions described in small blood vessels (Grainger et al., 1980). A statistically significant increase in circulating immune complexes was observed in workers exposed to VC, compared to unexposed workers (Ward et al, 1976) . The increase in circulating immune complexes was greatest in women and

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in those with duties involving exposure to relatively higher levels of VC (Bogdanikowa & Zawilska, 1984).

Bencko et al. (1988) found significantly elevated IgA, IgG and IgM levels in the serum of workers exposed to low levels of VC (< 10 mg/m^3), but found that in workers with excessive exposures to VC (> 10 mg/m^3) there was a significant drop in IgG level.

The antinuclear antibody (ANA) test is negative or at low titre in VC disease (Ward et al., 1976), whereas it is often positive in other scleroderma-like disorders.

There is much heterogeneity within VC disease, in terms of skin involvement, severity, and organ involvement, and it is clear that this could have an immunological background. Systemic sclerosis may be a genetically linked autoimmune disease. Many autoimmune diseases show statistically significant associations with certain human-leukocyte-associated antigen (HLA) alleles. Black et al. (1983, 1986) compared the HLA frequencies and autoantibodies in workers with VC disease (n=44), asymptomatic workers (n=30), systemic sclerosis (n=50) and normal (blood donor) controls (n=200). The HLA-DR5 allele occurred significantly more frequently in VC disease (36%) and systemic sclerosis (30%) compared to asymptomatic workers (3%) and normal controls (16%). Eleven out of 21 men with severe VC disease had HLA markers B8, DR3 whereas none of the 23 workers with mild disease were positive for these markers, suggesting that this haplotype favours progression of the disease.

Splenomegaly has been detected in a number of VC-exposed workers (Falk et al, 1974; Suciu et al., 1975; Veltmann et al., 1975; Makk et al., 1976; Ho et al., 1991). Hyperplastic sinusoidal cells were found in some specimens.

g) *Reproductive toxicity*

The reproductive effects of VC have been reviewed (Uzych, 1988; Little, 1993; Olsen et al., 1995).

VC has been cited in several early case series from different countries as being responsible for male sexual dysfunctions such as

potency troubles, "pathological changes in the ejaculates", decreased androgen secretion or undefined sexual disorders (Suciu et al., 1975; Veltman et al., 1975; Walker, 1976; Sanotsky et al., 1980; Makarov, 1984) in exposed workers, but there is a lack of controlled studies. Similarly, various female sexual dysfunctions have been reported after long term exposure to VC (Makarov et al., 1984).

The possible risk, arising from human male exposure to VC, for pregnancy and fetal loss among the wives of workers was first raised after a report by Infante et al. (1976a,b) suggesting that fetal loss was significantly more among wives of exposed workers. Data for the wives of 95 VC polymerization workers in the USA were contrasted with data for the partners of PVC fabrication workers and rubber workers (total 158). Prior to exposure, the fetal death rates for controls and polymerization workers were 6.9 and 3.1% (age adjusted, respectively). After exposure, the rates were 6.8 and 10.8%, respectively. Weaknesses in the study were in the method of age adjustment, that information was obtained from interviews with male workers only (and not their wives), and that there were no data on maternal age or on smoking and other abuses.

In a study on 534 VC production and polymerization workers whose wives were under 45 on 1 January 1984, 82 men were exposed to VC before their spouses' pregnancies. The crude rate of abortions (no. of spontaneous abortions / no. of pregnancies) was 8.9 for exposed and 8.8 for unexposed (total number of pregnancies: 90 and 1027, respectively). Adjustment for confounders did not suggest a significant relationship between spontaneous abortion and paternal exposure to VC (Mur et al., 1992).

No statistically significant correlation could be found between exposure to VC and congenital central nervous system (CNS) defects among the children of fathers working at VC polymerization facilities in Kanawha County, USA (Edmonds et al., 1975, 1978), but the study data were not sufficient for a clear evaluation (Uzych, 1988).

In a Chinese study of 236 female workers exposed for more than 1 year to VC and 239 controls using retrospective (levels 3.9 to 89.3 ppm) and prospective (0.2 to 130.7 ppm) epidemiology, VC did not appear to influence involuntary infertility, pregnancy outcome or

course of parturition, although the incidence of toxaemia in pregnancy was found to be higher among female workers exposed to higher concentrations in the prospective study (Bao et al., 1988; Jiangl, 1990).

An investigation into reproductive function in 2736 workers exposed to VC in 13 PVC factories and 3442 workers in other factories not exposed to VC showed no significant differences in reproductive outcome. However, in the female exposed group, the incidence of pregnancy complication was significantly higher than that of the control group, suggesting that VC may effect the pregnancy process in female workers (Huang, 1994).

There have been studies on female workers in the PVC processing industry (Lindbohm et al., 1985; Ahlborg et al., 1987), but, as VC was not the only source of exposure, these studies were not considered here.

8.3.3 Neoplastic effects

After the case series published in 1974 (Creech & Johnson, 1974) on hepatic angiosarcoma among workers exposed to vinyl chloride, several further case series and small epidemiological studies, mainly with emphasis on hepatic tumours, were published in the 1970s and 1980s. They show that VC can cause the rare liver tumour (ASL). Other (non-ASL) cancer sites/types reported for which some of these studies have indicated an association with VC exposure are: liver (e.g., non-angiosarcoma) tumours, particularly hepatocellular carcinoma; respiratory system; digestive system other than the liver; lymph and haematopoietic tissue; brain and other central nervous system; malignant melanoma.

The early studies, together with a prepublication report of the USA cohort study (see below) were summarized by Sir Richard Doll (Doll, 1988). More recently, the studies performed in Sweden, Italy, the United Kingdom and Norway were updated and analysed together (L'Abbé et al., 1989; Simonato et al., 1991). Parts of the European study have also been published separately. An updated American study (Wong et al., 1991) combined many smaller studies conducted earlier in the USA. These two studies provide the most informative data on the health effects associated with exposure to VC. Four

smaller prospective studies on VC exposure workers have been conducted in Canada (Thériault & Allard, 1981), Germany (Weber et al., 1981; Greiser et al., 1982), France (Laplanche, 1987, 1992) and the former-USSR (Smulevich et al., 1988). The complete description of two additional studies (Frentzel-Beyme et al., 1978; Huang, 1993a,b) was not available to the Task Group and were not further considered.

The epidemiological studies on VC/PVC workers are described as follows:

C Simonato et al. (1991) (European/IARC study), which incorporates populations reported by: Byrén et al. (1976), Molina et al. (1981), Hagmar et al. (1990) (Sweden); Fox & Collier (1977), Jones et al. (1988) (United Kingdom); Heldaas et al. (1984, 1987) (Norway); Belli et al. (1987), Pirastu et al. (1990, 1991, 1998) (Italy);

C Wong et al. (1991) (USA study)[a], which incorporates populations reported by Tabershaw & Gaffey (1974), Monson et al. (1975); Nicholson et al. (1975), Ott et al. (1975), Waxweiler et al. (1976), Buffler et al. (1979), Cooper (1981), Dahar et al. (1988), Wu et al. (1989);

C Thériault & Allard (1981) Canada;

C Weber et al. (1981), Greiser et al. (1982) Germany;

C Laplanche et al. (1987, 1992) France;

C Smulevich et al. (1988) former-USSR

The USA study consisted of 10 173 men who had worked for at least one year in jobs involving exposure to VC prior to January 1973 in 37 plants in the USA. Observation covered the years 1942–1982, and the observed mortality was compared with the expected rates, based on USA national rates for white males, standardized for age, and calendar time. The race was actually known for only 666 workers, among which 3% were African. Altogether 1536 members of the

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[a] After the Task Group meeting, a report of an update of the USA study became available. A summary of it is presented in Appendix 3.

cohort were identified as having died, the vital status of 725 individuals (7.88%) remained unknown, and death certificates were not obtained for 97 (6.3%). These deaths were included in the calculation of the overall SMR, but not in any cause-specific SMRs (which leads to an underestimation of all disease-specific SMRs by 6.3%).The deaths were coded using the 7th ICD revision, where the numbers 155 and 156 comprise liver (155, both primary and secondary) and bile duct and gall bladder tumours (156). The average length of employment was approximately 16 years, and 46% of the cohort were employed before 1955, thus providing a possible latency of more than 27 years for this group. The levels of exposure were not known. The all-causes SMR was 90.1 (95% CI 85.6–94.7), based on a total of 1536 deaths. The SMR for all cancers was 105.1 (94.4–116.5).

The European/IARC study comprised a total of 14 351 subjects from 19 factories. After exclusion of short-term employees (< 1 year), females, deaths outside the observation period, members of more than one cohort, 12 706 subjects remained for the analysis. The follow-up was 97.7% complete, the average length of follow up 17 years, and the total number of person-years 222 746. National rates of mortality, specific for age and five-year calendar periods, were used for the comparison. The observation period was different for different factories, starting for most from 1955, and extended until 1986. Calendar period-specific job exposure matrices (JEMs) were developed for 13 of the 19 factories. These JEMs were developed using job title as a basic unit in which exposure is assessed. Estimates of exposure were assigned, *a priori*, by a group of industrial hygienists on the basis of the historical information available from the companies.

These estimates have been used both for qualitative and quantitative dose-response analysis. In particular, a cumulative dose was computed for each subject by multiplying the number of years spent in a specific job by the time-specific estimates in ppm and then summing up all the periods.

The 7th (for liver tumours, codes 155–156), 8th and 9th revisions (155) of ICD were used (thus combining primary and secondary tumours of the liver and tumours of extrahepatic bile ducts). A statistically significant deficit in over-all mortality was observed (SMR 88, 95% CI 83–93), while for all malignant neoplasms, the SMR was 104 (CI 95–114), with 445 cancer deaths observed.

The Canadian study (Thériault & Allard, 1981) studied the mortality of 1659 workers in a chemical industry complex in Schwanigan who had worked for no less than 5 years in the company between 1943 and 1972. Out of the total, 48 (2.9%) could not be traced. The observation period was 20 years or more for 315 workers (70%), and the duration of exposure no less than 10 years for 340 (75%). Since several episodes of unconsciousness among workers were reported, the exposure to VC had probably been high: no measurement data were available. The causes of death during 1948–1972 of the cohort was determined from death certificates. In the analysis, those exposed to VC for more than 5 years (451) were compared with those exposed for less than 6 months (870). In addition, the mortality of the exposed subcohort was compared to the age-standardized mortality expected for Quebec in the year 1971. For cancer cases, medical records were consulted for the verification of the diagnosis. The overall mortality was similar in the exposed and non-exposed cohorts, and gave an SMR of 0.83 for the VC-exposed cohort in comparison to the Quebec figures.

Smulevich et al. (1988) reported results from a retrospective cohort study of workers employed in some of the oldest Soviet chemical plants producing VC and PVC. The study comprised 2195 men and 1037 women employed for at least one month in the plants. Subjects were followed from 1939 to 1977. Information on specific occupation within the plant, duration of exposure, date and cause of death, and postmortem results (for cancer deaths) were collected for all member of the cohort. No information was provided on the means for doing the follow-up nor on losses to follow-up. Workers were classified into those with high level exposure to VC (> 300 mg/m^3), moderate levels (30–300 mg/m^3) and low levels (< 30 mg/m^3). Mortality for the cohorts was compared with rates of the city of the plant for the years 1959, 1969 and 1975. There were 288 deaths registered in the cohort, including 63 from cancer. The SMR for all cancers was 1.06.

A prospective cohort study of 1100 workers exposed to VC in various French plants and 1100 unexposed subjects was initiated in 1980 (Laplanche et al., 1987, 1992). Unexposed controls were matched to cases by age, plant and physician. Subjects were followed until December 1988 for vital status, other health outcomes and

occupation. Information was collected on complete occupational history, smoking and drinking habits, and medical history (see also section 8.3.2.3c and Table 39).

Weber et al. (1981) and Greiser et al. (1982) reported a historic prospective cohort study of 7021 male workers who had been or were working on 31 December 1974 in VC/PVC plants in Germany and Austria (follow-up 10.5 years). The control cohort consisted of 4910 Germans and Austrians from the same chemical companies but not having contact with VC (follow-up 15.5 years). SMR for liver tumours was 1523, with no details of the number of ASL. For lymphatic tumours and leukaemia there was a SMR of 214. No information was given on subtypes. A summary of findings on selected neoplasms for the epidemiological studies on workers exposed to VC is given in Tables 39 and 40.

8.3.3.1 Liver and biliary tract cancers

a) *Features of angiosarcoma*

Angiosarcoma of the liver (ASL), also known as haemangio-endothelial sarcoma, is an extremely rare liver tumour and is difficult to diagnose. ASL constitutes only 2% of all primary tumours of the liver in the general population. It has been associated only with exposure to VC, Thorotrast (a contrast medium used in X-ray radiography in the 1930s–1950s) and arsenic (Creech & Johnson, 1974; Falk et al., 1974). In England and Wales, from 1975 to 1987, there was an annual incidence of 1.4 cases per 10 million population (Elliott & Kleinschmidt, 1997). Regular international surveillance of cases of ASL from VC exposure show that 118 cases were registered by 1985 (Forman et al., 1985), 173 by 1993 (Lee et al., 1996), and 197 by 1999 (Association of Plastics Manufacturers in Europe, 1999) (Table 38).

The most prominent clinical symptoms are abdominal pain, weakness, fatigue and weight loss with hepatosplenomegaly, ascites and jaundice being the common clinical signs. It is suggested that patients with non-cirrhotic portal fibrosis and a history of VC exposure should be followed-up for likely ASL (Lee et al., 1996). However, Lelbach (1996) noted that, strikingly, except for the final

Table 38. Number of vinyl chloride-associated ASL cases
reported per country in 1972

Country	ASL cases up to 1985[a]	ASL cases up to 1993[b]	ASL cases up to 1999 [changes since 1993] [c]
USA	35	44	50 [+6]
Germany	26 (West)	41	40 [-1]
France	18	28	31 [+3]
United Kingdom	9	20	21 [+1]
Canada	10	13	13
Croatia	4	4	12 [+8]
Slovakia	2	2	6 [+4]
Italy	4	8	8
Sweden	5	5	5
Japan	2	3	4 [+1]
Belgium	2	2	2
Norway	1	1	1
Spain		1	1
Australia		1	1
Brazil			1 [+1]
Israel			1 [+1]
Total [d]	118	173	197

[a]   From: Forman et al. (1985)
[b]   From: Lee et al. (1996)
[c]   Association of Plastics Manufacturers in Europe (1999)
[d]   It should be noted that from several countries known to be producers of PVC, there is no information regarding ASL cases. Furthermore, some plants have contributed disproportionately to the total

stages, there was little impairment of hepatic function in ASL patients. The average latent period between starting work in an occupation involving VC exposure and ASL diagnosis/death for 99 cases was 22 years (Purchase et al., 1987; Lelbach, 1996).

Any treatment is generally unsuccessful and survival after diagnosis usually averages less than 12 months. Hepatic failure and

intra-abdominal haemorrhage are the usual terminal effects (Riordan et al., 1991; Lee et al., 1996). Liver transplantation might be the only chance of survival (Hayashi et al., 1990). If ASL is detected early enough, surgical resection and adjuvant chemotherapy is a possibility; subsequent hepatic recurrence could be treated by radiation therapy and chemoembolization (Paliard et al., 1991; Neshiwat et al., 1992; Hozo et al., 1997).

b) *Results of epidemiological studies*

In addition to the index tumour, ASL, several case series have been published on VC-exposed workers who had liver tumours other than ASL, in particular hepatocellular carcinoma (HCC) (Koischwitz et al., 1981; Evans et al., 1983; Dietz et al., 1985; Pirastu et al., 1990, 1991; Lelbach, 1996; Makita et al., 1997; Saurin et al., 1997). In the USA study, statistically significantly elevated relative risk was observed for the cancers of liver and biliary tract (SMR 641, CI 450–884). Mortality was related to the duration of exposure (SMR 182, 1235, and 1284 for workers with exposure duration of < 10, 10–20 and > 20 years, respectively), and to the latency period (SMR 386, 590, and 1218 for latency periods of < 20, 20–30 and > 30 years, respectively. The risk was higher for workers hired before 1950 (SMR 780) than in for those hired 1950–1959 (SMR 440) or since 1960 (SMR 419). The risk was highest among workers hired at an early age (SMR 1611, 813 and 346 for those hired at < 25, 25–34 and $ 35 years of age. The authors noted, however, that those hired early and young were likely to have longer duration of exposure and latency.

A total of 15 angiosarcomas were recorded on the death certificates. Although no expected numbers were calculated, this must be in a very marked excess, since the annual incidence of liver angiosarcoma is approximately 2 per 10 million, which would in this cohort lead to an expected number of ~0.05. The authors noted that, when the 15 angiosarcomas were excluded, there remained 22 other liver and biliary tract tumours; this represents an excess (5.7 expected, SMR 386, P < 0.02). This is likely to be an overestimate, since some of these other liver cancers were likely to be angiosarcomas.

Table 39. Summary of findings on selected neoplasms for the epidemiological studies on workers exposed to VC

Cause of mortality	European/IARC study (Simonato et al., 1991) Obs/Exp *SMR* (95% CI)	USA study (Wong et al., 1991) Obs/Exp *SMR* (95% CI)	Weber et al. (1981) Obs/Exp *SMR* (95% CI)	Smulevich et al. (1988) Obs/Exp *SMR* (95% CI)	Thériault & Allardt (1981) Obs/Exp *SMR* (95% CI)	Laplanche et al. (1992) Exposed/Non-expos. *RR* (95% CI)	All studies [d] Obs/Exp *SMR* (95% CI)
All causes	1438/1636.4 *88* (83–93)	1536/1705.27 *90* (86–95)	414/434.7 *95*	-	59/71.07 *83*	40/43 *1.0* (0.6–1.5)	
All malignant neoplasms	445/427.8 *104* (95–114)	359/341.7 *105* (94–116)	79/82.9 *103* [b]	63/58.88 *107*	20/16.37 *122*	*1.3* (0.7–2.3)	966/927.65 *104* (98–111)
Liver cancer/ angiosarcoma (ASL)	24/8.4 *286* (183–425) 16 ASL out of 17 liver cancer deaths with histopathology	37/5.77 *641* (450–884) 15 ASL in death certificates. 21 ASL in international register	12/0.9 *1523*	0/n.a	8/0.14 *5714* 8 ASL (+2 ASL undiagnosed)	3 3 ASL	81/19.21 *533* (423–662)

Table 39 (contd).

Brain	14/13.1 **107** (59–180)	23/12.76 **181** (114–271)	2/1.3 **162**	4/2.61 **153**	0/0.6 **0**	43/30.37 **142** (103–191)
Lung	144/148.3 **97** (82–114)	111/115.87 **96** (79–116)	24/26.6 **96**	1/1.2 **83**	2/5.78 [c] **34**	282/297.75 **95** (84–106)
Lymphatic and haematopoietic	29/32.7 **89**	37/36.28 **102** (72–141)	15/7.7 **214**	10/2.2 **454**	1/1.67 **60**	92/80.55 **114** (92–140)
Lymphomas	18/19.3 [a] **93**	24/21.8 [a] **110**		5/1.2 **417**		
Stomach	49/45.1 **109** (80–144)	10/16.01 **63** (30–115)	18/14.4 **138**	21/24.7 **85**	-	98/100.21 **98** (79–119)

[a] Lymphoma and malignant myeloma
[b] As reported in original paper
[c] All respiratory neoplasms
[d] Calculated by the Task Group. All studies except Laplanche et al. (1992) who did not provide observed and expected values

Table 40. Analysis of liver, brain and lung cancer mortality in the USA and European cohort by duration of exposure

Organ	Study	< 10 years SMR	(observed)	10–19 years SMR	(observed)	20 + years SMR	(observed)
Liver	USA (Wong et al., 1991)	182	(6)	1236	(20)	1285	(11)
	Europe (Simonato et al., 1991)	0	(0)	253	(8)	432	(16)
Brain	USA	165	(13)	121	(4)	386	(6)
	Europe	59	(2)	113	(6)	136	(6)
Lung	USA	93	(59)	114	(37)	75	(15)
	Europe	95	(73)	107	(51)	83	(20)

In the European study, the SMR for liver neoplasms was 286 (95% CI 183–425, and it increased with increasing latency (SMR 0, 253, 388 and 561 for latencies < 10, 10–19, 20–29 and $ 30 years, respectively), duration of exposure (SMR 94, 327, 310, 714 and 1111 for duration of employment of < 10, 10–14, 15–19, 20–24 and $ 25 years, respectively), ranked level of exposure, and cumulative exposure (SMR 348, 400, 1429 and 1667 for < 2000, 2000–6000, 6000–10 000 and $ 10 000 ppm-years, allowing for a 15-year latency). A clear exposure-response relationship was seen between ranked level of exposure (ppm) as well as cumulative exposure (ppm-years) to VC and liver cancer mortality, with autoclave workers having the highest risk (Table 41; Simonato et al., 1991). This relationship is even more evident taking only those liver cancers defined histologically as ASL. In addition, for those VC workers not defined as autoclave workers, an exposure-response relationship could be seen for those diagnosed as having ASL and non-ASL liver cancers (Pirastu et al., 1990, 1991; Simonato et al., 1991).

Of the 17 liver cancer deaths, for which histopathological data were available, 16 were classified as angiosarcomas. For the remaining seven, the histological type remained unknown. The Task

Group noted that even if they all had been cancers other than angiosarcoma, the relative risk of liver tumours other than angiosarcoma would not have been elevated (expected number − 8).

For 2643 workers from Norway and Sweden, cancer incidence information was also available. The only site for which a statistically significantly elevated risk was observed was the liver (SIR 303, CI 122–623).

In the Canadian study, there was an excess of digestive tract cancers (14 cases, SMR 259, $P < 0.01$) that was fully accounted for by cancers of the liver (8 cases). All liver cancers were angiosarcomas.

Hospital admission diagnoses were studied among 714 present and 1575 previous workers, identified from national Labour Insurance Bureau records, with exposure to VC (Du & Wang, 1998). The frequencies of different diagnoses were compared with similar data on workers in the manufacture of optical instruments or of motorcycles. Eight cases of primary liver cancer were observed among the VC-exposed workers (out of 1044 admissions), while the number was 9/3667 for the optical workers, and 9/5861 for motorcycle manufacturers, which gave 4.5 (95% CI 1.5 to 13.3) and 6.5 (2.3–18.4) as age-adjusted morbidity odds ratios (MOR), calculated from a linear regression model, for the VC-exposed workers, compared to the two comparison groups. Increased MORs (of borderline significant) were also observed for haematopoietic cancer, chronic liver disease and liver cirrhosis, as well as other chronic diseases, and accidents.

Two updates of parts of the Italian cohort (Pirastu et al., 1991) have recently appeared. An elevated mortality of liver cancer (11 observed, 5.7 expected cases, SMR 193) was observed in Marghera. In an extended survey for hepatic cancers, four further cases were uncovered. There were 5 angiosarcomas, 5 hepatocellular carcinomas, 3 cirrhotic carcinomas, and in two cases the histology was not known (Pirastu et al., 1997). In three other subcohorts (Pirastu et al., 1998), the pooled SMR for liver cancer was 364 (7 observed cases, 90% CI 108–390).

A survey of 5291 workers from 13 PVC manufacturing plants in 12 cities in China using 6276 workers unexposed to VC as controls

Table 41. Mortality data for liver cancer according to the exposure variables [a]

Exposure variable	O	SMR	95% CI	15 years of latency	
				SMR	95% CI
Job title					
Ever autoclave worker	11	896	447–1603	1358	678–2430
Never autoclave worker [b]	13	181	97–130	284	151–485
Duration of employment (years)					
1–9	4	94	26–239	205	56–525
10–14	5	327	106–763	602	196–1406
15–19	4	310	84–794	310	84–794
20–24	6	714	262–1555	714	162–1555
$ 25	5	1111	361–2593	1111	361–2593

Table 41 (contd).

Ranked level of exposure (ppm)					
Low (< 50)	3 (4)	119	25–347	227 (244)	47–664 (67–625)
Intermediate (50–499)	3 (7)	161	33–471	250 (551)	52–731 (222–1136)
High ($ 500)	12 (12)	567	293–991	719 (719)	371–1255 (371–1255)
Unknown	6 (1)	317	177–691	486 (125)	182–1079 (3–697)
Cumulative exposure (ppm–years)					
0–1999	4 (9)	99	27–254	191 (348)	52–490 (159–662)
2000–5999	4 (4)	351	96–898	460 (400)	125–1177 (109–1024)
6000–9999	4 (7)	800	218–2048	851 (1429)	232–2179 (574–2943)
$ 10 000	3 (3)	1429	295–4175	1667 (1667)	344–4871 (344–4871)
Unknown	9 (1)	357	163–678	536 (100)	245–1017 (2–557)
Whole cohort	24	286	183–425	445	285–663

[a] From: Simonato et al. (1991); O = observed number of deaths; SMR = standardized mortality ratio; CI = confidence interval. The values in parentheses were determined in analyses including the estimated job-exposure matrices

[b] In Norway, the longest-held job was used. In Sweden job rotation was practiced, and no one was classified as an autoclave worker

was carried out between 1982 and 1989. Although no cases of ASL were reported, the mortality from liver cancer in male workers exposed to VC was significantly higher than those of the control group and of the male general population in the middle cities in China. Among malignant tumours, liver cancer ranked first in exposed males. The authors found that the average age for persons who were diagnosed with liver cancer was significantly lower than that of the control group (Huang, 1993a,b).

8.3.3.2 Brain and central nervous system (CNS)

Statistically significant increases of brain and CNS tumours after occupational exposure to VC were reported in USA surveys by Waxweiler et al. (1977) and Cooper (1981), as well as in Sweden (Byrén et al., 1976) and Germany (Greiser et al., 1982).

In the USA (study of Wong et al., 1991), the relative risk was elevated for cancers of the brain and other CNS cancers (SMR 180.2, CI 114.1–270.6). Mortality was highest in the group with the longest duration of exposure (SMR 164.7, 120.8 and 385.9, for workers with the duration of exposure < 10 years, 10–20 years and > 20 years, respectively), while no trend with latency was observed (SMR 183.8, 158.3 and 210.7, for latencies of < 20, 20–30 and > 30 years). Workers hired early did not exhibit higher risk than those hired late (SMR 156, 164 and 256, for employees hired before 1950, 1950–1960 and after 1960, respectively. It was noted that most of the cases came from the two plants with the highest rate of ASL.

In the European study, the SMR for brain cancer was 107 (CI 59–180). The small number of cases (total 14) made the assessment of the relationship between duration of exposure and latency difficult, but the risk was highest after longest latency (SMR 59, 113, 59 and 407 after a latency of # 10, 10–20, 20–30 and $ 30 years) and after longest duration of exposure (SMR 106, 78 and 183 for a duration of exposure of # 10, 10–20 and $ 20 years). There were even fewer cases for the assessment of the relationship between estimated exposure and cancer risk (8 cases altogether), but the point estimates were higher for higher estimated exposures (SMR 91, 42 and 128 for low, intermediate and high exposure), while little covariation between estimated cumulative exposure and relative brain cancer risk was observed (SMR 0, 162 and 120 for cumulative exposures of < 50, 50–499 and $ 500 ppm-years).

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In the cancer incidence aspect of the European study, a non-significantly elevated SIR was observed for cancer of the brain (SIR 159 CI 68–312).

8.3.3.3 Respiratory tract

The study by Monson et al. (1974) first suggested an association between VC and lung cancer.

In the USA study, the SMR for lung cancer was 95.8 (CI 78.7–115.5).

In the European study, the SMR for lung cancer was 97 (CI 82–114). It did not show any consistent relationship with duration of employment, latency, ranked level of exposure or cumulative exposure; the SMR was similar for ever- and never-autoclave workers.

In the cancer incidence aspect of the European study, a non-significantly elevated SIR was observed for cancer of the lung (SIR 152, CI 95–230).

In the Canadian study, the mortality from respiratory cancer was low (relative risk in comparison to the unexposed cohort 0.36, and SMR based on Quebec data, 34, based on two cases). Smoking habits, as studied by a questionnaire, were similar in the exposed and non-exposed cohorts.

8.3.3.4 Lymphatic and haematopoietic cancers

There were indications of increased risk of cancer of the lymphatic and haematopoietic systems in several early studies (Monson et al., 1975; Waxweiler et al., 1976; Greiser et al., 1982; Smulevich et al., 1988).

In the Wong et al. (1991) USA study, the SMR for lymphatic and haematopoietic cancer was 102 (CI 71.6–140.7, while that for lymphoma and reticulosarcoma was 102.0 (CI 71.6–140.7).

In the European study, the overall SMR for lymphosarcoma was 170 (CI 69–351), based on seven cases. No cases were observed in the

groups with a latency of 20–30 or $ 30 years, and six out of the seven subjects had worked less than 10 years in VC-exposure conditions.

8.3.3.5 Malignant melanoma

There was a relationship between VC exposure and malignant melanoma of the skin in PVC production workers in the early Norwegian study (Heldaas et al., 1984, 1987).

In the European study, a non-significant, elevated risk was observed for melanoma, and the risk was higher in the incidence part of the study (SIR 184, CI 79–302). However, the risk was limited to one country only (Norway).

8.3.3.6 Breast cancer

Infante & Pesák (1994) noted that there had been no follow-up study to that of Chiazze et al. (1977), who observed an excess in breast cancer mortality. Although a subsequent study among these researchers (Chiazze et al.,1980) did not identify a significantly elevated odds ratio in relation to VC exposure, the statistical power used in the study has been questioned (Infante & Pesák, 1994). There have been no other reports on breast cancer in humans, but in most Western countries women have not been working in jobs involving VC exposure. In some countries, however, e.g., China and Eastern Europe, women are/were probably exposed to higher VC levels than in Western countries (see Table 21) but epidemiological studies are not available. Mammary carcinoma has been reported in animal studies with inhalative and oral exposure to VC (see section 7.7.2).

No breast cancer was observed in the study by Smulevich et al. (1988).

8.3.3.7 Other cancer sites

In the European study, a non-significantly elevated risk was also observed for urinary bladder (21 deaths observed, SMR 146, CI 91–224) and, in the incidence part, for cancer of the stomach (SIR 150, CI 80–256).

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8.4 Genotoxicity studies

8.4.1 Cytogenetic studies of VC-exposed workers

Table 42 summarizes the results of cytogenetic studies of chromosomal aberrations (CA), micronucleus formation (MN) and sister-chromatid exchanges (SCEs) in the peripheral blood lymphocytes of VC workers compared to controls. Studies on the genotoxicity of VC have been reviewed (Uzych, 1988; Giri, 1995). Although in many studies the exposure concentrations and duration of exposure were only estimated, a dose-response relationship and a "normalization" of genotoxic levels with time after reduction of exposure can be seen.

There was a clear relationship between incidence of CA and the exposure concentrations/type of work (Purchase et al., 1978). The same groups of workers showed lower or no effects after the exposure concentration was reduced to < 13 mg/m^3 (< 5 ppm) (Hansteen et al., 1978; Anderson et al., 1980; Fucic et al., 1996). That such levels do not cause an increase in CA was confirmed by several studies (Picciano et al., 1977; Rössner et al., 1980; de Jong et al., 1988).

SCEs increased with the level of exposure to VC of workers (Sinués et al., 1991). SCEs were generally not detected in blood samples from workers exposed to VC at < 5 ppm.

In a micronucleus assay, workers exposed to VC had a much higher frequency of micronucleated lymphocytes than the controls. However, a significant decrease in the number of micronucleated lymphocytes was found within 15 days after the last exposure, but even 90 days after the last exposure (peak of 780 mg/m^3) the frequency, although decreased, was still above the control value (Fucic et al., 1994). A similar effect had been shown with SCE frequencies (Fucic et al., 1992).

Chromosomal aberrations were measured in peripheral blood lymphocytes from 29 subjects potentially exposed to VC after an accidental release into the environment (Hüttner & Nikolova, 1998). The control group consisted of 29 non-exposed people, matched regarding age, gender and smoking habits. The exposed group

Table 42. Chromosome analysis in human T-lymphocytes (*in vivo*) after vinyl chloride exposure during work at
PVC polymerization plants or due to other accidental exposure [a]

Test	No. workers; No. controls	Additional information	Duration of exposure (years)	Exposure level (mg/m^3)	Result	Reference
HPRT mutation using T-cell cloning assay	24; 23	worked on post-chlorination of PVC in an open system where free VC evaporated	average 7	average < 13	-	Hüttner & Holzapfel (1996)
DNA single strand breakage	16	3 groups of VC/PVC workers	average 13	average 150	-	Du et al. (1995)
	104		average 16	5	-	
	122		average 16	2	-	
Chromosomal aberrations	11; 10	PVC workers	4–28 (average 15)	peaks >1300	+	Ducatman et al. (1975)
	7; 3		9–29	50–75	+	Funes-Cravioto et al. (1975)
	45; 93		0.5–12	n.g.	+	Szentesi et al. (1976)
	57; 24	VC/PVC workers classified according to type of work (1974)	10.7 (average for autoclave workers)	10–100	+	Purchase et al. (1978)
	21; 6			< 13	+	Anderson et al. (1980)
	23; 8	same as Purchase et al. (1978)		< 13	-	

Table 42 (contd).

Chromosomal aberrations (contd).	20; 20	with clinical symptoms; without clinical symptoms			+ -	Fleig & Thiess (1974, 1978)
	39; 16	1974	> 10	> 65	+	Hansteen et al. (1978)
	37; 32	same workers 1977		2.6	-	
	3; 9		10–27	50–400	+	Kucerová et al. (1979)
	37; 12		n.g.	2–111	+	Katosova & Pavlenko (1985)
	43; 22		average 11.2	2–41	+	Hrivnak et al. (1990)
	19; 20		average 15	130; peaks of 5000	+	Fucic et al. (1990b)
	67; n.g.	breaks occurring at non-random sites	average 15	13; peaks of 5000	+	Fucic et al. (1990a)
	10; n.g.		8–25; average 15	av 13; short peaks higher	+	Garaj-Vrhovac et al. (1990)
	n.g	PVC workers	5	26	+	Zhao et al. (1994)
		PVC workers	2	26	-	
		PVC workers	> 7	4	-	
		residents on site	> 8	0.2	-	
	209; 295	3 groups	average 4	< 2 to > 13	-	Picciano et al. (1977)
	31; 35	1977	2–3	< 10	-	Rössner et al. (1980)
		same group 1978		peak < 30	-	
	66; 39	1976–1977	1–11; average 6	3 peaks up to 26	-	de Jong et al. (1988)
	29; 29	exposure of general population after accidental release of VC	for short time (~1 h)	unknown concentration	+	Hüttner & Nikolova (1998)

Table 42 (contd).

Test	No. workers; No. controls	Additional information	Duration of exposure (years)	Exposure level (mg/m^3)	Result	Reference
Micronucleus assay	19; 20		average 15	130; peaks of 5000	+	Fucic et al. (1990b)
	32	24 h to 90 days following a peak exposure of 780 mg/m^3	10 5	peak of 780 mg/m^3 every 3 months	+ +	Fucic et al. (1994)
Sister-chromatid exchange	9; 8		10–27	50–400	+	Kucerová et al. (1979)
	16, 16		> 10	2.6	-	Hansteen et al. (1978)
	21; 6		3.5	< 13	(-)	Anderson et al. (1981)
	31; 35		2–3	< 10	-	Rössner et al. (1980)
	31; 41		> 2	3–44; peaks of 130	+	Sinués et al. (1991)
	21; 41			1–20		
	15; 10		1.5–35	13; peaks of 5000	+	Fucic et al. (1992)
				0.3; peaks of 130	-	Fucic et al. (1996)

[a]   HPRT = hypoxanthine guanine phosphoribosyltransferase; n.g. = not given

showed a statistically significant increase in the mean frequency of aberrant cells (1.47% versus 1.07% in the control group).

8.4.2 Mutations at the hypoxanthine guanine phosphoribosyltransferase (hprt) locus

With the use of the hprt lymphocyte clonal assay it is possible to determine the mutation frequency of the *hprt* gene and to characterize its mutant spectra. Induced mutagenesis in the lymphocytes of PVC production workers was measured by selecting mutant T-cells with the *hprt* gene in medium containing 6-thioguanine. The exposed workers had similar mutation frequencies (about 8×10^{-6}) as controls (Hüttner & Holzapfel, 1996).

The types and frequencies of mutations caused by VC in a human B-lymphoblastoid line expressing cytochrome P-450 2EI (H2E1 cells) were investigated by Chiang et al. (1997). VC was found to be toxic and mutagenic to H2E1 cells as a function of incubation time when they were exposed to 7.5% VC in air. This exposure resulted in 75% survival and an hprt mutant frequency of 42×10^{-6} after 48 h, compared to 6×10^{-6} for unexposed cells. Exposure to 0.8 to 15.0% VC in air produced similar mutation frequencies but without a clear dose-response relationship, perhaps due to saturation of metabolic activation. Ten percent (5/50) of VC-induced mutations showed detectable deletions. Both CEO and CAA showed dose-dependent increases in cell killing and mutant frequency. VC and CEO displayed similar toxicity/mutation profiles and a similar frequency of large deletions, whereas CAA showed greater toxicity and a larger frequency of deletion mutations.

8.4.3 Mutations in ASL from VC-exposed workers

8.4.3.1 p53 *gene*

Normal and cancer cells appear to differ through discrete changes in specific genes controlling proliferation and tissue homoeostasis. The *p53* tumour suppressor gene is present in every cell of the human body and is located on the short arm of the human chromosome 17 p. (Lane, 1994). It is mutated in about half of all cancer types arising from a wide spectrum of tissues (Harris, 1996).

The encoded wild-type p53 protein, a 393 amino acid nuclear phosphoprotein, activates the transcription of several genes, including

some involved in cell cycle control (e.g., p21), and has been implicated in DNA repair processes, DNA replication and apoptosis (Lane, 1994; Semenza & Weasel, 1997). The majority of cancer-related mutations in *p53* cluster in several "hot-spot" regions of the protein that have been highly conserved through evolution. These regions occur in the sequence-specific DNA-binding core domain of the protein between amino acid residues 102 and 292 (Lane, 1994). The mutations in *p53* found in malignancies could thus result in substitutions of amino acid residues in these regions that are critical for the determination of its structure and function (Cho et al., 1994; Brandt-Rauf et al., 1996).

The *p53* gene was examined in tumours from four highly exposed (before 1974) autoclave workers with ASL and one other VC worker with hepatocellular carcinoma (HCC) (Hollstein et al., 1994). Two A to T mutations in a highly conserved domain of the coding sequence (codon 249: AGG to TGG, Arg to Trp; and codon 255: ATC to TTC, Ile to Phe) were found one each in the tumour but not in other normal cells of two of the ASL patients (both smokers). A further A to T missense *p53* mutation (codon 179: CAT to CTT) was found in a cell line from a further VC-associated liver tumour patient (Boivin et al., 1997; see Table 43). Such mutations are uncommon in human cancers (2.7% of a total of 5085 cancers and 8% of a total of 290 primary liver cancers; Hollstein et al., 1996). Furthermore, *p53* mutations are uncommon in sporadic (non-VC-induced) ASL (2/21 cases, 9%), supporting the evidence linking VC exposure and ASL containing an increased frequency of *p53* mutations with a mutational spectrum (A to T) (Soini et al., 1995). To date (1998) 11 out of 15 (73%) ASL from VC-exposed workers have been shown immunohistochemically to have mutant p53 protein. Further, a statistically significant trend for mutant p53 protein has been found in the serum of VC-exposed workers (Smith et al., 1998); this study is continuing (Li et al., 1998a,b).

p53 gene mutations were also found in 11 out of 25 (44%) ASL in Sprague-Dawley rats induced by VC and 1 in 8 HCCs (Barbin et al., 1997; see Table 43). This is a higher mutation rate than that found in humans but again the majority of missense mutations involved were A:T base pairs. The A:T 6 T:A transversion observed in the first nucleotide of codon 253 in two rat ASL is equivalent to the same transversion characterized previously in codon 255 in one human ASL associated with VC exposure (Trivers et al., 1995).

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Table 43. Comparison of mutation spectra in the *p53* gene
in liver tumours in humans and rats [a]

Species	Tumour origin	No. mutations/ no. of cases	No. and types of mutations	References
Humans	VC-associated ASL	3/6	3 A:T → T:A	Hollstein et al. (1994)
	cells cultured from VC-associated liver tumour		[CAT → CTT] (codon 179)	Boivin et al. (1997)
Rats	VC-associated ASL	11/25	5 A:T → T:A 2 A:T → G:C 2 A:T → C:G 3 G:C → A:T one 12 base-pair deletion 1 deletion	Barbin et al. (1997)
	HCC	1/8	1 A:T → T:A	

[a]   Adapted from Barbin et al. (1997); ASL = angiosarcoma of the liver;
HCC = hepatocellular carcinoma

8.4.3.2 ras *genes*

The *ras* gene family, Ha-*ras*, Ki-*ras* and N-*ras*, are genes coding
for p21 and are frequently activated by point mutations in codons 12,
13 and 61. These activated genes seem to play a key role in the
development of spontaneous or carcinogen-induced mammalian
tumours (Barbacid, 1987). In a study of *ras* oncogene mutations in
tumours of VC-exposed workers, 15 of 18 ASLs were found to contain
a G to A transition at the second base of codon 13 (GGC to GAC) of
the Ki-*ras*-2 gene (Marion et al., 1991, 1996; see Table 44). This
mutation leads to the substitution of glycine by aspartic acid at amino
acid residue 13 in the encoded p21 protein.

Ki-*ras*-2 gene mutations were found in codon 12 in 5/19 sporadic
ASL and in 2/5 thorotrast-induced ASL in humans. All seven
mutated tumours contained a G → A transition at base 2. In addition,

Table 44. Mutagenesis of *ras* proto-oncogenes in VC-associated liver tumours in humans and rats

Tumour origin [a]	Gene involved	Codon	No. mutations/ No. tumours	Base pair change/ Codon change	References
Human ASL	Ki-*ras* 2 gene	Codon 13	15/18	G → A/ GGC → GAC	Marion et al. (1991, 1996); DeVivo et al. (1994)
Rat ASL	Ki-*ras* 2 gene		0/10		Froment et al. (1994); Boivin-Angèle et al. (in press)
Rat HCC	Ha-*ras* gene	Codon 61	5/8	AT → TA/ AT → TA	Froment et al. (1994); Boivin-Angèle et al. (in press)

[a] ASL = angiosarcoma of the liver; HCC = hepatocellular carcinoma

4 of these tumours (3 sporadic, 1 thorotrast-induced) contained a second mutation in the Ki-*ras* gene, a G → T transversion of the first base of codon 12 (Przygodzki et al., 1997).

In studies in VC-induced ASL and HCC tumours in rats, no mutations were found in Ki-*ras* genes but there were mutations at codon 61 of the Ha-*ras* proto-oncogene (Froment et al., 1994; Boivin-Angèle et al., in press).

8.5 Studies on biological markers

8.5.1 Excretion of metabolites

The concentration of the VC metabolite thiodiglycolic acid in the urine has been found to correlate with VC exposure in workers and has been suggested as a biological marker for VC (Müller et al., 1978) (see also section 5.3).

8.5.2 Genetic assays

Increased levels of chromosomal abnormalities, compared to control populations, were found in workers exposed to high levels of VC but not in workers exposed to less than 13 mg/m^3 (5 ppm) (see Table 42). The micronucleus assay and mitotic activity have been suggested as methods for determining recent VC exposure (Fucic & Garaj-Vrhovac, 1997; see section 8.4).

8.5.3 Enzyme studies

Ever since the 1970s there has been disagreement as to the value of monitoring levels of enzymes as a measure of VC exposure or as a sign of VC disease. Liver function tests may be of limited value in detecting VC-induced liver disease because, although hepatocytes are the primary site of VC metabolism, they are not the target of toxicity (Lelbach & Marsteller, 1981). Individual studies of VC-exposed populations have reported abnormalities in one or more liver function tests, such as aspartate aminotransferase (ASAT), alanine amino-transferase (ALAT) and alkaline phosphatase (AP) (Lilis et al., 1975; Waxweiler et al., 1977). However, Sugita et al. (1986) concluded that VC probably had not affected these enzymes after adjusting for confounding factors. This was confirmed by Du et al. (1995) who showed that ASAT, ALAT and AP were mainly affected by the presence of hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (anti-HCV).

Gamma glutamyl transpeptidase (GGT) is thought to be associated with VC exposure (Langauer-Lewowicka et al., 1983; Du et al., 1995) and, according to the latter, this is the only enzyme that correlates with VC exposure levels. It should be noted that GGT is readily elevated in alcohol drinkers, so the value of this enzyme as a biomarker of VC-induced liver injury becomes questionable. In workers showing VC-induced liver dysfunction (VC levels 2.6–54 mg/m^3; 1 to 21 ppm), ALAT was the earliest parameter raised, then serum GGT (Ho et al., 1991). Ho et al. (1991) also reported that 10 of 12 workers with VC-induced liver dysfunction showed improvements in liver function tests after removal from exposure. There are case reports of individuals whose angiosarcomas were first detected by abnormal liver function tests (Makk et al., 1976), but liver function abnormalities appear to be a relatively late finding (Falk &

Steenland, 1998). No published studies have been identified that evaluate the effectiveness of medical surveillance in occupational groups with VC exposures below 2.6 mg/m³ (1 ppm).

8.5.4 von Willebrand factor

The immunoquantitation of the level of the von Willebrand factor (vWf; factor VIII-related antigen, a large multimeric plasma glycoprotein in the blood clotting system) in 107 VC exposed workers was performed using an enzyme-linked immunosorbent assay (ELISA) (Froment et al., 1991). The vWf level was slightly but significantly higher in the VC-exposed workers than in the control group. The vWf serum level of three patients with hepatic angiosarcoma was markedly elevated.

8.5.5 p53 *and* ras *proteins*

Mutant p53 and p21 proteins or their antibodies can be detected in sera from healthy workers exposed to VC (Marion et al., 1996; Semenza & Weasel, 1997; Smith et al., 1998; Li et al., 1998a,b). A dose-response relationship between estimated cumulative exposure and the frequency of these onco-proteins has been reported (Table 45). Statistically significantly elevated frequencies were observed even in the group with lowest estimated exposure (cumulative exposure < 40 ppm-years) (Li et al., 1998b). However, exposure estimations were crude. In addition, similar findings have not been reported for other VC-exposed groups.

8.6 Susceptible subpopulations

8.6.1 Age susceptibility

Evidence from animal studies suggests that there may be early-life sensitivity to VC (section 7.7.3), but there is also contradictory evidence. There has been concern that children living near landfill sites might be particularly susceptible to VC formed and released there (Hiatt et al., 1994; Cogliano et al., 1996). However, there is no epidemiological evidence to support this.

Table 45. p53 and p21 mutations (as detected by serum biomarkers analysis) in relation to estimated vinyl chloride exposure (Li et al., 1998a)

Estimated exposure (ppm–years)	Total no. of workers	Both biomarkers negative	No. of workers with mutation in either p53 or p21	No. of workers with mutation in both p21 and p53	Adjusted OR	95% CI
0	43	38	5	0	1	
# 500	42	20	21	1	11.1	3.3–37.5
501–2500	45	20	21	4	12.8	4.1–40.2
2501–5000	31	6	19	6	29.9	9.0–99.1
> 5000	54	15	22	17	31.2	10.4–94.2

8.6.2 Immunological susceptibility

Individual susceptibility may influence the development of VC disease, since not all highly exposed workers developed clinical symptoms or signs (Wilson et al., 1967; Black et al., 1986). Studies conducted in a single population of VC-exposed workers have shown that susceptibility for the disorder seems to be increased in the presence of the human-leukocyte-associated antigen HLA-DR 5 or a gene in linkage disequilibrium with it and an antigen associated with the haplotype A1, B8, while DR3 seems to favour progression of the disease (section 8.3.2.3e). The significance of this finding is unclear without replication in another VC-exposed population.

8.6.3 Polymorphic genes in VC metabolism

Levels of CYP2E1 can vary considerably among individual humans (Guengerich et al., 1991) and are a possible cause of differences of susceptibility to VC.

El Ghissassi et al. (1995b) analysed the *GSTM1* genotype in 133 Caucasian individuals who had had a high exposure to VC for several years and had (or had not) clinical signs of chronic injury (see also Froment et al., 1991, section 8.5.4). Of the 133 individuals, 62 workers had non-neoplastic symptoms, while 8 had liver cancer. The frequency of *GSTM1* null genotype in the whole group of exposed workers was 61.7% (82 of 133) and 62.5% in patients with liver cancer. In case-control studies reported by others, the frequency of *GSTM1* null genotype ranged from 41 to 53% for Caucasians.

9. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

9.1 Laboratory experiments

VC has been shown to be mutagenic in several *in vitro* and *in vivo* test systems derived from organisms belonging to different taxonomic levels. The details referring to bacterial, fungal and mammalian cell lines or to whole organisms like insects or plants are discussed in section 7.6. The carcinogenic effects of VC are addressed in section 7.7. The following chapter focuses on investigations of other signs of toxicity relevant to organisms that may be exposed to VC in the environment. Standard tests on survival and reproduction were not available. Care must be taken when interpreting the toxicity results available as many were obtained from static tests using nominal exposure concentrations. Such tests will have large losses of VC due to volatilization, thus reducing the actual exposure to VC.

9.1.1 Microorganisms

9.1.1.1 Water

A consortium of anaerobic microorganisms (species not identified; initially obtained from municipal sludge) was used for testing VC toxicity. Both batch and semi-continuous assays were conducted. VC had an inhibitory effect on the total gas production, beginning at a concentration of 5.4 mg/litre and resulting in an EC_{50} value of approximately 40 mg/litre, as seen in the batch assay over 3.5 days. In the semi-continuous assay lasting 15 days, the threshold was greater than 64 mg/litre (the highest concentration tested), probably due to volatilization of VC (Stuckey et al., 1980).

The growth of five mixed bacterial populations (isolated from natural aquatic systems) was not affected, as compared to controls, in liquid cultures (closed flasks; 21 °C; over 5 weeks) containing up to 900 mg VC/litre (Hill et al., 1976b).

The toxicity of waste effluents of a VC production plant to the green alga *Chlorella sp.* was tested before and after the wastes were

treated by neutralization procedures (addition of aqueous solutions of NaOH and catalysts). The crude effluents consisted of VC (15–18%, weight), di-, tri- and pentachloroethanes (45%), dichloroethylene (27%), dichloropropane (6%), ethyl chloride (1%) and unidentified substances (1%). This mixture led to a weak inhibition of algal growth (measured by changes in optical density at 678 nm), with a 72-h EC_{50} value of 1495 mg/litre (which corresponds to a VC concentration of 224 mg/litre). It should be noted that other compounds present in the effluent may also have contributed to the toxicity. The corresponding EC_{50} values of the neutralized waste samples (filtrates and extracts of precipitates; composition not analysed) ranged from 4000 to > 100 000 mg/litre (Demkowicz-Dobrzanski et al., 1993).

9.1.1.2 Soil

Soil (aquifer) microcosms enriched for methanotrophic activity transformed up to 90% of the 1–17 mg/litre influent VC with no apparent toxic effects (Dolan & McCarty, 1995a,b). However, when both VC and 1,1-dichloroethylene were present, about 75% less transformation of VC and a marked decrease in methane oxidation rate was observed (Dolan & McCarty, 1995a). Toxic effects, measured as decreased methane uptake, were seen during degradation of VC (VC concentrations: up to saturated solutions; solubility: 2.7 mg/ml) by a culture of mixed methanotrophs (seeded with soil from a defunct landfill). A mixture of VC and trichloroethylene (TCE) and a triple mixture of VC, cis-dichloroethylene (c-DCE) and TCE showed cumulative toxicity (Chang & Alvarez-Cohen, 1996).

The nitrifying soil bacterium *Nitrosomonas europaea* had a turnover-dependent loss of (ammonia-dependent) O_2 uptake activity after co-metabolic transformation of VC (Rasche et al., 1991).

9.1.2 Aquatic organisms

9.1.2.1 Invertebrates

VC reduced the population doubling time of a ciliated protozoon, *Tetrahymena pyriformis,* population cultured *in vitro* (Sauvant et al., 1995). The IC_{50} value was 540 mg/litre (8.6 mmol/litre).

During a 96-h assay VC had no effect on the survival of the free-living nematode *Panagrellus redivivus* at concentrations ranging from 10^{-3} to 10^{-8} mol/litre (0.6–62 500 ：g/litre), but it reduced the developmental success of this species. The molting rate from the fourth larval stage to adult (determined on progeny of 150 to 300 gravid females per assay; three replications) was significantly decreased relative to controls, and that primarily at VC concentrations of 6.3–6300 ：g/litre (Samoiloff et al., 1980).

The effects of waste effluents from a VC plant described in section 9.1.1.1 (test with *Chlorella sp.*) were also tested with the crustacean *Daphnia magna* (n = 3 × 10 per experiment; age: 6–24 h). The test parameter for the latter was lethality, which was determined by procedures based on ISO 6341-1982 (ISO, 1989). Crude waste produced a 24-h LC_{50} value of 80.7 mg/litre (related to VC: 12 mg/litre). The neutralized wastes (filtrates and extracts of precipitates) were less toxic, reflected by the higher LC_{50} values ranging from 445 to > 100 000 mg/litre (Demkowicz-Dobrzanski et al., 1993).

9.1.2.2 Vertebrates

The acute toxicity of VC to fish was examined with a few freshwater species; 96-h LC_{50} values of 1.22 g VC/litre and 1.06 g VC/litre were reported for bluegill (*Lepomis macrochirus*) and largemouth bass (*Micropterus salmoides)*, respectively, but without giving further details (Hann & Jensen, 1974). Brown et al. (1977) exposed Northern pikes (*Esox lucius*) to 388 mg VC/litre; 10 days after exposure all test animals (n=15) were dead (versus 1 of 20 in controls during 120 days of observation). However, the test conditions (e.g., handling of controls, water quality) were not sufficiently described in this study. Tests of zebra fish (*Brachydanio rerio*; n = 10 per group) according to OECD guideline 203 (OECD, 1984), which was adapted to volatile chemicals, resulted in LC_{50} values (based on mean measured test concentrations) of 240 mg/litre (24 h) or 210 mg/litre (48 h, 72 h and 96 h). The no-observed-effect concentration (NOEC) regarding mortality was 128 mg/litre (Groeneveld et al., 1993).

Estimated benchmark values, concentrations believed to be non-hazardous, to freshwater fish derived by several methods ranged from

87.8 to 28 879 ：g/litre (Suter, 1996). The Tier II secondary acute value and secondary chronic value were reported to be 1570 ：g/litre and 87.8 ：g/litre, respectively. The lowest chronic benchmark for fish was estimated to be 28 879 ：g/litre, with a corresponding fish EC_{20} of 14 520 ：g/litre.

9.2 Field observations

9.2.1 Aquatic organisms

A field study of benthic invertebrates (Dickman et al., 1989; Dickman & Rygiel, 1993) was carried out during 1986–1991 at 15 sites of the Niagara River watershed (Canada) near a PVC plant. The VC discharge in 1986 was estimated to be more than 32 kg (accompanied by unknown quantities of organotin). The density and diversity of several invertebrate groups (Amphipoda, Culicoidae, Chironomidae, Isopoda, Hirudinea, Oligochaeta, Gastropoda, Trichoptera) was found to be low as compared to a reference site. Chironomids (Diptera) turned out to be the best indicators. They were absent at the sampling site closest to the factory's discharge pipe, and their numbers increased with increasing distances. Those collected nearest to the discharge site primarily belonged to the genus *Polypedilum*, which is known to be pollution tolerant. Nevertheless, individuals of this genus showed a high proportion of larval mentum (labial plate) deformities (38% versus 1.7–5.7% at reference sites). Altogether, the frequencies of deformities at the discharge site fell significantly ($P = 0.05$) from 47% measured in 1986–1989 to 25% in 1991, which correlated with the lower levels of VC (figures not given) being released into the river in 1990–1991 (Dickman & Rygiel, 1993).

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of human health effects

10.1.1 Hazard identification

10.1.1.1 Non-neoplastic effects

a) *Human data*

i) *Skin, connective tissue and bone*

Among the non-neoplastic effects of vinyl chloride (VC) exposure, disorders of the skin, connective tissue and bone are the most specific and well-characterized. These include acroosteolysis, Raynaud's phenomenon and sclerodermoid skin lesions. These conditions were quite common in early studies, which may have involved exposures to high levels of several hundred ppm. Acroosteolysis occurred primarily in PVC production workers who had been involved in reactor cleaning. Data on mortality from connective tissue disorders, a relatively rare category of death, have not been provided in published studies, nor are there sufficient data to estimate an exposure–response relationship.

ii) *Non-neoplastic liver disease*

Non-neoplastic liver disease was also well-documented in early studies of workers with high levels of exposure to VC. In one carefully described study, "advanced portal hypertension" with histological findings of non-cirrhotic fibrosis was diagnosed in 17 out of 180 VC polymerization workers. Histological alterations reported in liver biopsy specimens obtained from VC monomer workers in another series included focal hepatocytic hyperplasia and focal mixed hyperplasia; these lesions were infrequent in the comparison group. Reversible changes in liver function tests have been reported in VC workers exposed to 2.6–54 mg/m^3 (1–21 ppm). Despite evidence for the induction of non-malignant liver disease from clinical studies, there has been no evidence of excess mortality from studies of large cohorts. There are also insufficient data to estimate exposure response.

iii) *Respiratory disease*

There is some evidence for respiratory effects from both morbidity and mortality studies of VC workers, but this may be related to PVC-resin dust rather than VC monomer. Positive findings from mortality studies are limited to one cohort. Therefore, the literature does not clearly implicate respiratory disease as an effect of exposure to VC monomer.

iv) *Reproductive effects*

Although animal studies implicate the reproductive system as a potential target organ for vinyl chloride toxicity, studies in humans have not been adequate to confirm these effects or to rule them out.

v) *Cardiovascular disease*

A few morbidity studies have reported an elevated incidence of circulatory diseases among VC-exposed workers. Cardiovascular disease mortality is significantly lower than expected in the two large cohorts.

vi) *Susceptible subpopulations*

There is no strong evidence for the existence of susceptible sub-populations in humans. It has been suggested that specific HLA types and genetic polymorphisms in VC-metabolizing enzymes may be factors in human susceptibility to VC-related diseases.

b) *Experimental animal data*

VC has been tested in several animals species and strains for acute, short-term and long-term effects. Signs of acute toxicity include congestion of internal organs, neurotoxic effects and circulatory disturbances. In short-term studies VC caused mainly liver damage, degenerative changes in the testes, degeneration and inflammation in the lungs and degenerative lesion in the kidneys. Immunological alterations in connection with VC exposure have also been described. Reproductive performance or fertility were not affected.

10.1.1.2 Neoplastics effects

a) *Human data*

In 1974, a case report associated exposure to VC with the occurrence of angiosarcoma of the liver (ASL). Further case series and small epidemiological studies were reported shortly thereafter. At a later stage two studies, one in the USA and one in Europe, combined data from those studies and updated the mortality follow-up. Apart from these two large studies, four more smaller studies have been conducted and fully reported and were also considered by the Task Group.

There is a five-fold excess risk for liver cancer among workers exposed to VC, mostly in PVC polymerization plants where the highest exposures to VC occurs. The largest part of this excess risk is due to the excess risk for ASL. In the European study, there was a 45-fold excess risk for ASL in workers exposed to more than 10 000 ppm-years compared to those exposed to less than 2000 ppm-years. In the European study histopathological confirmation was available for 17 out of 24 liver cancers; of those confirmed 16 were ASL. In the USA study 21 out of 37 liver cancer deaths were registered as ASL. In the Canadian study all 8 liver cancer deaths were ASL, as was the case for the 3 liver cancer deaths in the French study. No information is available concerning ASLs in the German study while no liver cancers were diagnosed in the Russian study. It is probable that some ASLs occurring among VC-exposed workers have remained undiagnosed and have been coded in the death certificates as liver cancers unspecified or as other liver-associated disease.

Several studies examined the risk specifically for hepatocellular carcinoma (HCC) of the liver. No excess was observed in the European study, nor in the Canadian or French studies. Data from the USA study and also from the update of the Italian component of the European cohort seem, however, to indicate that there is also an excess for HCC. This is of smaller magnitude than that observed for ASL. The interpretation of the results for HCC is complicated because of the uncertainties concerning the accuracy of diagnosis of angiosarcomas and HCC using death certificate information and the absence of compete histopathological confirmation of the diagnoses

of liver cancer in the studies. Although the results are not fully consistent between studies, the data suggest that there may be a small excess risk for HCC.

Four out of five studies reporting results for brain tumours identified a moderate excess risk with an SMR of 1.42 for the combined data from five studies (43 observed, 95% CI 1.03–1.91). The risk tended to increase with duration of exposure/employment in the European and USA study. Furthermore, in the USA study, the highest risk occurred in the two plants where most ASL cases had been diagnosed, and where presumably the highest VC exposure had occurred. In the European study where the dose–response relationship was examined, no association was seen with cumulative exposure to VC. The overall epidemiological evidence is suggestive of a possible risk among VC workers.

Some of the smaller early studies had reported an increase in lung cancer among VC workers. There was no indication of an excess risk, however, in the two largest studies (European and USA) or in the other four smaller studies. There was no association either with duration of exposure/employment in the USA or the European study, nor with cumulative exposure to VC in the European study.

Excess risk for malignant lymphomas had been reported in some early small studies. No excess risk, however, was observed in the two largest cohorts (USA and European) or in the Canadian cohort. An excess risk for the combined category leukaemia and lymphoma was observed in the Russian and the German study. In interpreting these results it should be noted that the studies used different disease classification and in some occasions grouped lymphomas with malignant myeloma. The overall results exclude the presence of any large increased risk for lymphomas or leukaemia.

b)   *Experimental animal data*

VC is a multispecies, multiorgan carcinogen. It induces benign and malignant tumours in several organs of various species, both in males and females. The most prominent feature is the induction of the rare angiosarcomas, especially in the liver. This phenomenon has been demonstrated in different strains of mice and rats, as well as in hamsters. Other tumours include nephroblastomas and neuro-

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blastomas, hepatocellular carcinomas, mammary gland carcinomas and lung adenomas.

VC is genotoxic, causing alterations and damage to DNA. VC metabolites bind to the DNA yielding promutagenic DNA adducts. Mutations and chromosomal abnormalities have been described in many *in vitro* and *in vivo* systems. These genotoxic processes play a significant role in tumorigenesis, while cell proliferation, secondary to the VC-induced cell toxicity, may also be involved in the process.

10.1.2 Dose-response analysis

10.1.2.1 Non-neoplastic effects

a) *Human data*

The published studies examining non-neoplastic diseases in VC-exposed subjects do not provide dose-response information.

b) *Experimental animal data*

Several short-term and long-term studies have been assessed for establishing the NOAEL of VC. Liver cell polymorphism (variation in size and shape of hepatocytes and their nuclei) reported in the feeding study by Til et al. (1991) is recommended for quantifying non-cancer risks from oral exposure to VC. The severity and incidences of this liver lesion were statistically significantly increased at a daily dose of 1.3 mg/kg body weight but not at 0.13 mg/kg per day (Table 46), the no-observed-adverse-effect level (NOAEL) therefore being 0.13 mg/kg per day. Basophilic liver cell foci induction in the study of Til et al. (1991) occurred at lower concentrations, but it was not considered by the Task Group to be a manifestation of hepatocytic toxicity.

A lowest-observed-adverse-effect level (LOAEL) of 26 mg/m^3 was established based on a subchronic (3–12 months) inhalation toxicity study in male rats by Bi et al. (1985). The basis for the estimation was the increased relative liver weight and mild testicular degeneration (Table 47), both effects being more pronounced in a dose-related manner at the two higher dose levels tested (260 and 7800 mg/m^3). A recent inhalation two-generation reproduction study with VC in rats,

Table 46. Type and incidence of treatment-related liver-cell polymorphism
of rats orally exposed to vinyl chloride (from Til et al., 1991)

	Males				Females			
N (total/group)	100	100	100	50	100	100	100	50
Dose mg/kg per day	0	0.014	0.13	1.3	0	0.014	0.13	1.3
Liver cell polymorphisms	No of animals with liver cell polymorphism of varying severity							
Slight	27	23	26	19	46	41	49	23
Moderate	4	4	7	10[b]	14	13	8	15[a]
Severe	1	1	1	3	2	3	4	9[c]

[a] $P < 0.05$ [b] $P < 0.01$ [c] $P < 0.001$

Table 47. Damage of testes induced by different concentration
of vinyl chloride (from Bi et al., 1985)

Group	No. of animals	Slight damage	Moderate damage	Severe damage	Total	%
Control	74	9	3	2	14	18.9
10 ppm [a]	74	14	5	3	22	29.7
100 ppm [b]	74	19	5	3	27	36.5 [d]
3000 ppm [c]	75	29	8	5	42	56.0 [e]

[a]   26 mg/m^3 [b]   260 mg/m^3 [c]   7770 mg/m^3
[d]   P < 0.05   [e]   P < 0.001

using exposure concentrations of 26, 260 and 2860 mg/m^3 (Shah, 1998), yielded the same LOAEL value. In this study, increased relative liver weights and hypertrophy of centrilobular hepatocytes were found in parental animals at all dose levels and a dose-dependent manner.

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10.1.2.2 Neoplastic effects

a) *Human data*

In most epidemiological studies dose–response analyses were not available. Of the two largest studies conducted in the USA and Europe, the USA study examined only duration of exposure and did not examine dose–response. In the European study a calendar period-, job- and plant-specific job exposure matrix was used. Expert judgement was used to estimate exposures for the early time periods when no measurements were available. The use of such a matrix implies that, when assigning the exposure index to individuals in the cohorts, a certain degree of misclassification occurs tending to underestimate the strength of a dose–response relationship.

All of the results in this section are from the European study (Simonato et al., 1991) unless otherwise noted. A clear dose-response relationship was found only for ASL alone or in combination with other primary liver cancers.

In all the analyses of liver cancer in the European cohort there is a clear relationship with increasing estimated doses. The effect is most evident for ASL, for which the risk estimate in the highest exposure groups is two and half times larger than for all liver cancers (Tables 48 and 49). These results are consistent with the analyses published by Wu and colleagues in the updating of one of the USA subcohorts. In this study, the average cumulative exposure score to VC was 6 times higher for ASL cases than for other liver cancer cases and control subjects.

Results from the regression models in the European study indicated that cumulative dose appears as the most powerful determinant of ASL, followed by time since first exposure. This can also be seen from Table 50. The results from the regression models indicated that there was only a small or no effect of calendar period and age of hire. Both duration and intensity of exposure correlated with liver cancer risk (see Table 41).

Dose–response analyses for lung cancer, brain tumours and lymphomas are reported in section 8.3.

Table 48. Maximum likelihood estimates for final model with
cumulative exposure and years since first employment
for deaths from liver cancer (N = 24) [a]

Exposure variable	Relative risk	95% confidence interval
Cumulative exposure (ppm–years)		
< 500	1.0	
500–1999	1.2	0.1–11.4
2000–5999	4.6	1.0–21.0
6000–9999	12.2	2.5–59.6
$ 10 000	17.1	3.1–93.6
Years since first employment		
0–19	1.0	
20–24	5.6	1.4–22.4
$ 25	6.8	1.7–27.4

[a]   From: Simonato et al. (1991)

Table 49. Maximum likelihood estimates for final model with
cumulative exposure and years since first employment
for deaths from angiosarcoma of the liver (N = 22) [a]

Exposure variable	Relative risk	95% confidence interval
Cumulative exposure (ppm–years)		
< 2000	1.0	
2000–5999	6.8	1.1–41.7
6000–9999	24.7	4.1–150.1
$10 000	45.4	7.3–281.1
Years since first employment		
0–19	1.0	
20–24	4.7	1.0–22.8
$25	6.2	1.4–29.0

[a]   From: Simonato et al. (1991)

Table 50. Absolute risk of angiosarcoma of the liver
per 100 000 (Simonato et al., 1991)

Years since first employment	Cumulative exposure (ppm–years)			
	< 2000	2000–5999	6000–9999	$10 000
0–19	1.0	6.8	24.4	44.8
20–24	4.7	32.0	115.6	212.5
$25	6.2	42.2	152.3	280.0

b) *Experimental animals data*

Studies using short- and long-term oral and inhalation exposure were carried out to assess the carcinogenic activity of VC (section 7.7.) For assessing carcinogenic risk, pivotal studies have been selected where the study design, exposure levels, observation period and histopathological examinations are regarded as suitable for assessing risk.

For oral exposure, it is recommended that female rats from the Feron et al. (1981) study be used to quantify risk for VC, because the incidence of liver tumour-bearing animals is greater than in males, giving a more conservative estimate. Rats with either neoplastic liver nodules, hepatocellular carcinomas and/or ASLs should be included for quantification. These lesions are all dose-related. The neoplastic nodules, while not malignant, have the potential to progress to malignancy. While it is uncertain that VC induces tumour types other than ASL in humans, tumour type concordance is not considered to be necessary, and thus inclusion of all liver tumours is desirable as a conservative approach.

If quantification is desired for ASL only, then the male rat is recommended because the incidences for this end-point are higher in males (Table 51). Including animals with angiosarcomas in other organs is unnecessary because the only other site with significantly increased incidences of this tumour type is the lung, and, with one exception, all animals with ASL also had liver tumours.

Table 51. Tumour incidences in oral feed study with vinyl chloride
in Wistar rats (from Feron et al., 1981)

Dose (mg/kg bw)	Neoplastic liver nodules	Hepato-cellular carcinomas	Liver angio-sarcomas	Liver tumour-bearing rats	Mammary adeno-carcinomas
Females					
0	2/57	0/57	0/57	2/57	3/57
1.7	26/57	4/58	0/57	28/58	2/58
5.0	39/59	19/59	2/59	49/59	4/59
14.1	44/57	29/57	9/57	56/57	7/57
Males					
0	0/55	0/55	0/55	0/55	
1.7	1/58	1/58	0/58	2/58	
5.0	7/56	2/56	6/56	11/56	
14.1	23/59	8/59	27/59	41/59	

For inhalation exposure, several studies have been conducted in different species (section 7.7). Four experiments with similar design and experimental conditions, carried out by Maltoni et al. (1981, 1984) in rats, were used for assessing carcinogenic risk after VC inhalation exposure. Out of the treatment-related carcinogenic responses, ASL, all vascular tumours of the liver and all liver tumours combined were considered to be suitable for assessing risk (Table 52). Induction of ASL is a special feature of VC and since this tumour type was also observed in exposed humans, this end-point was considered especially relevant for quantification of risk.

For ASL, increased incidence was observed in both males and females. A clear dose–response relationship could be established in female rats, and the effect was also suggestive in males. A similar trend could be observed if all vascular tumours or all liver tumours were considered. The other tumours, however, occurred only at low incidences. The lowest dose at which ASL and other vascular tumours were detected was 26 mg/m^3 in females and 65 mg/m^3 in males.

Table 52. Liver tumours in inhalation studies on rats
(from Maltoni et al., 1981, 1984)

Exposure (mg/m^3, 4 h/d, 5 d/w)	Exposure (mg/m^3, continuous) [a]	Number of animals	% ASL	% liver vascular tumours [b]	% all liver tumours [b]
Males					
0	0	222	0	0	0
2.6	0.3	58	0	0	0
13	2	59	0	0	0
26	3	59	0	0	0
65	8	60	1.7	1.7	1.7
130	15	174	1.1	2.3	2.3
260	31	60	0	1.7	1.7
390	46	60	1.7	1.7	1.7
520	62	60	11.7	15.0	16.0
650	77	29	3.4	3.4	4.4
1300	155	30	0	0	0
6500	774	30	20.0	20.0	20.0
15 600	1857	29	10.3	10.3	10.3
26 000	3095	30	10.0	10.0	11.0
Females					
0	0	239	0	0	0
2.6	0.3	60	0	0	0
13	2	60	0	0	0
26	3	60	6.7	6.7	6.7
65	8	60	6.7	8.3	8.3
130	15	180	7.2	10.6	10.6
260	31	60	1.7	1.7	1.7
390	46	60	8.3	8.3	8.3
520	62	60	8.3	11.7	15.0
650	77	30	6.7	10.0	10.0
1300	155	30	20.0	20.0	36.7
6500	774	30	23.3	23.3	30.0
15 600	1857	30	33.3	40.0	43.3
26 000	3095	30	13.3	13.3	13.3

[a]   Exposure calculated to correspond to 24 h/day, 7 days/week
[b]   % of animals with tumours were added, because no individual animal data
were available.

Nephroblastomas and neuroblastomas have also been observed in some studies in rats after VC exposure. These rare tumours appeared in a dose- and time-dependent manner; the doses required for tumour induction were, however, higher than those for ASL.

Several inhalation studies of VC in mice have been carried out. The induced spectrum of tumours was similar to that in rats: angiosarcomas and angiomas of the liver and other organs, mammary gland and lung tumours. In one study (Maltoni et al., 1981, 1984), a clear dose–response relationship was observed for ASL as well as for all vascular tumours in the female mice (Table 53). The lowest carcinogenic dose was 130 mg/m^3, higher than that in rats.

Mammary gland adenocarcinomas were observed in several VC studies. Four inhalation studies with VC in Sprague-Dawley rats (Maltoni et al., 1981, 1984) were evaluated (Table 54). A statistically significantly increased incidence in mammary gland carcinoma was observed in three of the four studies. However, in none of these studies was a clear dose–response relationship observed. Increased incidences of mammary carcinomas, without a dose–response relationship, were also observed in Swiss mice after inhalation exposure (Maltoni et al., 1981, 1984). Drew et al. (1983) exposed Fischer-344 rats to 0 or 261 mg/m^3 either for 6 or 12 months. Increased incidences of mammary adenocarcinomas were observed in the animals exposed at different ages but, since only one exposure level was used, a dose–response relationship could not be established. In Syrian hamsters, using similar study design but an exposure level of 520 mg/m^3 (Drew et al., 1983), a high incidence of mammary tumours was observed in animals exposed early in life.

In two other mouse studies (Lee et al., 1978; Drew et al., 1983), elevated incidences of both mammary gland carcinomas and other mammary tumours were observed. However, these studies were also inadequate for risk assessment. In summary, increased incidence of mammary gland carcinomas were observed in several experiments where animals were exposed to VC, either orally or by inhalation, indicating treatment-related carcinogenic effect. However, the lack of dose–response or the use of a single dose excluded the use of these data for risk assessment.

Table 53. Incidences of different tumour types in Swiss mice after inhalation exposure to vinyl chloride (from Maltoni et al., 1981, 1984 BT4)

Exposure (mg/m^3)	Effective number	ASL	Angiosarcoma (other organs)	Angioma (liver)	Angioma (other organs)	Total vascular tumours	Mammary gland	Lung adenoma
Males								
0	80	0	0	0	1	1	0	8
130	30	1	1	0	1	3	0	3
650	30	9	2	6	2	17	0	24
1300	30	6	2	1	1	10	1	24
6500	29	6	4	2	0	12	0	18
15 600	30	2	0	2	2	6	0	23
26 000	26	1	0	1	2	4	0	20
Females								
0	70	0	1	0	0	1	1	7
130	30	0	0	1	4	5	13	3
650	30	9	1	5	1	17	12	17
1300	30	8	5	4	2	10	9	26
6500	30	10	4	3	1	12	10	22
15 600	30	11	1	5	1	6	9	24
26 000	30	9	1	5	2	4	14	26

Table 54. Incidence of mammary gland carcinomas in Sprague-Dawley rats and Swiss mice after inhalation exposure to vinyl chloride (from Maltoni et al., 1981, 1984) [a]

Exposure (mg/m^3)	BT15 (rat)	BT1 (rat)	BT2 (rat)	BT9 (rat)	BT4 (mouse)
0	6/60 (10)	0/29	1/100 (1)	5/50 (10)	1/70 (1.4)
2.6	12/60 (20)				
13	22/60 (36.6) [d]				
26	21/60 (35) [c]				
65	15/60 (25)				
130		2/30 (6.6)		59/150 (39) [d]	13/30 (43.3) [d]
260			3/60 (5)		
390			6/60 (10) [c]		
520			5/60 (8) [b]		
650		2/30 (6.6)			12/30 (40) [d]
1300		1/30 (3.3)			9/30 (30) [d]
6500		2/30 (6.6)			10/30 (33.3) [d]
15 600		0/30			9/30 (30) [d]
26 000		3/30 (10)			14/30 (46.6) [c]

[a]   Values are no. of tumour / no. of animals, with percentages in parentheses; statistical significance compared to the concurrent control group (two tailed Fischer)
[b] $P \# 0.05$
[c] $P \# 0.01$
[d] $P \# 0.001$

10.1.3 *Human exposure*

The aim of this section is to estimate present levels of exposure to VC of the general population and of subpopulations with special exposure, such as those living near point sources of VC and those exposed at work. The purpose is to indicate worst-case scenarios rather than average or most likely exposures.

The data available are very limited both in time and space. Often the distance of the sampler from the point source or the sampling and

averaging times have not been reported. This makes the comparison of results from different studies difficult.

10.1.3.1 General population

The main sources of VC exposure for the general population are VC/PVC plants, biodegradation of chlorinated solvents in landfills, spills of chlorinated solvents from, for instance, dry cleaning shops, and the metal and electronic industry. In addition, small amounts of VC may be liberated from PVC.

There are no known natural sources of VC. Concentrations of VC in ambient air samples were reported to range from < 0.013 to 26 : g/m^3. These data were collected in the 1970s and 1980s from rural, remote, suburban and urban sites. The concentrations measured in rural and suburban/urban sites were similar. There is a lack of recent data on ambient air, making it difficult to conclude whether there has been a historical reduction in ambient concentrations. The exposure to VC via inhalation by the general population (non-occupational exposure) is estimated not to exceed 10 : g/kg body weight per day, using the derivation method described in Environmental Health Criteria 170: Assessing Human Health Risks of Chemicals: Derivation of Guidance Values for Health-based Exposure Limits (IPCS, 1994).

Concentrations (probably daily means) of VC measured in ambient air from industrial areas were reported to be < 8000 : g/m^3 in the 1970s and < 200 : g/m^3 and 4800 : g/m^3 in the 1980s in different geographical areas. Monthly mean concentrations measured in the vicinity of one plant during the 1990s ranged from 0.1 to 1.3 : g/m^3. Exposure of the general population living in the vicinity of industrial areas was estimated not to exceed 3000 : g/kg per day in the 1970s, 70–1800 : g/kg per day in the 1980s and 0.5 : g/kg per day in the 1990s.

VC concentrations in air sampled from the vicinity of waste sites ranged from < 0.08 to 104 : g/m^3. These concentrations were reported in air sampled during the 1980s and 1990s; no historical trend could be established. Exposure of the general population living in the vicinity of landfills was estimated to be # 300 : g/kg per day.

There are no data on VC concentrations in air from other areas contaminated with chlorinated hydrocarbons.

Sources of VC in indoor air have included PVC products, smoking, paints and aerosol propellants. Up to the 1970s, the VC concentration in PVC exceeded 1000 mg/kg, and consequently VC was detected in indoor air and cars. Since the late 1970s the VC content in PVC has been regulated to approximately 1 mg/kg, therefore VC concentrations are now unlikely to be significant in indoor air, except where there are nearby external sources such as landfills, etc.

The general population may be exposed to VC in drinking-water. In the majority of water samples analysed, VC was not present at detectable concentrations. The maximum VC concentration reported in drinking-water was 10 : g/litre, leading to a maximum exposure of 0.2 : g/kg per day. There is a lack of recent data on concentrations in drinking-water, but these levels are expected to be below 10 : g/litre. In groundwater near point sources, very high (up to 200 mg/litre) concentrations of VC have been observed and well water nearby may be a very significant source of VC: daily intakes may reach 5000 : g/kg per day. Some recent studies have identified VC in PVC-bottled drinking-water at levels below 1 : g/litre. The frequency of occurrence of VC in such water is expected to be higher than in tap water.

Dietary exposure to VC from PVC packages used for food has been calculated by several agencies, and, based upon estimated average intakes in the United Kingdom and USA, an exposure of < 0.0004 : g/kg per day was estimated for the late 1970s and early 1980s.

Exposure of the general population may be higher in situations where large amounts of VC are accidentally released to the environment, such as a spill during transportation. However, such exposure is likely to be transient.

10.1.3.2 Occupational exposure

Staff working in plants where VC is manufactured or polymerized into PVC or at landfills may be occupationally exposed to VC. Occupational exposure to VC has continually decreased since the

1940s. Since the 1970s, occupational exposure level (OEL) values have been set at 2.6 to 18 mg/m^3 in most European countries and the USA. Few data are available to determine how frequently the actual workplace exposures are within the OEL. Where data are available, compliance during the 1990s was reported in some European countries. Based upon an OEL of 18 mg/m^3, an occupational exposure of 3000 : g/kg per day can be calculated. The most recently reported average occupational exposure in these countries was 0.3 mg/m^3. This gives a daily dose of 50 : g/kg per day. However, concurrent exposure levels of more than 300 mg/m^3 have also recently been reported in some countries. Exposure to VC in PVC processing plants has been historically, and is probably currently, much lower than in PVC/VC production plants.

10.1.4 Risk characterization

VC has been shown to be carcinogenic and toxic in both oral and inhalation experimental bioassays, as well as in human epidemiological studies. Experimental studies have also shown that it is genotoxic and must be activated through a rate-limited pathway. In order to perform quantitative risk assessment using animal bioassays, it will be necessary to utilize a physiologically based pharmacokinetic model (PBPK) to derive the concentration of active metabolite at the critical target site, the liver, as well as to extrapolate dose from animals to humans. The PBPK model should be validated, taking into account the known metabolic pathways and using metabolic constants determined experimentally, and should not introduce too many unknown parameters. The Task Group was not in a position to evaluate accurately the available pharmacokinetic models for their suitability for risk assessment. Furthermore, in order to estimate the risk predictions from epidemiological studies, original data on exposed human populations, at the level of the individual, are required.

Some of the published PBPK models and risk assessments are reviewed in Annex 2.

10.2 Evaluation of effects on the environment

VC is released to the environment from plants where it is manufactured and/or used in the production of PVC. The most

important releases are emissions to the atmosphere, but VC may also be released in waste water. It may also be formed in the environment as a product of the biodegradation of chlorinated C_2 solvents. This route of VC formation may lead to emissions of VC from areas contaminated with chlorinated C_2 solvents, such as landfills.

The maximum VC concentration reported in surface water is 0.6 mg/litre. VC is unlikely to be bioaccumulated to a significant extent in aquatic organisms.

The only toxicity study which was deemed of sufficient quality to evaluate the effects of VC on aquatic organisms gave a 48-h LC_{50} of 210 mg/litre for a freshwater fish. There is a paucity of chronic toxicity data for aquatic organisms. Despite these limitations, owing to the rapid volatilization of VC, the low concentrations in surface water and the low acute toxicity to fish, VC is not expected to present a hazard to aquatic organisms.

There is a paucity of data for terrestrial organisms.

11. RECOMMENDATIONS FOR PROTECTION OF HUMAN HEALTH

11.1 Public health

The following measures should be taken:

C   worldwide application of production technologies leading to low residual VC levels in PVC;

C   implementation and enforcement worldwide of steps that guarantee minimal emissions of VC at production sites;

C   identification, surveillance and emission and exposure control of contaminated areas such as landfill sites.

11.2 Occupational health

Since VC is a genotoxic carcinogen, exposures should be kept as low as possible, using the best available technology worldwide.

More information, education and training of workers potentially exposed to VC regarding the risks involved and safe working procedures and habits is required.

Monitoring and record-keeping of exposure and record-keeping of exposed workers are needed.

12. FURTHER RESEARCH

The following topics need further research:

C follow-up of existing VC cohorts with quantitative exposure assessment;

C epidemiological studies of populations with defined and low exposure to VC;

C evaluation of the efficacy and usefulness of the medical surveillance of VC-exposed workers;

C validation of effects and susceptibility biomarkers for VC;

C the role of post-DNA-damage events in the carcinogenicity of VC and their relationships with target organ or cell type specificity;

C evaluation of the sensitivity to VC in early childhood and determination of possible mechanisms involved;

C the possibility of carcinogenicity of VC in mammary gland tumours and the mechanism involved;

C optimization of remediation of contaminated sites;

C studies on the toxicity of VC to aquatic and terrestrial organisms.

13. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

Vinyl chloride was evaluated by the International Agency for Research on Cancer (IARC, 1979) and the evaluation was updated in Supplement 7 (IARC, 1987). There was sufficient evidence for carcinogenicity of vinyl chloride in humans and sufficient evidence for carcinogenicity in animals; the overall evaluation was that vinyl chloride is carcinogenic to humans.

In the WHO Guidelines for Drinking-water Quality (WHO, 1996), using results from the rat bioassay of Til et al. (1983) and applying the linearized multistage model, the human lifetime exposure for a 10^{-5} excess risk of ASL was calculated to be 20 ：g/day. It was also assumed that in humans the number of cancers at other sites may equal that of ASL, so that a correction (factor of 2) for cancers other than ASL is justified. VC concentrations in drinking-water of 5 ：g/litre were calculated as being associated with excess risks of 10^{-5}.

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ANNEX 1. REGULATIONS CONCERNING VINYL CHLORIDE

1. Regulations regarding VC levels in PVC materials and food and drink

According to EC regulations PVC materials intended to come in contact with foodstuffs must not contain VC at levels > 1 mg/kg; the limit in the packed food is 10 : g/kg (CEC, 1978). The corresponding German regulation additionally includes commodities, toys and tricks, and articles which are for toiletry use (German Federal Health Office, 1998). The US FDA proposed to restrict the VC content of polymers used for food contact to 5–50 : g/kg (US FDA, 1986).

A limit value of 2 : g/litre was issued by the US EPA for drinking-water (US EPA, 1995b) and by the US FDA for bottled water (Anon, 1993). The Maximum Contaminant Level of the Californian Department of Health Services (DOHS) is 0.5 : g/litre (US EPA, 1995b). In Germany, there are recommendations to tolerate 2 : g/litre in drinking-water (German Federal Health Office, 1992).

2. Occupational exposure limit values for vinyl chloride

Some examples of present exposure limit values are given in Table 55.

Table 55. Occupational exposure limit values for vinyl chloride

Country/organization	Exposure limit description	Value (ppm)	Value (mg/m^3)	Reference
Europe; United Kingdom; Germany; Finland	personal 8-h TWA	7	18.2	CEC (1978); HSC (1995); BIA (1997)
		5	12.8	Finnish Government (1992)
Europe; United Kingdom; Germany; Finland	working area (annual)	3	8	CEC (1978); Finnish Government (1992); HSC (1995); BIA (1997)
Czech Republic, Slovakia, Hungary and Poland	MAC$_K$[a]		10	Bencko & Ungváry (1994)
USA	15 min	5	12.8	OSHA (1998)
	8 h	1	2.6	OSHA (1998)
	TLV 8-h TWA	1	2.6	ACGIH (1999)
		0[b]		NIOSH (1997)

[a] Maximal allowable concentration (K indicates the carcinogenic properties of VC)
[b] No detectable exposure
TLV = threshold limit value; TWA = time weighted average; OSHA = US Occupational Safety and Health Administration; ACGIH = US American Conference of Governmental and Industrial Hygienists Inc.; HSC = UK Health and Safety Commission; BIA = German Professional Associations Institute for Occupational Safety; Finnish Government = Government Resolution 919/92, Finland

ANNEX 2. PHYSIOLOGICAL MODELLING AND RECENT RISK ASSESSMENTS

1. Physiological modelling of toxicokinetic data for vinyl chloride

Physiologically based toxicokinetic (PBTK) models intend to predict the dose of active metabolites reaching target tissues in different species, including humans, and thereby to improve the toxicokinetic extrapolation in cancer risk assessments. PBTK models have also been used as a tool to examine the behaviour of VC in mammalian systems.

The model of Chen & Blancato (1989), also cited as a US EPA (1987) model, proposed a PBTK model based on the styrene model of Ramsey & Andersen (1984) with four compartments, representing the liver, a fat compartment that includes all of the fatty tissues, a richly-perfused tissue compartment that includes all organs except the liver, and a slowly perfused compartment that includes muscular and skin tissues. Liver was assumed to be the sole metabolizing organ, and the metabolism of VC was assumed to occur via one pathway following Michaelis-Menten-kinetics and saturable at high concentration levels. Physiological parameters (e.g., body weight, lung weight, ventilation rate, tissue volume and blood flows to various tissue groups) were reference values from US EPA. This model was validated by Clement International Corporation (1990) with gas uptake experiments in rats and with data sets available in the literature (Gehring et al., 1978). At concentrations # 65 mg/m³ the model fitted observed data, but at higher concentrations the model predicted a greater amount of VC metabolism than observed.

A second model (Gargas et al., 1990) was a generic model of volatile chemical kinetics in a recirculated closed chamber, which was used to identify global metabolic parameters in the rat for a number of chemicals including VC. It incorporated a second, linear metabolic pathway (presumed to be glutathione conjugation) in parallel with the saturable (oxidative) pathway.

Continuing on from these above models, Clement International Corporation (1990) re-fitted the one- and two-pathway descriptions to

gas uptake data and then compared their predictions to measurements of total metabolism by Gehring et al. (1978) and Watanabe et al. (1976b). Two refinements to the model were investigated: 1) reaction of VC with glutathione (GSH), or 2) the products of both the saturable and the linear pathways were assumed to react with GSH. Neither description fitted both total metabolism and GSH depletion data and the authors suggested a new PBTK model featuring two saturable oxidative pathways, both producing reactive metabolites. Clewell et al. (1995a) developed a more elaborate model of VC based on the suggestions from Clement International Corporation (1990). The initial metabolism of VC was hypothesized to occur via two saturable pathways (one representing high affinity, low capacity oxidation by CYP2E1 and one representing low affinity, high capacity oxidation by other P-450 isozymes), producing in both cases chloroethylene oxide (CEO) as an intermediate product. CAA (from CEO) was modelled as the major substrate in GSH conjugation, with a lesser amount of CEO as the glutathione transferase substrate. The model was similar to that proposed by Chen & Blancato (1989) with regard to number and type of compartments, physiological parameters and the assumption that metabolism of VC takes place solely in the liver. Partition coefficients taken from literature data (Gargas et al., 1989) were used. The metabolic parameters for the two oxidative pathways were estimated from gas uptake experiments conducted by Clement International Corporation (1990). In this model it is assumed that the reactive VC metabolites were further degraded to carbon dioxide, or reacted with GSH or with cellular material. Parameters for subsequent metabolism were taken from the PBTK model for vinylidene chloride (D'Souza & Andersen, 1988) and were also used for species other than the rat after appropriate allometric scaling, i.e., metabolic capacity scales approximately according to body weight raised to ¾ power (Andersen et al., 1987). Support for the use of this principle for VC comes from data on the metabolism of VC in non-human primates (Buchter et al., 1980). In humans there is no evidence of a low-affinity high-capacity oxidation by other P-450 isozymes so this parameter was set at zero for humans. There is a wide variability of human CYP2E1 activity of about an order of magnitude, whereas in inbred strains typically used in animal studies the variability in CYP2E1 activity is small. The Clewell model was then used to calculate dose metrics for ASL in animal bioassays (Maltoni et al., 1981, 1984; Feron et al., 1981) as well as for human inhalation exposure (see Table 56).

Reitz et al. (1996) developed a PBTK model for VC similar to that proposed by Clewell et al. (1995a) with a single saturable pathway based on a model for methylene chloride (Andersen et al., 1987) with modifications on the size of liver compartment and allometric constants. Partition coefficients were obtained from Gargas et al. (1989). Metabolic parameters were calculated from gas uptake experiments with male and female Sprague-Dawley rats. Metabolic parameters for mice and humans were estimated from these experimental data on rats and interspecies ratios obtained from literature (Andersen et al., 1987). The model has been validated against data on total metabolism in the rat (Watanabe et al., 1976b), gas uptake data in the mouse, and inhalation data in the human on exhaled concentrations of VC following VC exposure (Baretta et al., 1969).

2. Recent risk assessments of VC

2.1 Simonato et al. (1991)

Simonato et al. (1991) performed a regression analysis from epidemiological data (see sections 8.2 and 8.3) to assess the relative risk of liver cancer and ASL in occupational exposure to VC using the variables cumulative exposure (ppm-years) and years since first employment (Tables 48 and 49). On the basis of this regression analysis and including cumulative exposure and years since first exposure in the model, the absolute risk of ASL per 100 000 was calculated (Table 50).

2.2 Clewell et al. (1995b)

A PBTK model was used to predict the total production of reactive metabolites from VC in the animal bioassays and in human exposure scenarios. These measures of internal exposure were then used in the linearized multistage model (LMS) (Crump, 1984) to predict the risk associated with lifetime exposure to VC in air or drinking-water.

The most appropriate toxicokinetic dose metric for a reactive metabolite was considered to be the total amount of the metabolite generated divided by the volume of the tissue in which it is produced (Andersen et al., 1987), which, in the case of VC and ASL, would be the total amount of metabolism divided by the volume of the liver.

Specifically, the average amount generated in a single day is used, averaged over the lifetime (i.e., the lifetime average daily dose, or LADD). The use of a dose rate such as LADD, rather than total lifetime dose, has been reported to provide a better cross-species extrapolation of chemical carcinogenic potency (D'Souza & Andersen, 1988). According to the authors, a body surface area adjustment is no longer necessary when using a LADD.

The animal bioassays used are shown in Table 56. The 95% upper confidence limits on the human risk estimates for lifetime exposure to 2.6 : g VC/m^3 (1 ppb) were then calculated on the basis of each of the sets of bioassay data, using the LMS model. The risk estimates on inhalation studies in rats agreed with those in mice and were also comparable with those from studies on rat diet. The estimates on oral gavage were much higher ($\times$ 6), which the authors suggested might be due to the use of corn oil.

Table 56. Human risk estimates (per million) for lifetime exposure to
2.6 : g VC/m^3 (1 ppb) air based on the incidence
of ASL in animal bioassay [a]

Animal bioassay study	95% UCL risk/million per ppb		Reference
	Males	Females	
Mouse inhalation	1.52	3.27	Maltoni et al. (1981, 1984)
Rat inhalation	5.17	2.24	Maltoni et al. (1981, 1984)
Rat diet	3.05	1.10	Feron et al. (1981)
Rat gavage	8.68	15.70	Maltoni et al. (1981, 1984)

[a] From: Clewell et al. (1995b); UCL = the 95% upper confidence limit of the human risk estimates for lifetime exposure to 2.6 : g VC/m^3 (1 ppb)

Risk calculations were also carried out on the basis of epidemiological data using a linear relative risk dose-response model (see Table 57). A PBTK model was run for the exposure scenario appropriate to each of the selected subcohorts from each of the studies.

Table 57. Human risk estimates (per million) for lifetime inhalation
of 2.6 : g VC/m^3 (1 ppb) air based on the incidence of
ASL in human epidemiological studies [a]

95% UCL risk/million per ppb [b]	Epidemiological study
0.71–4.22	Fox & Collier (1977)
0.97–3.60	Jones et al. (1988)
0.40–0.79	Simonato et al. (1991)

[a] From: Clewell et al. (1995b)

[b] The range of risk estimates reflects uncertainty in the appropriate value for P_0, the background probability of death from liver cancer. The lower risk estimate was calculated using the value of P_0 used in the study of Fox & Collier (1977), while the higher risk estimate was calculated using an estimate of the lifetime liver cancer mortality in the USA population (Chen & Blancato, 1989). Therefore there is not a true range but a reflection of two assumptions about the background rate of liver cancer in humans.

To obtain an estimate of the carcinogenic potency, the resulting internal dose metrics were multiplied by the appropriate durations to obtain the cumulative internal doses, which were then input into the relative risk model together with observed and expected liver cancer deaths for each subcohort. A 95% upper confidence limit on the lifetime risk per ppb of VC was estimated to compare results with the animal-based results obtained with the LMS model. The estimates from the three epidemiological studies compared well with those from the toxicokinetic animal-based studies. From the Simonato data, a 0.4 to 0.8×10^{-6} risk per ppm VC was estimated, which Clewell et al. (1995b) noted is about 30 below the published inhalation unit risk of 8.4×10^{-6} (: g/m^3)$^{-1}$. A carcinogenic risk estimate of ASL from a lifetime exposure to 1 : g VC/litre in human drinking-water was 1.14×10^{-6} (: g/litre)$^{-1}$ and was derived from Feron's study on male rats after dietary administration of VC. This value was compared with the published unit risk of 5.4×10^{-5} (: g/litre)$^{-1}$ (US EPA, 1995a).

2.3   Reitz et al. (1996)

Reitz et al. (1996) used a PBTK model to calculate LADDs and these were fit to a LMS model. The data generated in rats were used

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to predict ASL incidence in mice and were found to fit with the data from Maltoni's experiment BT 4 and those of Lee et al. (1978).

The PBTK model was used to calculate LADDs for humans: mg VC metabolites formed/day per litre of liver tissue for conditions thought likely to have been present in the workplace in past years (i.e., VC concentrations 50–2000 ppm; 8 h/day; 5 days/week and 10 or 20 years/70 years). From these estimates of dose the LMS model was used to estimate the likelihood that tumours would be produced based on the rat model. These results were then compared with the actual data from Simonato et al. (1991). Predictions using this PBTK model were substantially higher (10–35 fold) than actually observed in humans (see Table 58). But the PBTK-based value for the 95% UCL for excess lifetime risk associated with continuous inhalation of $1 : g/m^3$ was 5.7×10^{-7}, compared with the much higher risk, 8.4×10^{-5}, using conventional risk estimates (US EPA, 1995a). Reitz et al. (1996) concluded that even using the PBTK model, the risk of ASL is overestimated and suggested that the livers of humans are less sensitive to the carcinogenic effect of reactive VC metabolites than the livers of the commonly used inbred laboratory rodents.

2.4 *Storm & Rozman (1997)*

Storm & Rozman (1997) use a no-threshold (LMS model and benchmark dose approach with linear extrapolation) and threshold (NOEL/LOEL and benchmark dose uncertainty factor approaches) models and compare them with the present occupational exposure limits in the 0.5 to 5 ppm range (Table 59). Although VC is a genotoxic carcinogen, the authors argued that for VC a threshold exists because DNA adducts formed by reaction with vinyl chloride metabolites are repaired by DNA glycosylase in both rat and human liver *in vitro* (Dosanjh et al., 1994; Saparbaev et al., 1995), and only when repair capability is exceeded does cancer develop (Swenberg et al., 1995).

Storm & Rozman (1997) used Maltoni's inhalation study with Sprague-Dawley rats (Maltoni et al., 1981) and, after adjusting all exposures to reflect equivalent continuous human exposures and then to LADD in mg/kg-day, used these dose measures in the low-dose extrapolation models. (Occupational exposures were derived by converting appropriately derived LADDs to equivalent occupational

Table 58. Predicted versus observed ASL incidence for humans
assuming occupational exposure to VC [a]

Ppm	Years exposed	Ppm-years	Linearized multistage prediction based on animal studies (incidence/100 000)	Human observed (incidence/100 000)
100	10	1000	374 [b]	6.2 [e]
50	20	1000	376 [b]	6.2 [e]
200	20	4000	1465 [b]	42.2 [f]
1	45	45	21 [c]	0 [g]
			6–11 [d]	

[a] From: Storm & Rozman (1997)

[b] Derived by Reitz et al. (1996) assuming an occupational exposure of 5 days/week, 50 weeks/year

[c] Calculated from unit risk derived by Reitz et al. (1996), assuming occupational rather than continuous exposures

[d] Calculated from human risk/million per ppb based on Simonato et al. (1991) derived by Clewell et al. (1995b), assuming occupational rather than continuous exposures

[e] Derived by Simonato et al. (1991) for exposure < 2000 ppm-years and $ 25 years since first employment

[f] Derived by Simonato et al. (1991) for exposure 2000–5999 ppm-years and $ 25 years since first employment

[g] No ASL reported among workers first exposed in or after 1974 when the OSHA permissible exposure limit (PEL) of 1 ppm was promulgated.

exposures, assuming an inhalation rate of 10 m^3/working day and that exposures occurred 8 h/day, 50 weeks/year for 45 years).

No-threshold models evaluated were the LMS model for extrapolation of genetic carcinogen dose–response curves to low doses, and the benchmark dose approach (BMD) with linear extrapolation (US EPA, 1996). Maximum likelihood estimates (MLE) and 95% UCL (q_i*) on the linear coefficient (q_i) were derived using a LMS model. The resultant linear coefficients from these and the results from Reitz et al. (1996) described above using the PBTK model were then used to derive safe levels of occupational exposure. For the BMD approach, a computer programme was used to derive MLEs as well as 95% lower bound (LB) estimates for specified risk

levels along with X^2 goodness-of-fit statistics, in this case $P > 0.01$. The MLE and LB of both the exposure associated with 10% incidence (ED_{10} and LED_{10}) and the exposure associated with 1% incidence (ED_{01} and LED_{01}), respectively, were used for linear extrapolation to zero (US EPA, 1996). "Safe" levels of occupational exposure were derived from the slopes of these lines.

Threshold models evaluated included a) the LOEL/NOEL uncertainty factor approach traditionally used for non-carcinogenic effects and b) the BMD and uncertainty factor approach being developed as a replacement for the former. A NOEL of 13 mg/m^3 (5 ppm) was derived from the Maltoni et al. (1981) bioassay in rats. An uncertainty factor of 2 was applied to account for the half-lifetime exposure duration of the VC study, a standard uncertainty factor of 10 to account for potential intraspecies variability in susceptibility, an interspecies uncertainty factor of 3 or 0.3 to cover the assumption that humans were more or less sensitive than rats in this study giving total uncertainty factors of 60 or 6, respectively. The same factors were applied to MLE and LB estimates of dose using the BMD curve-fitting approach.

The X^2 goodness-of-fit P value for the BMD curve was only acceptable when the apparent outliers at 100 and 250 ppm and high-dose responses at 500, 2500 and 6000 ppm were eliminated, and these values were therefore also eliminated in the LMS model for purpose of comparison.

Both no-threshold models based on administered dose provide estimates of occupational safe levels of about 0.004 ppm, at least two orders of magnitude lower than the present accepted "safety" limit value of 0.5–5 ppm when using an acceptable level of risk of 1 in 100 000 (1×10^{-5}). With the PBTK model, estimates were about 0.04 ppm. For threshold models, using the BMD curve-fitting approach, with an ED_{01} and LED_{01} point of departure, occupational levels of 0.1 to 0.7 ppm, respectively, were estimated for humans less or more sensitive than rats. Estimations based on the rat NOEL approach gave values of 0.4 to 4 ppm, respectively, for humans more and less sensitive than rats.

Table 59. Comparison of estimated safe levels for occupational
exposure to VC (from Storm & Rozman, 1997)

No-threshold models			Slope $(mg/kg\text{-}day)^{-1}$	Risk 1/100 000 assuming occupational exposure [a] (ppb)
Linearized multistage	Administered dose [b]	MLE	1.4×10^{-2}	4.3
		UCL	1.8×10^{-2}	3.4
	PBTK dose [c]	MLE	1.6×10^{-3}	39.4
		UCL	2.0×10^{-3}	31.2
	US EPA [d]	UCL	2.9×10^{-1}	0.2
Benchmark dose	ED_{01}-Point of departure	MLE	1.4×10^{-2}	4.3
		LB	1.8×10^{-2}	3.4

Threshold models			BMD [b] $(mg/kg\text{-}day)$	Uncertainty factor	Risk 1/100 000 assuming occupational exposure [a] (ppm)
Benchmark dose-ED_{01}	Humans less sensitive	MLE	0.7	6 [e]	0.7
		LB	0.5	6 [e]	0.7
	Human = rat sensitivity	MLE	0.7	20 [f]	0.2
		LB	0.5	20 [f]	0.2
	Humans more sensitive	MLE	0.7	60 [g]	0.1
		LB	0.5	60 [g]	0.1

			LADD $(mg/kg\text{-}day)$	Uncertainty factor	Risk 1/100 000 assuming occupational exposure [a] (ppm)
Rat NOEL (5 ppm)	Humans less sensitive		3.6	6 [e]	3.8
	Human = rat sensitivity		3.6	20 [f]	1.1
	Humans more sensitive		3.6	60 [g]	0.4

[a] Occupational exposures assume 10 m^3/day inhalation rate, 5 days/week, 50 weeks/year, for 45 years averaged over a lifetime of 70 years (Note: Levels are ppb for no-threshold models, ppm for threshold models)

[b]   Derived using a computer programme

[c]   Slope from Reitz et al. (1996)

[d]   Slope from US EPA Health Effects Assessment Summary Tables (US EPA, 1995)

[e]   Safety factors of 10 for intraspecies, 0.3 for interspecies extrapolation and 2 for half-lifetime exposure

[f]   Safety factors of 10 for intraspecies extrapolation and 2 for half-lifetime exposure

[g]   Safety factors of 10 for intraspecies, 3 for interspecies extrapolation, and 2 for half-lifetime exposure

MLE = maximum likelihood estimate; UCL = 95% upper confidence limit;

LB = 95% lower bound on dose

ANNEX 3. EXECUTIVE SUMMARY OF VINYL CHLORIDE PANEL REPORT

Executive summary of

Mundt KA, Dell LD, Austin RA, Luippold RS, Noess R & Bigelow C. *Epidemiological study of men employed in the vinyl chloride industry between 1942 and 1972: I. Re-analysis of mortality through December 31, 1982; and II. Update of mortality through December 31, 1995.* Final Report. Arlington, Virginia: The Vinyl Chloride Panel, Chemical Manufacturers Association, January 8, 1999. 178 pages [a]

A cohort of 10 109 men who were employed for at least one year in vinyl chloride exposed jobs between 1942 and 1972 at any one of 37 facilities in the USA or Canada was followed for mortality. Through December 31, 1995, a total of 3191 deaths had occurred among cohort members. A re-analysis of mortality through December 1982, at which time 1569 deaths had occurred, was conducted to establish baseline results against which the updated mortality results could be compared. The re-analysis of mortality through December 1982 was necessary for four reasons: (1) the cohort was reduced from 10 173 to 10 109 after the removal of study subjects who were duplicates or were not eligible for cohort inclusion; (2) a substantial proportion of cohort members previously lost to follow-up were identified and restored to the cohort; (3) an appropriate referent population, based on regional mortality rates, was constructed and used for the mortality update through 1995; and (4) the number of categories of death that could be evaluated in the analysis increased from 61 to 92 causes of death.

Through 1995, mortality from all causes of death was 17% lower than state mortality weighted according to person-years accumulated

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among employees in the state where the plant was located. This result was similar to the 16% deficit seen for mortality from all causes of death through 1982. Mortality from all cancers, however, showed a deficit of 4% through 1995, in contrast with the 2% excess seen as of 1982. Specific cancers showing meaningful excesses both through 1982 and through 1995 included cancers of the liver and biliary tract, brain, and connective and soft tissues. However, several causes of death previously believed to be related to vinyl chloride exposure were not seen in excess, including lung cancer, cancers of lymphatic and haematopoietic tissue, emphysema and pneumoconioses and other lung diseases, including chronic obstructive pulmonary disease (COPD).

Through 1995, mortality from liver and biliary tract cancer, including angiosarcoma of the liver, was significantly increased (SMR=359; 95% CI: 284–446) although the excess was smaller than that observed through 1982 (SMR=428; 95% CI: 304–585). The SMR for liver and biliary tract cancer increased with duration of exposure from 83 (95% CI: 33–171) to 215 (95% CI: 103–396) to 679 (95% CI: 483–929) to 688 (95% CI: 440–1023) for those exposed from 1 to 4 years, 5 to 9 years, 10 to 19 years and 20 years or more, respectively. The SMR for liver and biliary tract cancer also increased with time since first exposure from 0 (no deaths observed) to 287 (95% CI: 131–544) to 323 (95% CI: 200–493) to 434 (95% CI: 322–572) for those 1 to 9 years, 10 to 19 years, 20 to 29 years, and 30 or more years since first exposure, respectively. Results of a Cox proportional hazards model that fitted age at first exposure, duration of exposure, and year of first exposure indicated that duration of exposure was most strongly associated with increased risk of mortality from liver and biliary tract cancer. The adjusted hazards ratio for 1 to 4 years, 5 to 9 years, 10 to 19 years and 20 years or more duration of exposure were 1.0 (referent group), 2.8 (95% CI: 1.0–7.3), 9.0 (95% CI: 4.0–20.7) and 6.0 (95% CI: 2.5–14.4), respectively. This confirms the recognized association between vinyl chloride exposure and liver and biliary tract cancer, mainly due to a large excess of angiosarcoma of the liver.

Mortality from brain cancer showed an excess (SMR=142; 95% CI: 100–197) that was slightly smaller than that seen in the re-analysis through 1982 (SMR=169; 95% CI: 105–255). Since 1982, an additional 14 brain cancer deaths were observed (12.2 expected). The SMRs for brain cancer were elevated among those exposed for 5 to

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9 years (SMR=193; 95% CI: 96–346) and those exposed for 20 years or more (SMR=290; 95% CI: 132–551). Results of a Cox proportional hazards model adjusted for duration of employment showed that age at employment of 35 years or older and longer duration of employment were both associated with increased risk of mortality from brain cancer, and these associations were not confounded. The association of brain cancer deaths with vinyl chloride exposure is uncertain, as the older age at first employment in the vinyl chloride industry suggests that these cohort members might have sustained exposure to some other carcinogen prior to employment in vinyl chloride.

Mortality from cancers of the connective and soft tissues also showed an excess (SMR=270; 95% CI: 139–472), based on 12 deaths. Through 1982, mortality from connective and soft tissue cancers was also elevated (SMR=367; 95% CI: 147–755), based on seven observed deaths. This result was not reported in earlier investigations of this cohort because mortality for this cause of death category had not been previously evaluated. Although the total number of deaths due to this rare cause was small, the observed excess is potentially important for two reasons. First, very little is known about the risk factors for connective and soft tissue cancers, a category including numerous histological types of cancer. Second, some of these cancers may have been mis-diagnosed or mis-reported angiosarcomas of the liver, one form of soft tissue sarcoma known to be related to vinyl chloride exposure.

No excesses in mortality were seen for lung cancer or cancers of the lymphatic and haematopoietic system. In contrast to the previous report which showed an excess of mortality from emphysema and chronic obstructive disease, mortality from emphysema and mortality from pneumoconioses and other respiratory diseases (PORD), the category which included chronic obstructive pulmonary disease, each showed deficits (SMR=61; 95% CI: 40–89 for emphysema and SMR=73; 95% CI: 60–88 for PORD). The previously published findings with respect to mortality due to these causes of death may have resulted from methodological errors.

In conclusion, this update of the industry-wide cohort confirmed a strong association between duration of employment in the vinyl chloride industry prior to 1974 and cancers of the liver and biliary

tract, mostly resulting from a large excess of deaths due to angiosarcoma of the liver. This association has been observed in all similar studies and represents one of the most consistent effects observed in the occupational health literature. Cancers of the connective and soft tissues, though occurring in relatively small numbers, also appear to be related to employment in the industry. The elucidation of the actual mechanism for this observed association will require further investigation. The brain cancer mortality excess observed in the analyses through 1982 is less clearly associated with vinyl chloride, and may reflect risk factors other than vinyl chloride present in the early years of the industry or reflecting exposures sustained prior to employment in this industry. Since 1982, no such excess has occurred.

This study represents one of the largest and longest-followed cohorts potentially exposed to substantial levels of vinyl chloride. The brain cancer and emphysema excesses previously reported are not sustained, however, the brain cancer excess remains unexplained. Except for deaths due [to] cancers of the liver and biliary tract, and to a lesser extent cancers of connective and soft tissues, the mortality patterns for this cohort remain at or below that expected in the general population.

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RESUME

La présente monographie traite du chlorure de vinyle monomère lui-même, à l'exclusion de son polymère, le chlorure de polyvinyle (PVC). Le problème de l'exposition à des mélanges contenant du chlorure de vinyle n'est pas abordé.

1. Identité, propriétés physiques et chimiques et méthodes d'analyse

Dans les conditions ambiantes, le chlorure de vinyle se présente sous la forme d'un gaz incolore inflammable à l'odeur douceâtre. Sa tension de vapeur est élevée, de même que la valeur de sa constante pour la loi d'Henry; sa solubilité dans l'eau est relativement faible. Il est plus lourd que l'air et il est soluble dans presque tous les solvants organiques. On le transporte à l'état liquide sous pression.

A la température ambiante et en l'absence d'air, le chlorure de vinyle pur et sec est très stable et non corrosif. Toutefois, au-dessus de 450 °C ou en présence d'hydroxyde de sodium ou de potassium, il peut subir une décomposition partielle. Sa combustion dans l'air donne naissance à du dioxyde de carbone et à du chlorure d'hydrogène. En présence d'air et d'oxygène, des peroxydes très explosifs peuvent se former, ce qui exige une surveillance permanente et la limitation de la teneur en oxygène, en particulier dans les installations de récupération du chlorure de vinyle. En présence d'eau, il se forme de l'acide chlorhydrique.

Du point de vue industriel, ce sont les réactions de polymérisation conduisant au chlorure de polyvinyle qui sont techniquement les plus importantes, mais les réactions d'addition des halogènes sur la double liaison, qui conduisent au 1,1,2-trichloréthane ou au 1,1-dichloréthane, ont aussi leur importance.

On peut surveiller la concentration de chlorure de vinyle dans l'atmosphère en piégeant le composé sur un support adsorbant et en procédant à une analyse par chromatographie en phase gazeuse après désorption liquide ou thermique. Pour le dosage dans l'air ambiant, il peut être nécessaire d'utiliser plusieurs supports adsorbants ou pièges froids disposés en série pour mieux capter le composé. Les pics

de concentration sur les lieux de travail peuvent se mesurer au moyen d'instruments à lecture directe utilisant notamment des détecteurs à ionisation de flamme ou à photo-ionisation. Pour le contrôle en continu, ont utilise des analyseurs basés sur la spectrophotométrie infrarouge ou sur la chromatographie en phase gazeuse avec détection par ionisation de flamme et qui sont munis d'un système d'enregistrement et de traitement des données. Pour doser le chlorure de vinyle dans les liquides et les solides, on a recours à l'injection directe, à l'extraction et de plus en plus, à la technique de l'espace de tête ou à celle de purgeage-piégeage. Pour l'analyse de ces échantillons, on utilise aussi la chromatographie en phase gazeuse avec détection par ionisation de flamme ou spectrométrie de masse.

2. Sources d'exposition humaine dans l'environnement

Le chlorure de vinyle n'existe pas à l'état naturel, même si on en a décelé la présence dans les gaz qui s'échappent des décharges et dans les eaux souterraines, par suite de la décomposition de rejets de solvants constitués d'hydrocarbures chlorés, ou encore dans l'environnement des lieux de travail où on fait usage de ce genre de solvants. Il y a également du chlorure de vinyle dans la fumée de cigarette.

La production industrielle du chlorure de vinyle utilise deux réactions principales: a) l'hydrochloration de l'acétylène et b) le craquage thermique (à environ 500 °C) du 1,2-dichloréthane produit par chloration ou oxychloration directes de l'éthylène par le chlore ou par un mélange HCl + air/O_2. Ce procédé est actuellement le plus couramment utilisé.

La production mondiale de PVC et par conséquent celle de chlorure de vinyle monomère a été d'environ 27 millions de tonnes en 1998. Vingt pour cent des matières plastiques utilisées dans le monde sont à base de PVC et ce polymère se retrouve dans presque tous les secteurs de l'industrie. Environ 95% de la production mondiale de chlorure de vinyle sert à la fabrication de PVC. Le reste est utilisé pour la production de solvants chlorés, essentiellement du 1,1,1-trichloréthane (10 000 tonnes par an).

Trois procédés principaux sont utilisés pour la production industrielle du PVC: la polymérisation en suspension (80% de la production mondiale), la polymérisation en émulsion (12%) et la polymérisation en masse (8%). La plupart des études de cas faisant état des effets nocifs du chlorure de vinyle concernent des usines produisant du PVC par polymérisation en suspension (on dit aussi *polymérisation en perles*).

On a signalé des émissions de chlorure de vinyle lors d'accidents survenus dans des usines produisant du PVC ou pendant le transport. Dans de nombreux pays, on récupère le chlorure de vinyle résiduel non polymérisé lors de la production de PVC ou qui se trouve dans les rejets gazeux ou les eaux usées. Faute de certaines précautions, il est possible de retrouver du chlorure de vinyle dans les résines et autres produits à base de PVC.

Le taux de chlorure de vinyle résiduel présent dans le PVC est réglementé dans de nombreux pays depuis la fin des années 1970. Depuis lors, les émissions de chlorure de vinyle dues à la décomposition thermique du PVC sont soit indétectables, soit très faibles.

Des dioxines peuvent se former lors de la production de chlorure de vinyle. Les quantités qui sont répandues dans l'environnement sont controversées.

3. Transport, distribution et transformation dans l'environnement

En raison de sa forte tension de vapeur, le chlorure de vinyle libéré dans l'environnement devrait exister presque uniquement en phase gazeuse. Il existe des indices de dépôts sous forme liquide.

Le chlorure de vinyle est relativement peu soluble dans l'eau et sa capacité d'adsorption aux particules et aux solides en suspension est faible. C'est par volatilisation que le composé s'élimine le plus rapidement des eaux de surface. La demi-vie de volatilisation à partir des eaux de surface varie d'environ 1h à 40 h.

A partir du sol, la demi-vie de volatilisation est, selon les calculs, égale à 0,2–0,5 jours. On estime que les pertes de chlorure de vinyle (au bout d'un an sous un mètre de terre) vont de 0,1 à 45%, selon le type de sol. Le coefficient de sorption pédologique tiré des données physico-chimiques indique que le potentiel de sorption du composé est faible et que par conséquent il est très mobile dans le sol. Il existe une autre voie importante de distribution dans l'environnement, à savoir le lessivage qui peut entraîner le chlorure de vinyle jusqu'aux nappes d'eau souterraines où il est susceptible de persister pendant des années.

Les études de laboratoire portant sur des organismes aquatiques révèlent une certaine tendance à la bioaccumulation, mais pas de bioamplification le long de la chaîne alimentaire.

A quelques exceptions près, le chlorure de vinyle ne se laisse pas facilement dégrader par les groupements de microorganismes inadaptés dans les conditions ambiantes. On estime que la demi-vie de biodégradation par des micro-organismes non acclimatés est de l'ordre de plusieurs mois ou années. Toutefois, certaines cultures microbiennes enrichies ou pures (par exemple *Mycobacterium* sp.) sont capables de décomposer le chlorure de vinyle lorsque les conditions culturales sont optimales. Les principaux produits de dégradation sont l'acide glycolique ou le dioxyde de carbone après conversion aérobie et l'éthane, l'éthylène, le méthane ou le chlorométhane après transformation anaérobie. Souvent, les microorganismes aérobies décomposent plus rapidement le chlorure de vinyle que les microorganismes anaérobies.

Le principal processus atmosphérique est la réaction avec les radicaux OH produits par voie photochimique; la demi-vie troposphérique résultant de ce processus est de 1 à 4 jours. Les réactions de photolyse réalisées dans des conditions expérimentales donnent naissance à plusieurs composés importants, comme le chloracétaldéhyde, le formaldéhyde et le chlorure de formyle.

On pense que les réactions de photolyse, de même que l'hydrolyse chimique, sont de peu d'importance en milieu aqueux. Toutefois, la présence de photosensibilisateurs peut faciliter la transformation du chlorure de vinyle.

On a des raisons de penser que le chlorure de vinyle réagit avec le chlore ou les chlorures utilisés pour la désinfection de l'eau pour donner du chloracétaldéhyde et autres composés indésirables. Il existe d'autres interactions possibles, notamment avec les sels, dont un grand nombre sont susceptibles de former des complexes avec le chlorure de vinyle, ce qui peut en accroître la solubilité.

Parmi les méthodes utilisées (avec des succès divers) pour éliminer le chlorure de vinyle présent dans l'eau, on peut citer le lavage, l'extraction, l'adsorption et l'oxydation. Certaines méthodes de biopurification (applicables aux eaux souterraines et aux sols) associent l'évaporation ou d'autres techniques à un traitement microbien. Le chlorure de vinyle présent dans les rejets gazeux peut être recyclé, incinéré ou décomposé par voie microbienne. La majeure partie du chlorure de vinyle produit industriellement se retrouve à l'état lié dans des articles en PVC. L'incinération de ces produits comporte un risque de formation de PCDD, de PCDF et d'autres dérivés chlorés indésirables.

4. Concentrations dans l'environnement et exposition humaine

La population dans son ensemble est très peu exposée au chlorure de vinyle.

La concentration de chlorure de vinyle dans l'air ambiant est faible, généralement inférieure à 3 : g/m^3. La population peut être davantage exposée lorsque de grandes quantités de chlorure de vinyle sont libérées accidentellement dans l'environnement, par exemple en cas de déversement pendant le transport. Il s'agit cependant d'une exposition qui a toutes chances d'être passagère. A proximité de sites industriels où l'on produit du chlorure de vinyle et du PVC ou près de décharges, on a enregistré des concentrations beaucoup plus élevées (pouvant aller respectivement jusqu'à 8000 : g/m^3 et 100 : g/m^3).

La principale voie d'exposition professionnelle est la voie respiratoire et elle intervient principalement dans les usines qui produisent du chlorure de vinyle et du PVC. Dans les années 1940 et 1950, l'exposition professionnelle au chlorure de vinyle était de plusieurs milliers de mg/m^3; elle atteignait encore plusieurs centaines

de mg/m^3 dans les années 1960 et au début des années 1970.Une fois reconnu le risque cancérogène inhérent au chlorure de vinyle, la norme d'exposition à ce composé a été fixée au cours des années 1970 à environ 13–26 mg/m^3 (5–10 ppm) dans la plupart des pays. Le respect de ces directives a fait fortement chuter la concentration du chlorure de vinyle sur les lieux de travail, mais au cours des années 1990 on a tout de même fait état de concentrations plus élevées et ce pourrait encore être le cas actuellement dans quelques pays.

Il est arrivé que l'on trouve du chlorure de vinyle dans les eaux de surface, dans les sédiments et dans les boues d'égout, avec des concentrations maximales respectivement égales à 570 : g/litre, 580 : g/kg et 62 000 : g/litre. Des échantillons de sol prélevés près d'une teinturerie abandonnée se sont révélés présenter une forte teneur en chlorure de vinyle (jusqu'à 900 mg/kg) . On a mis en évidence des concentrations de l'ordre de 60 000 : g/litre ou davantage dans des eaux souterraines ou dans des eaux de lessivage provenant de zones contaminées par des hydrocarbures chlorés. Des teneurs élevées (jusqu'à 200 mg/litre) ont également été mises en évidence, 10 ans après le repérage des premières fuites, dans l'eau de puits situés à proximité d'une usine de PVC.

Les quelques données disponibles montrent que les tissus des petits vertébrés aquatiques et des poissons peuvent contenir du chlorure de vinyle.

Dans la majorité des échantillons d'eau de boisson analysés, le chlorure de vinyle n'était pas présent à des concentrations décelables. La concentration maximale dont il ait été fait état était de 10 : g/litre dans de l'eau prête à être consommée. On manque de données récentes sur la concentration du composé dans l'eau de boisson, mais elle devrait être inférieure à 10 : g/litre. Si la source utilisée pour la boisson est contaminée, l'exposition peut être plus importante. Des études récentes ont permis de déceler la présence de chlorure de vinyle dans de l'eau minérale en bouteilles de PVC à une concentration inférieure à 1 : g/litre. On peut penser que la présence de chlorure de vinyle est plus fréquente dans ces eaux en bouteilles que dans l'eau du robinet.

L'utilisation de PVC pour l'emballage peut entraîner la présence de chlorure de vinyle dans les denrées alimentaires, les produits

pharmaceutiques et les cosmétiques. On en a décelé jusqu'à 20 mg/kg dans des liqueurs, jusqu'à 18 mg/kg dans des huiles végétales et jusqu'à 9,8 mg/kg dans du vinaigre. Depuis le début des années 1970, le nombre d'échantillons contrôlés positifs pour le chlorure de vinyle est moindre et la concentration est plus faible qu'auparavant, grâce aux mesures législatives prises par un certain nombre de pays.

Plusieurs organismes ont calculé l'exposition au chlorure de vinyle due à la contamination des denrées alimentaires par leur emballage de PVC. En se basant sur valeur estimative moyenne de la dose ingérée au Royaume-Uni et aux Etats-Unis, on a calculé qu'à la fin des années 1970 et au début des années 1980, l'exposition devait être inférieure à 0,0004 : g/kg par jour. Une étude ancienne a mis évidence du chlorure de vinyle dans la fumée de tabac à des concentrations de quelques ng par cigarette.

5. Cinétique et métabolisme chez les animaux de laboratoire et l'Homme

Après inhalation ou ingestion, le chlorure de vinyle est facilement et rapidement absorbé. Des études effectuées sur des animaux et des sujets humains, dans des conditions d'équilibre dynamique, ont montré qu'environ 40% de la dose inhalée étaient absorbés après exposition par la voie respiratoire. L'expérimentation animale montre que l'absorption peut dépasser 95% après ingestion. L'absorption percutanée de chlorure de vinyle à l'état gazeux est peu importante.

Les données fournies par les études sur l'inhalation et l'ingestion de chlorure de vinyle par des rats montrent que le composé se répartit rapidement et largement dans l'organisme. Par suite d'une métabolisation et d'une excrétion rapides, son accumulation est limitée. Chez le rat, le passage transplacentaire se produit rapidement. On n'a pas connaissance d'études consacrées à la répartition du composé dans l'organisme après exposition par voie percutanée.

Après inhalation ou ingestion, la principale voie métabolique consiste en une oxydation par le cytochrome P-450 (CYP2E1) qui conduit à la formation d'oxyde de chloréthylène, un époxyde à courte vie extrêmement réactif, qui se transpose très vite en chloracétaldéhyde. La principale réaction de détoxication de ces deux

métabolites réactifs ainsi que de l'acide chloracétique, produit de déshydrogénation du chloracétaldéhyde, consiste en une conjugaison avec le glutathion catalysée par la glutathion-*S*-transférase. Les conjugués sont ensuite transformés en dérivés de la cystéine [*S*-(2-hydroxyéthyl)cystéine, *N*-acétyl-*S*-(2-hydroxyéthyl)cystéine, *S*-carboxyméthylcystéine et acide thiodiglycolique] et ils sont excrétés dans l'urine. Un autre métabolite, le dioxyde de carbone, est excrété dans l'air exhalé.

Les isozymes de la CYP2E1 et de la glutathion-*S*-transférase présentent d'importantes variations d'activité interspécifiques et interindividuelles.

Après exposition par inhalation ou ingestion de faibles doses de chlorure de vinyle, le composé est éliminé par métabolisation et ses métabolites non volatils sont principalement excrétés par la voie urinaire. L'étude comparée de l'absorption après inhalation montre que relativement au poids corporel, le chlorure de vinyle est métabolisé moins rapidement par l'organisme humain que par l'organisme animal. Toutefois, si on tient compte de la superficie du corps, on constate que la clairance métabolique est comparable chez l'Homme et chez les autres mammifères. Lorsque l'exposition - toujours par inhalation ou ingestion – est plus importante, la principale voie d'excrétion chez l'animal consiste dans l'élimination du composé initial dans l'air expiré, ce qui témoigne de la saturation des voies métaboliques. Quelle que soit la dose, l'excrétion par la voie fécale est secondaire. On n'a pas trouvé d'étude qui soit spécialement consacrée à l'excrétion par la voie biliaire.

On estime que l'oxyde de chloréthylène est le métabolite le plus important *in vivo*, pour ce qui est des effets cancérogènes et mutagènes du chlorure de vinyle. Cet époxyde réagit sur d'ADN pour former un certain nombre d'adduits, principalement de la 7-(2*N*-oxoéthyl)guanine (7-OEG) et, en moindre quantité, des éthénoadduits exocycliques comme la 1,*N*^{6}-éthénoadénine (, A), la 3,*N*^{4}-éthénocytosine (, C) et la *N*^{2},3-éthénoguanine (, G). Contrairement à l'adduit principal, la 7-OEG, ces éthénoadduits avec l'ADN ont des propriétés promutagènes . On a pu doser la 7-OEG, la , A, la , C et la , G dans les divers tissus de rongeurs exposés à du chlorure de vinyle. On a mis au point des modèles toxicocinétiques à base physiologique

pour rendre compte de la relation entre la dose aux tissus cibles et les points d'aboutissement toxicologique du chlorure de vinyle.

6. Effets sur les mammifères de laboratoire et les systèmes d'épreuve *in vitro*

Administré par inhalation à des animaux de plusieurs espèces, le chlorure de vinyle s'est révélé d'une faible toxicité aiguë. La CL_{50} à 2 h pour le rat, la souris, le cobaye et le lapin a été trouvée respectivement égale à 390 000, 293 000, 595 000 et 295 000 mg/m^3. On ne possède aucune donnée sur la toxicité aiguë du composé par voie orale ou percutanée. L'inhalation brutale de chlorure de vinyle a un effet stuporeux. Chez des rats, des souris et des hamsters, la mort a été précédée d'un accroissement de l'activité motrice, d'ataxie et de convulsions suivies d'une défaillance respiratoire. Chez des chiens plongés dans un état stuporeux après exposition brutale à une concentration de 260 000 mg/m^3, on a noté de graves arythmies cardiaques. Des rats, exposés par la voie respiratoire à du chlorure de vinyle, ont présenté un certain nombre d'anomalies anatomopathologiques telles que congestion des organes internes, notamment des poumons, du foie et des reins, et oedème pulmonaire.

On ne dispose pas d'études ni de données appropriées qui permettent d'évaluer les effets de l'exposition par voie percutanée ou encore le pouvoir irritant ou sensibilisateur au niveau cutané.

Une exposition de courte durée (13 semaines) au chlorure de vinyle par la voie orale a permis d'obtenir une valeur de 30 mg/kg pour la NOEL, c'est-à-dire la dose sans effet observable, le critère retenu étant l'augmentation du poids du foie.

Chez plusieurs espèces, le principal organe cible après exposition de courte durée (jusqu'à 6 mois) par voie respiratoire se révèle être le foie. Chez des rats soumis à une dose de 26 mg/m^3 (la dose la plus faible utilisée) on a constaté une augmentation du poids relatif du foie et des modification hépatocellulaires; à dose plus élevée ($ 260 mg/m^3), les anomalies hépatiques étaient plus prononcées et dépendaient de la dose. Les autres organes cibles étaient le rein, le poumon et le testicule. Les rats, les souris et les lapins se sont révélés plus sensibles que les cobayes et les chiens.

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Une exposition de longue durée par la voie respiratoire a entraîné une augmentation statistiquement significative de la mortalité chez certaines souches de rats à des doses ne dépassant pas 260 mg/m³, chez des souris à la dose de 130 mg/m³ et chez des hamsters à la dose de 520 mg/m³ sur des durées d'exposition variables. Des rats exposés à une dose de 130 mg/m³ ont présenté une diminution du poids corporel et une augmentation du poids relatif de la rate ainsi qu'une dégénérescence hépatocellulaire et une prolifération des cellules pariétales des capillaires sinusoïdes. A dose plus élevée, on a noté une dégénérescence testiculaire, une néphrose tubulaire et des foyers de dégénérescence au niveau du myocarde. Chez des rats et des souris exposés par la voie respiratoire la dose sans effet nocif observable (NOAEL) est inférieure à 130 mg/m³ pour ce qui est des effets cancérogènes.

Des études d'alimentation de longue durée ont fait ressortir une augmentation de la mortalité, un accroissement du poids du foie et une modification de la morphologie de cet organe.

Après exposition par la voie orale, on a observé un polymorphisme hépatocellulaire (variation de la taille et de la forme des hépatocytes et de leur noyau) chez des rats soumis à des doses de chlorure de vinyle ne dépassant pas 1,3 mg/kg de poids corporel. La NOAEL était égale à 0,13 mg/kg de poids corporel.

Après administration prolongée à des rats de chlorure de vinyle dans des granulés de PVC par la voie alimentaire, on a observé un accroissement significatif de l'incidence des tumeurs au niveau du foie. Il s'agissait d'angiosarcomes à la dose quotidienne de 5,0 mg/kg p.c., et de nodules néoplasiques (femelles) ou de carcinomes hépato-cellulaires (mâles) à la dose de 1,3 mg/kg p.c.

Des études au cours desquelles on a fait inhaler du chlorure de vinyle à des rats Sprague-Dawley ont fait ressortir une relation dose-réponse dans le cas des angiosarcomes du foie et, à forte concentration, pour les carcinomes de la glande de Zymbal. En revanche, on n'a pas observé de relation dose-réponse bien nette dans le cas des hépatomes ou des angiosarcomes extrahépatiques, des néphroblastomes, des neuroblastomes ou des tumeurs des glandes mammaires. Chez la souris, le spectre tumoral induit par une

exposition respiratoire de longue durée est analogue à celui que l'on observe chez le rat, mais on a aussi noté une augmentation des tumeurs pulmonaires propre à la souris. Chez des hamsters, on a relevé une augmentation de l'incidence des angiosarcomes hépatiques, des tumeurs des glandes mammaires et du conduit auditif, des mélanomes et des épithéliomas gastriques et cutanés.

Un certain nombre de systèmes d'épreuve *in vitro* ont permis de mettre en évidence les effets mutagènes et génotoxiques du chlorure de vinyle, surtout après activation métabolique. Le composé s'est révélé mutagène dans le test d'Ames sur les souches TA100, TA1530 et TA1535 de *S. typhimurium*, à l'exclusion des souches TA98, TA1537 et TA1538, ce qui dénote des mutations par substitution de paires de bases (transversion et transition) plutôt que des mutations par décalage du cadre de lecture. Ces résultats concordent avec une autre observation, à savoir que les éthénoadduits qui se forment lors de l'attaque de l'ADN par l'oxyde de chloréthylène et par le chloracétaldéhyde aboutissent effectivement à des mutations par substitution de paires de bases.

D'autres tests de mutation génique effectués sur des bactéries, des levures et des cellules mammaliennes ont donné des résultats positifs, mais seulement en présence d'activation métabolique. Des effets mutagènes ont également été observés dans des lignées cellulaires humaines contenant le cytochrome P-450IIE1 obtenu par clonage, qui est capable de métaboliser le chlorure de vinyle. On a aussi décelé des mutations dans des fragments d'un végétal (*Tradescantia*) mis en présence de chlorure de vinyle. Des tests de conversion génique ont donné des résultats positifs dans le cas de *Saccharomyces cerevisiae* en présence d'un système d'activation métabolique. En présence de chlorure de vinyle, des hépatocytes de rat ont été le siège d'une synthèse non programmée de l'ADN et un accroissement des échanges entre chromatides-soeurs a été observé dans des lymphocytes humains après addition d'un système activateur exogène. Chez des bactéries dont le système de réparation de l'ADN était défectueux, on n'a pas décelé d'inhibition de la croissance en l'absence de système activateur. Les tests de transformation cellulaire ont donné des résultats positifs avec ou sans activation métabolique.

Chez *Drosophila melanogaster*, l'exposition au chlorure de vinyle a provoqué des mutations géniques et des recombinaisons mitotiques, mais ces effets n'ont pas été observés sur des cellules germinales de mammifères. Le composé a des effets clastogènes chez des rongeurs, il augmente les échanges entre chromatides-soeurs chez le hamster et provoque la rupture des brins de l'ADN chez la souris. Des tests par passage sur hôte (rat) ont montré que le chlorure de vinyle provoquait une conversion génique et les mutations directes chez des levures.

L'oxyde de chloréthylène et le chloracétaldéhyde se sont révélés mutagènes dans un certain nombre de systèmes. L'oxyde de chloréthylène est un mutagène puissant, alors que le chloracétaldéhyde est fortement toxique. Ces deux composés sont cancérogènes pour la souris, l'oxyde de chloréthylène étant de loin le plus actif.

Les mutations observées au niveau des gènes *ras* et *p53* ont été analysées sur des tumeurs hépatiques induites chez des rats Sprague-Dawley par du chlorure de vinyle: dans les carcinomes, on a constaté la présence de substitutions de paires de bases au niveau du gène Ha-*ras;* dans les angiosarcomes, ces substitutions intéressaient le gène *p53*. La présence de ces mutations concorde avec la formation, observée après exposition au chlorure de vinyle, d'éthénoadduits persistants dans l'ADN des hépatocytes, éthénoadduits dont on connaît le caractère promutagène.

L'étude du mécanisme par lequel s'exerce l'effet cancérogène du chlorure de vinyle donne à penser que l'intermédiaire réactif que constitue l'oxyde de chloréthylène attaque l'ADN pour former des éthénoadduits, ce qui conduit à la substitution de paires de bases et à la transformation néoplasique.

7. Effets sur l'Homme

L'exposition à des concentrations de l'ordre de 2590 mg/m^3 (1000 ppm), qui n'étaient pas rares avant 1974, pendant des périodes de 1 mois à plusieurs années, seraient à l'origine d'un syndrome pathologique particulier observé chez des ouvriers travaillant sur le chlorure de vinyle et appelé "maladie du chlorure de vinyle". Les symptômes évoqués consistaient en douleurs auriculaires et céphalées, étourdissements, troubles visuels, fatigue et perte d'appétit, nausées,

insomnies, essoufflement, douleurs au niveau de l'estomac et dans la région du foie et de la rate, douleurs et picotements dans les membres, sensation de froid aux extrémités, diminution de la libido et perte de poids. Sur le plan clinique, on a relevé au niveau des doigts des modifications à type de sclérodermie évoluant vers des anomalies osseuses qualifiées d'acro-ostéolyse, avec des anomalies de la circulation périphérique identiques à celles qui sont caractéristiques de la maladie de Raynaud, une hypertrophie du foie et de la rate d'histologie particulière et des manifestations respiratoires.

Les études sur l'Homme ne sont pas suffisantes pour pouvoir confirmer la présence d'effets sur la fonction de reproduction. Un certain nombre d'études font état d'une augmentation de l'incidence des affections de l'appareil circulatoire chez des ouvriers travaillant sur le chlorure de vinyle. Toutefois, les études effectuées sur des cohortes d'effectif plus important ont mis en évidence une diminution de la mortalité due aux maladies cardiovasculaires.

Les études épidémiologiques fournissent une argumentation solide et cohérente tendant à prouver que l'exposition au chlorure de vinyle provoque une forme rare de cancer, l'angiosarcome du foie. On a également établi un lien entre certaines tumeurs cérébrales ou carcinomes hépatocellulaires et le chlorure de vinyle, sans qu'on puisse considérer les données obtenues à cet égard comme définitives. Les autres localisations où l'on a observé une augmentation des cancers sont le poumon, les tissus lymphatiques et hématopoïétiques et la peau.

Le chlorure de vinyle a des effets mutagènes et clastogènes chez l'Homme. On a ainsi constaté que chez des ouvriers exposés à de fortes concentrations de chlorure de vinyle, la fréquence des aberrations chromosomiques, des micronoyaux et des échanges entre chromatides-soeurs dans les lymphocytes du sang périphériques, était plus élevée que chez les témoins. Dans de nombreuses études, l'intensité et la durée de l'exposition ne sont qu'estimatives, mais on peut néanmoins observer l'existence d'une relation dose–réponse et une "normalisation" des effets génotoxiques avec le temps lorsque l'exposition diminue.

Des mutations ponctuelles ont été décelées au niveau des gènes *p53* et *ras* dans des tumeurs (angiosarcomes du foie) prélevées sur des

ouvriers très exposés travaillant sur des autoclaves (avant 1974) ainsi que dans un carcinome hépatocellulaire dont était porteur un autre ouvrier également exposé au chlorure de vinyle.

Parmi les marqueurs biologiques dont on a étudié la possibilité d'utilisation comme indicateurs d'une exposition au chlorure de vinyle, on peut citer a) l'excrétion de métabolites (par exemple l'acide thiodiglycolique), b) des marqueurs génétiques comme la présence d'anomalies chromosomiques ou de micronoyaux, c) le taux de certaines enzymes (par exemple celles qui sont mesurées dans les tests de la fonction hépatique), d) les oncoprotéines sériques et leurs anticorps en tant que biomarqueurs des effets induits par le chlorure de vinyle.

Les enfants qui vivent à proximité de décharges et autres sources ponctuelles d'exposition au chlorure de vinyle pourraient courir un risque accru, compte tenu de la sensibilité plus forte constatée chez les jeunes animaux. On n'a toutefois pas de preuves directes d'une telle sensibilité chez l'Homme.

C'est seulement dans le cas de l'angiosarcome du foie-seul ou en association avec d'autres tumeurs hépatiques - qu'une relation dose–réponse claire ressort des études épidémiologiques. Il n'existe qu'une seule étude épidémiologique qui ait produit des données suffisantes pour une estimation quantitative de la relation dose–réponse.

8. Effets sur les autres êtres vivants au laboratoire et dans leur milieu naturel

On manque des données toxicologiques habituelles au sujet de la survie et de la reproduction des organismes aquatiques exposés au chlorure de vinyle. Il faut interpréter avec prudence les données disponibles car pour la plupart, elles proviennent de tests au cours desquels on n'a pas mesuré les concentrations auxquelles ces organismes étaient exposés et il n'a donc pas été tenu compte des pertes par volatilisation.

La concentration la plus faible de chlorure de vinyle qui produise un effet sur des microorganismes a été trouvée égale à 40 mg/litre. Il

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s'agit d'une valeur de la CE_{50} obtenue lors d'un test statique de 3,5 jours sur des microorganismes anaérobies pour lequel le critère retenu était l'inhibition de la respiration.

La concentration la plus faible qui produise un effet sur des organismes supérieurs a été trouvée égale à 210 mg/litre (CL_{50} à 48 h pour un poisson d'eau douce); avec une concentration sans effet nocif observable (NOAEC) de 128 mg/litre. Chez d'autres espèces, on a constaté des effets à plus faible concentration, mais la portée écologique de ces effets n'a pas été vérifiée.

On peut prévoir que la concentration de chlorure de vinyle sans effet nocif pour les poissons d'eau douce se situe entre 0,088 et 29 mg/litre.

On manque de données concernant des effets du chlorure de vinyle sur les organismes terrestres.

RESUMEN

Esta monografía se ocupa exclusivamente del cloruro de vinilo
(VC) como monómero y no es una evaluación del cloruro de polivinilo
(PVC), polímero del VC. No se tratan las exposiciones a mezclas con
VC.

1. Identidad, propiedades físicas y químicas y métodos analíticos

En condiciones normales, el VC es un gas incoloro, inflamable,
con un olor ligeramente dulce. Tiene una presión de vapor alta, un
valor elevado para la constante de la Ley de Henry y una solubilidad
en agua relativamente baja. Es más pesado que el aire y soluble en
casi todos los disolventes orgánicos. Se transporta en forma líquida
bajo presión.

A temperatura ambiente en ausencia de aire, el VC purificado
seco es muy estable y no corrosivo, pero por encima de 450 °C, o en
presencia de hidróxido sódico o potásico, se puede producir una
descomposición parcial. La combustión del VC en el aire produce
anhídrido carbónico y cloruro de hidrógeno. En presencia de aire y de
oxígeno, se pueden formar peróxidos muy explosivos, por lo que hay
que mantener una vigilancia constante y limitar el contenido de
oxígeno, en particular en las plantas de recuperación de VC. En
presencia de agua se forma ácido clorhídrico.

Desde el punto de vista industrial, las reacciones de
polimerización para obtener PVC son técnicamente las más
importantes, aunque también lo son las reacciones de adición con
otros halógenos en el doble enlace, por ejemplo, para obtener 1,1,2-
tricloroetano o 1,1-dicloroetano.

La concentración de VC en el aire se puede vigilar mediante su
retención en adsorbentes y, tras la desorción líquida o térmica, el
análisis por cromatografía de gases. En las mediciones del aire
ambiente, se pueden necesitar varios adsorbentes en serie o colectores
refrigerados para aumentar la eficacia de la retención. Las
concentraciones máximas en los lugares de trabajo se pueden medir
con instrumentos de lectura directa, por ejemplo basados en la

detección por FID o la PID. En la vigilancia continua se han utilizado analizadores de rayos infrarrojos y de cromatografía de gases/detección de ionización de llama combinados con el registro y procesamiento de datos. En el análisis del VC en líquidos y sólidos se utilizan la inyección directa, la extracción y cada vez más las técnicas del espacio libre superior y de purga y retención. En estas muestras también se analiza el VC mediante cromatografía de gases, combinada, por ejemplo, con detectores de ionización de llama o de espectrometría de masas.

2. Fuentes de exposición humana y ambiental

No se tiene conocimiento de que el VC se produzca de forma natural, aunque se ha encontrado en los gases de vertedero y en el agua freática como producto de la degradación de hidrocarburos clorados depositados como residuos de disolventes en los vertederos o en el entorno de lugares de trabajo en los que se utilizan dichos disolventes. El VC también está presente en el humo de los cigarrillos.

La producción industrial de VC se lleva a cabo mediante dos reacciones principales: a) hidrocloración del acetileno; y b) descomposición térmica (a unos 500 °C) del 1,2-dicloroetano producido mediante cloración directa (etileno y cloro) o la oxicloración (etileno, ClH y aire/O_2) de etileno en el "proceso equilibrado". En la actualidad se utiliza más el segundo proceso.

La producción mundial de PVC (y por consiguiente de VC) en 1998 fue de unos 27 millones de toneladas. El PVC representa el 20% del material plástico utilizado y se emplea en la mayoría de los sectores industriales. Alrededor del 95% de la producción mundial de VC se utiliza para la fabricación de PVC. El resto se destina a la producción de disolventes clorados, fundamentalmente de 1,1,1-tricloroetano (10 000 toneladas/año).

Son tres los procesos principales que se utilizan en la fabricación comercial de PVC: suspensión (equivalente al 80% de la producción mundial), emulsión (12%) y en masa o a granel (8%). La mayoría de los estudios monográficos en los que se describen efectos adversos del VC se refieren a instalaciones que utilizan el proceso de suspensión (llamado también de dispersión).

Hay varios informes de liberación de VC a causa de accidentes en instalaciones de fabricación de PVC o durante el transporte. En numerosos países se ha introducido la recuperación del VC no convertido residual procedente de la polimerización y de otras fuentes del proceso, como por ejemplo los efluentes de gases residuales y de agua. Cuando no se toman precauciones especiales, se puede detectar VC en resinas y productos de PVC.

La concentración residual de VC en el PVC está reglamentada en muchos países desde finales de los años setenta. Desde entonces, la liberación de VC a partir de la degradación térmica del PVC no es detectable o se produce a niveles muy bajos.

En la producción de VC se pueden formar dioxinas como contaminantes. Las concentraciones de dioxinas liberadas al medio ambiente son un tema polémico.

3. Transporte, distribución y transformación en el medio ambiente

Debido a su alta presión de vapor, cabe esperar que el VC que se libera a la atmósfera se mantenga casi totalmente en la fase de vapor. Hay indicios de deposición húmeda.

La solubilidad del VC en agua es relativamente baja y su capacidad de adsorción a la materia particulada y los sedimentos escasa. La volatilización es el proceso más rápido de eliminación del VC que se incorpora al agua superficial. Se han notificado semividas para la volatilización del agua superficial que oscilan entre alrededor de una y 40 horas.

Las semividas de volatilización a partir del suelo se calcularon en 0,2–0,5 días. Las pérdidas estimadas de VC (tras un año bajo una cubierta de suelo de 1 m) oscilaron entre el 0,1% y el 45%, en función del tipo de suelo. Los coeficientes de sorción en el suelo estimados a partir de datos fisicoquímicos indican un potencial escaso y, por consiguiente, una movilidad alta en el suelo. Otra vía importante de distribución es la lixiviación a través del suelo hacia el agua freática, donde el VC puede persistir durante años.

En experimentos de laboratorio con organismos acuáticos se observó una cierta bioacumulación, pero no hubo bioamplificación en la cadena alimentaria.

Salvo en un pequeño número de excepciones, las agrupaciones microbianas no adaptadas no degradan fácilmente el VC en condiciones normales. Se estimó que las semividas de biodegradación máxima sin adaptación del VC eran del orden de varios meses o años. Sin embargo, los cultivos enriquecidos especiales o puros (por ejemplo, *Mycobacterium* spp.) son capaces de degradar el CV en condiciones de cultivo óptimas. Los productos principales de degradación fueron el ácido glicólico o el anhídrido carbónico tras la conversión aerobia y etano, eteno, metano o clorometano mediante transformación anaerobia. Con frecuencia, la reacción de degradación del CV es más rápida por vía aerobia que anaerobia.

El proceso predominante de transformación en la atmósfera es la reacción con radicales OH producidos por vía fotoquímica, dando lugar a semividas en la troposfera estimadas en 1–4 días. Durante las reacciones experimentales de fotolisis se generan varios compuestos críticos, como cloroacetaldehído, formaldehído y cloruro de formilo.

Se considera que las relaciones fotolíticas, así como la hidrólisis química, tienen escasa importancia en los medios acuosos. Sin embargo, la presencia de fotosensibilizadores puede potenciar la transformación del VC.

Hay indicios de que el VC reacciona con el cloro o el cloruro utilizado en la desinfección del agua, produciendo de esta manera cloroacetaldehído y otros compuestos no deseados. Otra posibilidad de interacción es con las sales, muchas de las cuales tienen la capacidad de formar complejos con el VC, aumentando tal vez su solubilidad.

Los métodos utilizados (con diferente éxito) para la eliminación del VC de las aguas contaminadas son la separación, la extracción, la adsorción y la oxidación. Algunas técnicas de biocorrección *in situ* (para el agua freática o el suelo) combinan la evaporación y otros métodos con el tratamiento microbiano. El VC de los gases de desecho se puede reciclar, incinerar o degradar por medios microbiológicos. La mayor parte del CV de producción industrial se

encuentra en los artículos de PVC. Con su incineración se corre el riesgo de que se formen dibenzodioxinas policloradas/dibenzofuranos policlorados y otros compuestos orgánicos clorados perjudiciales.

4. Niveles medioambientales y exposición humana

La exposición de la población general al VC es muy pequeña.

Las concentraciones atmosféricas de VC en el aire ambiente son bajas, normalmente inferiores a 3 : g/m^3. La exposición de la población general puede ser mayor en situaciones en las cuales se haya producido una liberación accidental de grandes cantidades de VC a la atmósfera, por ejemplo por un escape durante el transporte. Sin embargo, esta exposición probablemente es transitoria. Cerca de zonas industriales y de eliminación de desechos de VC/PVC se han registrado concentraciones mucho más altas (hasta 8000 : g/m^3 y 100 : g/m^3, respectivamente).

Las concentraciones en el aire de los espacios cerrados en casas adyacentes a vertederos alcanzaron concentraciones máximas de 1000 : g/m^3.

La vía más importante de exposición ocupacional es la inhalación y se produce fundamentalmente en instalaciones de VC/PVC. La exposición ocupacional al VC ascendió a varios miles de mg/m^3 en los años cuarenta y cincuenta y fue de varios cientos de mg/m^3 en los sesenta y comienzo de los setenta. Tras el reconocimiento del peligro carcinogénico del VC, en los años setenta se establecieron en la mayoría de los países normas de exposición ocupacional de alrededor de 13–26 mg/m^3 (5–10 ppm). El cumplimiento de estas directrices ha reducido considerablemente las concentraciones de VC en los lugares de trabajo, pero incluso en los años noventa se han notificado concentraciones más altas, que se pueden encontrar todavía en algunos países.

Ocasionalmente se ha detectado VC en aguas superficiales, sedimento y fangos cloacales, con máximos de 570 : g/litro, 580 : g/kg y 62 000 : g/litro, respectivamente. Las muestras de suelo recogidas cerca de una tienda de productos químicos de limpieza abandonada contenían concentraciones muy elevadas de VC (hasta

900 mg/kg). Las concentraciones máximas de VC en el agua freática o lixiviada de zonas contaminadas por hidrocarburos clorados ascendieron a 60 000 : g/litro (o más). Se detectaron concentraciones altas (hasta 200 mg/litro) en el agua de un pozo cercano a una instalación de PVC 10 años después de las filtraciones.

Los escasos datos disponibles ponen de manifiesto que el VC puede estar presente en los tejidos de pequeños invertebrados acuáticos y de peces.

En la mayoría de las muestras de agua de bebida analizadas, no había VC presente en concentraciones detectables. La concentración máxima de VC notificada en agua de bebida tratada fue de 10 : g/litro. No se dispone de datos recientes sobre las concentraciones de VC en el agua de bebida, pero cabe prever que sean inferiores a 10 : g/litro. Si se utiliza agua contaminada como fuente de agua de bebida, se podrían producir exposiciones más elevadas. En algunos estudios recientes se ha identificado VC en agua de bebida embotellada en envases de PVC en concentraciones inferiores a 1 : g/litro. Probablemente sea más frecuente la presencia de VC en este tipo de agua que en la de grifo.

El envasado con ciertos materiales de PVC puede producir la contaminación por CV de productos alimenticios, farmacéuticos o cosméticos, incluso licores (hasta 20 mg/kg), aceites vegetales (hasta 18 mg/kg), vinagres (hasta 9,8 mg/kg) y colutorios (hasta 7,9 mg/kg). Gracias a las medidas legislativas adoptadas por numerosos países, desde comienzos de los años setenta se ha logrado una reducción significativa de las concentraciones de VC y/o en el número de muestras positivas.

Varios organismos han calculado la exposición al VC a través de los envases de PVC utilizados para productos alimenticios y, teniendo cuenta el promedio de ingesta estimado en el Reino Unido y en los Estados Unidos, se calculó una exposición < 0,0004 : g/kg para finales de los años setenta y comienzos de los ochenta. En un estudio inicial se identificó VC en el humo del tabaco en concentraciones del orden de ng/cigarrillo.

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5. Cinética y metabolismo en animales de laboratorio y en el ser humano

Tras las exposición por inhalación o por vía oral, el VC se absorbe con rapidez y facilidad. La vía primaria de exposición al VC es la inhalación. En estudios realizados con animales y con personas en condiciones estables, después de la exposición por inhalación se absorbe aproximadamente el 40% del VC inspirado. En estudios de exposición oral con animales se observó una absorción de más del 95%. La absorción cutánea al VC en estado gaseoso no es significativa.

Los datos obtenidos en estudios de administración oral y por inhalación en ratas indican una distribución rápida y generalizada del VC. La rapidez del metabolismo y la excreción limita la acumulación de VC en el organismo. En las ratas se produce un desplazamiento rápido del VC a través de la placenta. No se ha informado de estudios sobre distribución tras la exposición cutánea.

La principal ruta de metabolismo del CV después de la inhalación o la ingestión oral consiste en la oxidación por el citocromo P-450 (CYP2E1) para formar óxido de cloroetileno (CEO), epóxido muy reactivo de vida breve que reacciona de nuevo rápidamente para formar cloroacetaldehído (CAA). La reacción primaria de desintoxicación de estos dos metabolitos reactivos, así como del ácido cloroacético, producto de la deshidrogenación del CAA, es la conjugación con el glutatión en una reacción catalizada por la glutatión-*S*-transferasa. Los productos de la conjugación sufren ulteriores modificaciones para formar derivados de la cisteína con sustituciones (*S*-(2-hidroxietil)-cisteína, *N*-acetil-*S*-(2-hidroxietil) cisteína, *S*-carboximetil cisteína y ácido tiodiglicólico) y se excretan en la orina. Otro metabolito, el anhídrido carbónico, se exhala en el aire.

Se sabe que el CYP2E1 y las isoenzimas de la glutatión-S-transferasa tienen variaciones individuales importantes de actividad interespecíficas e intraespecíficas.

Tras la exposición por inhalación o por vía oral a dosis bajas, el CV se elimina metabólicamente y los metabolitos no volátiles se excretan fundamentalmente en la orina. En investigaciones comparativas de la absorción de VC por inhalación se puso de

manifiesto una velocidad de eliminación metabólica en el ser humano menor que en los animales de laboratorio, en función del peso corporal. Sin embargo, una vez corregida con arreglo a la superficie corporal, la eliminación metabólica del VC en el ser humano es comparable a la observada en otras especies de mamíferos. Al aumentar la exposición oral o por inhalación, la vía más importante de excreción en los animales es la exhalación de VC inalterado, lo cual indica que hay una saturación de las rutas metabólicas. Con independencia de la dosis aplicada, la excreción de metabolitos por las heces es sólo una vía secundaria. No se encontraron estudios en los que se investigase específicamente la excreción por la bilis.

Se considera que el CEO es el metabolito más importante *in vivo* con respecto a los efectos mutagénicos y carcinogénicos del VC. El CEO reacciona con el ADN para producir el aducto principal 7-(2N-oxoetil)guanina (7-OEG) y, a niveles más bajos, los aductos exocíclicos de eteno, $1,N^6$-etenoadenina ($,$ A), $3,N^4$-etenocitosina ($,$ C) y $N^2,3$-etenoguanina ($,$ G). Los aductos de eteno del ADN tienen propiedades promutagénicas, a diferencia del aducto principal 7-OEG. Se han medido las concentraciones de 7-OEG, $,$ A, $,$ C y $,$ G en diversos tejidos de roedores expuestos al VC. Se han creado modelos toxicocinéticos con una base fisiológica para describir la relación entre la concentración en el tejido destinatario y los efectos finales tóxicos del VC.

6. Efectos en mamíferos de laboratorio y en sistemas de prueba *in vitro*

La toxicidad aguda del VC administrado por inhalación a diversas especies parece ser baja. Se notificaron CL_{50} a las 2 horas para ratas, ratones, cobayas y conejos de 390 000, 293 000, 595 000 y 295 000 mg/m³, respectivamente. No hay datos disponibles sobre la toxicidad aguda tras la administración oral o la aplicación cutánea. El VC tiene un efecto estupefaciente después de la administración aguda por inhalación. En ratas, ratones y hámsteres, la muerte estuvo precedida por un aumento de la actividad motora, ataxia y convulsiones, y a continuación colapso respiratorio. En perros se produjo una arritmia cardíaca grave en estado de narcosis tras la exposición por inhalación a 260 000 mg/m³. Después de la exposición aguda de ratas al VC por inhalación se observaron diversos efectos

patológicos, entre ellos congestión de los órganos internos, sobre todo los pulmones, el hígado y los riñones, así como edema pulmonar.

No hay estudios o datos importantes disponibles para la evaluación de los efectos de la exposición cutánea, la irritación de la piel o la propiedad de sensibilización del VC.

De la exposición oral de ratas al VC durante un período breve de 13 semanas se obtuvo una concentración sin efectos observados (NOEL), basada en el aumento de peso del hígado, de 30 mg/kg.

En diversas especies, el principal órgano destinatario en la exposición breve (hasta 6 meses) al VC por inhalación fue el hígado. Con una concentración de 26 mg/m^3 (la dosis más baja utilizada) se observaron en ratas un aumento del peso relativo del hígado y cambios hepatocelulares; a concentraciones superiores ($ 260 mg/m^3) se produjeron también cambios hepáticos más acentuados dependientes de la dosis. Otros órganos destinatarios fueron los riñones, los pulmones y los testículos. Las ratas, los ratones y los conejos parecen ser más sensibles que los cobayas y los perros.

La exposición prolongada al VC por inhalación produjo un aumento estadísticamente significativo de la mortalidad en algunas estirpes de ratas con concentraciones de sólo 260 mg/m^3, en ratones con 130 mg/m^3 y en hámsteres con 520 mg/m^3 para diversos períodos de exposición. Las ratas expuestas a 130 mg/m^3 mostraron una reducción del peso corporal y un aumento del peso relativo del bazo, degeneración hepatocelular y proliferación de las células de revestimiento de los sinusoides del hígado. La exposición de ratas a concentraciones más elevadas produjo una alteración degenerativa de los testículos, nefrosis tubular y degeneración focal del miocardio. En ratas y ratones expuestos por inhalación, la concentración sin efectos adversos observados (NOAEL) para los efectos no neoplásicos es inferior a 130 mg/m^3.

En estudios de alimentación crónica se puso de manifiesto un aumento de la mortalidad, un peso mayor del hígado y una alteración morfológica del hígado.

Tras la exposición oral de ratas a concentraciones de sólo 1,3 mg/kg de peso corporal se pudo observar polimorfismo de las células hepáticas (variación del tamaño y la forma de los hepatocitos y sus núcleos). La NOAEL fue de 0,13 mg/kg de peso corporal.

En estudios prolongados de alimentación realizados en ratas con gránulos de VC y PVC se produjo un aumento significativo de la incidencia del angiosarcoma hepático (ASH) con 5,0 mg/kg de peso corporal al día y nódulos neoplásicos en el hígado (hembras) y carcinoma hepatocelular (CHC) (machos) con 1,3 mg/kg de peso corporal al día.

En estudios de inhalación de VC en ratas Sprague-Dawley se observó una relación dosis-respuesta en el caso del ASH y, a concentraciones más altas, carcinoma de las glándulas de Zymbal. No se observó una dependencia clara de la dosis para el hepatoma o el angiosarcoma extrahepático, los nefroblastomas, los neuroblastomas o los tumores mamarios malignos. En ratones, el espectro de tumores inducidos por la exposición prolongada mediante inhalación es semejante al observado en ratas, pero se detectó sólo en ratones un aumento de los tumores pulmonares. En hámsteres se notificó un aumento de la incidencia de tumores de ASH, tumores de las glándulas mamarias y el conducto acústico, melanomas, tumores de estómago y del epitelio cutáneo.

Se han detectado efectos mutagénicos y genotóxicos del VC en varios sistemas de prueba *in vitro*, fundamentalmente después de la activación metabólica. El VC tiene un efecto mutagénico en la prueba de Ames con las cepas TA100, TA1530 y TA1535 de *S. typhimurium*, pero no con las cepas TA98, TA1537 y TA1538, lo cual indica que las mutaciones son el resultado de la sustitución de pares de bases (transversión y transición) más que de mutaciones por desfase. Esto está en consonancia con el resultado de que los aductos de eteno del ADN formados por los metabolitos reactivos CEO y CAA se convierten en mutaciones reales mediante las sustituciones de pares de bases.

Otras valoraciones de mutaciones genéticas en bacterias, levaduras y células de mamíferos han puesto de manifiesto resultados positivos exclusivamente en presencia de una activación metabólica.

Se notificaron asimismo efectos mutagénicos en una línea de células humanas con citocromo P-450IIE1 clonado, que es capaz de metabolizar el VC. También se detectó una mutación genética en esquejes de plantas (*Tradescantia*) expuestos al VC. En las valoraciones de la conversión genética, se notificaron resultados positivos con *Saccharomyces cerevisiae* en presencia de un sistema de activación metabólica. La exposición al VC indujo síntesis no programada de ADN en hepatocitos de rata y un aumento del intercambio de crómatidas hermanas en linfocitos humanos tras la adición del sistema de activación exógeno. No se detectó inhibición del crecimiento en bacterias deficientes en enzimas de reparación del ADN sin activación metabólica. En valoraciones de la transformación celular se obtuvieron resultados positivos con activación metabólica y sin ella.

La exposición al VC indujo mutaciones genéticas y recombinación mitótica en *Drosophila melanogaster*, pero no produjo ninguna mutación genética en células germinales de mamíferos. El VC mostró efectos clastogénicos en roedores, aumentó el intercambio de cromátidas hermanas de hámster e indujo el fraccionamiento del ADN en ratones. En valoraciones mediadas por huéspedes (ratas), el VC indujo una conversión genética y mutaciones adaptativas en levaduras.

Se observó un efecto mutagénico del CEO y el CAA en diferentes sistemas de prueba. El CEO es un mutágeno potente, mientras que el CAA es muy tóxico. Ambos mostraron efectos carcinogénicos en ratones, siendo el CEO mucho más activo que el CAA.

Se analizaron las mutaciones de los genes *ras* y *p53* en tumores de hígado inducidos por el VC en ratas Sprague-Dawley: se encontraron sustiticiones de pares de bases en el gen Ha-*ras* en el carcinoma hepatocelular y en el gen *p-53* en el ASH. Estas mutaciones coinciden con la formación observada y la persistencia de aductos de eteno en el ADN del hígado, tras la exposición de ratas a VC, y con las propiedades promutagénicas conocidas de los aductos de eteno.

Los estudios sobre los mecanismos de la carcinogenicidad del VC parecen indicar que el epóxido intermedio reactivo CEO tiene una interacción con el ADN para formar aductos de eteno, que dan lugar a una sustitución de pares de bases que lleva a una transformación neoplásica.

7. Efectos en el ser humano

Se ha notificado que concentraciones de VC del orden de 2590 mg/m^3 (1000 ppm), que no eran raras antes de 1974, durante periodos comprendidos entre un mes y varios años provocaban un síndrome patológico específico observado en los trabajadores del VC, llamado "enfermedad del cloruro de vinilo". Los síntomas descritos fueron dolor de oídos y de cabeza, vértigo, visión borrosa, cansancio y falta de apetito, náuseas, insomnio, dificultad respiratoria, dolor de estómago, dolor en la zona del hígado/bazo, dolor y sensación de hormigueo en los brazos y las piernas, sensación de frío en las extremidades, pérdida de la libido y disminución del peso. Entre los resultados clínicos figuraron cambios en los dedos del tipo del escleroderma, con modificaciones óseas posteriores en la punta de los dedos descritas como acroosteólisis, cambios en la circulación periférica idénticos a los clásicos de la enfermedad de Raynaud y agrandamiento del hígado y del bazo con una aspecto histológico específico, así como manifestaciones respiratorias.

Los estudios en seres humanos no han sido adecuados para confirmar los efectos en el sistema reproductor. En un pequeño número de estudios de morbilidad se ha notificado una elevada incidencia de enfermedades circulatorias entre los trabajadores relacionados con el cloruro de vinilo. Sin embargo, en estudios de cohortes amplios se ha observado una mortalidad más baja que la debida a enfermedades cardiovasculares.

Hay pruebas manifiestas y convincentes obtenidas de estudios epidemiológicos de que la exposición al VC produce un tumor raro, el angiosarcoma hepático. También pueden asociarse con el VC casos de tumores cerebrales y carcinoma hepatocelular, aunque las pruebas no pueden considerarse definitivas. Otros puntos notificados como de una mayor incidencia de cáncer, pero de manera menos convincente, son el pulmón, los tejidos linfático y hematopoyético y la piel.

El VC es mutagénico y clastogénico en el ser humano. Se ha observado un aumento de la frecuencia de aberraciones cromosómicas, micronúcleos e intercambio de cromátidas hermanas en los linfocitos de la sangre periférica de los trabajadores expuestos a concentraciones elevadas de VC en comparación con los testigos. Aunque en muchos

estudios solamente se estimaron las concentraciones y la duración de la exposición, se puede observar una relación dosis-respuesta y la "normalización" de los efectos genotóxicos con el paso del tiempo después de la reducción de la exposición.

Se han detectado mutaciones puntuales en los genes *p 53* y *ras* en tumores de personas que trabajaban con autoclaves y que estaban muy expuestas (antes de 1974) afectadas de angiosarcoma hepático y en otro trabajador relacionado con el CV con carcinoma hepatocelular.

Los marcadores biológicos investigados como indicadores de la exposición al VC o de los efectos inducidos por el VC son los siguientes: a) excreción de metabolitos del VC (por ejemplo, ácido tiodiglicólico), b) valoraciones genéticas (por ejemplo, anomalías cromosómicas o valoración de micronúcleos), c) concentraciones de enzimas (por ejemplo, en pruebas de la función hepática), d) oncoproteínas séricas (p21 y p53) y/o sus anticuerpos como biomarcadores de los efectos inducidos por el VC.

Los niños que viven en lugares cercanos a vertederos y otras fuentes puntuales pueden correr un riesgo mayor, tomando como base las pruebas que parecen derivarse de la sensibilidad en las primeras fases de la vida en estudios realizados con animales. Sin embargo, no hay pruebas directas en el ser humano.

En los estudios epidemiológicos solamente hay una relación dosis-respuesta clara para el angiocarcinoma hepático solo o en combinación con otros tumores del hígado. Sólo en un estudio epidemiológico hay datos suficientes para una estimación cuantitativa de la relación dosis-respuesta.

8. Efectos en otros organismos en el laboratorio y en el medio ambiente

Se carece de datos normalizados de toxicidad relativos a la supervivencia y la reproducción de los organismos acuáticos expuestos al VC. Hay que interpretar con cautela los datos disponibles, porque la mayoría de ellos se obtuvieron en pruebas en las cuales no se midió la concentración de la exposición, por lo que no se tuvieron en cuenta las pérdidas debidas a la volatilización.

La concentración más baja de VC que produjo un efecto en los microorganismos fue de 40 mg/litro. Fue un valor de la CE_{50} basado en la inhibición de la respiración de microorganismos anaerobios en la valoración de un lote durante 3,5 días.

La concentración más baja que produjo un efecto en organismos superiores fue de 210 mg/litro (CL_{50} a las 48 horas para un pez de agua dulce), con una concentración sin efectos adversos observados (NOAEC) correspondiente de 128 mg/litro. Se han notificado efectos en otras especies debidos a concentraciones más bajas de VC, pero no se comprobó la importancia ecológica de dichos efectos.

Las concentraciones de VC estimadas como no peligrosas para los peces de agua dulce se calculó que oscilaban entre 0,088 y 29 mg/litro.

Hay pocos datos sobre los efectos del VC en los organismos terrestres.

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