ECHA Scientific report

for evaluation of limit values for 2-chloro-1,3-butadiene (chloroprene) at the workplace

Prepared by the European Chemicals Agency

26 January 2023

Telakkakatu 6, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

Preamble

The Commission, in view of the preparation of the proposals for amendment of Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work (CMRD, and in line with the 2017 Commission Communication '*Safer and Healthier Work for All' - Modernisation of the EU Occupational Safety and Health Legislation and Policy*[1], asked the advice of RAC to assess the scientific relevance of occupational exposure limits

Therefore, the Commission made a request on 23 February 2022 to ECHA in accordance with the Service Level Agreement (SLA) (Ares (2022)711149), to evaluate, in accordance with the Directive 2004/37/EC, the following substances: 2-chloro-1,3-butadiene (chloroprene).

In support of the Commission's request, ECHA has prepared a scientific report concerning occupational limit values for 2-Chloro-1,3-butadiene (Chloroprene, EC number 204-818-0) at the workplace.

In the preparatory phase of making this report, a call for evidence was started on 2 May 2022 to invite interested parties to submit comments and evidence by 1 August 2022.

This scientific report is made available at: Occupational exposure limits-Consultations on OEL recommendation on **26 January 2023** and interested parties are invited to submit comments by **28 March 2023**.

The Committee for Risk Assessment (RAC) will develop its opinion on the basis of the scientific report submitted by ECHA.

[1] http://ec.europa.eu/social/main.jsp?langId=en&catId=148&newsId=2709&furtherNews=yes

Table of Contents

List of figures

List of tables

List of abbreviations

Abbreviation	Definition
ACGIH	American Conference of Governmental Industrial Hygienists (USA)
ACGIH TLV	ACGIH Threshold Limit Value
ADME	Absorption, distribution, metabolism and excretion
AGS	Ausschuss für Gefahrstoffe (German Committee on Hazardous Substances)
AGW	Arbeitsplatzgrenzwerte (Occupational Limit Values)
BAR	Biologische Arbeitsstoff-Referenzwerte (Biological reference value; corresponds to the background level present concurrently, in a reference population of persons of working age who are not occupationally exposed to this substance).
BAT	Biologische Arbeitsplatztoleranzwert (German biological tolerance value for occupational exposure)
BAuA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (German Federal Institute for Occupational Safety and Health)
BGV	Biological Guidance Value
BLV	Biological Limit Value
BMD	Benchmark dose
BOEL(s)	Binding Occupational Exposure Limit(s)
bw	Body weight
CAD	Chemical Agents Directive 98/24/EC
CAS RN	CAS Registry Number (unique identifier that provides an unambiguous means to distinguish chemical substances or molecular structures when there are many possible systematic, generic, proprietary or otherwise trivial names).
CEO	(1-chloroethenyl) oxirane
CI	Confidence Interval
Cl-MA-III	3-Chloro-2-hydroxy-3-butenyl mercapturic acid
CLP	Regulation EC No 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures (CLP Regulation)
CMD / CMRD	Carcinogens and Mutagens Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work. The amendment of the CMD, Directive 2022/431/EU also brought reprotoxic substances within the scope of the directive, changing the original title on the protection of workers from the risks related to exposure to carcinogens or mutagens at work to the protection of workers from the risks related to exposure to carcinogens, mutagens or reprotoxic substances at work (CMRD).
CMR	Carcinogens, Mutagens or substances toxic to Reproduction
CNS	Central nervous system
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DHBMA	3,4-Dihydroxybutyl mercapturic acid
EC	European Commission
ECHA	European Chemicals Agency
EEA	European Economic Area
EPA	Environmental Protection Agency
ERR	Exposure-risk relationship

Abbreviation	Definition
EU	European Union
GC/ECD	Gas chromatography with electron capture detector
GC/HS-FID	Headspace gas chromatography with flame ionization detection
GESTIS Substance Database	GEfahrSToffInformationsSystem (German information system for the safe handling of hazardous substances and other chemical substances at work) Substance Database
GLP	Good Laboratory Practice
HOBMA	4-Hydroxy-3-oxobutyl mercapturic acid
IARC	International Agency for Research on Cancer (World Health Organization)
IOELV(s)	Indicative Occupational Exposure Limit Value(s)
LC-MS/MS	Liquid Chromatography with tandem mass spectrometry
LOAEC	Lowest observed adverse effect concentration
LOD	Limit of detection
LOQ	Limit of quantification
MHBMA	2-Hydroxy-3-butenyl mercapturic acid
MoA	Mode of action
MRL(s)	Maximum residue level(s)
NIOSH	National Institute for Occupational Safety and Health (USA)
NOAEC	No observed adverse effect concentration
OECD	Organisation for Economic Co-operation and Development
OEL(s)	Occupational exposure limit(s)
OSHA	Occupational Safety and Health Administration (USA)
OSHA PEL	OSHA Permissible Exposure Limit
POD	Point of departure
RAC	Committee for Risk Assessment
REACH	Regulation (EC) No 1907/2006 of the European Union concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
RR	Risk ratio
SIR	Standardised incidence ratio
SLA	Service Level Agreement
SMR	Standardised mortality ratio
STEL	Short term exposure limit
TRGS	Technische Regeln für Gefahrstoffe (German Technical regulations for hazardous substances)
TWA	Time-Weighted-Average
USA	United States of America
WHO	World Health Organisation

Scope of the task and literature search

ECHA has been tasked by the European Commission to evaluate the exposure to 2-Chloro-1,3-butadiene (Chloroprene) to assess the option of an airborne occupational exposure limit, other limit values (BLV/BGV) and notations.

This report is based on international assessments such as AGS (2019), DFG (2001), EPA (1985), EPA (2010), IARC (1999). This has been complemented by a literature search of published papers from the last ten years.

ECHA evaluation and recommendation

2-Chloro-1,3-butadiene (Chloroprene) is a non-threshold carcinogen.
Consequently, no health-based OEL can be identified and an exposure-risk relationship (ERR) expressing the excess risk for cancer in function of air concentration is derived.

The table below presents the outcome of the scientific evaluation to derive limit values for 2-chloro-1,3-butadiene (chloroprene).

Outcome of the scientific evaluation

Derived Limit Values	Value
OEL as 8-hour TWA	Not proposed
STEL	Not proposed
BLV	Not proposed
BGV	Not proposed

Notations	Value
Notations	None proposed

Cancer exposure-risk relationship*

2-Chloro-1,3-butadiene concentration in air (ppm)	2-chloro-1,3-butadiene concentration in air (mg/m³)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.0035	0.013	1
0.014	0.052	4
0.035	0.13	10
0.14	0.52	40
0.35	1.3	100
1.4	5.2	400
3.5	13	1000

* Assuming exposure 8 hours per day and 5 days per week over a 40-year working life period. 1 ppm = 3.68 mg/m³ (at 20°C) (see Table 1, section 1)

1. Chemical Agent Identification and Physico-Chemical Properties

Chloroprene belongs to the group of chlorobutenes.

As explained in Ullmann's Encyclopaedia of Industrial Chemistry[2], "*Chloroprene is a colorless liquid with a characteristic ethereal odor. It is soluble in most organic solvents*."

The chemical identifiers and main physico-chemical properties of chloroprene are listed in tables 1 and 2.

Table 1: Chemical Identifications

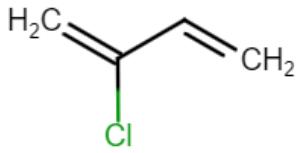
Identifier	
IUPAC Name	2-chlorobuta-1,3-diene
Synonyms	Chloroprene β-chloroprene 2-chloro-1,3-butadiene
EC/ List No	204-818-0
CAS RN	126-99-8
Chemical structure	
Chemical formula	C_4H_5Cl
Molecular weight	88.54 g/mol

Table 2: Physico-chemical properties[3]

Endpoint	Value
Appearance	colourless liquid
Boiling point	59.4°C at 101,3 kPa
Density	0.96 g/cm3 at 20°C
Vapour pressure	25.0 kPa at 20°C
Partition coefficient (log Pow)	2.525 at 20°C
Water solubility	256 mg/L at 20°C
Viscosity	0.71 mPa · s at 20°C
Conversion factor	1 ppm = 3.68 mg/m^3 (at 20°C)[4] 1 mg/m^3 = 0.27 ppm (at 20°C)

[2] Ullmann's Encyclopaedia of Industrial Chemistry 2022 - Chloropropanes, Chlorobutanes, and Chlorobutenes

[3] Values obtained from registration data published on www.echa.europa.eu

[4] $concentration\left[\frac{mg}{m^3}\right] = 88.5355\ \frac{g}{mol} \cdot \frac{1.013 \cdot 10^5 Pa \cdot 1m^3}{8.314 \cdot \frac{Pa \cdot m^3}{mol \cdot K} \cdot 293.15K} \cdot 10^{-3} \cdot concentration[ppm]$

2. EU Harmonised Classification and Labelling - CLP (EC) 1272/2008

The harmonised classification and labelling of chloroprene is described in Table 3.

Table 3: EU classification: Summary of existing classification

Index No	International chemical ID	EC number	CAS RN	Annex VI of CLP hazard class and category	Hazard statement code
602-036-00-8	Chloroprene, 2-chlorobuta-1,3-diene	204-818-0	126-99-8	Flam. Liq. 2 Acute Tox. 4 Skin Irrit. 2 Eye Irrit. 2 Acute Tox. 4 STOT SE 3 Carc. 1B STOT RE 2	H225 H302 H315 H319 H332 H335 H350 H373

3. Chemical Agent and Scope of Legislation - Regulated uses of 2-chlorobuta-1,3-diene (Chloroprene) in the EU

3.1 Directive 98/24/EC and Directive 2004/37/EC

There is currently no binding or indicative occupational exposure limit value for 2-chlorobuta-1,3-diene (Chloroprene) under Directives 98/24/EC [5] or 2004/37/EC [6].

3.2 REACH Registrations

Table 4: REACH Registrations and tonnage

Substance(s)		Tonnage (tonnes/annum)	
Name	EC number	Full registration	Intermediate use
2-chlorobuta-1,3-diene (chloroprene)	204-818-0	>1000 (12 registrants)	Polymerisation of 2-chlorobuta-1,3-diene (Chloroprene) for manufacture of thermoplastics

3.3 Authorised uses under Annex XIV of REACH

2-Chlorobuta-1,3-diene (Chloroprene) is not currently listed in Annex XIV of REACH ("Authorisation List").

3.4 Restricted uses under Annex XVII of REACH

2-Chlorobuta-1,3-diene (Chloroprene) is not currently listed in Annex XVII of REACH.

3.5 Plant Protection Products Regulation (EC) 1107/2009

There are no plant protection products authorised under Regulation (EC) No 1107/2009[7] and Directive 91/414/EEC[8] which are based on or include 2-chlorobuta-1,3-diene

[5] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A31998L0024
[6] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02004L0037-20220405
[7] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02009R1107-20210327
[8] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A01991L0414-20110601

(Chloroprene). 2-chlorobuta-1,3-diene (Chloroprene) is not listed as an active substance in the Annex of Commission Implementing Regulation (EU) No 540/2011[9].

3.6 Human and Veterinary Medicinal Products Directives 2001/83/EC and 2004/28/EC respectively

2-Chlorobuta-1,3-diene (Chloroprene) is not listed among authorised medicines contained in the Article 57 of Regulation (EC) No 726/2004[10]. It is also not subject to maximum residue levels (MRLs) and are therefore not included in Annex II of Council Regulation (EEC) No 2377/90[11], in accordance with Directive 2004/28/EC.

3.7 Biocidal Products Regulation (EU) 528/2012

There are no biocidal products authorised on the EU/EEA market which are based on or include 2-chlorobuta-1,3-diene (chloroprene). This is not listed as an active substance under Regulation (EC) No 528/2012[12] or Directive 98/8/EC[13].

4. Existing Occupational Exposure Limits

Several EU Member States have established OEL values for 2-chloro-1,3-butadiene (chloroprene). Some Member States have additionally established short-term limit values (STEL).

Table 5 presents these values along with those established in Australia, Canada, China, New Zealand, Norway, Singapore, South Africa, South Korea, Switzerland, the United Kingdom and the USA. The list should not be considered as exhaustive.

Table 5: Existing Occupational Exposure Limits (OELs) indicated as 8-h Time-Weighted Average (TWA) for 2-chloro-1,3-butadiene (chloroprene)

Country	TWA (8 hrs)		STEL (15 min)		Remarks	Reference
	ppm	mg/m³	ppm	mg/m³		
EU countries						
Austria	5	18	20	72		
Belgium	10 (1)	37 (1)				(1) Additional indication "D" means that the absorption of the agent through the skin, mucous membranes or eyes is an important part of the total exposure. It can be the result of both direct contact and its presence in the air.
Denmark	1 (1)	3.6 (1)	1 (1)(2)	3.6 (1) (2)		(1) Skin (2) Ceiling limit value

[9] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32011R0540
[10] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32004R0726
[11] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A01990R2377-20080816
[12] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32012R0528
[13] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A31998L0008

Country	TWA (8 hrs)		STEL (15 min)		Remarks	Reference
	ppm	mg/m³	ppm	mg/m³		
Finland	1	3.7	5 (1)	18 (1)		(1) 15 minutes average value
France	10	36				
Germany (AGS[1])	1.4 (1) 0.14 (2)	5.15 (1) 0.51 (2)	1.4 (1)(3)	5.15 (1)(3)		(1) Workplace exposure concentration corresponding to the proposed tolerable cancer risk. (2) Workplace exposure concentration corresponding to the proposed acceptable cancer risk. (3) 15 minutes average value
Hungary		18				
Ireland	10	36				
Poland		2				
Romania	8	30	14 (1)	50 (1)		(1) 15 minutes average value
Spain	10 (1)	37 (1)				(1) Skin
Sweden	1	3.5	5 (1)	18 (1)		(1) 15 minutes average value
Non-EU countries						
Australia	10	36				
Canada-Ontario	10					
Canada-Québec	10 (1)	36 (1)				(1) Skin
China		4				
New Zealand	10	36				
Norway	1 (1)	3.6 (1)				(1) Skin
Singapore	10	36				
South Africa	2 (1)					(1) Skin
South Africa Mining	10 (1)	36 (1)				(1) Skin
South Korea	10 (1)					(1) Skin
Switzerland	5	18				

Country	TWA (8 hrs)		STEL (15 min)		Remarks	Reference
	ppm	mg/m³	ppm	mg/m³		
United Kingdom	10	37				The UK Advisory Committee on Toxic Substances has expressed concern that these OELs may not be adequately protected because of doubts that the limit was not soundly-based. These OELs were included in the published UK 2002 list and its 2003 supplement, but are omitted from the published 2005 list.
USA-NIOSH[2]			1 (1)	3.6 (1)		(1) Ceiling limit value
USA-OSHA[3]	25 (1)	90 (1)				(1) Skin

Source: GESTIS - International limit values for chemical agents (Occupational exposure limits, OELs); https://www.dguv.de/ifa/gestis/gestis-internationale-grenzwerte-fuer-chemische-substanzen-limit-values-for-chemical-agents/index-2.jsp (accessed August 2022; searched for '2-chloro-1,3-butadiene (chloroprene)')

Notes:[1] AGS, Ausschuss für Gefahrstoffe; [2] NIOSH, National Institute for Occupational Safety and Health; [3] OSHA, Occupational Safety and Health Administration

One EU Member State has established a biological limit value for 2-chloro-1,3-butadiene (chloroprene) in the urine (Table 6). No BGV has been found.

Table 6: Biological limit values (BLV) for 2-chloro-1,3-butadiene (chloroprene)

Country	Biological Limit Value in Urine	Specifications	Reference
Germany	400 µg 3,4-dihydroxybutyl mercap-turic acid (DHBMA)/g creatinine	(BAR): Sampling time: end of exposure or end of shift; for long-term exposures: at the end of the shift after several previous shifts	(DFG, 2021a)

Notes: BAR: Biological reference value

5. Occurrence, Use and Occupational Exposure

2-Chloro-1,3-butadiene (Chloroprene) is an important chemical raw material, a precursor for polymers, which is mainly used in the production of synthetic rubber ('neoprene') (AGS, 2019). It is produced by the chlorination of 1,3-butadiene. The monomer is almost exclusively used for the production of the elastomer polychloroprene. Only a small quantity is used in the production of 2,3-dichlorobutadiene to manufacture special copolymers. Chloroprene rubber has excellent insulation properties and is, for example, used as

material for thermoprotective suits, in electric insulators, and in the automotive industry. (IARC, 1999).

5.1 Occurrence

Chloroprene is not known to occur as a natural product.

5.2 Production and Use Information

The only commercial use of chloroprene is for polymer manufacture. Chloroprene is either reacted directly to produce a polymer or converted into a comonomer that is subsequently co-polymerized for polymer manufacture.
The polymerisation of chloroprene is also the only use identified for chloroprene in the REACH registrations. Other sources also support that chloroprene is used almost exclusively in the production of the specialized elastomer known as polychloroprene.

Chloroprene was first obtained as a by-product from the synthesis of divinylacetylene. It was found that chloroprene polymerises spontaneously, and since then synthesis of chloroprene has been the basis of commercial production, and the first successful synthetic elastomer, Neoprene, or DuPrene as it was first called, was introduced in 1932.
Chloroprene is also used in the synthesis of 2,3-dichloro-1,3-butadiene, which is used as a monomer in selected copolymerizations with chloroprene. The original commercial production of polychloroprene was from acetylene through monovinylacetylene. Since the 1960s, because of the increasing price of acetylene and decreasing price of butadiene, the latter has replaced acetylene as the feedstock in most countries (IARC, 1999).

In Germany all the chloroprene produced is used as an intermediate in chemical industry for the synthesis of polychloroprene. There is no export. In Sweden as well, chloroprene is used as an intermediate for polymers (no information about volumes). In Denmark, it is found in 35 products with a typical concentration of 10%. In Finland it is found in two adhesives with a content of 15-18% (no further data available). According to the producer such high contents of monomers are very unlikely and probably reflect polymeric chloroprene contents. The residual contents of monomeric chloroprene in polymeric products is at maximum 500 ppm (polychloroprene latices)(OECD, 1998).
Articles made with chloroprene rubber have excellent resistance to weathering and ozone and they include electrical insulating and sheathing materials, hoses, conveyor belts, flexible bellows, transmission belts, sealing materials, diving suits and other protective suits. Adhesive grades of polychloroprene are used mainly in the footwear industry. Polychloroprene latexes have been used for dipped goods (balloons, gloves), latex foam, fibre binders, adhesives and rug backing (IARC, 1999).

5.3 Occupational exposure

Potential occupational exposure to chloroprene with many other monomers, solvents additives etc. may occur in the manufacture of butadiene-based polymers and butadiene derivatives.

The exposure levels to chloroprene have been from 6 to 6760 ppm (22–24 470 mg/m^3) in the US polymerization plant in the 1970s. The average chloroprene concentrations have decreased from that time and they were mainly below 5 ppm for process operators and mechanics and below 2 ppm for other workers in the 1990s (IARC, 1999).

Exposure to residual chloroprene monomer in polychloroprene latex and polymer has also been described from the 1970s. Airborne chloroprene, concentrations between 0.2 to 7 ppm (0.7–25 mg/m^3) have been measured in a roll building area at a metal fabricating plant in the United States where polychloroprene was applied extensively to metal cylinders before vulcanization and in a Russian shoe factory.(IARC, 1999)

Dry polychloroprene contains no detectable chloroprene, while polychloroprene latex contains minimal chloroprene. Most commercial polychloroprene latexes contain <0.1%

residual chloroprene, although some (<20%) may contain up to 0.7%. The residual chloroprene is intimately dissolved in the polychloroprene polymer and does not vaporize readily. Thus, there is very little potential for chloroprene exposure from use of polychloroprene latex. (Lynch, 2001b)

Consequently, the only opportunity for exposure to chloroprene should be in the manufacture of chloroprene and/or polychloroprene. There is no employee exposure to chloroprene during the initial monomer manufacturing steps due to the absence of chloroprene. Similarly, there is virtually no exposure during polychloroprene isolation due to the minimal level of chloroprene in the emulsion fed to this process. Significant concentrations of chloroprene are present in the final chloroprene-manufacturing step, but employee exposure is very low because the reaction is conducted inside the sealed process with minimal employee intervention. The polymerization and monomer removal steps are contained, but not completely sealed. There is a non-trivial exposure potential, but the actual employee exposure is minimized by use of engineering controls, work practices and personal protective equipment. Measured exposures are below regulatory limits and actual employee exposures are even lower.(Lynch, 2001b)

Worker exposures have reduced largely as a result of engineering and work-practice improvements applied in polymer plants over the years. Some of these improvements are as follows:

- Dry connectors are used on hoses for transfer operations from tank cars and tank trucks.
- Double mechanical pump seals and improved valve packings have been installed.
- Reactors, towers and drums can now be cleaned with high-pressure water systems mostly eliminating the need for workers to enter the vessels.
- Improved process control has reduced fouling and unwanted polymerization so that vessels are cleaned less frequently, and there is less frequent filter changing.
- Better level of control on draw-off from drums reduces the amount of monomer released.
- Better sampling techniques such as closed loop sampling reduce the exposure of laboratory technicians and general releases in the plant.
- Better polymer stripping results in less monomer in latex, finishing and in fouled towers and less exposure for users (Lynch, 2001a)

The air contamination with chloroprene at a German workplace producing polychloroprene was estimated to be low since the measured air concentrations of chloroprene were below 0.1 ppm. However, the occupational hygienist of the plant assumed that dermal exposure was significant (Eckert et al., 2013).

5.4 Routes of exposure and uptake

5.4.1 Worker exposure

Exposure is primarily by the inhalation route, but dermal contact may also be a relevant route of exposure. Chloroprene is absorbed, both through the skin and via the lungs and the gastrointestinal tract. Owing to the physico-chemical properties, skin absorption is assumed to make a considerable contribution to the total exposure to chloroprene. However, no direct quantification of dermal absorption is available (see section 7.1). Exposure at the workplace occurs mainly during production or polymerization of 2-chloroprene, where inhalation and dermal absorption are assumed to be of major importance. (DFG, 2021a)

5.4.2 General population

General population is not exposed to chloroprene via use of articles made from polychloroprene. It is reported that dry polychloroprene no longer contains detectable chloroprene (detection limit, 0.5 ppm). In polychloroprene latexes, residual chloroprene is

less than 1%, varying with the manufacturing process and intended use (IARC, 1999). Solid polychloroprene polymer products contain less than 1 ppm chloroprene and most polychloroprene polymer latexes contain less than 0.1% residual chloroprene (Lynch, 2001b).

The highest exposure to the general population via the environment would be expected through ambient air in the vicinity of a production/processing plant and through drinking water processed from groundwater. The local concentration in air was estimated at 2.3-23 µg/m^3 and the concentration in drinking water is assumed to be 1-10 µg/l. (OECD, 1998)

6. Monitoring Exposure

6.1 External exposure

Several validated methods are available for measuring chloroprene. The principle of the methods is as follows: air sampling is performed by passing air actively through a sorbent tube. The retained chloroprene is then extracted for analysis by chemical desorption followed by analysis via gas chromatography with different detectors.

Table 7 lists two of the available methods for measuring chloroprene in air. It is possible to measure chloroprene in air in the range of the µg/m^3 or ppb.

Table 7: Methods for measurement of chloroprene in air

Sampling methods/desorption	Analytical technique	LOQ, flowrate, sampling volume and time	Reference
Charcoal tube (active) N,N dimethylacetamide	GC/HS-FID (1)	0.3 mg/m^3 Flow rate: 0.5 l/min 30L (1 hour)	(DFG, 2013)
Chromosorb 106 tube (active)	GC/ECD (2)	80 µg/m^3 Flow rate: 0.05 l/min 6L (2 hour)	(OSHA, 1998)

(1) Headspace gas chromatography with flame ionization detection
(2) Gas chromatography with electron capture detector

6.2 Biomonitoring of exposure (internal exposure)

(DFG, 2021a) considers different mercapturic acids in urine as biomarkers of exposure to chloroprene. See details on metabolism of chloroprene in section 7.1.

The biomarkers considered are:

- 3,4-Dihydroxybutyl mercapturic acid (DHBMA)
- 2-Hydroxy-3-butenyl mercapturic acid (MHBMA)
- 4-Hydroxy-3-oxobutyl mercapturic acid (HOBMA)
- 3-Chloro-2-hydroxy-3-butenyl mercapturic acid (Cl-MA-III)

The non-chlorinated mercapturic acids are not specific biomarkers of chloroprene and may be formed also from other compounds such 1,3 butadiene. However, the level of DHBMA formed is much higher than that of Cl-MA-III.

6.2.1 Background levels

(DFG, 2021a) reports studies on background levels of the four biomarkers. The findings are summarized in Table 8.

Table 8: Summary of studies on background levels for chloroprene biomarkers

Biomarker	Median level	95th percentile	References
DHBMA			Several, see review by (DFG, 2021b)
Non-smokers	100-300 µg/l creatinine	760 µg/l	
Smokers	150–400 µg/g creatinine	329 µg/l creatinine	
MHBMA			Several, see review by (DFG, 2021b)
Non-smokers	< 2 µg/g creatinine		
Smokers	10 µg/g creatinine		
HOBMA	111 µg HOBMA/g creatinine	305 µg HOBMA/g creatinine	(Eckert et al., 2012)
Cl-MA-III	All below the limit of detection < 1.4 µg/g creatinine)		(Eckert et al., 2012)

DFG concluded on using DHBMA as biomarker of exposure and established a BAR (Biologische Arbeitsstoff-Referenzwerte, Biological reference value) of 400 µg/DHBMA)/g creatinine. However, it is to be noted that DHBMA is a main metabolite both of chloroprene and of 1,3-butadiene (DFG 2021).

In the case of Cl-MA-III and HOBMA not enough human data were available for the derivation of a reference value. MHBMA could be demonstrated in low concentrations only in the group of chloroprene-exposed persons while DHBMA was identified the main urinary metabolite of 2-chloroprene in humans (Eckert et al., 2012).

In the studies mentioned in Table 8, only those persons were included in the reference populations who were occupationally not exposed to alkylating substances such as 1,3-butadiene and 2-chloroprene.

6.2.2 Occupational exposure

So far, no human studies are available that enable the derivation of a correlation between external and internal exposure to chloroprene (DFG, 2021a).

6.2.3 Biomonitoring analytical methods

There are analytical method available for the determination of the biomarkers described at the beginning of section 6.2. Table 9 provides an overview of the methods.

Table 9: Analytical methods for chloroprene biomarkers

Biomarker	Method	Analytical technique	LOQ
DHBMA in urine	(DFG, 2007)	LC–MS/MS(1)	75.9 µg/L
MHBMA in urine	(DFG, 2007)	LC–MS/MS(1)	2.73 µg/L
HOBMA in urine	(Eckert et al., 2012)	LC–MS/MS(1)	13.2 µg/L
Cl-MA-III in urine	(Eckert et al., 2012)	LC–MS/MS(1)	4.5 µg/L

(1) Liquid Chromatography with tandem mass spectrometry

7. Health Effects

7.1 Toxicokinetics (Absorption, distribution, metabolism and excretion - ADME)

7.1.1 Human data

Systemic adverse effects of 2-chloro-1,3-butadiene (chloroprene) have been observed in exposed workers, thus indicating absorption and distribution. However, no relevant quantitative human toxicokinetics data are available.

7.1.2 Animal data

7.1.2.1 Absorption

No quantitative data on chloroprene absorption via the oral, inhalation or dermal route were found.

7.1.2.2 Distribution

Repeated dose studies with chloroprene have showed effects in several organs, confirming systemic distribution (see section 7.3). No animal studies investigating the distribution of chloroprene were found.

7.1.2.3 Metabolism

The involvement of glutathione (GSH) conjugation in the detoxification was studied by Summer and Greim (1980). Male Wistar rats received oral doses of 100 or 200 mg/kg bw and three hours after the exposure, the GSH levels were measured as 55% and 39%, respectively, of the levels in control animals. No extensive studies investigating chloroprene metabolism in animals were found.

7.1.2.4 Excretion

In the study by Summer and Greim (1980) a non-linear, but dose-dependent increase in urinary thioesters of Wistar rats exposed to 100 or 200 mg /kg bw was observed. The measured thioesters were presumably mercapturic acid and glutathione conjugates of chloroprene. The elimination was considered rapid as the levels of these thioesters returned to control levels within 24 hours after exposure. No other animal studies focusing on chloroprene elimination were found

7.1.3 *In vitro* data

7.1.3.1 Absorption

No data were found.

7.1.3.2 Distribution

Tissue-to-air partition coefficients were determined for chloroprene in mouse, rat and hamster tissues using a vial equilibration method. The results indicated that chloroprene would mainly be distributed to adipose tissue. (Himmelstein et al., 2004a)

7.1.3.3 Metabolism

The metabolic pathway of chloroprene has been extensively studied *in vitro*, and discussed in detail by AGS and EPA (AGS, 2019, EPA, 2010). Key studies investigating the metabolism in lung and liver tissue cell fractions were conducted by Cottrell et al. and Himmelstein et al. (Cottrell et al., 2001, Himmelstein et al., 2001a).

The P450 enzyme CYP2E1 is involved in the chloroprene metabolism, resulting in the formation of a predominant epoxide metabolite, (1-chloroethenyl)oxirane, and a minor metabolite, 2-chloro-2-ethenyloxirane (Cottrell et al., 2001, Himmelstein et al., 2001a). These are then further metabolised (detoxified) in reactions involving epoxide hydrolase.

At higher concentrations, the dose-response becomes supra-linear due to saturation, and almost reaches a plateau. The metabolic pathway is illustrated Figure 1.

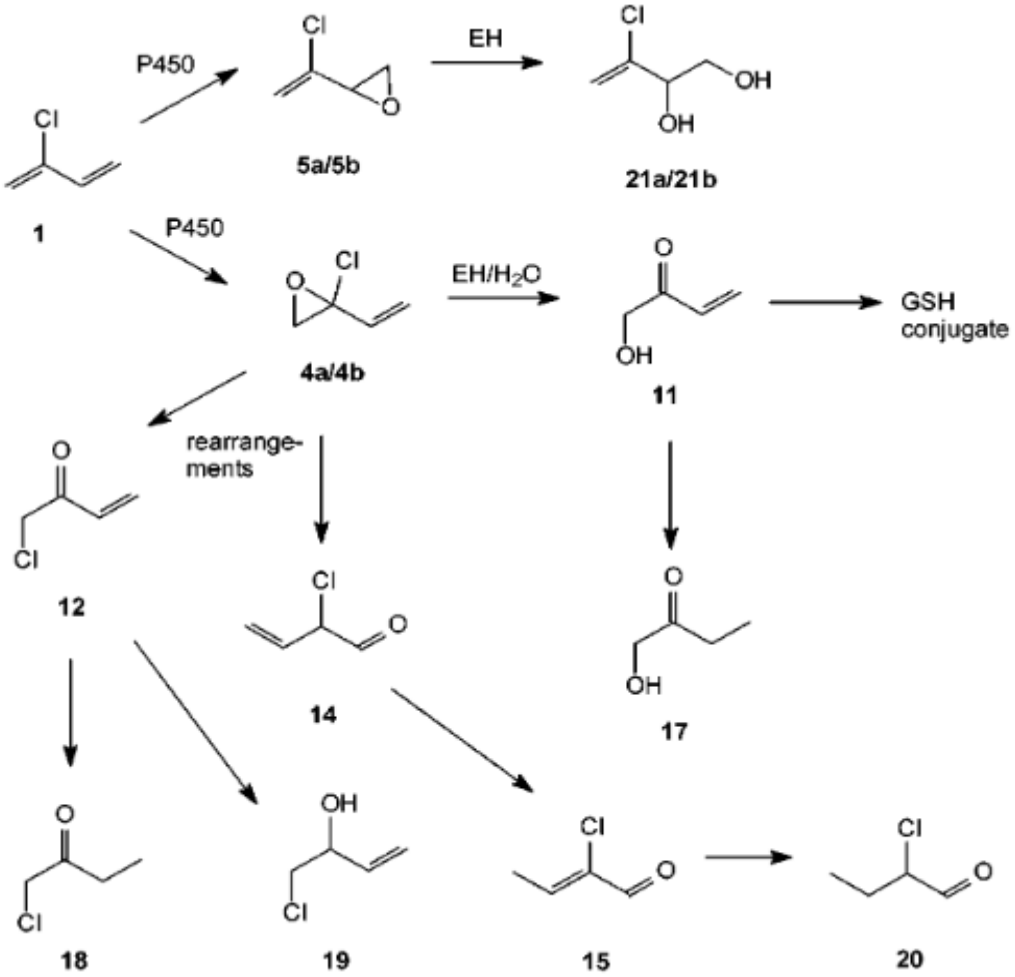


Figure 1: Proposed scheme for the *in vitro* microsomal metabolic pathway of chloroprene
Notes: [1] chloroprene; [5a/5b] (1-chloroethenyl)oxirane, R- and S- enantiomers; [4a/4b] 2-chloro-2-ethenyloxirane, R- and S- enantiomers. (Cottrell et al., 2001)

Some metabolic differences between species have been observed regarding the formation of the two optical isomers of (1-chloroethenyl)oxirane. As a result of the mono-epoxidation measured in liver microsomes from rats, (1-chloroethenyl)oxirane was mainly occurring as an R-enantiomer, whereas in mouse and human cell preparations there was a slight enantioselectivity towards the S-enantiomer (Cottrell et al., 2001).

In the studies by Himmelstein et al. (Himmelstein et al., 2004a, Himmelstein et al., 2004b, Himmelstein et al., 2001a) and Cottrell et al. (2001), much more (1-chloroethenyl)oxirane was formed by lung microsomes from B6C3F1 mice than by microsomes from rats, hamsters or humans (B6C3F1 mice >Fischer 344 rats > Wistar rats, hamsters, humans). However, it is noted that human lung microsomes used in the studies were collected from one person only. Furthermore, the detoxification of (1-chloroethenyl)oxirane by epoxide hydrolases is slower in liver microsomes of B6C3F1 mice than with microsomes of rats, and particularly slower than hamsters or humans.

This can explain the differences in organ toxicity and carcinogenicity in different species (AGS, 2019, EPA, 2010) see Section 7.7.2.

7.1.3.4 Elimination

No data were found.

7.1.4 Toxicokinetic modelling

A physiologically bases toxicokinetic (PBPK) model was first published by (Himmelstein et al., 2004a, Himmelstein et al., 2004b). Lung and liver were identified as the main organs where metabolism takes place. Later, the models have been further refined (Clewell et al., 2019, Yang et al., 2012).

7.1.5 Summary

There is limited information on the absorption, distribution and elimination of chloroprene. The metabolic pathway has been extensively studied, showing that chloroprene is mainly metabolised to the reactive epoxide (1-chloroethenyl)oxirane, and to a lesser extent 2-chloro-2-ethenyloxirane. Species differences have been identified, indicating that the detoxification of the metabolites is markedly slower in mice than in other species.

7.2 Acute toxicity

7.2.1 Human data

7.2.1.1 Acute oral toxicity

No human data are available.

7.2.1.2 Acute dermal toxicity

No human data are available.

7.2.1.3 Acute inhalation toxicity

Rickert et al. (2012) described a 29-year-old chemical company worker who was found unconscious in an empty vessel used for chloroprene and died 3 hours later despite of resuscitation and hospitalization. The exposure time was about 30 minutes or less. During autopsy the corpse and especially the interior organs gave off an intense acute smell causing drowsiness and dizziness in the medical examiners. The cause of death could not be determined as the macromorphological findings were unspecific. Lungs were heavy and oedematous. The brain showed signs of a severely increased intracranial pressure. Cortex and marrow of the kidneys were significantly demarcated. All internal organs were highly congested with blood. Furthermore, it was noted that slight lesions like everting the lids caused excessive bleedings.

Also histopathology confirmed that all internal organs were highly blood congested. Chloroprene was found in nearly all tissues and body fluids except in the urine and lung. The highest concentrations were detected in the kidney, liver, myocardial muscle and especially in the brain. Furthermore, hexanal was found in all samples except in the urine. The amount of hexanal in some specimens was high, especially in the lung, bile, gastric content and myocardial muscle. The authors suspected that the lack of chloroprene in the lungs was probably due to the reanimation and in the urine most likely due acute cardiac arrest preventing excretion. No estimates of air concentration of chloroprene in the vessel were available, but the authors assumed that a significant amount of chloroprene was not only inhaled but also absorbed through the skin because the man wore a respiratory mask. The reason why high concentrations of hexanal were found in the tissues could not be clarified.

According to DFG (2001), Nystrom (1948) described vomiting and dizziness in workers with 15 minute or less of exposure to 1000ppm of chloroprene.

7.2.2 Animal data

7.2.2.1 Acute oral toxicity

2-Chloro-1,3-butadiene (chloroprene) has a harmonised classification as Acute Tox 4 via the oral route.
An LD50-value of 251 mg/kg bw has been reported in rats (ECHA, 2022).

7.2.2.2 Acute dermal toxicity

No data are available.

7.2.2.3 Acute inhalation toxicity

2-Chloro-1,3-butadiene (chloroprene) has a harmonised classification as Acute Tox 4 via inhalation.
Clary et al. (1978) derived an LC50-value of 2280 ppm (8227 mg/m^3) from acute (4 hours) exposure data in male rats.

7.2.3 Summary

Human data on acute toxicity are limited to one case report with presumably heavy but not further quantified exposure and an undefined exact cause of death, and one old study reporting dizziness and vomiting after 15 minute or less of exposure to 1000 ppm of chloroprene. Chloroprene has been reported to induce mortality in rats after acute oral and inhalation exposure.

7.3 Specific target organ toxicity/Repeated dose toxicity

7.3.1 Human data

AGS (2019) referred to the study of Ritter and Carter (1948) and Nystrom (1948) which reported hair loss among workers exposed to 2-chloro-1,3-butadiene (chloroprene) in neoprene production, but exposure levels were not reported. AGS (2019) also referred to Lejhancova (1967) who reported hair loss in chloroprene exposed workers. Subsequent measurements in the air of the work areas concerned revealed concentrations of 60-290 mg chloroprene/m^3 (approx. 16.6-80.3 ppm); no information on dermal exposure and exposure to oligomers were reported. Histologically, there were also changes in the hair roots and localized decomposition of keratin. According to AGS (2019), Nystrom (1948) also reported headache, fatigue, chest pain, tachycardia, irritability, and nervousness as well as evidence of hypochromic but reversible anemia in individuals exposed to chloroprene. However, exposure levels were not characterized.

Lloyd et al. (1975) reviewed human data and noted that irritation to the respiratory organs but also systemic-toxic effects such as central nervous system depression and damage to the kidneys and liver occur in humans exposed to chloroprene, but did not characterize the exposure levels.

Gooch and Hawn (1981) compared biochemical and hematological parameters according to exposure status in workers in a chloroprene manufacturing plant (Louisville Kentucky plant, also described in cancer section 7.7.1). All workers employed as of December 31, 1977 were included. Workers were categorized into three exposure groups: currently exposed (n = 336), not currently exposed but with past exposure (n = 227); and never exposed (n = 283). The exposure groups were based on a job description indicating if the worker was assigned to the chloroprene polymerization area of the plant. Additionally, seven employees in supervisory roles familiar with chloroprene manufacture independently rated each job as "high," "medium," "low," or "varied" in regard to the actual potential for exposure to chloroprene. In the plant, all new hires were required to undergo a physical examination upon employment and annually thereafter that included also clinical chemistry and hematological analyses. The results for tests conducted between 1974 and 1977 were included in the analysis. When clinical chemistry parameters were compared between exposure groups no effect was seen in currently exposed workers and those workers never exposed to chloroprene; this lack of effect was also observed when currently exposed workers with "high" potential for chloroprene exposure were compared to workers never exposed to chloroprene. Paired analyses (comparisons of clinical chemistry in workers with test results before and after being assigned to chloroprene manufacture) showed that glucose and cholesterol values were lower and LDH values were higher in workers after being assigned to chloroprene manufacture compared to test results before assignment. However, all values were within normal ranges. When currently exposed

workers were compared to never exposed workers stratified by duration of exposure (<1 year, 1–5 years, 6–10 years, >10 years), cholesterol and alkaline phosphatase were higher in workers exposed >10 years (cholesterol) and 6–10 years (alkaline phosphatase). This pattern was also observed when only workers with a "high" potential for exposure were analyzed. When cholesterol values were adjusted for the age of the workers, no chloroprene-related effect was observed. The differences seen in alkaline phosphatase were attributed to two workers with abnormally high alkaline phosphatase levels due to bone injury and blood pressure medication. No hematological effects were observed. No levels of estimated exposure level for the exposed workers were presented.

EPA (2010) referred to a subsequent NIOSH industrial hygiene investigation of the above-mentioned Louisville plant, where ambient and personal monitoring was conducted to assess worker exposure to chloroprene (McGlothlin et al., 1984). Additionally, medical interviews and medical record examinations were conducted to determine if adverse health outcomes due to workplace exposures could be detected. In the air quality monitoring portion of the study, personal breathing zone and area air samples were collected in the manufacturing areas that dealt with both the monomer (chloroprene) and polymer (polychloroprene). The range of chloroprene air concentrations detected by fixed location area samples ranged from below detection limits (32 out of 79 total samples) to 1200 ppm. The two highest concentrations (910 and 1200 ppm) were detected at "drainage trenches" and may not have been representative of normal workday exposures experienced in the manufacture areas. In the remaining fixed location samples, the average chloroprene concentration (over 6–7 hours) was 5.6 ppm, which was below the OSHA PEL of 25 ppm for an 8-hour workday. Only one fixed location area air sample (excluding those taken at the drainage trenches) exceeded the OSHA PEL (26 ppm). Of the 194 personal air samples taken from workers in the monomer and polymer portions of the plant, 103 (54%) exceeded the NIOSH 15-minute recommendation of 1 ppm, 5 (3%) exceeded the ACGIH TLV of 10 ppm, and only 1 (0.5%) exceeded the OSHA PEL of 25 ppm. EPA (2010) noted that it is important to note that the magnitude of worker exposure detected in this study may not be representative of exposures workers experience currently due to increased safety procedures and improved manufacturing processes. In the medical examination portion of the study, 37 workers were interviewed, and demographic and occupational information was collected. Smoking histories, medical problems, past illnesses, and current symptoms were covered in the interviews and any relation to current work exposures was sought. None of the workers indicated in the interviews that they felt that their current health status was related to their workplace exposure to chloroprene. Some workers indicated that they had occasionally experienced lightheadedness and eye, nose, and throat irritation. Workers experiencing respiratory disease had medical histories indicating heavy smoking, heart disease, or other medical issues.

As noted by EPA (2010) Sanotskii (1976) reviewed Russian studies on chloroprene exposed workers and reported that medical examinations of chloroprene production workers had found changes in the nervous system, hepatic and renal function, cardiovascular system, and hematology. Assessment of exposures in Russian latex and rubber manufacturing plants showed that chloroprene was the main hazard and that exposures ranged from 1 to 7 mg/m^3 (0.28–1.93 ppm) in exposed work areas. One of the studies reviewed included medical examinations of 12 men and 53 women, of whom two-thirds had been employed in a chloroprene production plant for less than 5 years. Cardiovascular examinations found muffled heart sounds in 30 workers, reduced arterial pressure in 14, and tachycardia in 9. There was also a reduction in RBC counts, with hemoglobin substantially below the limit of physiological variation. Erythrocytopenia, leucopenia, and thrombocytopenia were observed. Increases in vestibular function disturbance were associated with duration of work. In another study reviewed by Sanotskii (1976), women aged 19–23 employed in jobs with chloroprene exposure for 2–4 years had abnormal diurnal variation in arterial pressure, with reduced systolic and diastolic components at the end of the workday when compared with controls. Their pulse rates were considerably higher than those of controls ($p < 0.01$). Central nervous system (CNS)

function was also affected with lengthening of sensorimotor response to visual cues compared with controls. Olfactory thresholds increased with duration of employment. It is noted that the review does not allow to assess how potential confounding from other exposures was taken into account in the above analyses (the original studies are in Russian).

There was no increase in mortality for any of the non-malignant diseases studied in the follow-up studies among chloroprene workers in two US plants, a French plant and a plant in Northern Ireland (Marsh et al. 2007a) or in the extended follow-up of the workers of the two US plants (Marsh et al., 2021). In the latest follow-ups of those cohorts, the person-years of follow-up in was the highest in the Louisville, US plant (245 218 person-years), compared to 127 036, 50 602 and 17 057 in the Northern Ireland, Pontchartrain, US and French cohorts, respectively. The results of the cancer follow-up of these cohorts are further described in section 7.7.1.

7.3.2 Animal data

Subacute, sub-chronic and chronic inhalation studies have been conducted by NTP in rats and mice (Melnick et al., 1996, NTP, 1998).

In a repeated dose 16-day study, male and female F344 rats were exposed to chloroprene via inhalation 6 h/day, 5 days/week at concentrations of 0, 32, 80, 200, 500 ppm (0, 120, 290, 740, 1800 mg/m^3 respectively). Hypoactivity and shallow breathing was observed in the high-dose group at the first days of exposure and to some degree also in the mid-dose group animals. Three male rats died on the first three days of the study. On day 5, 10 males and 13 females died when blood was collected for clinical pathology evaluations. Statistically significant non-neoplastic findings reported were degeneration of the olfactory epithelium at all doses, and squamous metaplasia of the respiratory epithelium at the highest dose in both sexes. Centrilobular hepatocellular necrosis was reported at the two highest doses (statistically significant in females at 200 ppm and males at 500 ppm). Mean body weight gains were significantly less in the 200 ppm males and females and 500 ppm females as compared to controls. Other findings included increased scattered chronic centrilobular inflammation (aggregates of lymphocytes and macrophages in livers of female rats at 200 and 500 ppm and in one male at 500 ppm), increased liver weights and increased kidney weights in females at 80 ppm and 500 ppm. Normocytic and normochromic anaemia and thrombocytopenia was seen in both sexes at 500 ppm and in females at 200 ppm. Furthermore, the activities of alanine aminotransferase, glutamate dehydrogenase and sorbitol dehydrogenase decreased at 500 ppm (males and females) and 200 ppm (females). (NTP, 1998)

Following the same 16-day study protocol as above, NTP investigated the effects in B6C3F1 mice. Dose levels selected were 0, 12, 32, 80, 200 ppm (0, 44, 120, 290, 740 mg/m^3 respectively), but at the top dose, all animals died during the first three days. Myocardial enlargement and necrosis in liver and thymus were identified in examinations of those animals. Decreased body weight gain was seen in males at 32 and 90 ppm. Other findings included increased liver weights (females) and a few animals with hyperplasia of the forestomach epithelium (males and females) (NTP, 1998).

A 13-week inhalation study in F344 rats was conducted at concentrations of 0, 5, 12, 32, 80, 200 ppm (0, 20, 44, 120, 290, 740 mg/m^3 respectively), 6 h/day, 5 days/ week. Respiratory metaplasia and minimal to mild olfactory epithelial degeneration were observed in male and female rats exposed at concentrations of 80 and 200 ppm. In females, the incidence of olfactory epithelium degeneration (specifically in the posterior part of the nasal cavity) was also increased at 32 ppm. At 200 ppm, minimal to mild hepatocellular necrosis was observed in male and female animals. The incidence of scattered chronic inflammation was increased in females at 200 ppm. Slightly increased kidney weights were seen at 80 and 200 ppm in females and 200 ppm in males. Further findings included decreased liver GSH (glutathione) levels at 200 ppm, reversible thrombocytopenia (200 ppm, observed at days 2 and 22 but not at termination) and

anaemia (200 ppm, week 13). (NTP, 1998). Based on the local nasal effects at 32 ppm, a NOAEC of 12 ppm can be identified.

In the 13-week mouse study (B6C3F1), the dose levels were 0, 5, 12, 32, 80 ppm (0, 20, 44, 120, 290 mg/m^3 respectively; 6 h/day, 5 days/week). The mean body weight gain of male mice at 80 ppm was significantly lower compared to control animals. The incidence of squamous epithelial hyperplasia of the forestomach was increased in both sexes at 80 ppm (NOAEC 32 ppm). A minimal anaemia and increased platelet production were identified in female mice at 32 and 80 ppm. (NTP, 1998)

The 2-year NTP study (NTP, 1998) in F344 rats and B6C3F1 mice is described in section 7.7.2. The animals were exposed to 0, 12.8, 32, 80 ppm, 6 h/day, 5 days/ week. The main findings included:

- Starting at the lowest dose of 12.8 ppm, a significant increase in hyperplasia of the alveolar epithelium in male and female rats was noted. Furthermore, significantly increased incidences of atrophy, basal cell hyperplasia, metaplasia and necrosis of the olfactory epithelium were observed in rats of both sexes as 32 and 80 ppm (necrosis in males already at 12 ppm). No NOAEC can be identified; LOAEC is 12.8 ppm.
- In mice, increased incidences of bronchial hyperplasia were recorded at all dose levels in both sexes. Hyperplasia of the renal tubules was also found in male mice in all exposed groups. At the highest dose of 80 ppm, there was a significantly increased incidence of atrophy and metaplasia of the nasal olfactory epithelium in female and male animals. Hyperplasia of the forestomach was also found. Chloroprene exposure resulted in significantly decreased survival rates of females at all dose levels and males at 32 and 80 ppm. Decreased body weights of females were observed at 80 ppm. (NTP, 1998)

In addition to the NTP studies, TNO (Clary et al., 1978) conducted subacute studies with chloroprene. Wistar rats were exposed for 4 weeks (6 h/d, 5 days/week) at 0, 40, 160, 625 ppm (0, 150, 590, 2300 mg/m^3 respectively). 5 out of 10 males and 3 out of 10 females in the top-dose group died during the exposure period. The lungs of those animals showed perivascular oedema and haemorrhagic zones. Liver necrosis and centrilobular degeneration, and slightly enlarged kidney tubular epithelial cells were found at the highest dose. In the same study, Syrian golden hamsters were exposed at the same doses and conditions as the rats. All animals in the top-dose group died withing 24 h after the beginning of the exposure. At 160 ppm, hepatocellular necrosis was identified. Other findings, starting at the lowest dose of 40 ppm, included decreased body weight, skin and eye irritation, restlessness and lethargy. (Clary et al., 1978)

7.3.3 Summary

Hair loss, irritation of mucous membranes and neurological effects have been observed in humans after long-term heavy exposure to chloroprene. However, type of contact as well as duration and level of exposure were not characterised and adjustment for the effect of potential confounders is lacking in those studies. Animal effects include local nasal effects in chloroprene inhalation studies. At higher doses, anaemia, liver and kidney effects were reported.

7.4 Irritancy and corrosivity

7.4.1 Human data

AGS (2019) cited Nystrom (1948), who described that chloroprene can cause dermatitis on skin contact. However, the type of dermatitis and type of contact as well as duration and level of exposure were not characterised.

7.4.2 Animal data

Chloroprene has a harmonised classification as irritant (Skin irrit.2, Eye irrit. 2). Mild to moderate skin erythema and oedema were reported when shaved rabbit skin was exposed

to 200 mg/kg bw chloroprene (semiocclusive coverage) for 24 hours (ECHA, 2022). Skin irritation has also been reported in some old studies (DFG, 2001).

Mucosal irritation was reported in rats upon inhalation of high doses of chloroprene (Clary et al., 1978).

7.4.3 Summary

Chloroprene is classified as irritating to the skin and eyes. Human data on irritation effects of chloroprene are limited to one old report which described dermatitis on skin contact. However, the type of dermatitis and type of contact and duration and level of exposure were not characterised.

7.5 Sensitisation

7.5.1 Human data

7.5.1.1 Respiratory sensitisation

No human data are available concerning respiratory sensitisation of chloroprene.

7.5.1.2 Skin sensitisation

No human data are available concerning skin sensitisation of chloroprene.

7.5.2 Animal data

7.5.2.1 Respiratory sensitisation

No animal data are available concerning respiratory sensitisation of chloroprene.

7.5.2.2 Skin sensitisation

No animal data are available concerning skin sensitisation of chloroprene.

7.5.3 Summary

No data are available concerning respiratory or skin sensitisation of chloroprene.

7.6 Genotoxicity

7.6.1 Human data

Only original studies in non-English literature were identified.

EPA (2010) referred to the Russian review of Sanotskii (1976) which also reported a study (in Russian) of chromosome aberrations in leukocyte cultures prepared from blood cells of chloroprene production employees. The occurrence of chromosomal aberrations were significantly higher ($p < 0.001$) in the exposed group compared to the control group, as well as elevated compared to reported levels among healthy persons. Similar results were reported for a different study of two sets of female employees: (1) 20 women aged 19–23 and exposed to 3–7 mg/m^3 (0.83–1.93 ppm) chloroprene for 1–4 years; and (2) 8 women aged 19–50 and exposed to 1–4 mg/m^3 (0.28–1.1 ppm) for 1–20 years. EPA (2010) concluded that insufficient data on analytical methods and exposure ascertainment used in the investigation of chromosomal aberrations in chloroprene workers preclude drawing conclusions from the results presented by Sanotskii (1976). Similar conclusions on adequacy of the human data were drawn by AGS (2019).

DFG (2001) referred to a study performed among workers of a Chinese factory, where the number of sister chromatid exchanges in those exposed to chloroprene were no higher than in those not exposed (Hesbert et al., 1983). DFG (2001) considered, however, that due to lack of documentation, an undefined reference population and not being able to rule out mixed chemical exposure the study was not suitable for reliably assessing genotoxicity in humans.

7.6.2 Animal data (*in vivo*)

A number of studies assessing the genotoxic potential of chloroprene have been reported and are presented in Table 10. Chloroprene was shown to induce recessive lethal mutations in *Drosophila melanogaster* in earlier studies, but this finding was not corroborated by a NTP-conducted study. Cytogenetic assays assessing the induction of chromosomal aberrations, sister chromatid exchange and micronuclei were predominantly negative, including all relevant NTP inhalation studies in $B6C3D_1$ mice which however responded with multiple carcinogenic effects at the same dose levels. Mutational analysis of the *ras* proto-oncogenes revealed a higher frequency and unique pattern of of K-*ras* and H-*ras* mutations in chloroprene-induced tumours, over spontaneous neoplasms.

Table 10: Summary of *in vivo* genotoxicity studies

Species (test system), strain, sex; No/group	Dose range, route, duration	Study endpoints	Study results	References
Drosophila melanogaster; Berlin-K males (and *Basc* females)	22.9 and 34.3 mM for 48 h; 5.7 and 11.4 mM for 66 h; 5.7, 11.4, 22.9, 34.3 mM for 72 h Feeding to male flies; 7 experiments; two chloroprene batches tested: 99% and >99.7% purity	X-linked recessive lethal mutations	**positive** spontaneous mutation frequency significantly exceeded, when all data were pooled and compared to controls; no dose-response relationship	(Vogel, 1979)
Drosophila melanogaster; adult Canton-S wild-type males (and *Basc* females)	First by feeding for 72 h, retested by injection; Feed: 1800 ppm Injection:1800 ppm; 50% pure	Sex-linked recessive lethal mutations in male germ cells (No. of lethals/No. of X chromosomes tested)	negative	(NTP, 1998); (Foureman et al., 1994)
C57BL/6 mice, M (n=8-15) and F (n=24-35)	Series I: 0, 0.064, 0.32, 3.5 mg/m^3 and Series II: 0, 0.054, 0.13 and 1.85 mg/m^3 Inhalation; 2 months	Dominant lethal mutations in germ cells of male rats	**positive** at ≥0.13 mg/m^3 increases in death before/after implantation and total embryonic death rate (significant at 1.85 and 3.5 mg/m^3)	(Sanotskii, 1976)
Swiss mice; M, n=12	10 or 100 ppm Inhalation; 6 h per day, 5 days per week, for 2 weeks	Dominant lethal mutations	negative	Immel and Willems, 1978a cited in (DFG, 2001)
White Rats M (n=10) and F (n=10-11)	0, 0.057 and 0.14 mg/m^3 Inhalation for 2.5 or 4.5 months	Dominant lethal mutations in germ cells of male rats	**positive** at 0.14 mg/m^3 significant increases in death after implantation and total embryonic death rate	(Sanotskii, 1976)
Wistar rats,	50 or 100 ml/m^3	Dominant lethal	negative	(Immel and

Species (test system), strain, sex; No/group	Dose range, route, duration	Study endpoints	Study results	References
n=12	Inhalation; 6 h daily, 5 days	test		Willems, 1978b/1978 c cited in (DFG, 2001)
C57BL/6 mice, bone marrow, (n=6-10)	Series I: 0, 0.064, 0.32, 3.5 mg/m^3 and Series II: 0, 0.054, 0.13 and 1.85 mg/m^3 Inhalation for 2 months	Chromosomal aberrations	**positive**	(Sanotskii, 1976)
B6C3F$_1$ mice; bone marrow; M (n=8/group)	0, 12, 32 or 80 ppm Inhalation;6 h per day, 12 days	Chromosomal aberrations	negative	(NTP, 1998) (Tice et al., 1988)
Rats, male	3.8 mg /m^3 (≈ 1 ppm) or 39 mg/m^3 (≈ 11 ppm); inhalation; 4 h daily for 48 days	Chromosomal aberrations	**positive**	Davtjan et al, 1973 cited in (DFG, 2001)
B6C3F$_1$ mice; bone marrow M (n=4/group)	0, 12, 32 or 80 ppm Inhalation; 6 h per day, 12 days	Sister-chromatid exchange	negative	(NTP, 1998) (Tice et al., 1988)
Mice, bone marrow	Inhalation up to 760 mg/m^3, 2 h for 2 consecutive days	Micronucleus test	**positive** significantly increased frequency of micronuclei in bone marrow PCE	Li and Xue, 1986 cited in (DFG, 2001)
B6C3F$_1$ mice; peripheral blood; M (n=14-15/group)	0, 12, 32, or 80 ppm Inhalation; 6 h per day, 5 days per week for a total of 12 exposure days (over a 16-day period)	Micronucleus assay; frequency of micronucleated cells/1000 PCEs and 1000 NCEs	negative	(NTP, 1998) (Tice et al., 1988)
B6C3F$_1$ mice; peripheral blood; M and F (n=10/group)	0, 5, 12, 32 or 80 ppm 6 h per day, 5 days per week in a 13-week inhalation study	Micronucleus assay; frequency of micronucleated cells/2000 PCEs and 10000 NCEs	negative	(NTP, 1998)
Wistar rats, bone marrow cells	100 ml/m^3 (368 mg/m^3) Inhalation; 6 h/day, 5 consecutive days	Micronucleus assay	negative	Willems and Immel cited in (DFG, 2001)
B6C3F$_1$ mice; lung and Harderian	0, 12.8, 32, or 80 ppm	Molecular analysis of genetic	**positive** **Lung neoplasms:**	(NTP, 1998) (Sills et al., 1999, Ton et

Species (test system), strain, sex; No/group	Dose range, route, duration	Study endpoints	Study results	References
gland neoplasms; M/F	Inhalation, 6 h per day, 5 days per week for 2 years	alterations in cancer-related genes	higher frequency (80%) of *K-ras* mutations detected in chloroprene-induced lung tumours than in spontaneous lung neoplasms in control mice (30%); predominant mutation: K-*ras* codon 61, A to T transversion (CAA to CTA) (22/46); most abundant in the 12.8 and 32 ppm dose groups High frequency of Loss of heterozygosity on chromosome 6 in the region of K-*ras* **Harderian Gland neoplasms:** higher frequency (100%) of *ras* mutations (K-*ras* and H-*ras*) in chloroprene-induced harderian gland tumours than in spontaneous neoplasms in control mice (56%); predominant mutation K-*ras* codon 61, A to T transversions (CAA to CTA) (25/27); similar incidences in the 12.8, 32, or 80 ppm dose groups (100%, 80%, and 100%, respectively)	al., 2007)

7.6.3 *In vitro* data

A number of *in vitro* genotoxicity studies of chloroprene have been reported (Table 11). NTP evaluation yielded negative results in the *Salmonella typhimurium* mutagenicity test in the presence or absence of metabolic activation (NTP, 1998, Zeiger et al., 1987). No activity in strain TA100 was reported with freshly distilled chloroprene. However a mutagenic effect occurring linearly with increasing age of chloroprene distillates was attributed to dimers formed as by-products (Westphal et al., 1994). In earlier studies, chloroprene was mutagenic in strains TA100, TA1535, TA98, and negative in TA1537 and TA1538 (Bartsch et al., 1975, Bartsch et al., 1979), Willems 1978, 1980 as cited in (EPA, 2010) (DFG, 2001). When testing positive, the addition of a metabolic activation system generally enhanced the mutagenic effect and in cases the toxicity of chloroprene, possibly conferred by the formation of metabolites.

Table 11: Summary of *in vitro* genotoxicity studies

Species (test system)	Dose levels	Study endpoints	Results		References*
			With metabolic activation	Without metabolic activation	
Salmonella typhimurium TA100 TA100, TA1535	0, 0.5, 2, and 8 % chloroprene in air (v/v) for 4 h at 37° C Dimers mixture (0.1- 1mM)	Bacterial reverse mutation	**positive** (weakly) **positive**	**positive** concentration-dependent negative	(Bartsch et al., 1975) (Bartsch et al., 1979)
Salmonella typhimurium TA100 TA1535	10,000-40,000 ppm 24 or 48 h	Bacterial reverse mutation	**positive**	**positive**	Willems 1978, Willems 1980, as cited in (EPA, 2010)
Salmonella typhimurium TA98 TA1537 TA1538	10,000-40,000 ppm 24 or 48 h	Bacterial reverse mutation	negative	negative	Willems 1978, Willems 1980, as cited in (EPA, 2010)
Salmonella typhimurium TA98, TA100, TA1535, TA1537	0, 310, 33, 100, 333, 1000, or 3,333 mg/plate (provided as aliquots, 50% purity) 20 mins, at 37°C	Bacterial reverse mutation	negative	negative	(NTP, 1998) (Zeiger et al., 1987)
Salmonella typhimurium TA100	Chloroprene purified by distillation immediately before the study; 5 mmol/plate Gas-tight preincubation in ethanol of dissolved in DMSO Aged chloroprene; 4 decomposition products (cyclic dimers) identified as major by-products	Bacterial reverse mutation	negative **positive** (2-3-fold enhanced effect)	negative **positive**	(Westphal et al., 1994)
Chinese hamster V79 cells	0.2, 1.0, 2.0 and 10% (v/v) chloroprene vapour in air for 5 h	Mammalian cell gene mutation; 8-azaguanine and ouabain resistance	negative enhanced dose-related toxicity	negative	(Drevon and Kuroki, 1979)

The *in vitro* mutagenic and clastogenic potential of chloroprene's metabolite (1-chloroethenyl) oxirane (CEO) has been evaluated by(Himmelstein et al., 2001b). In the bacterial reverse mutation assay, CEO (0-69 mM) caused toxicity at ≥14 mM and ≥34 mM, in the absence or presence of S9 metabolism, respectively. CEO caused positive mutagenic responses in the *Salmonella typhimurium* tester strains TA97a, TA98, TA100 and TA1535 both with and without metabolic activation, exhibiting greater activity in the base pair substitution strains TA100 (active at 0.7 mM), followed by TA1535. In the *in vitro* micronucleus assay, following an initial incubation of Chinese hamster V79 cells for 3 hours with 0-0943 mM CEO, cytotoxicity and altered cell morphology became evident at ≥0.175 mM. No discernible clastogenic response , evaluated only in the absence of S9 metabolism, was evident up to the cytotoxic concentrations (0.02-0.20) of the metabolite. CEO has been shown to preferentially alkylate DNA at the G-N7 and N3-cytosine positions, with N7-(3-chloro-2-hydroxy-3-buten-1-yl)-guanine (dGI), and N3-(3-chloro-2-hydroxy-3-buten-1-yl)-2′-deoxyuridine (dCI), identified as the predominant adducts (Munter et al., 2002). Additionally, CEO produces *in vitro* DNA interstrand crosslink at deoxyguanosine residues within 5′-GC and 5′-GGC sites. The observed correlation between DNA cross-linking efficiency and *in vitro* cytotoxicity, when comparing CEO to structural analogues diepoxybutane and epichlorohydrin, renders the DNA interstrand crosslinks as key cytotoxic lesion (Wadugu et al., 2010). Collectively, these results suggest that CEO DNA reactivity/cross-linking efficiency and induced mutagenicity, but not clastogenicity, may contribute to the genotoxic effects of chloroprene and its carcinogenic activity reported in the rodent bioassay studies (see section 7.7.2).

7.6.4 Summary

Human data on genotoxicity are limited to studies with important methodological deficiencies.
Chloroprene has produced overall conflicting results in *Salmonella typhimurium* tester strains, showing no mutagenic activity in the relevant NTP-conducted studies. The purity, stability and solvent of the chloroprene solution appear to be relevant to the outcome. Dominant lethal mutations in mice and rats have been reported, with conflicting findings in *Drosophila melanogaster*. Negative results were yielded in all *in vivo* cytogenetic tests performed by the NTP, however tumours induced at the same dose levels, harboured a higher frequency of *ras*-mutations, compared to the spontaneous neoplasms in control animals. Chloroprene's metabolite CEO is mutagenic in *S. typhimurium* and alkylates DNA in a sequence-specific manner.

7.7 Carcinogenicity

IARC (1999) concluded that Chloroprene is *possibly carcinogenic to humans (Group 2B)*. The conclusion was based on combination of *inadequate evidence* in humans and *sufficient evidence* in experimental animals for the carcinogenicity of chloroprene.

7.7.1 Human data

The IARC (1999) conclusion that there is *inadequate evidence* in humans for the carcinogenicity of chloroprene" was justified as follows: "*The risk of cancer associated with occupational exposure to chloroprene has been examined in two well conducted studies, one in the United States and one in Russia. These investigations do not indicate a consistent excess of cancer at any site.*" It is noted that IARC assessed three cohort studies: one including two US neoprene production plants (Pell, 1978), a Chinese chloroprene monomer and neoprene production plant (Li et al., 1989) and a Russian shoe manufacturing plant (Bulbulyan et al., 1998).

- In one of the US plants there was indication of an increased risk of cancer of the urinary tract (5 observed cases vs 0.5 expected from national rates). However, three of these deaths were from bladder cancer in men who had worked with β-naphthylamine and two were from cancer of the kidney.
- In the Chinese cohort 16 cancer deaths were recorded among workers with a history of

exposure to chloroprene, giving an SMR of 2.4 in comparison with mortality rates in the local area during 1973–75. A significant excess of liver cancer was reported among workers in the monomer workshop (4 observed versus 0.83 expected; SMR, 4.8). IARC noted that the selection criteria for the cohort were not entirely clear and the use of reference rates from only a three year period may have led to bias.

- In the Russian shoe manufacturing plant chloroprene was the main solvent used in the glue and gluers were considered to be subject to high exposure. Workers employed in the same departments as gluers but indirectly exposed to chloroprene were considered to have medium exposure and workers only employed in other departments were considered to be unexposed to chloroprene. In the 1970s, chloroprene exposure for gluers was of the order of 20 mg/m^3 (5.4 ppm) Other solvents to which gluers were exposed were benzene until the 1950s, and ethyl acetate. Other workers were exposed to leather dust and formaldehyde. When Moscow mortality rates were used as reference there was an excess of mortality from liver cancer (SMR, 2.4; 95% CI, 1.1–4.3; 10 deaths) and leukaemia (SMR, 1.9; 95% CI, 1.0–3.3; 13 deaths). When workers exposed to chloroprene were compared with unexposed workers, the relative risks were 4.2 (95% CI, 0.5–33; 9 deaths) for liver cancer, 3.8 (95% CI, 0.5–31; 9 deaths) for kidney cancer and 1.1 (95% CI, 0.3–3.7; 9 deaths) for leukaemia. Liver cancer mortality increased with duration of employment as a gluer ($p = 0.02$) and with cumulative exposure index ($p = 0.07$). IARC noted that this trend may have included the unexposed group, in which case it would not provide evidence independent of the overall elevated relative risk for liver cancer. No such trend was present for any other neoplasm. No information was available on the histology of the cases of liver cancer.

In addition to the cohort studies IARC noted one case report on liver angiosarcoma in a worker exposed to polychloroprene (unclear if there was exposure to chloroprene monomer) who had no known occupational exposure to vinyl chloride or medical exposure to thorotrast and one case series of 18 lung cancer and 21 skin cancer cases among workers with heavy exposure to chloroprene.

After the IARC evaluation Rice and Boffetta (2001) assessed the outstanding issues and research priorities in the epidemiology for 1,3-Butadiene, isoprene and chloroprene. For chloroprene Rice and Boffetta noted that although some earlier epidemiological studies noted suggestive evidence of an association between chloroprene exposure and liver cancer risk, study limitations included possible bias from cohort selection, follow-up, and choice of reference population. Other study limitations noted included limited exposure assessment data, low statistical power and the possible confounding by unmeasured co-exposures. Rice and Boffetta also noted that two additional epidemiologic studies of chloroprene workers have been reported, from Armenia (Bulbulyan et al., 1999) and from France (Colonna and Laydevant, 2001). In the former study, an association with liver cancer was reported based on 6 cases. No such association was observed in the latter study, whose statistical power was limited and only one case of liver cancer was observed. Rice and Boffetta concluded that while it would be difficult to overcome all the methodological problems listed above, it would in particular, given the apparent excess of liver cancer in three of the available five studies studies, be important to obtain information on the diagnostic procedures and histological type(s) of such cases. Furthermore, the study from China should be re-analyzed with the use of proper reference rates or, alternatively, using an internal comparison group. The detailed results on liver cancer mortality should be made available from the US study.

It is noted that concerning the suggestions made by Rice and Boffetta (2001), Marsh et al. 2007 updated the cancer mortality of the US cohorts and also presented updated results of the French cohort and results from an Northern Ireland chloroprene production plant. Marsh et al. 2021 published a further update of the US cohorts. No further articles have been published on the Armenian, Chinese or Russian cohorts.

Tables in Appendix 1 summarise the results of the available cohorts, i.e. the Armenian, Chinese, French, Northern Ireland, Russian and two US cohorts Table 14: Summary of the

cohort studies assessing the association between exposure to chloroprene and overall cancer risk. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.0.for all cancer (Table 14), liver cancer (Table 15) and lung cancer (Table 16). There is no consistent pattern of an increased risk for cancer overall, or for lung cancer. For overall cancer it is noted that the risk (SMR) is below unity in two US cohorts, the Northern Ireland, French and Armenian cohorts indicating a healthy worker effect. For lung cancer it is further noted that none of the studies adjusted for potential confounding by smoking.

As regards liver cancer, most cohorts have very few or no cases. For the largest of the cohorts, US Louisville plant, an earlier follow-up by Marsh et al. (2007a) and Marsh et al. (2007b) observed a borderline significant (p = 0.09) trend of increasing risk of liver cancer by cumulative exposure to chloroprene in the internal analysis comparing to the lowest cumulative exposure category (RRs 1.0 = reference, 1.90, 5.10, and 3.33 across quartiles of exposure, based on 17 total cases). However, it is noted that the reference category had an unusually low mortality from liver cancer (SMR 0.4, 95% CI 0.05 – 1.6) based on only 2 observed cases thus complicating the interpretation of the trend observed in the internal analysis. The extended follow-up of the Louisville plant (Marsh et al., 2021) observed 31 liver cancer deaths and there was no increase overall (SMR 1.1, 95% CI 0.7 – 1.5). Nor was there statistically significant increased trend by duration of exposure, mean intensity of exposure or cumulative exposure either in external comparison to general population or in internal comparison to the lowest exposure/shortest duration internal comparison group. In this update, the number of liver cancer deaths in the lowest category of cumulative exposure was 9 thus allowing statistically more robust analyses of trends and the external comparison of that category showed a risk similar to the general population (SMR 0.9, 95% CI 0.4 – 1.7). Same exposure categorisation as in Marsh et al. (2007a,b) was used. It is also noted that none of the studies listed in Table 15 adjusted for potential confounding by alcohol consumption. There is, however, no direct indication that alcohol use would correlate with chloroprene exposure. As regards the Russian and Armenian cohorts it was, however, reported that there were quite many deaths from liver cirrhosis, 11 and 32 respectively, but no SMR was reported that would compare if those would reflect a higher incidence of heavy drinking in the study cohorts than in the local reference population used. Furthermore, the studies of Li et al. (1989) and Bulbulyan et al. (1998) calculated the liver cancer SMR based on reference rates available only for 3 or 1 years, respectively. It is noted that in the study by Marsh et al 2007b, there were quite important differences in median exposure intensity (ppm) and cumulative exposure (ppm-years) of exposure between Louisville, US (5.2 ppm, 18.4 ppm-years), Maydown, Northern Ireland (0.16 ppm, 0.084 ppm-years), Grenoble, France (0.15 ppm, 1.0 ppm-years) and Pontchartrain, US (0.028 ppm, 0.13 ppm-years) plants. In the Louisville plant 22.7% and in the Northern Ireland plant 5.5% of chloroprene exposed had also exposure to vinyl chloride, while in Pontchartrain plant and the French plant, none had vinyl chloride exposure due to a different manufacturing process used.

As the cohorts included in the above-mentioned studies were predominantly or exclusively male, they had limited possibilities to investigate female cancer types. More recently two studies have published results also concerning risk of breast cancer in chloroprene exposed. These are summarised in Appendix 1 (Table 17). It is noted that although a statistically significantly increased risk was observed in the study by Marsh et a. (2021) in the Louisville plant in the overall external comparison to general population, there was no statistically significant dose-response by duration or intensity of exposure or by cumulative exposure. No control for potential confounders was performed. In the study of Garcia et al. (2015), residential exposures of multiple suspected mammary carcinogens were modelled based on home address. After correcting for the multiple testing performed, the trend by increasing exposure of estimated residential chloroprene exposure was not significant.

Bukowski (2009) reviewed the quality of the epidemiological studies available and concluded that the four cohort studies included in the Marsh et al. (2007a,b), especially

the rigorous investigation of the large Louisville cohort, provide the highest quality evidence and would be the most likely candidates to serve as "principal studies" for purposes of risk assessment. However, these studies are largely negative and therefore provide no rational basis for a point of departure in exposure-response analysis. Bukowski (2009) reported that the statistical power to detect a twofold increase in lung cancer and liver cancer mortality in the Louisville cohort update of Marsh et al. (2007b) was 97-100%.

It is noted that no pooled analysis or meta-analysis of the existing cohorts has been published. Also in the studies of Marsh et al. (2007a,b) and Marsh et al. (2021) the results of each plant are reported separately. The exposure assessment is the most robust and reporting of results by metrics of intensity and cumulative exposure most detailed in the studies of Marsh et al. (2007a,b) and Marsh et al. (2021) (see Table 14, Table 15, Table 16 and Table 17 in Appendix 1 for details). In the latest follow-ups of those cohorts, the person-years of follow-up in was the highest in the Louisville plant (245 218 person-years), compared to 127 036, 50 602 and 17 057 in the Northern Ireland, Pontchartrain and French cohorts, respectively. Also, the intensity of exposure among the cohort members was the highest in the Louisville plant (median intensity 5.2 ppm, compared to 0.16, 0.15 and 0.028 ppm in the other plants. Consequently, the results of the Louisville plant in the most recent follow-up (Marsh et al. 2021) seem the most robust to compare the human cancer risk with the results of the rat and mouse cancer assays. No clear evidence of an increased risk of cancer overall, lung cancer or liver cancer was observed either in external comparison to the general population or in internal analysis of risk by increasing exposure. There were 974 cancers overall (SMR 0.9, 95% CI 0.8 – 1.0), 358 respiratory cancers (SMR 1.0, 95% CI 0.9 – 1.1) and 31 liver cancers (SMR 1.1, 95% CI 0.7 – 1.5). In this cohort the mean exposure duration was 12.2 years with mean and median exposure intensities of 5.2 and 8.4 ppm, respectively and the high exposure group used in the internal and external analyses had an exposure an intensity of > 16 ppm. A further description of exposure levels indicates that before 1979 the polymer workers, polymer clean-up workers and finishing workers had chloroprene exposure levels of 5 of 50 ppm and in 1950-1960s also other worker groups had such exposures and polymer, polymer clean-up workers and finishing workers exposures of 50-100 ppm (Esmen et al., 2007). It was also reported that frequent use of personal protective equipment to reduce peak exposures occurred only in post-1985 era. The updated follow-up of the Pontchartrain plant observed about 10 less cancer cases than in the Louisville cohort and has particularly low risks compared to the general population in the lowest exposure category complicating the interpretation of the internal analysis.

AGS (2019) noted that the median exposures in many operational procedures were around 5 ppm in the Louisville cohort for a long time. Before 1979 there were also many operations with exposures above 50 ppm (Esmen et al., 2007). AGS further noted that 5 ppm is approximately twice the BMD10 in the B6C3F1 mouse for lung tumours. At 12.5 ppm, the lung tumour rates in the B6C3F1 mouse had increased to two-fold that of the control. AGS (2019) therefore stated that it can be assumed that a tumour risk in humans that was quantitatively equivalent to that in mice should have been observed in the Louisville cohort. The AGS (2019) assessment is further described in section 9. Sax et al. (2020), compared the inhalation unit cancer risk (IUR) derived by EPA (2010) from a mice study with the epidemiological data by using PBPK modelling estimating internal doses that represent the concentration of the hypothesized toxic moiety (i.e., the chloroprene metabolite). Sax et al. (2020) concluded that the mice data based IUR overestimates the human cancer risk by two orders of magnitude. It is noted that both the AGS (2019) and Sax et al. (2020) reports were based on Louisville plant update of Marsh et al. (2007a,b) with 197 919 person-years of follow-up. Nevertheless, the latest update (Marsh et al. (2021) based on 245 218 person-years, does not indicate an increased cancer risk either.

7.7.2 Animal data

Two-year inhalation carcinogenicity studies in mice and rats have been conducted and reported by the NTP (NTP, 1998). The study design details and main findings of these GLP-

compliant studies (including type, site and incidence of neoplastic lesions in selected organs) are summarised in **Error! Reference source not found.**12.
In the mouse study, B6C3F$_1$ mice were exposed to concentrations of up to 80 ppm by inhalation. Survival of males exposed to 32 or 80 ppm and of females at all dose levels was significantly less than that of the chamber controls. The mean body weights of the high dosed females were reduced, compared to controls, after week 75.
Chloroprene caused significant (unless otherwise stated) increases compared to controls - generally exceeding the historical control ranges- in the incidences of a number of neoplasms at multiple sites:

a. in males and females:
- lung: alveolar/bronchiolar adenoma and alveolar/bronchiolar adenoma or carcinoma (combined) at all concentrations ((≥12.8 ppm)
- circulatory system (endothelial) neoplasms: hemangiosarcoma and hemangioma or hemangiosarcoma (combined) at multiple organ sites (males ≥12.8 ppm; females 32 ppm). Hemangiosarcomas occurred primarily in the mesentery, subcutis of the skin and liver; the bone and spleen were also affected. The increases in males remained significant at all doses, even when the liver lesions were excluded from the analysis, as their induction has been associated with *Helicobacter hepaticus* infections which in this study was present in males
- Harderian gland: adenoma and adenoma or carcinoma (combined) (males ≥32 ppm; females 80 ppm)
- forestomach: non-significant increases in the incidence of squamous cell papilloma in females exposed to 80 ppm and an overall positive trend in males

b. in male mice:
- kidney: renal tubule adenoma upon examination of either single or step-sections, the latter as part of or an extended verification analysis, at 80 ppm

c. in female mice:
- mammary gland: carcinoma and adenoacanthoma or carcinoma (combined) at 80 ppm
- liver: hepatocellular carcinoma in all exposed females (≥12.8 ppm) and hepatocellular adenoma or carcinoma (combined) at ≥32 ppm
- skin: sarcoma in all exposed groups (≥12.8 ppm), occurring primarily in the subcutis
- mesentery: sarcoma; incidence increased at all doses and significantly so at 32 ppm
- Zymbal's gland: carcinomas were observed in three high dosed females, with two
- of these carcinomas metastasising to the lung. No occurrence of this tumour type had been previously reported in control female mice in the NTP historical database.

In the rat study, F344/N rats were exposed to concentrations of up to 80 ppm by inhalation. Survival of males exposed to 32 or 80 ppm was significantly less than that of the chamber controls. The mean body weights of the high dosed males were reduced, compared to controls, after week 93. There were no differences in survival of body weights between exposed and chamber control female rats.
Chloroprene caused significant (unless otherwise stated) increases compared to controls - generally exceeding the historical control ranges- in the incidences of a number of neoplasms at multiple sites:

a. in males and females:
- oral cavity (oral mucosa, tongue, pharynx, gingiva): squamous cell papilloma and squamous cell papilloma or squamous cell carcinoma (combined) (males ≥32 ppm; females at 80 ppm)
- thyroid gland: follicular cell adenoma or carcinoma (combined) in males exposed to ≥ 32 ppm; a non-significant increase was noted in females exposed to 80 ppm

- lung: alveolar/bronchiolar carcinoma and alveolar/bronchiolar adenoma or carcinoma (combined): non-significant-yet exceeding the historical control range-small numerical increases in 80 ppm males; slight, non-significant increase in alveolar/bronchiolar adenoma noted in the 80 ppm females
- kidney: renal tubule adenoma and renal tubule adenoma or carcinoma (combined) in all exposed males (≥ 12.8 ppm), as per standard or extended evaluation; small numerical increase in the combined incidence in females (as per an extended evaluation)

b. in female rats:

- mammary gland: multiple fibroadenoma in all exposed groups, reaching statistical significance at ≥ 32 ppm

Two 80 ppm females and one 32 ppm male presented with transitional epithelium carcinomas in the urinary bladder. Although deemed "uncertain findings", these incidences were considered noteworthy as there was no occurrence of urinary bladder neoplasms in historical chamber controls of either sex.

Table 12: Summary of main neoplastic findings in animal inhalation studies

Species, strain, sex, number/ group	Doses, route, duration of exposure	Results	Remarks	References
Mouse, $B6C3F_1$, (M), n=50	0, 12.8, 32, 80 ppm, inhalation, 6 h/day, 5 days/wk; 2 years	Survival rates: 27/50, 27/50, 14/50, 13/50 **Lung:** alveolar/bronchiolar adenoma (includes multiple): 8/50[a], 18/50*, 22/50**, 28/50*** alveolar/bronchiolar carcinoma (includes multiple): 6/50, 12/50, 23/50***, 28/50*** alveolar/bronchiolar adenoma or carcinoma (combined) 13/50, 28/50***, 36/50***, 43/50*** **Circulatory system:** hemangiosarcoma (all organs) 3/50, 13/50**, 22/50***, 19/50*** hemangiosarcoma (excludes liver) 1/50, 11/50**, 16/50***, 15/50***	GLP-compliant study; survival of males exposed to 32 or 80 ppm was significantly reduced "clear evidence of carcinogenic activity"[b] "clear evidence of carcinogenic activity"	(NTP, 1998)

Species, strain, sex, number/ group	Doses, route, duration of exposure	Results	Remarks	References
		hemangioma or hemangiosarcoma (all organs) 3/50, 14/50**, 23/50***, 21/50*** hemangioma or hemangiosarcoma (excludes liver) 1/50, 12/50***, 18/50***, 17/50*** **Harderian gland:** adenoma 2/50, 5/50, 8/50*, 10/50* adenoma or carcinoma 2/50, 5/50, 10/50*, 12/50** **Forestomach:** squamous cell papilloma 1/50, 0/50, 2/50, 4/50 **Kidney:** renal tubule adenoma; step sections-extended evaluation 0/50, 1/49, 2/50, 6/50* single and step sections; standard and extended evaluation (combined) 0/50, 2/49, 3/50, 9/50**	"clear evidence of carcinogenic activity" "attributed to exposure to chloroprene" "attributed to exposure to chloroprene"	
Mouse, B6D2F$_1$, (F), n=50	0, 12.8, 32, 80 ppm, inhalation, 6 h/day, 5 days/wk; 2 years	Survival rates: 35/50, 16/50, 1/50, 3/50 **Lung:** alveolar/bronchiolar adenoma (includes multiple): 2/50, 16/49***, 29/50***, 26/50*** alveolar/bronchiolar carcinoma (includes multiple): 2/50, 14/49***, 16/50***, 28/50*** alveolar/bronchiolar adenoma or carcinoma (combined) 4/50, 28/49***, 34/50***, 42/50***	GLP-compliant study; survival of all groups of exposed females was significantly reduced "clear evidence of carcinogenic activity"	(NTP, 1998)

Species, strain, sex, number/ group	Doses, route, duration of exposure	Results	Remarks	References
		Circulatory system: hemangioma (all organs) 0/50, 0/50-, 2/50, 3/50 Hemangiosarcoma (all organs) 4/50, 6/50, 17/50***, 5/50 hemangioma or hemangiosarcoma (all organs) 4/50, 6/50, 18/50***, 8/50 **Harderian gland:** adenoma 1/50, 3/50, 3/50, 8/50* adenoma or carcinoma 2/50, 5/50, 3/50, 9/50* **Mammary gland:** carcinoma (includes multiple) 3/50, 4/50, 7/50, 12/50* adenoacanthoma or carcinoma 3/50, 5/50, 10/50, 14/50* **Liver:** hepatocellular carcinoma (includes multiple) 4/50, 11/49*, 14/50**, 19/50*** hepatocellular adenoma or carcinoma 20/50, 26/49, 20/50*, 30/50** **Skin:** sarcoma 0/50, 11/50***, 11/50***, 18/50*** **Mesentery:** sarcoma 0/50, 4/50, 8/50**, 3/50 **Forestomach:** Squamous cell papilloma 0/50, 0/50, 0/50, 4/50 **Zymbal's gland** carcinoma 0/50, 0/50-, 0/50-, 3/50	"clear evidence of carcinogenic activity" "clear evidence of carcinogenic activity" "clear evidence of carcinogenic activity" "clear evidence of carcinogenic activity" "clear evidence of carcinogenic activity" "clear evidence of carcinogenic activity" "attributed to exposure to chloroprene" "attributed to exposure to chloroprene"	
Rat, F344/ (M), n=50	0, 12.8, 32, 80 ppm;	Survival rates: 13/50, 09/50, 5/50, 4/50	GLP-compliant study;	(NTP, 1998)

Species, strain, sex, number/ group	Doses, route, duration of exposure	Results	Remarks	References
	inhalation, 6 h/day, 5 days/wk for 2 years	**Oral cavity:** Squamous cell papilloma 0/50, 2/50, 4/50*, 10/50*** squamous cell papilloma or squamous cell carcinoma 0/50, 2/50, 5/50*, 12/50*** **Thyroid gland:** Follicular cell adenoma or carcinoma 0/50, 2/50, 4/49*, 5/50* **Lung:** alveolar/bronchiolar carcinoma 0/50, 2/50, 1/49, 4/50 alveolar/bronchiolar adenoma or carcinoma 2/50, 2/50, 4/49, 6/50 **Kidney:** Renal tubule adenoma; step sections (extended evaluation) 1/50, 6/50*, 6/50**, 7/50** single and step sections (standard and extended evaluation; combined): 1/50, 7/50*, 6/50**, 8/50** renal tubule adenoma or carcinoma (combined); step sections (extended evaluation) 1/50, 7/50*, 6/50**, 7/50** single and step sections (standard and extended evaluations): 1/50, 8/50*, 6/50**, 8/50** **Urinary bladder:** transitional epithelium carcinoma	survival of males exposed to 32 or 80 ppm was significantly reduced "clear evidence of carcinogenic activity" "attributed to chloroprene exposure" "attributed to chloroprene exposure "attributed to chloroprene exposure "Uncertain finding; may have	

Species, strain, sex, number/ group	Doses, route, duration of exposure	Results	Remarks	References
		0/50, 0/50, 1/50, 0/49	been related to exposure"	
Rat, F344/N, (F), n=50	0, 12.8, 32, 80 ppm; inhalation, 6 h/day, 5 days/wk for 2 years	Survival rates: 29/49, 28/50, 26/50, 21/50 **Oral cavity:** squamous cell papilloma 1/49, 2/50, 2/50, 7/50* squamous cell papilloma or squamous cell carcinoma 1/49, 3/50, 5/50, 11/50** **Thyroid gland:** follicular cell adenoma or carcinoma 1/49, 1/50, 1/50, 5/50 **Mammary gland:** Fibroadenoma (includes multiple) 24/49, 32/50, 36/50*, 36/50** **Kidney:** renal tubule adenoma or carcinoma (combined); single and step sections (standard and extended evaluations; combined) 0/49, 0/50-, 0/50-, 4/50 **Urinary bladder:** transitional epithelium carcinoma 0/49, 0/50, 0/50, 2/50 **Lung:** alveolar/bronchiolar adenoma 1/49, 0/50, 0/50, 3/50	GLP-compliant study; "clear evidence of carcinogenic activity" "attributed to exposure to chloroprene" "attributed to exposure to chloroprene" "attributed to exposure to chloroprene" "Uncertain finding; may have been related to exposure" "Uncertain finding; may have been related to exposure"	(NTP, 1998)
Wistar rats, M+F, (n=100/sex/ group)	0, 10, 50 ppm v/ v) β-chloroprene (99.6% pure; freshly distilled); inhalation, 6 h/day, 5 days/wk for 24 months	Survival unaffected by exposure; accidental death of 87 male and 73 female at 10 ppm due to a technical fault in chamber operation; M: **Skin:** squamous cell carcinoma 0/97, 0/13-, 2/100 **Nose** (skin, nasal cavity, or maxillary sinus): Squamous-cell carcinoma 0/97, 0/13-, 3/100 skin squamous-cell carcinoma (combined)	"β -chloroprene was not considered to enhance the development of squamous-cell carcinomas in rats"	(Trochimowicz et al., 1998)

Species, strain, sex, number/ group	Doses, route, duration of exposure	Results	Remarks	References
		0/97, 0/13-, 5/100* F: **Skin/Nose** (skin, nasal cavity, or maxillary sinus) 1/99, 0/24-, 0/100 **Mammary gland** adenoma 3/99, 1/24-, 7/100 Fibroadenoma 24/99, 6/24-, 36/100*	"β-chloroprene exposure was not considered to enhance the development of benign mammary-gland tumours in rats"	

[a] overall rate: number of neoplasm-bearing animals/number of animals examined (necropsied or microscopically examined), [b]: statements in brackets are conclusions made by the authors of the respective studies, *p<0.05; **p<0.01, ***p≤0.001: significantly different from the chamber control group by: (NTP): Fischer exact test/Logistic regression test; (TNO): chi-square test; -:no incidence of tumour or value of statistic could not be computed

Based on the above observations, chloroprene shared a number of common sites of increased neoplastic incidences with 1,3-butadiene as reported in the respective NTP 2-year inhalation studies. In mice these comprised the lung, harderian gland, liver, forestomach, and mammary gland and in rats the thyroid and mammary glands. Similarly, the four organ sites where isoprene was reported to induce neoplasms in mice (lung, liver, harderian gland, and forestomach) were also affected by chloroprene. However, some carcinogenic effects of 1,3-butadiene were not seen in the chloroprene study (e.g., in mice: lack of lymphomas or granulosa cell tumours of the ovary) and some chloroprene-specific target sites such as the oral cavity were not reported in rats or mice exposed to either 1,3-butadiene or isoprene. These discrepancies may be related to differences in exposure to the parent compound and differences in target organ dosimetry and/or reactivity of metabolic intermediates ((NTP, 1998), references therein).

In a TNO lifetime inhalation study (conducted between 1976-1978), three groups of Wistar rats and Syrian golden hamsters of each sex were exposed to β-chloroprene for up to 24 and 18 months, respectively (Trochimowicz et al., 1998).
In rats, a slight but consistent growth retardation was found in males (~10%) and females (~5%) exposed to 50 ppm. Several statistically significant changes in relative organ weight (e.g., lung, liver, spleen, thyroid, kidney, pituitary) were not accompanied by chemical-related histopathological changes and were therefore considered to be unrelated to β-chloroprene exposure. With the exception of non-malignant mammary-gland tumours and squamous-cell carcinomas, no individual organ or tissue in exposed rats showed a statistically significant excess of tumours compared to controls. The number of females bearing benign fibroadenomas in the 50 ppm group was significantly increased and was attributed mainly to animals that were killed or died before the terminal sacrifice, since no difference was found between control and exposed rats killed at the end of the study. The 10 ppm group was not considered because of the small effective number of animals. Taking into account the incidence of palpable subcutaneous tissue masses in control groups from other concurrent life-span studies with this strain of rat, it was concluded that the fibroadenoma incidence increase was not exposure-related. There was no statistically significant difference in the incidence of other mammary-gland tumours (including adenoma, adenocarcinoma, and papillary carcinoma) between control and exposed animals. In the nose, 3/100 males in the 50 ppm group presented squamous-cell carcinomas of no clear aetiology. If originated as skin tumours, the total number of squamous-cell carcinomas of the skin would be 5/100 in the 50 ppm group; a significant incidence increase, compared to controls (1/97 occurrence in females) (Table 12). All other

tumours observed in rats were equally distributed between control and exposed animals and were typical of the neoplastic lesions occurring in these strains and animal age.
The same applied in hamsters, apart from a slight increase in cystadenomatous polyps of the gallbladder in the 10 ppm males.
Overall, there was no evidence of carcinogenicity in the TNO studies related to β-chloroprene exposure in either rats or hamsters at vapour concentrations as high as 50 ppm. This is in contrast to the NTP studies, and possible reasons have been proposed to be the difference in the purity of the test sample (99.6% in the TNO vs 98.5% in the NTP), whether it was freshly distilled or stored before use and the generation method employed to produce the chloroprene vapours (low vs high temperature vaporisation technique), which could have all impacted the thermally unstable chloroprene and the formation of promutagenic dimers. Other factors such as species/strain differences in e.g. metabolism were also conceivable.

In a short-term inhalation study in Kunming albino mice exposed to 0, 2.9, 19.2 and 189 mg/m^3, 4 h daily for 7 months, lung tumours were observed after month 6. Most lung tumours were papilloadenomas (50/57), and a few were adenomas (7/57). The increase in tumour incidence was significant between the 2.9 mg/m^3 group and controls (8.1% vs 1.3%). The incidence and multiplicity of tumour induction exhibited a dose-response relationship (Dong et al., 1989).

Finally, some early Soviet studies, with very limited experimental details, reported weak carcinogenic effects in mice and rats exposed by the oral, subcutaneous, and dermal routes in contrast to later studies (by the same routes and in the same species) which yielded negative results (Khachatryan, 1975; Zilfian et al., 1975, 1977, as cited by (AGS, 2019).

7.7.3 Summary

Earlier epidemiological studies noted suggestive evidence of an association between chloroprene exposure and liver cancer risk. The studies were, however, based on small numbers of exposed cases and were subject to methodological limitations like possible bias from cohort selection, follow-up, and choice of reference population. More recent, larger cohort studies with more detailed exposure information did not find consistent evidence of increased liver cancer risk overall, or a dose-response by duration, intensity or cumulative exposure. These studies did also not find consistent pattern of an increased risk for cancer overall, or for lung cancer. Due to the gender distribution of the cohorts, the studies had limited possibilities to investigate female cancer types. Although some studies found indications of an increased risk of breast cancer in chloroprene exposed, no consistent pattern of risk overall or a dose-response by duration, intensity or cumulative exposure was observed.

Exposure of B6C3F$_1$ mice and F344 rats to chloroprene produced potent, multisite carcinogenic responses, under the experimental conditions of the respective 2-year NTP studies, providing "clear evidence" of the carcinogenic potential of chloroprene in experimental animals.

- In mice, the lung was a major target organ of chloroprene-induced neoplasms with alveolar/bronchiolar adenomas or carcinomas occurring at a significant rate in both male and female mice, at all doses (≥12.8 ppm). Increased incidences of neoplasms in the circulatory system (hemangiomas/ hemangiosarcomas) and harderian gland (adenomas/carcinomas) were also observed in both sexes, with significance reached at both sites, at lower concentrations in males (≥12.8 ppm) than females (≥32 ppm). Female mice additionally presented significantly increased incidences of neoplasms in the liver and skin (≥12.8 ppm), mesentery (32 ppm) and mammary gland (80 ppm) providing further "clear evidence" for the carcinogenic activity of chloroprene. Other

exposure-related effects included neoplasms in the kidney in male mice, the Zymbal's gland in female mice and the forestomach in both sexes.

- In rats, "clear evidence" of carcinogenic activity of chloroprene was based on the increased incidences of neoplasms of the oral cavity (squamous cell papilloma or carcinoma), reaching significance in both male and female rats at ≥32 ppm and 80 ppm, respectively. Exposure-related effects comprised neoplasms of lung in male rats, of the mammary gland (fibroadenoma) in female mice and of the thyroid gland and kidney in both sexes. Male rats generally had a higher incidence of kidney neoplasms than females with renal adenomas or carcinomas becoming significant at all doses in males upon extended histopathologic evaluations. Slight numerical increases of urinary bladder neoplasms in male and female rats and lung neoplasms in female rats may have also been related to chloroprene exposure.

Collectively, tumour incidence and multisite distribution were generally greater among mice compared to rats. Although tumour incidences were statistically significantly increased at ≥32 ppm in rats - except for the kidney; increases in renal tubule adenomas/carcinomas were significant at ≥12.8 ppm in males- neoplastic lesions at multiple sites such as circulatory-system hemangioma/hemangiosarcoma in males, skin sarcoma in females, and lung adenoma and/or carcinoma in both sexes, were significantly increased at all exposure concentrations in mice ((≥12.8 ppm). The enhanced potency of chloroprene in mice compared to rats could be explained by the observed differences in metabolism (i.e. higher rate of chloroprene oxidation and slower rate of epoxide detoxification in mouse over rat microsomes) (see section 7.1.3.3).

A 2-year inhalation TNO study in Wistar rats contradicted the NTP findings, providing no evidence of carcinogenicity related to chloroprene exposure at vapor concentrations up to 50 ppm.

It is difficult to use negative human epidemiological data to rule out human cancer risk altogether. However, no increase in risk of overall, lung or liver cancer was observed in the largest cohort study, which also had the highest exposure, with a median and mean exposures of 5.2 and 8.4 ppm, respectively and the high exposure group used in the internal and external analyses had an exposure an intensity of > 16 ppm. At such exposure levels clear indications of increased risk would have been expected assuming that humans have a risk comparable to that observed in the cancer bioassay in mice, which seems to be the more sensitive species among the two rodents with available data (mouse and rat).

7.8 Reproductive toxicity

7.8.1 Human data

EPA (2010) discussed the Russian review of Sanotskii (1976) which referred to a study on chronic effects in exposed workers at an electrical engineering plant (the original study is in Russian). When compared to 118 unexposed controls, the chloroprene-exposed cohort (143 workers) exhibited an increased incidence of disturbances of spermatogenesis after 6–10 years of work and morphological disturbances after 11 years or more. A questionnaire showed that the rate of spontaneous abortion in the wives of chloroprene workers was more than threefold greater when compared to the control group. EPA (2010) noted that this study presents interpretational difficulties concerning the level of participation of the exposed workers and their wives, the quantitative interpretation of the reported sperm abnormalities, and the appropriate matching of exposed and control populations. In an earlier evaluation of this study, EPA (1985) concluded that recall bias associated with a retrospective questionnaire, was likely, and the likelihood that the study would have discovered a real increase in the rate of spontaneous abortions was remote, as embryos with chromosomal abnormalities are spontaneously aborted early in pregnancy. Many spontaneous abortions occur before a woman recognizes that she is

pregnant, with clinical signs of miscarriage often mistaken for heavy or late menstruation. EPA (1985) concluded that it was not reasonable to draw conclusions on the possible effect of chloroprene on early fetal losses based on the study referred by Sanotskii (1976) review. In addition, the EPA suggested that the low participation of male volunteers available for sperm analysis (9.5% participation, 15/143 workers) indicated that a large degree of selection bias may have been present. If Fmales with reproductive deficits self-selected themselves for participation, the meaningful interpretation of the study results may be limited. The final conclusion of the EPA (1985) analysis was that it is not possible to interpret the results in the Sanotskii (1976) review with any degree of reliability. Savitz et al. (1994) and Schrag and Dixon (1985) separately reviewed the study and also concluded that insufficient methodological details were available to critically evaluate the observation reported by Sanotskii (1976).

7.8.2 Animal data

Fertility

Two-generation reproductive toxicity studies by Appelman and Dreef-van der Meulen (1979) were reviewed in (EPA, 2010, Health_Council_of_the_Netherlands, 2003). No male fertility effects or effects on litter size intra-uterine mortality were observed in a study setting where male Wistar rats (F0 generation) were exposed to 0, 36, 120 or 360 mg/m^3 of freshly purified chloroprene via inhalation (6 h/day, 5 days/week during 13 weeks) before mating with untreated females. A reduction in body weight gain of males of the highest dose group was reported. Next, F1 male and female rats were exposed to chloroprene following the same protocol as for the F0 males, but with a duration of 10 weeks, starting at the age of four weeks. The only reported effects were related to reduced body weight gain and increased relative liver and ovary weight in females of the top dose group.

In the other, similar study (reviewed in (EPA, 2010, Health_Council_of_the_Netherlands, 2003)), female Wistar rats inhaled concentrations of 0, 36, 120 or 360 mg/m^3, 6 h/day, 5 days/week for 13 weeks. Next, they were mated with unexposed male rats. Decreased body weight gain was reported, but no other systemic or reproductive effects were observed. F1 male and female animals were exposed for 10 weeks as described above. No other findings than decreased body weight gain (at 119 and 360 mg/m^3) were reported.

(Culik et al., 1978) exposed male Charles River CD rats to 0 or 90 mg/m^3, 4 h/day, 22 days, after which the rats were mated with untreated females. No signs of changes in male rat fertility were observed. Mating index, litter size, viability index and lactation index were similar to the control group.

No effects on reproductive organs or parameters were reported in subchronic inhalation studies (approximately 6 h/day, 5 days/week, 13 weeks) with male and female F344 rats (0, 5, 12, 32, 80 ppm (0, 18, 115, 720 mg/m^3) or mice (0, 12, 32, 80 ppm (0, 43, 115, 288 mg/m^3). The parameters evaluated included sperm motility, sperm count, sperm morphology, testicular weight, epididymal weight, vaginal cytology, oestrus cycle. (NTP, 1998)

Developmental effects

Groups of pregnant rats were exposed to chloroprene via inhalation for 4 h/day at concentrations of 0, 3.4, 36 or 90 mg/m^3 on gestation days 1-12. They were sacrificed on day 17, and examinations to investigate maternal and embryotoxic effects. No exposure-related findings were identified. The report also describes another study setting in which pregnant rats were exposed during gestation days 19-24. The exposure concentrations and time where the same. A slight increase in average foetal body weight was observed among foetuses of the high dose group, and a significantly increased crown-rump length was measured at 36 and 90 mg/m^3. No major malformations (external, skeletal or soft tissue) were observed and no maternal toxicity effects were reported. (Culik et al., 1978)

In another study pregnant Wistar rats were exposed to chloroprene via inhalation (0, 36, 90, 270, 360 mg/m^3, 6 h/day) on gestation days 6-16 or 4-16 in a preliminary (n=7/dose group) or extended study (n=30/dose group), respectively. They were sacrificed on gestation day 21, whereafter investigations focusing on maternal toxicity, embryotoxicity and teratogenicity took place. No adverse effects were found; the only findings were reduced maternal food intake and growth reduction at the three highest dose levels and slight reductions foetal growth (Appelman and Koeter, 1980; reviewed in (Health_Council_of_the_Netherlands, 2003)).

In a study on pregnant New Zealand rabbits, developmental effects of chloroprene were examined after inhalation exposure to concentrations of 0, 37, 147, 644 mg/m^3 (0, 10, 40, 175 ppm), 6 h/day, 7 days/week on gestation days 6-28. On day 29 of gestation, uterine and foetal body weights were obtained and implants enumerated. No signs of maternal toxicity or foetal developmental effects were recorded in the extensive examinations conducted (Mast et al., 1994; reviewed in (Health_Council_of_the_Netherlands, 2003)).

7.8.3 Summary

Human data on reproductive and developmental effects are limited to one old study with several important methodological deficiencies. No significant effects on fertility or development were identified in animal studies with chloroprene exposure.

8. Other considerations

8.1 Mode of action (MoA) considerations

AGS (2019) recently concluded, after the review of the available evidence, that a primarily genotoxic mechanism of action must be assumed. AGS (2019) noted that "*The carcinogenicity of chloroprene in animal studies is very clearly species-and also strain-dependent. Tumours at the port of entry were observed as well as in systemic tissues. Often, there was no linkage with precursor effects; thus, stimulus effects, atrophies, and metaplasia were found in the nose in the NTP studies, but no tumours; on the other hand, tumours manifested in tissues in which no sub-chronic effects were evident. In addition, single, partly rare tumour forms without statistical significance and without a consistent target organ were also found.*

This picture becomes plausible in the light of kinetics. Individual organs or cell systems can form a mutagenic intermediate with appropriate enzyme equipment, essentially probably (1-chloroethenyl) oxirane, whose R-enantiomer is only slowly degraded or practically enriched by epoxide hydrolases with considerable species and strain differences.

Overall, this means that for carcinogenicity, a primarily genotoxic mechanism of action must be assumed. Furthermore, there is no indication that such a genotoxic effect is linked to a further prerequisite - such as high doses or cytotoxicity. In principle, this common mode of action is considered qualitatively independent of species and strain; however, quantitatively, there are significant differences in the bioavailability of (1-chloroethenyl) oxirane, and there is evidence from kinetic studies with animal and human microsomes that the bioavailability of the genotoxic metabolite is higher in B6C3F1 mice than in rats and humans. The limited metabolic capacities to produce the critical metabolite, depending on species and cell type, apparently form the background for the lack of detectability of genotoxic effects in vivo and for the overall flat, partly sublinear dose relationships, also for the few organ-specific effects in sub-chronic studies. For epidemiological studies in humans, this would mean that high exposures do not necessarily have to be more important than low exposures and that the duration of exposure should be of major importance."

As described in section 7 of this report, no more recent relevant animal or mechanistic data were identified since AGS (2019). As regards human data, the most recent cancer

follow-up update of the largest chloroprene exposed cohort published since AGS (Marsh et al., 2021, see section 7.7.1) consolidate, based on more person-years of observation and higher number of observed cancer cases, the findings of no consistent increase in cancer risk. A finding that was already observed in the earlier studies that were available to AGS. Consequently there is no reason to deviate from the non-threshold conclusion made by AGS as well as the conclusion that although in principle, the common mode of action is considered qualitatively independent of species and strain, quantitatively, there are significant differences in the bioavailability of (1-chloroethenyl) oxirane. In particular, there is evidence from kinetic studies with animal and human microsomes that the bioavailability of the genotoxic metabolite is higher in B6C3F1 mice than in rats and humans. This is related to more rapid generation of this metabolite, followed by slower detoxification by epoxide hydrolase in mice compared to rats or humans (see section 7.1.3).

As the toxicity of chloroprene is related to the formation of reactive metabolites, it is noted that for example CYP2E1 or epoxide hydrolase polymorphisms may influence the individual risks of workers exposed to chloroprene.

8.2 Lack of specific scientific information

Information is lacking to quantify the significance of dermal absorption of chloroprene.

8.3 Groups at Extra Risk

No groups at extra risk were identified.

9. Evaluation and recommendations

9.1 Cancer risk assessment

9.1.1 Published approaches for cancer risk assessment

9.1.1.1 AGS (2019)

AGS (2019) concluded, after the review of the available evidence, that a primarily genotoxic mechanism of action must be assumed (see section 8.1). AGS (2019) further noted that there is evidence from kinetic studies with animal and human microsomes that the bioavailability of the genotoxic metabolite is higher in B6C3F1 mice than in rats or humans.

AGS further concluded that "*The dose-response relationships for carcinogenic effects are mostly approximately linear up to intermediate dose ranges (32 ppm); at 80 ppm, the metabolic saturation phenomenon became partially apparent. However, some cell types are apparently transformed only at higher doses, so that linear, sublinear and supralinear curves can be found depending on the tumour type.*"

AGS performed BMD10 calculations based on the mice and rat NTP (1998) studies using the multistage model and noted that the selection of a point of departure (POD) for a linear extrapolation is usually based on the lowest BMD.

AGS noted that the BMD10 for the lung tumours on the B6C3F1 mouse according to the multistage model was 5 ppm for males and 4 ppm for females and, with mortality adjustment, 1.6 and 3.1 ppm, respectively. Because the tumour data themselves gave no indication that males are more sensitive, AGS noted that the possibility of computational artefacts must be considered, because of the high spontaneous rate and the partially supra-linear dose relationship.

In addition, AGS noted that there was considerable doubt about the relevance of the lung tumours in the B6C3F1 mouse to humans for the following reasons:

- The kinetic studies have shown an unusually high accumulation of the genotoxic metabolite for the mouse lung.

- No lung tumours were found in Fischer and Wistar rats, nor in hamsters, nor -within the resolution of the epidemiological studies- in humans.
- The structurally related butadiene, which has the same potency as chloroprene in the B6C3F1 mouse, has not led to lung tumours in humans according to comprehensive epidemiology studies.

As regards human data, AGS (2019) noted that the median exposures in many operational procedures were around 5 ppm in the Louisville cohort for a long time. Before 1979 there were also many operations with exposures above 50 ppm (Esmen et al., 2007).
AGS further noted that 5 ppm is approximately twice the BMD10 in the B6C3F1 mouse for lung tumours. At 12.5 ppm, the lung tumour rates in the B6C3F1 mouse had increased to two-fold that of the control. AGS further noted, referring to Bukowski (2009) that the statistical power to detect a two-fold increase in lung cancer and liver cancer mortality in the Louisville cohort update of Marsh et al. (2007b) was reported to be 97-100%. AGS (2019) stated that it can therefore be assumed that a tumour risk in humans that was quantitatively equivalent to that in mice should have been observed in the Louisville cohort.

Therefore, AGS considered more adequate, for quantitative considerations, to start from the oral cavity tumours in the Fischer rat which is a rare tumour with a very low background rate.

The BMD10 was 34.5 ppm and led to the following ERR:

Excess risk	Concentration
1: 1 000	0.345 ppm
4: 1 000	1.38 ppm
4: 10 000	0.138 ppm
4: 100 000	13.8 ppb

If the squamous cell carcinomas of the nose and skin at 50 ppm from the TNO study (i.e. Trochimowitcz et al., 1998) in Wistar rats were combined and their 5% incidence in males were taken as a starting point, the following figures would be obtained:

Excess risk	Concentration
1: 1 000	1 ppm
4: 1 000	4 ppm
4: 10 000	0.4 ppm
4: 100 000	40 ppb

AGS (2019) noted that the ERR based on the oral cavity tumours in the Fischer rat would differ from an ERR based on the tumours in the Wistar rat by a factor of 3 and that both tumour types could be assessed as similarly relevant.

AGS (2019) further concluded that an adjustment to modify the exposure in the animal experiment to the standard human exposure under working conditions could be omitted, since the consideration of the higher respiratory time volume (1/2) and the lower working lifetime of humans (75/40 x 52/48) compared to the lifetime exposure of the rat would almost cancel each other out. In addition, at low concentrations and slow kinetics, respiratory time volume is less important for local tumours than for systemic tumours.

AGS also noted that for the structurally related substance butadiene – using human leukaemia studies - a risk of 2: 1 000 per ppm and 1: 10 000 was determined for 0.05 ppm (AGS, 2010). AGS considered that this was similar to the above.

AGS concluded that various ERR derivations can be contrasted, differing by the selection of the POD, and that there is no fundamental contradiction among them (and in consideration of the kinetic data on biotransformation and epidemiological studies on chloroprene and butadiene).

AGS proposed as the main outcome the derivation based on oral cavity tumours in the Fischer rat and established the ERR as follows:

Tolerance value (risk-based 4: 1 000): 1.4 ppm

Acceptance risk (4: 10 000): 0.14 ppm

Acceptance risk (4: 100 000): 14 ppb

AGS (2019) further considered the need to define also an AGW analogue value (OEL analogue value) based on non-cancer effects (see 9.2.1.2).

9.1.2 Cancer risk assessment

A non-threshold mode of action is assumed for chloroprene (see section 8). No more recent relevant animal or mechanistic data were identified since AGS (2019). As regards human data, the most recent cancer follow-up update of the largest chloroprene exposed cohort published since AGS (Marsh et al., 2021, see section 7.7.1) consolidates, based on more person-years of observation and higher number of observed cancer cases, the findings of no consistent increase in cancer risk already observed in the earlier studies that were available to AGS. It is specifically noted that no indication of an increase in risk of lung cancer overall or any indication of an increasing trend by duration, intensity or cumulative exposure was observed in the largest cohort and the confidence interval of the overall lung cancer risk was very narrow around unity (SMR 1.0, 95% CI 0.9 – 1.1). Thus the approach and reasoning of AGS (2019) presented in section 9.1.1.1 are considered valid, i.e. mice being more sensitive than other species and selecting the more conservative of the two rat studies available in different strains (Fischer and Wistar), and not the lung tumours observed in mice, as point of departure. The BMD10 (34.5 ppm) calculated by AGS for the oral cavity tumours from the 2-year study in the Fischer rat (NTP 1998) is selected as the point of departure for deriving the exposure risk relationship (ERR).

The following standard correction for point of departure from a 2-year rat inhalation assay to occupational exposure was performed to reflect differences in exposure circumstances:

BMD10 (corrected) = BMD10 (animal) * (75/40 years) * (52/48 weeks) * (6/8 h) * (6.7/10 m^3) = 34.5 ppm * 1.0207 = 35.2 ppm.

Applying the corrected BMD10 and a linear extrapolation, the ERR presented in Table 13 was calculated.

Table 13. Cancer exposure-risk relationship*

2-chloro-1,3-butadiene concentration in air (ppm)	2-chloro-1,3-butadiene concentration in air (mg/m^3)	Excess life-time cancer risk (Cases per 100 000 exposed)
0.0035	0.013	1
0.014	0.052	4
0.035	0.13	10
0.14	0.52	40
0.35	1.3	100
1.4	5.2	400
3.5	13	1000

* Assuming exposure 8 hours per day and 5 days per week over a 40-year working life period. 1 ppm = 3.68 mg/m^3 (at 20°C) (see Table 1, section 1)

9.2 Derived Occupational Exposure Limit (OEL) Values

9.2.1 Published approaches to establishing OELs

9.2.1.1 DFG

No health based OEL has been set for chloroprene in Germany (DFG, 2022), while air concentrations are set up for tolerable and acceptable cancer risk levels as described in section 9.1.1.1. The German MAK Commission has derived a BAR applicable for non-smokers for urine concentration of 3,4-dihydroxybutylmercapturic acid (DHBMA) of 400 µg/g creatinine for chloroprene exposure. The BAR describes the background level in the working age population who are not occupationally exposed to chloroprene (DFG, 2021a). Also a skin notation is assigned to chloroprene (DFG, 2022). DFG (2001) noted that there is no quantitative data concerning dermal absorption of chloroprene. However, since chloroprene is a genotoxic substance, DFG considered that the previous skin notation (from 1975) should remain. DFG (2001) also noted that chloroprene is very lipophilic and thus likely absorbed via the dermal route

9.2.1.2 AGS

AGS (2019) calculated workplace air concentrations corresponding to the tolerable and acceptable cancer risk levels (see section 9.1.1.1). AGS further noted that the non-neoplastic effects observed in animal experiments, especially irritant effects on the respiratory tract and in the lungs, can in principle be assumed to be relevant for humans. Thus AGS considered if an AGW analogue value (OEL analogue value), i.e. a reference value for non-carcinogenic effects should also be established for chloroprene in addition to the tolerance and acceptance levels based on carcinogenic effects. AGS noted that an AGW-analogue value appears formally derivable from the sub-chronic studies (NOAEC 32 ppm in the mouse or NOAEC 12 ppm in the rat). At 32 ppm (LOAEC), the rat showed damage to the olfactory epithelium of low severity and isolated observations suggestive of systemic effects). In the chronic experiment, 12.8 ppm caused damage to the olfactory epithelium and oral cavity tumours in the Fischer rat. However, AGS considered that an exact determination of the effect thresholds in the sense of a POD for non-carcinogenic effects is subject to uncertainties at the cellular level in view of the kinetics of the substance and its mechanism of action.

However, the available data indicate that an ARW-analogue value would be near or just above the tolerance concentration. Based on these considerations for the AGW-analogue value, AGS concluded that the excursion factor for the tolerance value is 1 (excursion factor refers to short-term (15 minute) exposures with the full shift).

9.2.2 Occupational Exposure Limits (OELs) - 8h TWA

There is insufficient information available to conclude on a threshold MoA for carcinogenic action, which is considered the critical effect for exposure to chloroprene. Therefore, a non-threshold MoA is assumed. For that reason, it is not possible to derive a health-based OEL, and an exposure-risk relationship (ERR) was calculated from animal data (see section 9.1.2).

If an OEL was derived from data on threshold effects, the olfactory epithelium hyperplasia findings observed in the 13-week rat (inhalation exposure 6 h /day, 5 days/week) study (NTP, 1998) could be used as the starting point. Effects were seen at 32 ppm (120 mg/m^3; LOAEC) and the NOAEC was 12 ppm (44 mg/m^3). Other studies had higher NOAEC/LOAEC values.

A hypothetical limit value could be calculated as follows:

Correction of the starting point to correspond to worker exposure conditions:

44 mg/m^3 * 6h/8h * 6.7 m^3/10 m^3= 22.11 mg/m^3.

Assessment factors proposed to be applied include a factor of 2 for extrapolation for the duration from sub-chronic to chronic, 2.5 to cover interspecies differences, and 5 for worker intraspecies differences. Application of these factors would lead to:

OEL (8h TWA)= 22.11 mg/m^3 / 2*2.5*5 ≈ 0.9 mg/m^3 (0.24 ppm).

Alternatively, a hypothetical limit value for threshold effects can be derived for necrosis of the olfactory epithelium at 12.8 ppm (47 mg/m^3 LOAEC; no NOAEC identified) as seen in male rats of the 2-year inhalation study by NTP (1998).

Correction of the starting point to correspond to worker exposure conditions:

47 mg/m^3 * 6h/8h * 6.7 m^3/10 m^3= 23.6 mg/m^3.

Assessment factors proposed to be applied include a factor of 3 for the conversion from LOAEC to NOAEC, 2.5 to cover interspecies differences, and 5 for worker intraspecies differences. Application of these factors would lead to:

OEL (8h TWA)= 23.6 mg/m^3 / 3*2.5*5 ≈ 0.6 mg/m^3 (0.16 ppm).

As explained, a non-threshold MoA is assumed for the carcinogenic effects and thus the above OEL calculations should only be seen as comparative calculations. It is noted that according to the derived cancer ERR, the lowest of the above non-threshold effect OELs (0.16 ppm) would correspond to a residual cancer risk of about 4:10 0000.

9.2.3 Short Term Exposure Limits (STELs)

A non-threshold mode of action is assumed for the carcinogenic effects of chloroprene and an ERR is derived. There is no indication of short-term effects which would require to set up a STEL.

9.2.4 Biological Limit Value (BLV)

A non-threshold mode of action is assumed for the carcinogenic effects of chloroprene and it is not possible to identify a BLV under which no excess risk would occur. There are also no data to derive a correlation between the urine concentration of the biomarkers described in section 6.2 and (1) the excess cancer risk or (2) the workplace air chloroprene concentration used in the ERR derived in section 9.1.2.

No BLV is recommended.

9.2.5 Biological Guidance Value (BGV)

As described in section 6.2.1 the most robust data concerning biomonitoring background levels in the occupationally unexposed population concern DHBMA, which is the a metabolite of both 1,3-butadiene and chloroprene. However, such background data are available only for one EU country.

No BGV is proposed.

9.3 Notations

There are no quantitative data on dermal absorption of chloroprene. In addition, no dermal acute toxicity tests were found. Usually, a skin notation is applied where it can be assumed that dermal exposure may contribute to about 10 % or more of the body burden by inhalation exposure at the OEL (ECHA, 2019). Given that chloroprene is highly lipophilic it seems likely to be readily absorbed via the dermal route. However, as there is no data to quantify the assumed dermal absorption, no skin notation is proposed.

There are no data indicating skin or respiratory sensitisation effects after chloroprene exposure. Thus no notation is proposed for skin or respiratory sensitisation.

REFERENCES

AGS 2010. *Exposition-Risiko-Beziehung für 1,3-Butadien (Butadien, BD) (CAS-Nr. 106-99-0). Ausschuss für Gefahrstoffe - AGS-Geschäftsführung - BAuA.* https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Regelwerk/TRGS/pdf/910/910-1-3-butadien.pdf.

AGS 2019. *Begründung zu Chloropren in TRGS 910. Ausschuss für Gefahrstoffe - AGS-Geschäftsführung - BAuA -* www.baua.de/ags.

BARTSCH, H., MALAVEILLE, C., BARBIN, A. & PLANCHE, G. 1979. Mutagenic and alkylating metabolites of halo-ethylenes, chlorobutadienes and dichlorobutenes produced by rodent or human liver tissues. Evidence for oxirane formation by P450-linked microsomal mono-oxygenases. *Arch Toxicol,* 41**,** 249-77.

BARTSCH, H., MALAVEILLE, C., MONTESANO, R. & TOMATIS, L. 1975. Tissue-mediated mutagenicity of vinylidene chloride and 2-chlorobutadiene in Salmonella typhimurium. *Nature,* 255**,** 641-3.

BUKOWSKI, J. A. 2009. Epidemiologic evidence for chloroprene carcinogenicity: review of study quality and its application to risk assessment. *Risk Anal,* 29**,** 1203-16.

BULBULYAN, M. A., CHANGUINA, O. V., ZARIDZE, D. G., ASTASHEVSKY, S. V., COLIN, D. & BOFFETTA, P. 1998. Cancer mortality among Moscow shoe workers exposed to chloroprene (Russia). *Cancer Causes Control,* 9**,** 381-7.

BULBULYAN, M. A., MARGARYAN, A. G., ILYCHOVA, S. A., ASTASHEVSKY, S. V., ULOYAN, S. M., COGAN, V. Y., COLIN, D., BOFFETTA, P. & ZARIDZE, D. G. 1999. Cancer incidence and mortality in a cohort of chloroprene workers from Armenia. *Int J Cancer,* 81**,** 31-3.

CLARY, J. J., FERON, V. J. & REUZEL, P. G. 1978. Toxicity of beta-chloroprene (2-chlorobutadiene-1,3): acute and subacute toxicity. *Toxicol Appl Pharmacol,* 46**,** 375-84.

CLEWELL, H. J., 3RD, CAMPBELL, J. L., VAN LANDINGHAM, C., FRANZEN, A., YOON, M., DODD, D. E., ANDERSEN, M. E. & GENTRY, P. R. 2019. Incorporation of in vitro metabolism data and physiologically based pharmacokinetic modeling in a risk assessment for chloroprene. *Inhal Toxicol,* 31**,** 468-483.

COLONNA, M. & LAYDEVANT, G. 2001. A cohort study of workers exposed to chloroprene in the department of Isère, France. *Chem Biol Interact,* 135-136**,** 505-14.

COTTRELL, L., GOLDING, B. T., MUNTER, T. & WATSON, W. P. 2001. In vitro metabolism of chloroprene: species differences, epoxide stereochemistry and a de-chlorination pathway. *Chem Res Toxicol,* 14**,** 1552-62.

CULIK, R., KELLY, D. P. & CLARY, J. J. 1978. Inhalation studies to evaluate the teratogenic and embryotoxic potential of beta-chloroprene (2-chlorobutadiene-1,3). *Toxicol Appl Pharmacol,* 44**,** 81-8.

DFG 2001. *Gesundheitsschädliche Arbeitsstoffe. Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten: 2-Chloropren. MAK, 33. Lieferung.*

DFG 2007. Monohydroxybutenylmercapturic acid (MHBMA) and dihydroxybutylmercapturic acid (DHBMA) [Biomonitoring Methods, 2007]. *The MAK-Collection for Occupational Health and Safety.*

DFG 2013. Method for the determination of chloroprene [Air monitoring methods, 2013]. *The MAK-Collection for Occupational Health and Safety.*

DFG 2021a. Eckert E, Göen T. Chloroprene– Evaluation of a BAR Assessment Values in Biological Material– Translation of the German version from 2014. *MAK Collect Occup Health Saf.,* Dec:Doc919.

DFG 2021b. Göen T. 1,3-Butadiene – Addendum for re-evaluation of EKA and evaluation of BAR- Assessment Values in Biological Material – Translation of the German version from 2013. *MAK Collect Occup Health Saf.*

DFG 2022. MAK- und BAT-Werte-Liste 2022, Maximale Arbeitsplatzkonzentrationen und Biologische Arbeitsstofftoleranzwerte. German Medical Science, Düsseldorf, Germany: Deutsche Forschungsgemeinschaft, Ständige Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe.

DONG, Q. A., XIAO, B. L., HU, Y. H. & LI, S. Q. 1989. Short-term test for the induction of lung tumor in mouse by chloroprene. *Biomed Environ Sci,* 2**,** 150-3.

DREVON, C. & KUROKI, T. 1979. Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells. *Mutat Res,* 67**,** 173-82.

ECHA 2019. *Guidance on information requirements and chemical safety assessment. Appendix to Chapter R.8: Guidance for preparing a scientific report for health-based exposure limits at the workplace*.

ECHA 2022. *Registered substances dissemination site. https://echa.europa.eu/information-on-chemicals/registered-substances (last visited 22.11.2022). European Chemicals Agency.*

ECKERT, E., LENG, G., GRIES, W. & GÖEN, T. 2012. A method for the simultaneous determination of mercapturic acids as biomarkers of exposure to 2-chloroprene and epichlorohydrin in human urine. *Journal of Chromatography B,* 889-890**,** 69-76.

ECKERT, E., LENG, G., GRIES, W. & GÖEN, T. 2013. Excretion of mercapturic acids in human urine after occupational exposure to 2-chloroprene. *Arch Toxicol,* 87**,** 1095-1102.

EPA 1985. *Summary overview of health effects associated with chloroprene: Health issue assessment (Report No. EPA/600/8-85/011F). Research Triangle Park, NC: Environmental Criteria and Assessment Office; Office of Health and Environmental Assessment; Office of Research and Development; U.S. Environmental Protection Agency*.

EPA 2010. *Toxicological review of chloroprene. In Support of Summary Information on the Integrated Risk Information System (IRIS). U.S. Environmental Protection Agency, Washington, DC*.

ESMEN, N. A., HALL, T. A., PHILLIPS, M. L., JONES, E. P., BASARA, H., MARSH, G. M. & BUCHANICH, J. M. 2007. Chemical process-based reconstruction of exposures for an epidemiological study. Part II. Estimated exposures to chloroprene and vinyl chloride. *Chem Biol Interact,* 166**,** 264-76.

FOUREMAN, P., MASON, J. M., VALENCIA, R. & ZIMMERING, S. 1994. Chemical mutagenesis testing in Drosophila. X. Results of 70 coded chemicals tested for the National Toxicology Program. *Environ Mol Mutagen,* 23**,** 208-27.

GARCIA, E., HURLEY, S., NELSON, D. O., HERTZ, A. & REYNOLDS, P. 2015. Hazardous air pollutants and breast cancer risk in California teachers: a cohort study. *Environ Health,* 14**,** 14.

GOOCH, J. J. & HAWN, W. F. 1981. Biochemical and hematological evaluation of chloroprene workers. *J Occup Med,* 23**,** 268-72.

HEALTH_COUNCIL_OF_THE_NETHERLANDS 2003. *β-Cloroprene; Evaluation of the effects on reproduction, recommendation for classification. Health Council of the Netherlands: Committee for Compounds toxic to reproduction.*

HESBERT, A., LIMASSET, J. C. & DE CEAURRIZ, J. 1983. *Evaluation de la mutagenicite et de la cancerogenicite du chloroprene. Cahiers de notes documentaires - Securite et hygiene du travail, 4. Trimester 1983, No 113, 521-534*.

HIMMELSTEIN, M. W., CARPENTER, S. C., EVANS, M. V., HINDERLITER, P. M. & KENYON, E. M. 2004a. Kinetic modeling of beta-chloroprene metabolism: II. The application of physiologically based modeling for cancer dose response analysis. *Toxicol Sci,* 79**,** 28-37.

HIMMELSTEIN, M. W., CARPENTER, S. C. & HINDERLITER, P. M. 2004b. Kinetic modeling of beta-chloroprene metabolism: I. In vitro rates in liver and lung tissue fractions from mice, rats, hamsters, and humans. *Toxicol Sci,* 79**,** 18-27.

HIMMELSTEIN, M. W., CARPENTER, S. C., HINDERLITER, P. M., SNOW, T. A. & VALENTINE, R. 2001a. The metabolism of beta-chloroprene: preliminary in-vitro studies using liver microsomes. *Chem Biol Interact,* 135-136**,** 267-84.

HIMMELSTEIN, M. W., GLADNICK, N. L., DONNER, E. M., SNYDER, R. D. & VALENTINE, R. 2001b. In vitro genotoxicity testing of (1-chloroethenyl)oxirane, a metabolite of beta-chloroprene. *Chem Biol Interact,* 135-136**,** 703-13.

IARC 1999. WHO IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrgen Peroxide. *IARC Monographs,* 71**,** 227-250.

LEET, T. L. & SELEVAN, S. G. 1982. *Mortality analysis of workers exposed to chloroprene (Final report for EI DuPont deNemours & Company).Cincinnati, OH: National Institute for Occupational Safety and Health; Center for Disease Control; Public Health Service; Department of Health and Human Services*.

LEJHANCOVA, G. 1967. *Berufsbedingter Haarausfall durch Chloropren. Berufsdermatosen 15, 280-287*.

LI, S. Q., DONG, Q. N., LIU, Y. Q. & LIU, Y. G. 1989. Epidemiologic study of cancer mortality among chloroprene workers. *Biomed Environ Sci,* 2**,** 141-9.

LLOYD, J. W., DECOUFLE, P. & MOORE, R. M. 1975. Background information on chloroprene. *J Occup Med,* 17**,** 263-5.

LYNCH, J. 2001a. Occupational exposure to butadiene, isoprene and chloroprene. *Chemico-Biological Interactions,* 135-136**,** 207-214.

LYNCH, M. 2001b. Manufacture and use of chloroprene monomer. *Chemico-Biological Interactions,* 135-136**,** 155-167.

MARSH, G. M., KRUCHTEN, A. & BUCHANICH, J. M. 2021. Mortality Patterns Among Industrial Workers Exposed to Chloroprene and Other Substances: Extended Follow-Up. *J Occup Environ Med,* 63**,** 126-138.

MARSH, G. M., YOUK, A. O., BUCHANICH, J. M., CUNNINGHAM, M., ESMEN, N. A., HALL, T. A. & PHILLIPS, M. L. 2007a. Mortality patterns among industrial workers exposed to chloroprene and other substances. I. General mortality patterns. *Chem Biol Interact,* 166**,** 285-300.

MARSH, G. M., YOUK, A. O., BUCHANICH, J. M., CUNNINGHAM, M., ESMEN, N. A., HALL, T. A. & PHILLIPS, M. L. 2007b. Mortality patterns among industrial workers exposed to chloroprene and other substances. II. Mortality in relation to exposure. *Chem Biol Interact,* 166**,** 301-16.

MCGLOTHLIN, J. D., MEYER, C. & LEET, C. L. 1984. *Health hazard evaluation report for chlorprene, dichlorobuadiene, dichlorobutene, trichlorobutene, and toluene at E.I. du Pont de Nemours and Company, Inc. Louisville, Kentucky (Report No. HETA 79-027-1459; PB85-186757). Cincinnati, OH: National Institute for Occupational Safety and Health.*

MELNICK, R. L., ELWELL, M. R., ROYCROFT, J. H., CHOU, B. J., RAGAN, H. A. & MILLER, R. A. 1996. Toxicity of inhaled chloroprene (2-chloro-1,3-butadiene) in F344 rats and B6C3F(1) mice. *Toxicology,* 108**,** 79-91.

MUNTER, T., COTTRELL, L., HILL, S., KRONBERG, L., WATSON, W. P. & GOLDING, B. T. 2002. Identification of adducts derived from reactions of (1-chloroethenyl)oxirane with nucleosides and calf thymus DNA. *Chem Res Toxicol,* 15**,** 1549-60.

NTP 1998. *NTP Technical report on the toxicology and carcinogenesis of chloroprene (CAS No. 126-99-8) in F344/N rats and B6F3C1 mice (inhalation studies). NTP TR 467, NIH Publication No. 96-3957, US Department of Health and Human Services, Washington DC*.

NYSTROM, A. E. 1948. Health hazards in the chloroprene rubber industry and their prevention, a clinical and experimental study with special reference to chloroprene as well as oxidation and polymerization products thereof. *Acta Med Scand,* 131**,** 1-125.

OECD 1998. OECD SIDS Initial Assessment Report for 8th SIAM. Chloroprene. *UNEP Publications.*

OSHA 1998. OSHA Sampling and Analytical Methods. Method 112: beta-Chloroprene.

PELL, S. 1978. Mortality of workers exposed to chloroprene. *J Occup Med,* 20**,** 21-9.

RICE, J. M. & BOFFETTA, P. 2001. 1,3-Butadiene, isoprene and chloroprene: reviews by the IARC monographs programme, outstanding issues, and research priorities in epidemiology. *Chemico-Biological Interactions,* 135-136**,** 11-26.

RICKERT, A., HARTUNG, B., KARDEL, B., TELOH, J. & DALDRUP, T. 2012. A fatal intoxication by chloroprene. *Forensic Sci Int,* 215**,** 110-3.

RITTER, W. L. & CARTER, A. S. 1948. Hair loss in neoprene manufacture. *J Ind Hyg Toxicol,* 30**,** 192-5.

SANOTSKII, I. V. 1976. Aspects of the toxicology of chloroprene: immediate and long-term effects. *Environ Health Perspect,* 17**,** 85-93.

SAVITZ, D. A., SONNENFELD, N. L. & OLSHAN, A. F. 1994. Review of epidemiologic studies of paternal occupational exposure and spontaneous abortion. *Am J Ind Med,* 25**,** 361-83.

SAX, S. N., GENTRY, P. R., VAN LANDINGHAM, C., CLEWELL, H. J. & MUNDT, K. A. 2020. Extended Analysis and Evidence Integration of Chloroprene as a Human Carcinogen. *Risk Anal,* 40**,** 294-318.

SCHRAG, S. D. & DIXON, R. L. 1985. *Occupational exposures associated with male reproductive dysfunction. In R George; R Okun (Eds.), Annual Review of Pharmacology and Toxicology (pp. 567–592). Palo Alto, CA: Annual Reviews.*

SILLS, R. C., HONG, H. L., MELNICK, R. L., BOORMAN, G. A. & DEVEREUX, T. R. 1999. High frequency of codon 61 K-ras A-->T transversions in lung and Harderian gland neoplasms of B6C3F1 mice exposed to chloroprene (2-chloro-1,3-butadiene) for 2 years, and comparisons with the structurally related chemicals isoprene and 1,3-butadiene. *Carcinogenesis,* 20**,** 657-62.

SUMMER, K. H. & GREIM, H. 1980. Detoxification of chloroprene (2-chloro-1,3-butadiene) with glutathione in the rat. *Biochem Biophys Res Commun,* 96**,** 566-73.

TICE, R. R., BOUCHER, R., LUKE, C. A., PAQUETTE, D. E., MELNICK, R. L. & SHELBY, M. D. 1988. Chloroprene and isoprene: cytogenetic studies in mice. *Mutagenesis,* 3**,** 141-6.

TON, T. V., HONG, H. H., DEVEREUX, T. R., MELNICK, R. L., SILLS, R. C. & KIM, Y. 2007. Evaluation of genetic alterations in cancer-related genes in lung and brain tumors from B6C3F1 mice exposed to 1,3-butadiene or chloroprene. *Chem Biol Interact,* 166**,** 112-20.

TROCHIMOWICZ, H. J., LOSER, E., FERON, V. J., CLARY, J. J. & VALENTINE, R. 1998. CHRONIC INHALATION TOXICITY AND CARCINOGENICITY STUDIES ON-CHLOROPRENE IN RATS AND HAMSTERS. *Inhalation Toxicology,* 10**,** 443-472.

VOGEL, E. 1979. Mutagenicity of chloroprene, 1-chloro-1,3-trans-butadiene, 1-4-dichlorobutene-2 and 1,4-dichloro-2,3-epoxybutane in Drosophila melanogaster. *Mutat Res,* 67**,** 377-81.

WADUGU, B. A., NG, C., BARTLEY, B. L., ROWE, R. J. & MILLARD, J. T. 2010. DNA interstrand cross-linking activity of (1-Chloroethenyl)oxirane, a metabolite of beta-chloroprene. *Chem Res Toxicol,* 23**,** 235-9.

WESTPHAL, G. A., BLASZKEWICZ, M., LEUTBECHER, M., MULLER, A., HALLIER, E. & BOLT, H. M. 1994. Bacterial mutagenicity of 2-chloro-1,3-butadiene (chloroprene) caused by decomposition products. *Arch Toxicol,* 68**,** 79-84.

YANG, Y., HIMMELSTEIN, M. W. & CLEWELL, H. J. 2012. Kinetic modeling of beta-chloroprene metabolism: Probabilistic in vitro-in vivo extrapolation of metabolism in the lung, liver and kidneys of mice, rats and humans. *Toxicol In Vitro,* 26**,** 1047-55.

ZEIGER, E., ANDERSON, B., HAWORTH, S., LAWLOR, T., MORTELMANS, K. & SPECK, W. 1987. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ Mutagen,* 9 Suppl 9**,** 1-109.

Appendix 1. Summaries of epidemiological studies on chloroprene exposure and risk of overall cancer, liver cancer, lung/respiratory cancer and breast cancer.

Table 14: Summary of the cohort studies assessing the association between exposure to chloroprene and overall cancer risk. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.0.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
Bulbulyuan et al (1998).	Cohort of 5185 shoe factory workers who were employed for at least two years in the period 1960-76. Followed up during 1979-93 70 328 person-years of follow-up.	Semiquantitive exposure indexes (low=0, medium = 1, high = 10) were assigned based on 1970 chloroprene (CP) levels for 3 groups: cutting and fitting jobs (mean CP exposure 0 mg/m^3), workers who had no direct contact with CP but were in the same departments as gluers (CP exposure 0.4 – 1 mg/m^3) and gluers (CP exposure 20 mg/m^3). Semiquantitative cumulative exposures (unit years) were calculated summing periods in each exposure index job. Co-exposures: benzene, formaldehyde, ethylacetate, butylacetate, ethyleneglycol, acetone, chlorotrifluoromethane, leather dust depending on job. Not adjusted for in analyses.	Mortality External comparison Internal comparison	 All exposed No exp Any exp Medium exp High exp Cumulative exp (unit-years) 0 0.1 – 10 10.1 – 30 > 30 Duration in high exposure job (years) No exposure 1-9 10-19 20 -	 265 81 184 128 56 81 41 75 68 81 36 17 3	SMR 1.2 (1.1 - 1.4) RR 1.0 ref 1.0 (0.8 - 1.3) 1.0 (0.8 - 1.4) 1.2 (0.9 - 1.7) 1.0 ref 0.9 (0.6 - 1.3) 1.0 (0.8 - 1.4) 1.1 (0.8 - 1.6) 1.0 ref 1.1 (0.8 - 1.7) 1.4 (0.8 - 2.3) 1.1 (0.3 - 3.3)	 Adjusted for gender, age, calendar period of follow-up p for trend = 0.41 p for trend 0.31

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
Bulbulyan et al. (1999)	Cohort of 2314 workers of an Armenian CP production plant who were employed in the production departments for at least 2 months between 1940 and 1988 and were alive in 1979. Follow-up for cancer incidence in 1979-1990. 25 782 person-years for cancer incidence.	There was a sharp decline in maximum CP exposure levels in 1980 from above 500 to 0.5–5 mg/m^3. As the information on department specific exposure levels was not systematic, to calculate a cumulative index of CP exposure, semiquantitative exposure units from 1 to 6 (and 0 for no exposure) were assigned by depending on department and period and and then added up the units for each year of employment. Other exposures: vinyl acetate, toluidine, talc and mercaptans	Incidence Mortality No detailed results by exposure metric were presented for overall cancer	 All All	 37 20	SIR 0.7 (0.5 – 0.9) SMR 0.9 (0.6 – 1.4)	Adjusted for gender, age, calendar period of follow-up
Colonna and Laydevant (2001)	Cohort of all men who had been working for at least 2 years in a French CP production plant since it was founded in 1966. The follow-up for cancer incidence was complete for 1979-1997. Those who died or moved from the geographical area before 1979 could not be followed for cancer.	Based on existing industrial hygiene measurements by job category a semiquantitative exposure metric was assigned: low (< 2 ppm), medium (2-5 ppm), high (> 5 ppm). 75% of workers stayed in the same category for the entire period, for those who changed category, the highest was used.	Incidence External comparison	All Intensity Low Medium High Duration (years) <10 11-20 21 -	34 7 14 13 10 12 12	SIR 1.3 (0.9 – 1.8) 1.4 (0.6 – 2.8) 1.3 (0.7 – 2.1) 1.2 (0.6 – 2.1) 2.2 (1.0 – 4.0) 1.4 (0.7 – 2.4) 0.9 (0.5 – 1.5)	Adjusted for calendar period of follow-up and age. Only men included.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	7 950 person-years of follow-up.						
Leet and Selevan (1982)	Cohort of 1575 male workers employed on 30 June 1957 in the DuPont Louisville Kentucky neoprene production plant. Followed until 31 December 1974. 26 304 person-years of follow-up, 13 606 person-years in the high-exposure and 12 644 in the low-exposure category	Based on job title and working area the the exposure was classified as high (N=851) or low (N=823).	Mortality	All High Low	51 25 26	SMR 1.1 (0.8 – 1.4) 1.1 (0.7 – 1.6) 1.1 (0.7 – 1.6)	No adjustment for potential confounders. A worker with both low and high exposure jobs, contributed to person-years of high exposure since the first employment in such an occupation. Results by lag time were similar to overall results.
Li et al. (1989)	A cohort of 1258 workers in a Chinese plant producing chloroprene monomer and neoprene. The cohort was selected from the pay roll of the factory employees based on job title that allowed to grade the level of chloroprene exposure. Based on the total N of cancer deaths (55) the entire factory cohort seems larger than the studied cohort	Exposure was graded high or low based on job title, but SMRs were reported only by job title. Co-exposure to other known carcinogens was reported to concern benzene and N-phenyl-Z-naphtylamine.	Mortality	All Monomer workshop Polymer workshop Laboratory	16 8 5 3	SMR 2.4 3.5 1.6 2.2	 p < 0.01 p < 0.01 Non-significant Non-significant

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	of 1258 (16 cancer deaths). 1213 cohort members (96.4%) could be followed during 1969-83 and SMRs were calculated using local rates for 1973-75. The expected N of cancers was below one for all specific sites of cancer. Cancer deaths were searched from the death registries of the plant's hospital and the police substation and diagnoses verified from medical records in general and cancer hospitals. Person-years of follow-up not reported.						
Marsh et al. (2007a,b)	Four cohorts of CP producing plants. Followed until 2000. Louisville, US 5507 workers, exposure 1942-72 Pontchartrain, US 1357 workers, exposure 1969-2000 Maydown, Northern Ireland,	The exposure reconstruction was based on mathematical models which utilized exposure models based on the physics and chemistry associated with a given chemical process as determined from process documentation and task performance habits gleaned from	Mortality External comparison Pontchartrain Maydown Grenoble Louisville Louisville Detailed Results	 All All All All Duration (years) < 10 10 – 19	 34 128 20 652 324 64	SMR 0.7 (0.5 – 1.0) 0.7 (0.6 – 0.8) 0.6 (0.4 – 0.9) 0.9 (0.8 – 1.0) 0.7 (0.6 – 0.8) 0.7 (0.5 – 0.9)	

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	4848 workers exposure 1960-98 Grenoble, France, 717 workers, exposure 1966-2000 Person-years of follow-up L 197 919 P 30 660 M 127 036 G 17 057	interviews with knowledgeable plant personnel. In addition to a No exposure category, six exposure categories with the following nominal exposure (geometric mean of the class limits) were used: 0.0016 ppm 0.016 ppm 0.16 ppm 1.6 ppm 16 ppm 71 ppm 160 ppm Detailed work histories were used to link individual cohort members to exposure estimates and these were summed to estimate average and cumulative exposure. In Louisville 22.7% and in Maydown 5.5% of the CP exposed workers has also exposure to vinyl chloride. Median CP exposure L plant 5.2 ppm P plant 0.28 ppm M plant 0.16 ppm G plant 015 ppm Mean CP exposure L plant 8.4 ppm P plant 0.27 ppm M plant 1.4 ppm	External Internal comparison Louisville Pontchartrain Detailed Results External	20 – Intensity (ppm) < 3.6 3.6 – 8.1 8.1 – 15 16- Cumulative exposure (ppm-years) < 4.7 4.7 – 55.9 60 – 164 164 - Duration (years) < 10 10 – 19 20 – Intensity (ppm) < 3.6 3.6 – 8.1 8.1 – 15 16- Cumulative exposure (ppm-years) < 4.7 4.7 – 55.9 60 – 164 164 - Duration (years) < 10 10 – 19 20 – Intensity (ppm) < 0.0017 0.0017 – 0.133	262 163 163 97 229 163 163 163 163 RR 324 64 262 163 163 97 229 163 163 163 163 SMR 15 12 7 17 4	0.8 (0.7 – 0.9) 0.7 (0.6 – 0.8) 0.9 (0.8 – 1.0) 0.7 (0.5 – 0.8) 0.7 (0.6 – 0.8) 0.8 (0.6 – 0.9) 0.7 (0.6 – 0.8) 0.8 (0.7 – 0.9) 0.7 (0.6 – 0.8) 1.0 ref 0.7 (0.6 – 0.8) 1.1 (0.9 – 1.3) 1.0 ref 1.2 (0.9 - 1.5) 0.9 (0.7 – 1.2) 1.1 (0.9 – 1.3) 1.0 ref 1.0 (0.8 – 1.2) 1.1 (0.9 – 1.4) 0.9 (0.7 – 1.2) 0.8 (0.4 – 1.2) 0.6 (0.3 – 1.0) 0.6 (0.2 – 1.2) 0.6 (0.3 – 0.9) 2.8 (0.8 – 7.1)	 p global = 0.71 p trend = 0.42 p global = 0.27 p trend = 0.97 p global = 0.35 p trend = 0.83 Adjusted for age, time period, sex and worker type (blue/white collar)

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
		G plant 2.2 ppm		0.133 – 0.817	7	0.8 (0.3 – 1.6)	
				0.818 -	6	0.7 (0.3 – 1.5)	
				Cumulative exposure (ppm-years)			
				< 0.0193	15	0.8 (0.4 – 1.2)	
				0.0193 – 1.89	6	0.4 (0.2 – 0.9)	
				1.89 – 16.2	6	1.1 (0.4 –2.3)	
				16.2 -	7	0.6 (0.2 – 1.3)	
						RR	
			Internal comparison Pontchartrain	Duration (years)			
				< 10	15	1.0 ref	p global = 0.71
				10 – 19	12	0.7 (0.3 – 1.6)	p trend = 0.56
				20 –	7	0.8 (0.3 – 2.5)	
				Intensity (ppm)			
				< 0.0017	17	1.0 ref	p global = 0.17
				0.0017 – 0.133	4	4.8 (1.4 – 16)	p trend = 0.44
				0.133 – 0.817	7	1.6 (0.6 – 4.4)	
				0.818 -	6	1.3 (0.5 – 3.7)	
				Cumulative exposure (ppm-years)			
				< 0.0193	15	1.0 ref	p global = 0.31
				0.0193 – 1.89	6	0.5 (0.2 – 1.4)	p trend = 0.91
				1.89 – 16.2	6	1.5 (0.6 – 4.1)	
				16.2 -	7	0.8 (0.3 – 2.2)	
						SMR	
			Maydown Detailed Results External	Duration (years)			
				< 10	66	0.5 (0.4 – 0.7)	
				10 – 19	35	0.9 (0.6 – 1.2)	
				20 –	27	1.0 (0.6 – 1.4)	
				Intensity (ppm)			
				< 0.15	43	0.5 (0.4 – 0.7)	
				0.15 – 1.27	28	0.8 (0.6 – 1.2)	
				1.27 – 1.69	36	0.7 (0.5 – 1.0)	
				1.70 -	21	0.7 (0.4 – 1.1)	
				Cumulative exposure (ppm-years)			

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
				< 0.039	43	0.5 (0.4 – 0.7)	
				0.039 – 6.73	28	0.7 (0.5 – 1.1)	
				6.73 – 24.5	29	0.8 (0.5 – 1.1)	
				24.5 -	28	0.9 (0.6 – 1.2)	
			Internal comparison Maydown	Duration (years)		RR	
				< 10	66	1.0 ref	p global = 0.03
				10 – 19	35	1.5 (1.0 – 2.3)	p trend = 0.007
				20 –	27	1.8 (1.1 – 2.8)	
				Intensity (ppm)			
				< 0.15	43	1.0 ref	p global = 0.98
				0.15 – 1.27	28	1.0 (0.6 – 1.7)	p trend = 0.97
				1.27 – 1.69	36	1.1 (0.7 – 1.7)	
				1.70 -	21	1.0 (0.5 – 1.7)	
				Cumulative exposure (ppm-years)			
				< 0.039	43	1.0 ref	p global = 0.92
				0.039 – 6.73	28	1.1 (0.7 – 1.9)	p trend = 0.75
				6.73 – 24.5	29	0.9 (0.5 – 1.7)	
				24.5 -	28	1.0 (0.5 – 1.7)	
			Grenoble Detailed Results External	Duration (years)		SMR	
				< 10	9	0.6 (0.3 – 1.2)	
				10 – 19	5	0.4 (0.1 – 0.9)	
				20 –	6	0.8 (0.3 – 1.8)	
				Intensity (ppm)			
				< 0.0051	5	0.6 (0.2 – 1.4)	
				0.0051 – 0.088	5	0.6 (0.2 – 1.3)	
				0.088 – 1.22	5	0.7 (0.2 – 1.6)	
				1.22 -	5	0.6 (0.2 – 1.3)	
				Cumulative exposure (ppm-years)			
				< 0.050	5	0.6 (0.2 – 1.3)	
				0.050 – 1.415	5	0.5 (0.2 – 1.2)	
				1.415 – 23.9	5	0.6 (0.2 – 1.3)	
				23.9 -	5	0.8 (0.3 – 1.9)	
						RR	

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
			Internal comparison Grenoble	Duration (years) < 10 10 – 19 20 – Intensity (ppm) < 0.0051 0.0051 – 0.088 0.088 – 1.22 1.22 - Cumulative exposure (ppm-years) < 0.050 0.050 – 1.415 1.415 – 23.9 23.9 -	 9 5 6 5 5 5 5 5 5 5 5	 1.0 ref 0.6 (0.2 – 1.8) 1.3 (0.4 – 4.1) 1.0 ref 1.2 (0.4 – 4.2) 1.2 (0.3 – 4.4) 1.0 (0.3 – 3.8) 1.0 ref 1.2 (0.3 – 4.1) 1.1 (0.3 – 3.8) 1.5 (0.4 – 5.6)	 p global = 0.43 p trend = 0.82 p global = 0.99 p trend = 0.95 p global = 0.92 p trend = 0.57
Marsh et al. (2021)	Cohort of 6864 workers with CP exposure in two US CP production plants (Louisville plant N= 5507 exposure 1942-72, Pontchartrain plant N = 1357 exposure 1969-2000). Follow-up for cancer 1949-2017. About 23% of the Louisville plant workers had also exposure to vinyl chloride. Person-years of follow-up: L 245 218 P 50 602	The same exposure assessment as in Marsh (2007a,b) above was used and exposures since 2000 were neglected. I.e. only the cancer follow-up was updated. Median CP exposure L plant 5.2 ppm P plant 0.28 ppm Mean CP exposure L plant 8.4 ppm P plant 0.27 ppm	Mortality External comparison Pontchartrain Louisville Louisville Detailed results External comp, local	 All, comparison US All, comparison local All, comparison US All, comparison local Duration (years) < 10 10 – 19 20 – Intensity (ppm) < 3.6 3.6 – 8.1 8.1 – 15 16- Cumulative exposure (ppm-years)	 92 92 974 974 518 93 363 302 223 142 307	SMR 0.7 (0.6 – 0.9) 0.6 (0.5 – 0.8) 0.9 (0.8 – 1.0) 0.8 (0.7 – 0.8) 0.7 (0.7 – 0.8) 0.7 (0.6 – 0.9) 0.8 (0.8 – 0.9) 0.7 (0.7 – 0.8) 0.9 (0.8 – 1.0) 0.7 (0.6 – 0.9) 0.7 (0.6 – 0.8)	

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
				< 4.7	282	0.7 (0.7 – 0.8)	
				4.7 – 55.9	253	0.7 (0.6 – 0.8)	
				60 – 164	229	0.9 (0.8 – 1.0)	
				164 -	210	0.7 (0.6 – 0.8)	
			Internal comparison Louisville			RR	
				Duration (years)			
				< 10	518	1.0 ref	p global = 0.42
				10 – 19	93	1.1 (0.9 – 1.4)	p trend = 0.21
				20 –	363	1.1 (1.0 – 1.3)	
				Intensity (ppm)			
				< 3.6	302	1.0 ref	p global = 0.08
				3.6 – 8.1	223	1.3 (1.0 – 1.5)	p trend = 0.79
				8.1 – 15	142	1.1 (0.9 – 1.3)	
				16-	307	1.0 (0.9 – 1.2)	
				Cumulative exposure (ppm-years)			
				< 4.7	282	1.0 ref	p global = 0.10
				4.7 – 55.9	253	1.0 (0.9 – 1.2)	p trend = 0.40
				60 – 164	229	1.2 (1.0 – 1.5)	
				164 -	210	1.0 (0.8 – 1.2)	
				Duration (years)			Adjusted for age, time period, sex and worker type (blue/white collar)
			Detailed results Pontchartrain	< 10	33	0.7 (0.5 – 0.9)	
				10 – 19	23	0.6 (0.4 – 0.8)	
				20 –	36	0.7 (0.5 – 0.9)	
			External, comp, local	Intensity (ppm)			
				< 0.0017	40	0.5 (0.4 – 0.7)	
				0.0017 – 0.133	9	1.1 (0.5 – 2.1)	
				0.133 – 0.817	30	0.7 (0.5 – 1.0)	
				0.818 -	13	0.7 (0.4 – 1.3)	
				Cumulative exposure (ppm-years)			
				< 0.0193	29	0.6 (0.4 – 0.9)	
				0.0193 – 1.89	21	0.5 (0.3 – 0.8)	
				1.89 – 16.2	11	0.6 (0.3 – 1.1)	
				16.2 -	31	0.7 (0.5 – 1.0)	

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
			Internal comparison Pontchartrain	Duration (years) < 10 10 – 19 20 –	 33 23 36	 1.0 ref 1.1 (0.7 – 1.7) 0.6 (0.4 – 1.2)	 p global = 0.10 p trend = 0.63
				Intensity (ppm) < 0.0017 0.0017 – 0.133 0.133 – 0.817 0.818 -	 40 9 30 13	 1.0 ref 2.9 (1.3 – 6.5) 1.8 (1.0 – 3.4) 1.5 (0.7 – 3.1)	 p global = 0.07 p trend = 0.12
				Cumulative exposure (ppm-years) < 0.0193 0.0193 – 1.89 1.89 – 16.2 16.2 -	 29 21 11 31	 1.0 ref 0.7 (0.4 – 1.4) 1.2 (0.5 – 2.5) 1.5 (0.8 – 2.8)	 p global = 0.25 p trend = 0.20

Table 15: Summary of the cohort studies assessing the association between exposure to chloroprene and liver cancer risk. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.00..

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
Bulbulyuan et al (1998).	Cohort of 5185 shoe factory workers who were employed for at least two years in the period 1960-76. Followed up during 1979-93 Liver cancer reference rates were available only for 1992-93 and rates of 1992 were used in calculation of the SMRs. 70 328 person-years of follow-up.	Semi-quantitive exposure indexes (low=0, medium = 1, high = 10) were assigned based on 1970 CP levels for 3 groups: cutting and fitting jobs (mean CP exposure 0 mg/m^3), workers who had no direct contact with CP but were in the same departments as gluers (CP exposure 0.4 – 1 mg/m^3) and gluers (CP exposure 20 mg/m^3). Semiquantitative cumulative exposures (unit years) were calculated summing periods in each exposure index job. Co-exposures: benzene, formaldehyde, ethylacetate, butylacetate, ethyleneglycol, acetone, chlorotrifluoromethane, leather dust depending on job. Not adjusted for in analyses.	Mortality External comparison Internal comparison	 All exposed No exp Any exp Medium exp High exp Cumulative exp (unit-years) 0 0.2 – 10 10.1 – 30 > 30 Duration in high exposure job (years) No exposure 1-9 10-19 20 -	 10 1 9 6 3 1 0 6 3 1 1 1 1	SMR 2.4 (1.1 – 4.3) RR 1.0 ref 4.2 (0.5 – 33) 3.8 (0.5 – 34) 4.9 (0.5 – 47) 1.0 ref 0.0 7.1 (0.8 – 61) 4.4 (0.4 – 44) 1.0 ref 0.00 2.7 (0.2 -45) 8.3 (0.5 141)	 Adjusted for gender, age, calendar period of follow-up p for trend = 0.07 p for trend 0.02
Bulbulyan et al. (1999)	Cohort of 2314 workers of an Armenian CP production plant who were employed in the	There was a sharp decline in maximum CP exposure levels in 1980 from above 500 to 0.5–5 mg/m^3. As the information on	Incidence External comparison	 All Duration of CP exposure (years)	 6	SIR 3.3 (1.5 – 7.3)	Adjusted for gender, age, calendar period of follow-up

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	production departments for at least 2 months between 1940 and 1988 and were alive in 1979. Follow-up for cancer incidence in 1979-1990. 25 782 person-years for cancer incidence.	department specific exposure levels was not systematic, to calculate a cumulative index of CP exposure, semiquantitative exposure units from 1 to 6 (and 0 for no exposure) were assigned by depending on department and period and then added up the units for each year of employment. Other exposures: vinyl acetate, toluidine, talc and mercaptans		< 1 1 – 9 10 - Duration of high CP exposure (years) < 1 1 – 9 10 - Cumulative exposure (unit-years) 1 – 14 15 – 39 40 -	0 1 5 1 1 4 0 1 5	0.0 (exp 0.21) 1.9 (0.3 -14) 4.6. (1.9 – 11) 1.5 (0.2 – 10) 2.0 (0.3 – 14) 6.1 (2.3 – 16) 0.0 (exp 0.46) 2.9 (0.4 - 21) 4.9 (2.0 – 12)	
Colonna and Laydevant (2001)	Cohort of all men who had been working for at least 2 years in a French CP production plant since it was founded in 1966. The follow-up for cancer incidence was complete for 1979-1997. Those who died or moved from the geographical area before 1979 could not be followed for cancer. 7 950 person-years of follow-up.	Based on existing industrial hygiene measurements by job category a semiquantitative exposure metric was assigned: low (< 2 ppm), medium (2-5 ppm), high (> 5 ppm). 75% of workers stayed in the same category for the entire period, for those who changed category, the highest was used.	Incidence External comparison As only one case, risk not calculated by exposure level or duration of exposure. The only case occurred in medium exposure and > 20 years of exposure	All	1	SIR 1.4 (0.04 – 7.6)	Adjusted for calendar period of follow-up and age. Only men included.
Leet and Selevan (1982)	Cohort of 1575 male workers employed on 30 June 1957 in the	Based on job title and working area, the exposure was classified	Mortality	All High	4 3	SMR 5.7 (1.6 – 14.6) 7.5 (1.6 – 21.9)	SMR calculated only for groups with more than one observed

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	DuPont Louisville Kentucky neoprene production plant. Followed until 31 December 1974. 26 304 person-years of follow-up, 13 606 person-years in the high-exposure and 12 644 in the low-exposure category	as high (N=851) or low (N=823).		Low	1	-	case. No adjustment for potential confounders. A worker with both low and high exposure jobs, contributed to person-years of high exposure since the first employment in such an occupation.
Li et al. (1989)	A cohort of 1258 workers in a Chinese plant producing chloroprene monomer and neoprene. The cohort was selected from the pay roll of the factory employees based on job title that allowed to grade the level of chloroprene exposure. Based on the total N of cancer deaths (55) the entire factory cohort seems larger than the studied cohort of 1258 (16 cancer deaths). 1213 cohort members (96.4%) could be followed during 1969-83 and SMRs were	Exposure was graded high or low based on job title, but SMRs were reported only by job title. Co-exposure to other known carcinogens was reported to concern benzene and N-phenyl-Z-naphtylamine.	Mortality	All Monomer workshop Polymer workshop Laboratory	6 4 2 0	SMR 2.4 4.8 1.5	 Non-significant p < 0.05 Non-significant

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	calculated using local rates for 1973-75. The expected N of cancers was below one for all specific sites of cancer. Cancer deaths were searched from the death registries of the plant's hospital and the police substation and diagnoses verified from medical records in general and cancer hospitals. Person-years of follow-up not reported.						
Marsh et al. (2007a,b)	Four cohorts of CP producing plants. Followed until 2000. Louisville, US 5507 workers, exposure 1942-72 Pontchartrain, US 1357 workers, exposure 1969-2000 Maydown, Northern Ireland, 4848 workers exposure 1960-98 Grenoble, France, 717 workers, exposure 1966-2000	The exposure reconstruction was based on mathematical models which utilized exposure models based on the physics and chemistry associated with a given chemical process as determined from process documentation and task performance habits gleaned from interviews with knowledgeable plant personnel. In addition to a No exposure category, six exposure categories with the following nominal	Mortality External comparison Pontchartrain Maydown Grenoble Louisville Louisville Detailed Results	 All All All All Duration (years) < 10 10 – 19 20 – Intensity (ppm) < 3.6 3.6 – 8.1 8.1 – 15 16-	 0 1 1 17 6 4 7 3 7 3 4	SMR 0.0 (0.0 – 3.1) 0.2 (0.01 – 1.3) 0.6 (0.01 – 3.1) 1.0 (0.6 – 1.7) 0.6 (0.2 – 1.3) 2.1 (0.6 – 5.3) 1.0 (0.4 – 2.0) 0.6 (0.1 – 1.8) 1.7 (0.7 – 3.6) 0.9 (0.2 – 2.7) 0.6 (0.2 – 1.5)	

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	Person-years of follow-up L 197 919 P 30 660 M 127 036 G 17 057	exposure (geometric mean of the class limits) were used: 0.0016 ppm 0.016 ppm 0.16 ppm 1.6 ppm 16 ppm 71 ppm 160 ppm Detailed work histories were used to link individual cohort members to exposure estimates and these were summed to estimate average and cumulative exposure. In Louisville 22.7% and in Maydown 5.5% of the CP exposed workers has also exposure to vinyl chloride. Median CP exposure L plant 5.2 ppm P plant 0.28 ppm M plant 0.16 ppm G plant 015 ppm Mean CP exposure L plant 8.4 ppm P plant 0.27 ppm M plant 1.4 ppm G plant 2.2 ppm	Internal comparison Louisville	Cumulative exposure (ppm-years) < 4.7 4.7 – 55.9 60 – 164 164 - Duration (years) < 10 10 – 19 20 – Intensity (ppm) < 3.6 3.6 – 8.1 8.1 – 15 16- Cumulative exposure (ppm-years) < 4.7 4.7 – 55.9 60 – 164 164 -	 2 3 7 5 6 4 7 3 7 3 4 2 3 7 5	 0.4 (0.05 – 1.6) 0.6 (0.1 – 1.7) 1.6 (0.7 – 3.3) 1.0 (0.3 – 2.3) RR 1.0 ref 3.9 (0.8 – 17.1) 1.8 (0.5 – 6.4) 1.0 ref 3.8 (0.8 – 25.8) 1.8 (0.2 – 15.7) 1.3 (0.2 – 10.1) 1.0 ref 1.9 (0.2 – 23.8) 5.1 (0.9 – 54.6) 3.3 (0.5 – 39.3)	 p global = 0.24 p trend = 0.36 p global = 0.22 p trend = 0.84 p global = 0.17 p trend = 0.09 Adjusted for age, time period, sex and worker type (blue/white collar)
Marsh et al. (2021)	Cohort of 6864 workers with CP exposure in two US CP production plants (Louisville plant N= 5507	The same exposure assessment as in Marsh (2007a,b) above was used and exposures since 2000 were neglected. I.e.	Mortality External comparison Pontchartrain	 All, comparison US	 1	SMR 0.2 (0.01 – 1.1)	

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	exposure 1942-72, Pontchartrain plant N = 1357 exposure 1969-2000). Follow-up for cancer 1949-2017. About 23% of the Louisville plant workers had also exposure to vinyl chloride. Person-years of follow-up: L 245 218 P 50 602	only the cancer follow-up was updated. Median CP exposure L plant 5.2 ppm P plant 0.28 ppm Mean CP exposure L plant 8.4 ppm P plant 0.27 ppm		All, comparison local	1	0.2 (0.0 – 0.9)	
			Louisville	All, comparison US All, comparison local	31 31	1.1 (0.7 – 1.5) 1.0 (0.7 – 1.4)	
			Louisville Detailed results External comp, local	Duration (years) < 10 10 – 19 20 –	 15 6 10	 0.8 (0.5 – 1.4) 1.8 (0.7 – 3.8) 0.9 (0.4 – 1.7)	
				Intensity (ppm) < 3.6 3.6 – 8.1 8.1 – 15 16-	 9 8 5 9	 0.8 (0.4 – 1.5) 1.3 (0.6 – 2.3) 1.1 (0.4 – 2.6) 0.9 (0.4 – 1.7)	
				Cumulative exposure (ppm-years) < 4.7 4.7 – 55.9 60 – 164 164 -	 9 6 10 6	 0.9 (0.4 – 1.7) 0.7 (0.2 – 1.4) 1.5 (0.7 – 2.8) 0.9 (0.3 – 2.0)	
			Internal comparison Louisville	Duration (years) < 10 10 – 19 20 –	 15 6 10	RR 1.0 ref 2.4 (0.8 – 6.9) 1.2 (0.5 – 3.0)	p global = 0.19 p trend = 0.55
				Intensity (ppm) < 3.6 3.6 – 8.1 8.1 – 15 16-	 9 8 5 9	 1.0 ref 2.5 (0.8 – 7.8) 1.8 (0.4 – 6.8) 1.7 (0.5 – 5.4)	p global = 0.34 p trend = 0.43
				Cumulative exposure (ppm-years) < 4.7 4.7 – 55.9 60 – 164 164 -	 9 6 10 6	 1.0 ref 0.8 (0.2 – 2.7) 2.4 (0.8 – 7.1) 1.6 (0.4 – 5.7)	p global = 0.18 p trend = 0.18

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
							Adjusted for age, time period, sex and worker type (blue/white collar)

Table 16: Summary of the cohort studies assessing the association between exposure to chloroprene and lung/respiratory tract cancer risk. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.0.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
Bulbulyuan et al (1998).	Cohort of 5185 shoe factory workers who were employed for at least two years in the period 1960-76. Followed up during 1979-93 70 328 person-years of follow-up.	Semiquantitive exposure indexes (low=0, medium = 1, high = 10) were assigned based on 1970 CP levels for 3 groups: cutting and fitting jobs (mean CP exposure 0 mg/m^3), workers who had no direct contact with CP but were in the same departments as gluers (CP exposure 0.4 – 1 mg/m^3) and gluers (CP exposure 20 mg/m^3). Semiquantitative cumulative exposures (unit years) were calculated summing periods in each exposure index job. Co-exposures: benzene, formaldehyde, ethylacetate, butylacetate, ethyleneglycol, acetone, chlorotrifluoromethane, leather dust depending on job. Not adjusted for in analyses.	Mortality External comparison Internal comparison	 All exposed No exp Any exp Medium exp High exp Cumulative exp (unit-years) 0 0.3 – 10 10.1 – 30 > 30 Duration in high exposure job (years) No exposure 1-9 10-19 20 -	 31 8 23 18 5 8 7 9 7 8 3 2 0	SMR 1.4 (0.9 – 2.4) RR 1.0 ref 0.9 (0.4 – 2.2) 0.9 (0.4 – 2.1) 1.1 (0.4 – 3.5) 1.0 ref 1.1 (0.4 – 3.1) 1.0 (0.4 – 2.5) 0.8 (0.3 – 2.4) 1.0 ref 1.3 (0.3 – 5.1) 2.0 (0.4 - 9.6) 0	 Adjusted for gender, age, calendar period of follow-up p for trend = 0.7 p for trend 0.8
Bulbulyan et al. (1999)	Cohort of 2314 workers of an Armenian CP production plant who were	There was a sharp decline in maximum CP exposure levels in 1980 from above 500 to 0.5–5 mg/m^3. As	Incidence External comparison		6	SIR 0.5 (0.2 – 1.2)	Adjusted for gender, age, calendar period of follow-up

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	employed in the production departments for at least 2 months between 1940 and 1988 and were alive in 1979. Follow-up for cancer incidence in 1979-1990. 25 782 person-years for cancer incidence.	the information on department specific exposure levels was not systematic, to calculate a cumulative index of CP exposure, semiquantitative exposure units from 1 to 6 (and 0 for no exposure) were assigned by depending on department and period and and then added up the units for each year of employment. However, Lung cancer results were not presented according to any exposure metric. Other exposures: vinyl acetate, toluidine, talc and mercaptans					
Colonna and Laydevant (2001)	Cohort of all men who had been working for at least 2 years in a French CP production plant since it was founded in 1966. The follow-up for cancer incidence was complete for 1979-1997. Those who died or moved from the geographical area before 1979 could not be followed for cancer.	Based on existing industrial hygiene measurements by job category a semiquantitative exposure metric was assigned: low (< 2 ppm), medium (2-5 ppm), high (> 5 ppm). 75% of workers stayed in the same category for the entire period, for those who changed category, the highest was used.	Incidence External comparison	All Intensity Low Medium High Duration (years) <10 11-20 21 -	9 4 2 3 1 3 5	SIR 1.8 (0.8 – 3.5) 4.6 (1.3 – 12) 1.3 (0.2 – 4.5) 1.2 (0.3 – 3.6) 1.1 (0.03 – 5.9) 1.5 (0.3 – 4.4) 2.6 (0.8 – 6.0)	Adjusted for calendar period of follow-up and age. Only men included.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	7 950 person-years of follow-up.						
Leet and Selevan (1982)	Cohort of 1575 male workers employed on 30 June 1957 in the DuPont Louisville Kentucky neoprene production plant. Followed until 31 December 1974. 26 304 person-years of follow-up, 13 606 person-years in the high-exposure and 12 644 in the low-exposure category	Based on job title and working area the exposure was classified as high (N=851) or low (N=823).	Mortality	All High Low	17 10 7	SMR 1.1 (0.6 – 1.7) 1.3 (0.6 – 2.4) 0.9 (0.4 – 1.8)	No adjustment for potential confounders. A worker with both low and high exposure jobs, contributed to person-years of high exposure since the first employment in such an occupation. Results by lag time were similar to overall results.
Li et al. (1989)	A cohort of 1258 workers in a Chinese plant producing chloroprene monomer and neoprene. The cohort was selected from the pay roll of the factory employees based on job title that allowed to grade the level of chloroprene exposure. Based on the total N of cancer deaths (55) the entire factory cohort seems larger than the studied cohort	Exposure was graded high or low based on job title, but SMRs were reported only by job title. Co-exposure to other known carcinogens was reported to concern benzene and N-phenyl-Z-naphtylamine.	Mortality	All Monomer workshop Polymer workshop Laboratory	2 1 1 0	SMR 5.1 7.1 5.6	 Non-significant Non-significant Non-significant

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	of 1258 (16 cancer deaths). 1213 cohort members (96.4%) could be followed during 1969-83 and SMRs were calculated using local rates for 1973-75. The expected N of cancers was below one for all specific sites of cancer. Cancer deaths were searched from the death registries of the plant's hospital and the police substation and diagnoses verified from medical records in general and cancer hospitals. Person-years of follow-up not reported.						
Marsh et al. (2007a,b)	Four cohorts of CP producing plants. Followed until 2000. Louisville, US 5507 workers, exposure 1942-72 Pontchartrain, US 1357 workers, exposure 1969-2000 Maydown, Northern Ireland,	The exposure reconstruction was based on mathematical models which utilized exposure models based on the physics and chemistry associated with a given chemical process as determined from process documentation and task performance habits gleaned from	Mortality External comparison Pontchartrain Maydown Grenoble Louisville Louisville Detailed Results	 All All All All Duration (years) < 10 10 – 19	 12 48 10 266 137 23	SMR 0.7 (0.4 – 1.3) 0.8 (0.6 – 1.1) 0.9 (0.4 – 1.6) 1.1 (0.9 – 1.2) 0.7 (0.6 – 0.9) 0.7 (0.4 – 1.0)	

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	4848 workers exposure 1960-98 Grenoble, France, 717 workers, exposure 1966-2000 Person-years of follow-up L 197 919 P 30 660 M 127 036 G 17 057	interviews with knowledgeable plant personnel. In addition to a No exposure category, six exposure categories with the following nominal exposure (geometric mean of the class limits) were used: 0.0016 ppm 0.016 ppm 0.16 ppm 1.6 ppm 16 ppm 71 ppm 160 ppm Detailed work histories were used to link individual cohort members to exposure estimates and these were summed to estimate average and cumulative exposure. In Louisville 22.7% and in Maydown 5.5% of the CP exposed workers has also exposure to vinyl chloride. Median CP exposure L plant 5.2 ppm P plant 0.28 ppm M plant 0.16 ppm G plant 015 ppm Mean CP exposure L plant 8.4 ppm P plant 0.27 ppm M plant 1.4 ppm	Internal comparison Louisville Pontchartrain Detailed Results External	20 – Intensity (ppm) < 3.6 3.6 – 8.1 8.1 – 15 16- Cumulative exposure (ppm-years) < 4.7 4.7 – 55.9 60 – 164 164 - Duration (years) < 10 10 – 19 20 – Intensity (ppm) < 3.6 3.6 – 8.1 8.1 – 15 16- Cumulative exposure (ppm-years) < 4.7 4.7 – 55.9 60 – 164 164 - Duration (years) < 10 10 – 19 20 – Intensity (ppm) < 0.0017 0.0017 – 0.133 0.133 – 0.817	106 56 70 33 107 62 67 77 60 137 23 106 56 70 33 107 62 67 77 60 2 7 3 4 1 4	0.8 (0.7 – 1.0) 0.6 (0.5 – 0.8) 0.9 (0.7 – 1.1) 0.6 (0.4 – 0.8) 0.8 (0.7 – 1.0) 0.7 (0.6 – 0.9) 0.7 (0.6 – 0.9) 0.9 (0.7 – 1.2) 0.7 (0.5 – 0.8) RR 1.0 ref 1.0 (0.6 – 1.6) 1.0 (0.8 – 1.3) 1.0 ref 1.3 (0.9 – 2.0) 0.9 (0.6 – 1.4) 1.4 (1.0 – 1.9) 1.0 ref 1.0 (0.7 – 1.4) 1.3 (0.9 – 1.9) 0.9 (0.6 – 1.2) 0.3 (0.03 – 1.0) 0.9 (0.3 – 1.8) 0.6 (0.1 – 1.8) 0.3 (0.09 – 0.9) 2.1 (0.05 – 11) 1.1 (0.3 – 2.9)	 p global = 0.98 p trend = 0.84 p global = 0.06 p trend = 0.20 p global = 0.07 p trend = 0.71 Adjusted for age, time period, sex and worker type (blue/white collar)

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
		G plant 2.2 ppm		0.818 -	3	0.9 (0.2 – 2.6)	
				Cumulative exposure (ppm-years)			
				< 0.0193	3	0.4 (0.08 – 1.2)	
				0.0193 – 1.89	3	0.5 (0.1 – 1.5)	
				1.89 – 16.2	2	1.0 (0.1 – 3.5)	
				16.2 -	4	0.9 (0.2 – 2.2)	
			Internal comparison Pontchartrain	Duration (years)		1.0 ref	p global = 0.33
				< 10	2	3.1 (0.6 – 15)	p trend = 0.32
				10 – 19	7	2.1 (0.3 – 17)	
				20 –	3		
				Intensity (ppm)			
				< 0.0017	4	1.0 ref	p global = 0.25
				0.0017 – 0.133	1	7.3 (0.09 – 167)	p trend = 0.14
				0.133 – 0.817	4	5.0 (0.6 – 58)	
				0.818 -	3	3.5 (0.4 – 34)	
				Cumulative exposure (ppm-years)			
				< 0.0193	3	1.0 ref	p global = 0.70
				0.0193 – 1.89	3	1.6 (0.2 – 13)	p trend = 0.34
				1.89 – 16.2	2	2.9 (0.2 – 34)	
				16.2 -	4	2.3 (0.3 – 22)	
			Maydown Detailed Results External	Duration (years)			
				< 10	28	0.7 (0.5 – 1.1)	
				10 – 19	12	0.9 (0.4 – 1.5)	
				20 –	8	0.8 (0.4 – 1.6)	
				Intensity (ppm)			
				< 0.15	11	0.5 (0.2 – 0.8)	
				0.15 – 1.27	12	1.1 (0.6 – 1.9)	
				1.27 – 1.69	16	0.9 (0.5 – 1.5)	
				1.70 -	9	0.9 (0.4 – 1.7)	
				Cumulative exposure (ppm-years)			
				< 0.039	14	0.5 (0.3 – 0.9)	

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
				0.039 – 6.73	9	0.7 (0.3 – 1.4)	
				6.73 – 24.5	12	1.0 (0.5 – 1.7)	
				24.5 -	13	1.1 (0.6 – 1.9)	
			Internal comparison Maydown	Duration (years)			
				< 10	28	1.0 ref	p global = 0.82
				10 – 19	12	0.8 (0.4 – 1.8)	p trend = 0.84
				20 –	8	1.2 (0.2 – 5.9)	
				Intensity (ppm)			
				< 0.15	11	1.0 ref	p global = 0.08
				0.15 – 1.27	12	2.8 (1.1 – 7.4)	p trend = 0.09
				1.27 – 1.69	16	2.6 (1.1 – 6.2)	
				1.70 -	9	2.2 (0.8 – 6.0)	
				Cumulative exposure (ppm-years)			
				< 0.039	14	1.0 ref	p global = 0.39
				0.039 – 6.73	9	1.7 (0.7 – 4.2)	p trend = 0.10
				6.73 – 24.5	12	1.9 (0.7 – 5.0)	
				24.5 -	13	2.3 (0.9 – 6.0)	
			Grenoble Detailed Results External	Duration (years)			
				< 10	3	0.6 (0.1 – 1.9)	
				10 – 19	5	1.2 (0.4 – 2.7)	
				20 –	2	0.7 (0.09 – 2.6)	
				Intensity (ppm)			
				< 0.0051	2	0.8 (0.09 – 2.8)	
				0.0051 – 0.088	1	0.3 (0.01 – 1.8)	
				0.088 – 1.22	3	1.1 (0.2 – 3.1)	
				1.22 -	4	1.3 (0.3 – 3.2)	
				Cumulative exposure (ppm-years)			
				< 0.050	2	0.7 (0.09 – 2.6)	
				0.050 – 1.415	1	0.3 (0.01 – 1.7)	
				1.415 – 23.9	4	1.2 (0.3 – 3.0)	
				23.9 -	3	1.3 (0.3 – 3.7)	
				Duration (years)			

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
			Internal comparison Grenoble	< 10 10 – 19 20 – Intensity (ppm) < 0.0051 0.0051 – 0.088 0.088 – 1.22 1.22 - Cumulative exposure (ppm-years) < 0.050 0.050 – 1.415 1.415 – 23.9 23.9 -	3 5 2 2 1 3 4 2 1 4 3	1.0 ref 1.8 (0.4 – 7.8) 1.5 (0.2 –9 .6) 1.0 ref 0.6 (0.06 – 7.0) 2.3 (0.2 – 34) 3.0 (0.4 – 42) 1.0 ref 0.6 (0.05 – 6.8) 2.9 (0.4 – 40) 3.1 (0.3 – 48)	p global = 0.70 p trend = 0.58 p global = 0.45 p trend = 0.19 p global = 0.40 p trend = 0.17
Marsh et al. (2021)	Cohort of 6864 workers with CP exposure in two US CP production plants (Louisville plant N= 5507 exposure 1942-72, Pontchartrain plant N = 1357 exposure 1969-2000). Follow-up for cancer 1949-2017. About 23% of the Louisville plant workers had also exposure to vinyl chloride. Person-years of follow-up: L 245 218 P 50 602	The same exposure assessment as in Marsh (2007a,b) above was used and exposures since 2000 were neglected. I.e. only the cancer follow-up was updated. Median CP exposure L plant 5.2 ppm P plant 0.28 ppm Mean CP exposure L plant 8.4 ppm P plant 0.27 ppm	Mortality External comparison Pontchartrain Louisville Louisville Detailed results External comp, local	 All, comparison US All, comparison local All, comparison US All, comparison local Duration (years) < 10 10 – 19 20 – Intensity (ppm) < 3.6 3.6 – 8.1 8.1 – 15 16- Cumulative exposure (ppm-years) < 4.7 4.7 – 55.9 60 – 164	 32 32 358 358 196 30 132 96 83 49 130 95 97 96 70	SMR 0.7 (0.5 – 1.0) 0.6 (0.4 – 0.9) 1.0 (0.9 – 1.1) 0.7 (0.7 – 0.8) 0.7 (0.2 – 0.3) 0.6 (0.4 – 0.9) 0.8 (0.6 – 0.9) 0.6 (0.5 – 0.8) 0.9 (0.7 – 1.1) 0.7 (0.5 – 0.9) 0.8 (0.7 – 1.0) 0.7 (0.5 – 0.8) 0.7 (0.6 – 0.9) 0.9 (0.8 – 1.2) 0.7 (0.5 – 0.8)	

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
				164 -			
						RR	
			Internal comparison Louisville				p global = 0.98
				Duration (years)	196	1.0 ref	p trend = 0.85
				< 10	30	1.0 (0.7 – 1.5)	
				10 – 19	132	1.0 (0.8 – 1.2)	
				20 –			
							p global = 0.31
				Intensity (ppm)	96	1.0 ref	p trend = 0.29
				< 3.6	83	1.3 (0.9 – 1.8)	
				3.6 – 8.1	49	1.0 (0.7 – 1.5)	
				8.1 – 15	130	1.2 (0.9 – 1.7)	
				16-			
							p global = 0.04
				Cumulative exposure (ppm-years)	95	1.0 ref	p trend = 0.89
				< 4.7	97	1.1 (0.8 – 1.5)	
				4.7 – 55.9	96	1.4 (1.0 – 1.9)	
				60 – 164	70	0.9 (0.6 – 1.2)	Adjusted for age, time period, sex and worker type (blue/white collar)
				164 -			
			Pontchartrain Detailed results External comp, local	Duration (years)	4	0.3 (0.1 – 0.6)	
				< 10	12	0.8 (0.4 – 1.5)	
				10 – 19	16	0.8 (0.5 – 1.3)	
				20 –			
				Intensity (ppm)	10	0.4 (0.2 – 0.7)	
				< 3.6	2	0.8 (0.1 – 2.9)	
				3.6 – 8.1	14	0.9 (0.5 – 1.6)	
				8.1 – 15	6	1.0 (0.4 – 2.1)	
				16-			
				Cumulative exposure (ppm-years)	6	0.4 (0.1 – 0.8)	
				< 4.7	7	0.5 (0.2 – 1.5)	
				4.7 – 55.9	3	0.1 (0.1 – 1.4)	
				60 – 164	16	1.0 (0.6 – 1.6)	
				164 -			

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
			Internal comparison Pntchartrain			RR	
				Duration (years)	4	1.0 ref	p global = 0.09 p trend = 0.03
				< 10	12	2.5 (0.7 – 8.5)	
				10 – 19	16	3.7 (1.0 – 14)	
				20 –			
				Intensity (ppm)	10	1.0 ref	p global = 0.09 p trend = 0.05
				< 3.6	2	5.2 (1.0 – 28)	
				3.6 – 8.1	14	3.6 (1.1 – 12)	
				8.1 – 15	6	2.9 (0.8 – 10)	
				16-			
				Cumulative exposure (ppm-years)	6	1.0 ref	p global = 0.23 p trend = 0.04
				< 4.7	7	1.4 (0.4 – 4.6)	
				4.7 – 55.9	3	1.6 (0.3 – 7.4)	
				60 – 164	16	3.1 (0.9 – 10)	
				164 -			Adjusted for age, time period, sex and worker type (blue/white collar)

Table 17: Summary of the cohort studies assessing the association between exposure to chloroprene and breast cancer risk. Standardised mortality ratios (SMR) and other risk estimates are expressed in decimal form, i.e. no increase of risk equals a value of 1.0.

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
Bulbulyuan et al (1998).	Cohort of 5185 shoe factory workers who were employed for at least two years in the period 1960-76. Followed up during 1979-93 70 328 person-years of follow-up.	Semi-quantitive exposure indexes (low=0, medium = 1, high = 10) were assigned based on 1970 CP levels for 3 groups: cutting and fitting jobs (mean CP exposure 0 mg/m^3), workers who had no direct contact with CP but were in the same departments as gluers (CP exposure 0.4 – 1 mg/m^3) and gluers (CP exposure 20 mg/m^3). Semiquantitative cumulative exposures (unit years) were calculated summing periods in each exposure index job. Co-exposures: benzene, formaldehyde, ethylacetate, butylacetate, ethyleneglycol, acetone, chlorotrifluoromethane, leather dust depending on job. Not adjusted for in analyses.	Mortality External comparison Internal comparison More detailed results were not reported for breast cancer	 All exposed No exp Any exp Medium exp High exp	 33 13 20 14 6	SMR 1.1 (0.7 - 1.5) RR 1.0 ref 0.9 (0.5 - 1.8) 0.9 (0.4 - 2.0) 0.8 (0.3 - 2.1)	 Adjusted for gender, age, calendar period of follow-up
Bulbulyan et al. (1999)	Cohort of 2314 workers of an Armenian CP production plant who were employed in the	There was a sharp decline in maximum CP exposure levels in 1980 from above 500 to 0.5–5 mg/m^3. As the information on	Incidence External comparison		3	SIR 1.4 (0.4 – 4.3)	Adjusted for gender, age, calendar period of follow-up

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	production departments for at least 2 months between 1940 and 1988 and were alive in 1979. Follow-up for cancer incidence in 1979-1990. 25 782 person-years for cancer incidence.	department specific exposure levels was not systematic, to calculate a cumulative index of CP exposure, semiquantitative exposure units from 1 to 6 (and 0 for no exposure) were assigned by depending on department and period and then added up the units for each year of employment. However, Lung cancer results were not presented according to any exposure metric. Other exposures: vinyl acetate, toluidine, talc and mercaptans	More detailed results were not reported for breast cancer				
Marsh et al. (2007a,b)	Four cohorts of CP producing plants. Followed until 2000. Louisville, US 5507 workers, exposure 1942-72 Pontchartrain, US 1357 workers, exposure 1969-2000 Maydown, Northern Ireland, 4848 workers exposure 1960-98 Grenoble, France, 717 workers, exposure 1966-2000	The exposure reconstruction was based on mathematical models which utilized exposure models based on the physics and chemistry associated with a given chemical process as determined from process documentation and task performance habits gleaned from interviews with knowledgeable plant personnel. In addition to a No exposure category, six exposure categories with the following nominal exposure (geometric	Mortality External comparison Pontchartrain Maydown Grenoble Louisville More detailed results were not reported for breast cancer	 Not reported Not reported Not reported All	 10	SMR 1.0 (0.5 – 1.8)	

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
	Person-years of follow-up L 197 919 P 30 660 M 127 036 G 17 057	mean of the class limits) were used: 0.0016 ppm 0.016 ppm 0.16 ppm 1.6 ppm 16 ppm 71 ppm 160 ppm Detailed work histories were used to link individual cohort members to exposure estimates and these were summed to estimate average and cumulative exposure. In Louisville 22.7% and in Maydown 5.5% of the CP exposed workers has also exposure to vinyl chloride. Median CP exposure (overall, not reported for female workers only) L plant 5.2 ppm P plant 0.28 ppm M plant 0.16 ppm G plant 015 ppm Mean CP exposure (overall, not reported for female workers only) L plant 8.4 ppm P plant 0.27 ppm M plant 1.4 ppm G plant 2.2 ppm					

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
Marsh et al. (2021)	Cohort of 6864 workers with CP exposure in two US CP production plants (Louisville plant N= 612 female workers, exposure 1942-72, Pontchartrain plant N = 249 female workers, exposure 1969-2000). Follow-up for cancer 1949-2017. About 23% of the Louisville plant workers had also exposure to vinyl chloride. Person-years of follow-up: L 245 218 P 50 602	The same exposure assessment as in Marsh (2007a,b) above was used and exposures since 2000 were neglected. I.e. only the cancer follow-up was updated. Median CP exposure (overall, not reported for female workers only) L plant 5.2 ppm P plant 0.28 ppm Mean CP exposure (overall, not reported for female workers only) L plant 8.4 ppm P plant 0.27 ppm	Mortality External comparison Pontchartrain Louisville Louisville Detailed results External comp local	 Not reported All, comparison US All, comparison local Duration (years) < 10 10 – 19 20 – Intensity (ppm) < 0.6 0.6 – 7.1 7.1 – Cumulative exposure (ppm-years) < 0.0054 0.0054 – 2.4 2.4 – 36.6 36.7 -	 27 27 16 4 7 13 7 7 7 6 7 7	SMR 1.7 (1.1 – 2.5) 1.6 (1.1 – 2.3) 1.3 (0.8 – 2.2) 1.8 (0.5 – 4.5) 2.7 (1.1 – 5.5) 1.3 (0.7 – 2.2) 2.9 (1.2 – 6.0) 1.6 (0.6 – 3.3) 1.5 (0.6 – 3.0) 1.1 (0.4 – 2.5) 2.6 (1.1 – 5.4) 1.7 (0.7 – 3.5)	
			Internal comparison Louisville	RR Duration (years) < 10 10 – 19 20 – Intensity (ppm) < 0.6 0.6 – 7.1 7.1 – Cumulative exposure (ppm-years) < 0.0054 0.0054 – 2.4	 16 4 7 13 7 7 7 6 7	 1.0 ref 2.0 (0.5 – 6.7) 2.0 (0.6 – 5.5) 1.0 ref 2.8 (0.9 – 8.5) 1.7 (0.5 – 5.4) 1.0 ref 1.1 (0.3 – 4.0) 2.7 (0.7 – 11)	 p global = 0.22 p trend = 0.14 p global = 0.16 p trend = 0.18 p global = 0.32 p trend = 0.18

Reference	Description	Exposure assessment	Outcome	Exposure	N of cases	Risk estimate (95% CI)	Comments
				2.4 – 36.6 36.7 -	7	1.8 (0.4 – 7.9)	Adjusted for age, time period, sex and worker type (blue/white collar)
Garcia et al. (2015)	The study population of 112,378 California Teachers Study participants included 5,676 women diagnosed with invasive breast cancer.	Modelled annual average ambient air concentrations of 24 suspected mammary gland carcinogens (MCG) from the US EPA were linked to participants' addresses. Covariates adjusted for: age, race, family history of breast cancer, age at menarche, age at first full-term pregnancy, total lifetime breastfeeding months, hormone therapy use at baseline, physical activity, body mass index, current alcohol consumption, smoking status, and total pack-years of smoking	Incidence. Cox proportional hazards models were used to estimate hazard rate ratios and 95% confidence intervals associated with residential levels of 24 MCGs by quintiles of ambient air concentration. As thus resulted in multiple comparisons adjustments for this were performed.	Q1 Q2 Q3 Q4 Q5l	Not reported Not reported Not reported Not reported Not reported	HR 1.0 ref - - 1.05 (0.96, 1.15) 1.07 (1.00, 1.14) Some quintiles were combined as a large portion of the study participants had same concentration values	p for trend 0.04, but no longer significant after adjustment for multiple testing