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The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

152. Inorganic chloramines

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Preface

The main task of the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) is to produce criteria documents to be used by the regulatory authorities as the scientific basis for setting occupational exposure limits for chemical substances. For each document, NEG appoints one or several authors. An evaluation is made of all relevant published, peer-reviewed original literature found. The document aims at establishing dose-response/dose-effect relationships and defining a critical effect. Starting with this document, NEG will provide, when possible, recommendations for health-based occupational exposure limits. In the derivation of such limits, the ECHA Guidance on information requirements and chemical safety assessment[1] is taken into account. Whereas NEG adopts the document by consensus procedures, thereby granting the quality and conclusions, the authors are responsible for the factual content of the document.

The evaluation of the literature and the drafting of this document on inorganic chloramines were made by Drs Gunilla Wastensson at the University of Gothenburg and Kåre Eriksson at Umeå University, Sweden.

The draft versions were discussed within NEG and the final version was adopted at the NEG meeting 8 May 2019. Editorial work and technical editing were performed by the NEG secretariat. The following experts participated in the elaboration of the document:

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All criteria documents produced by NEG may be downloaded from www.nordicexpertgroup.org.

Gunnar Johanson, Chairman of NEG

[1] ECHA. Guidance on information requirements and chemical safety assessment. Chapter R.8: Characterisation of dose [concentration]-response for human health. Version 2.1. Helsinki, Finland: European Chemicals Agency, 2012.

Contents

Abbreviations and acronyms

AM	arithmetic mean
BALF	bronchoalveolar lavage fluid
CC16	club cell protein 16 kDa (formerly called Clara cell protein)
CI	confidence interval
CysLT	cysteinyl leukotriene
DENA	diethylnitrosamine
EIB	exercise induced bronchoconstriction
FENO	fraction of exhaled nitric oxide
FEV_1	forced expiratory volume in the first second
$FEV_{\%}$	$FEV_1/FVC \times 100$
FVC	forced vital capacity
GGT	γ-glutamyltranspeptidase
GM	geometric mean
GSH	glutathione
Ig	immunoglobulin
IL	interleukin
LC_{50}	lethal concentration for 50% of the exposed animals at single inhalation exposure
LDH	lactate dehydrogenase
L-eq	litre-equivalents
LOAEC	lowest observed adverse effect concentration (at inhalation)
LOD	limit of detection
LOQ	limit of quantification
LTB4	leukotriene B4
NEG	the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
NOAEC	no observed adverse effect concentration (at inhalation)
NOAEL	no observed adverse effect level
NTP	National Toxicology Program
OEL	occupational exposure limit
OR	odds ratio
PEF	peak expiratory flow
PR	prevalence ratio
RD_{50}	concentration causing a 50% decrease in respiratory frequency
S100-A8	S100 calcium binding protein A8 (also called calgranulin A)
SD	standard deviation
STEL	short-term exposure limit
SP	surfactant-associated protein
SPIN	Substances in Preparations in Nordic Countries
US	United States
WHO	World Health Organization

1. Introduction

Inorganic chloramines, i.e. monochloramine (NH_2Cl), dichloramine ($NHCl_2$) and trichloramine (NCl_3), are formed when free[1] chlorine reacts with nitrogen-containing substances present in e.g. chlorinated (disinfection) water sources. In the occupational setting, this may occur in swimming pool facilities (139) and in the food processing industry (63, 65, 76, 85). Inorganic chloramines may also be formed in industrial processes when liquid waste containing ammoniums ions is mixed with a sodium hypochlorite solution (100). Monochloramine, dichloramine and trichloramine are not known to be commercial products but monochloramine is generated *in situ* as needed to disinfect drinking water and waste water (68, 132).

Monochloramine and dichloramine are water soluble of which the former is the dominating inorganic chloramine in the chlorinated water sources mentioned above. Trichloramine is immiscible with water, has a relatively high vapour pressure at room temperature and thus evaporates relatively fast into the air compartment (67). Trichloramine is therefore the dominating inorganic chloramine in the indoor air of swimming pools (20, 64). In the food processing industry, the fraction of trichloramine in air is considerably lower (63, 65, 76, 85).

In recent years there has been an increased reporting of health problems such as irritation and pulmonary effects among staff in indoor chlorinated swimming pool facilities and in the food processing industry where chlorinated water is used. Chlorination of water gives rise to a number of disinfection by-products also in air, mainly inorganic chloramines (6, 83, 108, 138, 139). The aim of this document is to evaluate health effects associated with occupational exposure to inorganic chloramines, and if possible, to recommend health-based occupational exposure limits (OELs).

2. Substance identification

Substance identification data for the inorganic chloramines are presented in Table 1.

Table 1. Substance identification data for the inorganic chloramines (97).

Common name:	Monochloramine	Dichloramine	Trichloramine
CAS No.:	10599-90-3	3400-09-7	10025-85-1
EC No.:	234-217-9	–	233-045-1
Synonyms:	Monochlorammonia, monochloroamine	Dichloroamine	Nitrogen trichloride, nitrogen(III) chloride, trichloroazane, agene, trichlorine nitride
Molecular formula:	NH_2Cl	$NHCl_2$	NCl_3
Molecular weight:	51.47 g/mol	85.92 g/mol	120.36 g/mol

–: missing data.

[1] Free chlorine: chlorine available to sanitise water, i.e. chlorine and hypochlorite/hypochlorous acid.

3. Physical and chemical properties

Physical and chemical properties for the inorganic chloramines are presented in Table 2. Chloramines are powerful oxidants whose high redox potentials can oxidise many compounds including iodide ions, the latter being of interest for analytical purposes (Section 5.1.2) (26, 75).

3.1 Monochloramine

Monochloramine (NH_2Cl) is a colourless to yellow liquid with a melting point of - 66 °C. It is soluble in ethanol and ethyl ether, and slightly soluble in benzene and carbon tetrachloride. Pure monochloramine liquid and monochloramine vapours are unstable at room temperature, but the substance is readily soluble and stable in aqueous solution (68, 132, 135).

A threshold odour level of 0.65 mg/l as chlorine gas (Cl_2) in aqueous solution has been reported, but the substance rarely causes taste and odour problems in drinking water below 5 mg/l as Cl_2 (124).

Monochloramine oxidises sulphhydryls and disulphides in the same manner as hypochlorous acid (71).

3.2 Dichloramine

Dichloramine ($NHCl_2$) is a yellow gas (no boiling point data were located) at room temperature. The gas is unstable and reacts with many materials (66). Because of its instability it has been prepared only in aqueous solution (51).

The odour threshold is 0.15 mg/l as Cl_2 in aqueous solution, which is much lower than that of monochloramine. Most people perceive the unpleasant chlorinous smell when the concentration is above 0.5 mg/l (124).

Table 2. Physical and chemical properties of the inorganic chloramines (18, 51, 66, 67, 124, 132).

Parameter	Monochloramine	Dichloramine (unstable)	Trichloramine
Boiling point at 101.3 kPa:	- 50 °C, *dec.*	–	71 °C
Melting point at 101.3 kPa:	- 66 °C	–	- 40 °C
Vapour pressure at 25 °C:	–	–	150 mmHg (20.0 kPa)
Density, gas at 20 °C and 101.3 kPa:	–	–	1.72 g/ml
Density, liquid:	–	–	1.65 g/ml
Auto ignition temperature:	–	–	93 °C
Solubility in water:	Miscible	Soluble	Immiscible
Stability in water:	Stable	*Dec.*	*Dec.* slowly
Partition coefficient (air:water) at 20 °C:	0.45	1.52	435
Odour threshold in water as chlorine gas:	0.65 mg/l	0.15 mg/l	0.02 mg/l
Conversion factors at 20 °C: 1 mg/m^3 =	0.469 ppm	0.280 ppm	0.200 ppm
1 ppm =	2.13 mg/m^3	3.57 mg/m^3	4.99 mg/m^3

–: missing data, *dec.*: decomposes.

3.3 Trichloramine

Trichloramine (NCl_3) is an oily yellowish liquid at room temperature. It is immiscible with water and is soluble in benzene, chloroform, carbon tetrachloride, carbon disulphide and phosphorus trichloride. Trichloramine has a relatively high vapour pressure at ambient temperature and explodes when heated above 93 °C or when the liquid is exposed to sunlight (18). It evaporates approximately 300 times faster than monochloramine and 100 times faster than dichloramine from water into the air compartment (67).

Trichloramine has been said to produce a geranium-like and chlorinous odour. The odour threshold is low compared to the other inorganic chloramines, 0.02 mg/l in water as Cl_2 (124).

4. Occurrence, production and use

4.1 Occurrence

4.1.1 General

Inorganic chloramines are formed when free chlorine reacts with nitrogen containing substances such as urea and ammonia (139) present in chlorinated water sources such as drinking water and waste water, swimming pools and in the food processing industry where disinfecting or cleaning water is used (63-65, 76, 85, 132, 139). Inorganic chloramines may also be formed in industrial processes when liquid waste containing ammonium ions (NH_4^+) is mixed with a sodium hypochlorite solution (100).

The formation of inorganic chloramines is illustrated below exemplified with ammonia (NH_3) as a nitrogen-containing substance and hypochlorous acid (HClO) as a chlorinated disinfectant (64).

$$NH_3 + HClO \rightleftharpoons NH_2Cl + H_2O$$

$$NH_2Cl + HClO \rightleftharpoons NHCl_2 + H_2O$$

$$NHCl_2 + HClO \rightleftharpoons NCl_3 + H_2O$$

The formation of inorganic chloramines in water is dependent on the chlorine-to-nitrogen ratio and pH. In general, the optimal pH for the formation of monochloramine lies in the range 7.5–9.0. Under the conditions of water and waste water chlorination, monochloramine is the principle inorganic chloramine encountered. Dichloramine has a maximum of formation at pH 4–6, and a pH < 4.4 favours the formation of trichloramine (26, 75, 132).

National recommendations for pH values in chlorinated swimming pools vary slightly. All Nordic countries have a recommended upper pH limit of 7.6, with Norway and Sweden having the narrowest recommended range of 7.2–7.6 (37, 57,

94, 134). At a chlorine-to-nitrogen ratio of < 5:1 and a pH > 7, almost exclusively monochloramine is formed. At a chlorine-to-nitrogen ratio of > 5:1 and a pH < 7, dichloramine is formed. At pH < 7.2 an increased formation of trichloramine has been shown. When the chlorine-to-nitrogen molar ratio decreases, the formation of trichloramine decreases (52, 115, 132).

An increased number of swimmers in a swimming pool increases the air concentration of trichloramine (4, 16, 25, 36, 73, 136).

4.1.2 Monochloramine and dichloramine

Monochloramine and dichloramine are water soluble and thus present in chlorine disinfected drinking water, chlorine disinfected swimming pool water and chlorinated water used for cleaning or disinfection purposes in the food processing industry. In the latter, mono- and dichloramine may account for a substantial part of the inorganic chloramines in air (63, 65, 76).

4.1.3 Trichloramine

Trichloramine is immiscible with water and has a relatively high vapour pressure at room temperature and evaporates relatively fast from water. Trichloramine is the dominating inorganic chloramine in the air of indoor swimming pool facilities (20). In the food processing industry, trichloramine constitutes approximately 30–70% of the chlorine species in air (63, 64, 76, 85).

4.2 Production

4.2.1 Monochloramine

Monochloramine is not known to be a commercial product but is generated *in situ* as needed by the action of hypochlorous acid or chlorine gas on ammonia (68).

4.2.2 Dichloramine and trichloramine

No data were located.

4.3 Use

4.3.1 Monochloramine

Monochloramine is used as an alternative to chlorine as waste water and drinking water disinfectant and is formed *in situ* when free chlorine and ammonia is added to the water. This disinfection method results in less formation of trihalomethanes. Monochloramine is less effective as disinfectant than free chlorine, but is persistent and is therefore primarily used as secondary disinfectant to maintain a stable residual in water distribution systems (68, 132). Monochloramine has also been used in the synthesis of a wide range of chemicals including vicinal organic chloramines, *N*-chlorimines and hydrazine. In 1990, it was estimated that 55 000 tons of monochloramine was consumed worldwide in the production of hydrazine (141).

There has been no registered use of monochloramine in the SPIN (Substances in Preparations in Nordic Countries) database (123).

4.3.2 Dichloramine
No data were located.

4.3.3 Trichloramine
The agene process was formerly used for bleaching flour with trichloramine. The practice was discontinued in 1950 once it became known that agene-treated flour may cause severe neurological symptoms in dogs (canine hysteria) and other species. The denaturated protein (methionine sulphoximime) in the treated flour used for production of dog biscuits was identified as the toxic compound, and there were also concerns for potential adverse effects on human health (119).

There has been no registered use of trichloramine in the SPIN database (123).

5. Measurements and analysis of workplace exposure

5.1 Air monitoring

The method most often used today to determine inorganic chloramines in air was developed by Héry and coworkers (63, 64). It is an indirect method as chloride ions are determined.

5.1.1 Monochloramine and dichloramine (soluble chlorine)
To determine soluble chlorine[2] by the method of Héry *et al*. (63, 64), air is sampled through a tube with silica gel coated with sulphamic acid. Following sampling the tube is desorbed in a sulphamic acid solution and the concentration of soluble chlorine is determined by potentiometry with a chlorine electrode and a pH/mV meter (63, 70) or by colorimetry (25).

5.1.2 Trichloramine
When determining the trichloramine concentration in air according to Héry *et al*., interference from soluble chlorine is avoided by the tube with silica gel impregnated with sulphamic acid (Section 5.1.1) in the front of a filter cassette which traps these substances. A Teflon filter prevents any chlorides contained in airborne water droplets from being included in the analysis of trichloramine and is discarded after sampling. For sampling of trichloramine, a quartz filter in the cassette is impregnated with a solution of sodium carbonate and diarsenic(III) trichloride. On the filter, trichloramine is reduced to chloride ions. Following desorption of the filter with deionised water, chloride is determined by ion chromatography with conductivity or capillary electrophoresis detection to estimate the air concentration of trichloramine (63, 64, 70).

The limit of detection (LOD) for trichloramine using the method developed by Héry *et al*. (63, 64) depends on the air volume sampled and the ion chromatographic

[2] Soluble chlorine: in occupational settings covered in this document, this means hypochlorite, hypochlorous acid, chlorine, monochloramine and dichloramine.

method used but is generally in the range of 0.0017–0.01 mg/m^3 (4, 16, 24, 25, 64, 98, 101).

Predieri *et al.* developed an impinger method for determination of trichloramine in the workplace atmosphere. In the impinger flask, trichloramine reacts with potassium iodide in water solution. The released iodine reacts with diethyl-*p*-phenylenediamine and produces a pink coloration. The coloration is proportional to the amount of trichloramine in sampled air and is determined by spectroscopy. The LOD was 0.0036 mg/m^3 at an air sampling volume of 100 litres (105). Other chlorinated inorganic or organic compounds such as dichloroacetonitrile, cyanogen chloride, dichloroacetic acid, trichloroacetic acid or dichloromethylamine present in the air (4, 22, 136) are suspected to interfere with the analysis leading to an overestimation of the trichloramine exposure. The percentage of interference was however not determined.

There is also a portable analysis tool that allows regular monitoring of trichloramine in air. The analyte is retained on quartz fibre filters, released in deionised water and subsequently analysed by colorimetry. The minimum required sampling time is 45 min (69, 126).

Air monitoring has mostly been performed as stationary sampling. The results may deviate from those obtained by personal sampling. Linear regression analysis based on data from 12 parallel 8-hour samplings of trichloramine in pool air suggested a relation between personal and stationary sampling of 1:1.6 (138). In a similar study by the same group, a linear regression based on 8 personal and 14 stationary 8-hour samplings showed a corresponding relation of 1:2.2 between personal and stationary sampling (137). Only data from personnel who spent > 50% of their workday in the pool area were included in the analyses.

5.2 Biological monitoring

For saliva and gastric fluid samples, membrane introduction mass spectrometry and tandem mass spectrometry has been used (132).

Monochloramine, dichloramine and monobromamine were determined in real-time in single human breaths by selected ion flow tube mass spectrometry. Preliminary measurements showed concentrations of 10–150 ppb of these substances in the breath of volunteers (healthy or with chronic obstructive pulmonary disease). Limits of detection approached 10 ppb (117). For trichloramine, 10 ppb corresponds to 0.05 mg/m^3.

6. Occupational exposure data

Trichloramine is the dominating inorganic chloramine in the indoor air of swimming pools. The remaining fraction as sampled by the method of Héry *et al*. (63, 64) is soluble chlorine (monochloramine, dichloramine, hypochlorite/hypochlorous acid and chlorine). Carbonelle *et al.* reported that trichloramine accounted for about 90% of the chlorine species in swimming pool air (20). In the food

processing industry, the corresponding figure is 30–70%. These lower percentages are due to intense stirring and spray washing of the chlorinated water, which may cause transfer of mono- and dichloramine into the atmosphere as vapours and aerosols (63, 64, 76, 85). Massin *et al*. carried out personal exposure measurements during different work tasks such as foaming and rinsing in the food industry. The exposure to the sum of soluble chlorine and trichloramine was 0.01–5.46 mg/m^3 (unclear if expressed as trichloramine, or chlorine, equivalents) (85).

6.1 Monochloramine and dichloramine (soluble chlorine)

Héry *et al.* performed air sampling of soluble chlorine in a green salad production plant. Personal air sampling was done during a half work shift and showed concentrations of < 0.1–3.7 mg/m^3. Stationary sampling for 1–8 hours showed air concentrations of 0.1–10.9 mg/m^3 (63).

Personal exposures to soluble chlorine were 0.02–0.16 mg/m^3 during fish curing, 0.03–0.85 mg/m^3 in slaughter houses, 0.04–1.33 mg/m^3 in poultry processing, 0.03–0.17 mg/m^3 in pet food production and < 0.01–0.30 mg/m^3 in delicatessen trade (65).

King *et al.* performed personal sampling of soluble chlorine among poultry processing workers with exposures of 0.010–0.13 mg/m^3 (76).

Chu *et al.* reported mean (± standard deviation; SD) air concentrations of soluble chlorine (stationary sampling) of 0.072 ± 0.052 mg/m^3 in 10 indoor swimming pools and 0.085 ± 0.056 mg/m^3 in 6 spa pools (25).

Air concentrations of soluble chlorine in an indoor waterpark resort ranged from non-detectable to 0.25 mg/m^3 (27).

6.2 Trichloramine

Air measurements of trichloramine have predominantly been performed in indoor swimming pool facilities (during pool work and swimming) and in the food processing industry (during cleaning and disinfection) (Table 3). The air measurement data presented in this section are retrieved from studies in which health effects of trichloramine were also studied.

Most stationary air measurements during pool work were made at spots where the personnel are likely to be located during a work day. The sampling times were typically 1.5–3 hours. The exposure levels (arithmetic mean; AM) were usually 0.15–0.65 mg/m^3 for public and school baths and 0.2–1.25 mg/m^3 for adventure baths (4, 16, 24, 25, 27, 36, 42, 64, 73, 79, 84, 98, 101, 129, 133, 136, 138). In two studies in indoor swimming pool facilities, personal sampling was used in parallel with stationary sampling. Overall, the personal exposure was approximately 50% of the levels obtained by stationary sampling (Section 5.1.2) (137, 138).

Air measurements of trichloramine during competitive and recreational swimming have been performed as stationary sampling at spots close to the swimming pool. Exposure levels during swimming were similar to those measured during pool work, i.e. 0.2–1.30 mg/m^3 (9-11, 15, 20, 21, 39, 47, 72, 78, 80, 118).

In a green salad processing plant, the personal exposure was < 0.1–2.3 mg/m^3 of trichloramine during a half work shift. Stationary sampling showed air concentrations of 0.1–5.9 mg/m^3. Sampling times were 1–8 hours (63).

In another study, personal exposures were < 0.05–1.31 mg/m^3 in slaughter houses, < 0.05–0.24 mg/m^3 during fish curing, 0.01–2.0 mg/m^3 in poultry production, < 0.01–0.11 mg/m^3 in pet food production and 0.03–0.59 mg/m^3 in delicatessen trade (65). Sampling times were 10–160 min and may thus not represent full-shift exposures. Short-time sampling is however useful to evaluate the exposure during specific work tasks.

King *et al.* performed full-shift personal sampling of trichloramine in the poultry industry. The geometric mean (GM) ranged from non-detectable to 0.16 mg/m^3 (76).

Table 3. Air concentrations of trichloramine in indoor swimming pool facilities and in the food processing industry in different countries.

Country	No. and type of pools/plants	Type of sampling	No. of samples	Sampling time, h	Exposure level, AM (range), mg/m^3	Reference
Swimming pool workers [a]						
Canada	2 public	Stationary [b]	19 18	2	0.22 (0.11–0.35) 0.14 (0.08–0.21)	(24)
Canada	1 public	Stationary [b]	26	3	0.38 (0.11–0.70)	(79)
Finland	16 (public, adventure and rehab)	Stationary [b]	16	1.5–2	0.06 (0.03–0.17)	(133)
France	15 public	Stationary [b, c]	–	3	0.19 (0.02–1.26) GM	(16)
France	7 public 5 adventure 1 rehab	Stationary [b]	129 176 4	≤3 ≤3 ≤3	0.15–0.39 [d] (0.06–0.90) 0.23–1.25 [d] (0.08–1.92) <0.05	(64)
France	46 public 17 adventure	Stationary [b]	860 402	3–4 3–4	0.24 (SD 0.17) 0.67 (SD 0.37)	(84)
Italy	20 public	Stationary [e]	20	1.7	0.65 (0.2–1.02)	(36)
Netherlands	6 public	Stationary [b]	119	6	0.56 (0.13–1.34)	(73)
Sweden	6 regular 3 adventure	Stationary [b]	18 9	3 3	0.19 (0.13–0.23) [d] 0.23 (0.04–0.36) [d]	(42)
Sweden	10 public (7 regular, 3 adventure)	Stationary [b]	129	3	0.21 (0.001–0.77)	(98)
Sweden	18 public (regular, adventure, whirlpools)	Stationary [b] Personal [b]	110 52	8 2–10	0.18 (<0.001–0.64), GM 0.10 0.071 (<0.001–0.24), GM 0.036	(138)
Sweden	10 habilitation or rehabilitation	Stationary [b] Personal [b]	32 21	8 8	0.023 (0.001–0.140), GM 0.009 0.019 (0.001–0.076), GM 0.008	(137)
Switzerland	10 public, 11 rehab, 8 school, 1 adventure	Stationary [b]	146	2	0.11 (0.02–0.52) [d] (18/30 pools <0.1)	(101)

Table 3. Air concentrations of trichloramine in indoor swimming pool facilities and in the food processing industry in different countries.

Country	No. and type of pools/plants	Type of sampling	No. of samples	Sampling time, h	Exposure level, AM (range), mg/m^3	Reference
Taiwan	6 public, 4 school 6 spa	Stationary [b]	54 –	1.5 1.5	0.035 (0.017–0.15) 0.059 (SD 0.042)	(25)
United Kingdom	3 public	Stationary [b]	15	–	(0.1–0.57)	(129)
Unites States	1 school	Stationary [e]	–	–	0.15 (< 0.01–0.62)	(4)
Unites States	1 adventure	Stationary [f]	99	8	(< LOQ–1.06)	(27)
Unites States	3 public, 1 school	Stationary [e]	–	0.5	(0.1–0.7)	(136)
Swimmers						
Belgium	1 public	Stationary [b]	19	2	(0.20–1.28)	(118)
Belgium	1 public	Stationary [g]	–	2	0.49	(11)
Belgium	4 public	Stationary [g]	–	–	(0.25–0.54)	(9)
Belgium	1 public	Stationary [g]	7	–	0.32 (0.17–0.54)	(10)
Belgium	Several public	Stationary [g]	–	–	(0.30–0.50)	(15)
Belgium	1 public	Stationary [b]	2	0.75; 2	0.36; 0.49	(21)
Belgium	1 public	Stationary [h]	2	0.75	0.16; 0.28	(20)
Canada	7 public	Stationary [b]	–	–	0.34 (0.26–0.41)	(78)
Netherlands	9 public	Stationary [b]	96	2	0.21 (0.03–0.78)	(72)
Spain	7 public	Stationary [b]	21	2	0.16 (median) (0.05–0.52)	(39)
Spain	3 public	Stationary [e]	9	0.3	0.4 (0.1–1.0) [i]	(80)
Spain	1 public 1 public	Stationary [j, l] Stationary [k, l]	26 17	– –	0.62 (SD 0.34) 0.38 (SD 0.19)	(47)

Table 3. Air concentrations of trichloramine in indoor swimming pool facilities and in the food processing industry in different countries.

Country	No. and type of pools/plants	Type of sampling	No. of samples	Sampling time, h	Exposure level, AM (range), mg/m^3	Reference
Food industry workers						
France	Green salad processing	Personal [b]	62	4	(< 0.1–2.3)	(63)
		Stationary [b]	31	1–8	(0.1–5.9)	
France	Slaughter house	Personal [b]	18	10–75 min	(< 0.05–1.31)	(65)
	Fish curing		7	14–69 min	(< 0.05–0.24)	
	Pet food processing		29	25–95 min	(< 0.01–0.11)	
	Delicatessen trade		19	30–160 min	(0.03–0.59)	
	Poultry production		12	30–140 min	(0.01–2.0)	
France	17 plants	Personal [b]				(85)
	Foaming		125	10 min–2 h	0.49 (0.05–5.46) [i]	
	Foaming/rinsing		40		0.48 (0.07–2.63) [i]	
	Rinsing		112		0.33 (0.01–2.94) [i]	
United States	Poultry production	Personal [f]			GM	(76)
	Evisceration area		18	8	0.0051 (ND–0.16)	
	Dark meat area		16	8	0.0012 (ND–0.05)	

[a] Stationary air sampling performed at the edge of the pool or within the area where the personnel spent most of the work shift.
[b] Filter sampling and analysis by ion chromatography (64).
[c] Sampling performed at 1.5 m or 0.25 m above the water surface respectively. No difference in air level between the sampling heights.
[d] Range of AMs.
[e] Impinger sampling and analysis by spectroscopy (105).
[f] Filter sampling and analysis by inductively coupled plasma atomic emission spectroscopy (96).
[g] Air sampling and analytical methods not given.
[h] High-performance liquid chromatography. Analytical parameters not given.
[i] Concentrations given as the sum of soluble chlorine and trichloramine (unclear if expressed as trichloramine, or chlorine, equivalents).
[j] Conventional chlorination method based on NaClO and HCl.
[k] New disinfection method based on NaClO and CO_2 followed by a phase combining saline electrolysis plus UV radiation added after filtering.
[l] Air sampling method not given. Analysis performed by an electrophoresis method; analytical parameters not given.
–: missing data, AM: arithmetic mean, GM: geometric mean, LOQ: limit of quantification, ND: non-detectable, SD: standard deviation, UV: ultraviolet.

7. Toxicokinetics

7.1 Human data

No human data were located, but inhalation is the dominating route of exposure to inorganic chloramines in the occupational setting. Exposure to monochloramine may also occur orally, via drinking water and via aspiration of water in swimming pools.

7.2 Animal data

7.2.1 Monochloramine

No inhalation or dermal data were located.

In the only study located, Abdel-Rahman *et al*. administered a single oral total dose of 1.1 mg (~ 5 mg/kg bw) radiolabelled monochloramine ($NH_2{}^{36}Cl$) to each of 4 male Sprague Dawley rats. Blood samples were collected at 15, 30 and 60 min and 2, 4, 8, 16, 24, 48, 72, 96 and 120 hours following administration. In a parallel experiment, a similar amount of radiolabelled monochloramine was administered to another 4 rats. Expired air samples and faecal and urine samples were collected at 8, 16, 24, 48, 72, 96 and 120 hours.

A peak ^{36}Cl plasma level was reached 8 hours after administration and the absorption rate constant was 0.278 mg/hour with an absorption half-time of 2.5 hours. The ^{36}Cl plasma level remained at a plateau 8–48 hours after administration. At 24 hours following administration, the ^{36}Cl plasma level was 0.87% of the administered dose. At 120 hours, the highest ^{36}Cl activity was measured in plasma and whole blood and the lowest in the liver, ileum and adipose tissue. After 48 hours, the radiolabel was eliminated from the plasma with a half-time of 38.8 hours. Most of the total ^{36}Cl was identified as $^{36}Cl^-$ which according to the authors indicated that the chlorine moiety was eliminated primarily in this form. Of the administered dose, 25% was excreted in urine and 1.98% in faeces within 120 hours. ^{36}Cl was not detected in expired air throughout the experiment (3).

There is a lack of information on the rate of chloramine-chloride exchange ($NH_2{}^{36}Cl + Cl^- \rightleftarrows NH_2Cl + {}^{36}Cl$) in solutions of high chloride concentrations. If the exchange rate is significant, the toxicokinetics of $NH_2{}^{36}Cl$ could appear to resemble that of chloride, when, in fact, the compound has lost its radiolabel through chloramine-chloride exchange.

7.2.2 Dichloramine and trichloramine

No data were located.

7.3 In vitro data

The persistence of monochloramine in saliva and gastric fluid was examined. Pooled samples of human saliva or gastric fluid samples were exposed to 1.0–20 mg/l of monochloramine. The samples were continuously monitored using

membrane introduction mass spectrometry and tandem mass spectrometry in a multiple monitoring procedure. Monochloramine in saliva was completely depleted in approximately 5 min at the 1-mg/l level. The 5-mg/l solution was incompletely depleted in 2 hours and the higher concentration solutions (not specified) were unaffected. Monochloramine in gastric fluid disappeared completely in <30 seconds at all concentrations. Dichloramine, trichloramine and molecular chlorine were not observed in saliva or gastric fluid during depletion (132).

8. Biological monitoring

As there are no human toxicokinetic data for inorganic chloramines, there is no basis for biological exposure monitoring of the substances at present.

Several effect markers have been suggested, none of which are specific for the inorganic chloramines.

Pneumoproteins, serum proteins especially produced in the respiratory tract, such as club cell protein 16 kDa (CC16) and surfactant-associated proteins (SP-A, SP-B and SP-D), have been suggested as biomarkers of the hyperpermeability that occurs in the deep lung (12). CC16 is an anti-inflammatory protein secreted by club cells (formerly called Clara cells) in the airways and predominantly in terminal bronchioles from where it leaks into serum (13). SP-A is the major surfactant-associated protein mainly secreted by alveolar type II cells and is considered to collaborate with SP-B and SP-C to spread and stabilise the phospholipid layer at the alveolar layer and thus reduce the surface tension (59). CC16 and SP-A are largely, and SP-B exclusively, confined to the lungs, whereas SP-D is expressed by a number of tissues (60). Small amounts of CC16, SP-A, SP-B and SP-D occur in blood, and these pneumoproteins have been validated as blood markers of lung hyperpermeability in a variety of lung disorders caused by different lung toxicants (58). CC16 can also be used as a peripheral marker of the integrity of club cells (61).

Elevated levels of *exhaled nitric oxide* are associated with increased release from epithelial cells of the bronchial wall and reflect chronic eosinophilic airway inflammation (74). Measurement of the fraction of exhaled nitric oxide (FENO) is a non-invasive and standardised test used in clinical practice for diagnosis and management of asthma (114). FENO has been suggested as a possible marker of airway inflammation due to exposure to irritant agents and has been associated with airway responsiveness in lifeguards (30).

Analysis of *protein changes in nasal lavage fluid* was applied in a study on pool workers by Fornander *et al*. Nasal lavage fluid was collected from 9 pool workers and 4 control subjects. Protein profiling of nasal lavage fluid showed altered distribution of three innate immunity proteins; the levels of α-1-antitrypsin and lactoferrin were significantly higher and that of S100 calcium binding protein A8 (S100-A8, also called calgranulin A) was significantly lower in the pool workers

than in the control subjects. These effects were most pronounced in subjects with airway irritation (42).

Evaluation of the predominating *cell types within the nasal mucosa* can indicate inflammation (rhinitis) due to occupational irritants. Nasal smear is collected for cytology and assessed using light microscopy. Erkul *et al.* used nasal cytology and found that pool workers had significantly more eosinophils in nasal smear than non-exposed workers, indicating allergic inflammation in the nasal mucosa (34).

9. Mechanisms of toxicity

Inorganic chloramines are potent sensory irritants that cause eye and upper respiratory tract irritation by interaction with neuronal sensors located in the mucous membranes of the respiratory tract and the eyes (shown for mono- and trichloramine) (33, 43).

Chloramines are membrane penetrating oxidants and react rapidly with sulphhydryl groups of proteins in the cytoskeleton and the extracellular matrix causing disruption of tight junctions and an almost immediate increase in epithelial permeability, as shown in *in vitro* studies [(91, 93, 128), as cited by (21)].

9.1 Monochloramine

Adverse health effects (methaemoglobinaemia resulting in haemolytic anaemia) have been shown in long-term haemodialysed patients exposed to monochloramine through chloraminated dialysis water (31, 77, 131). Monochloramine induces these effects through oxidation of haemoglobin and inhibition of the hexose mono-phosphate shunt which protect the red blood cells from oxidant damage through generation of reduced nicotinamide adenine dinucleotide phosphate (31, 77). However, these effects were reported following a specific route of exposure (dialysis) and are not considered relevant for workplace exposure.

Piva *et al*. investigated the effect of monochloramine on the glutamine and glucose transport systems in HeLa cells (human cervical cancer cell line) and rat mesenteric lymphocytes. Slight inhibition of both glutamine and glucose transport systems was initially observed in both the HeLa cells and lymphocytes. When the HeLa cells were pre-exposed to monochloramine, its inhibitory action increased. Similar results were obtained in the lymphocytes, suggesting that the effects of monochloramine are not cell specific. Only the sodium ion-independent (system L) component of the glutamine transport activity in HeLa cells was inhibited by monochloramine, and neither inhibition of cell metabolism nor enhanced cell lysis was observed suggesting that monochloramine inhibits cellular transport activity by binding to thiols (sulphhydryl groups) on the membrane (103).

9.2 Dichloramine

No data were located.

9.3 Trichloramine

Besides the established irritant potency of trichloramine, it has been hypothesised that exposure to chlorination products in indoor pools may promote the development of asthma in children and swimmers (11). A basic mechanism underlying the associations could be a repeated or chronic disruption of the lung epithelial barrier facilitating the penetration of allergens in the lung, and resulting in a loss of pneumoproteins (Chapter 8). In contrast to mono- and dichloramine, trichloramine is almost completely immiscible with water and cannot easily penetrate the ciliated surface and epithelial lining fluid of airways. Thus, trichloramine may exert its toxic action in the deep lung where the cells are non-ciliated and the tight junctions more accessible. This hypothesis is supported by the observation that allergic sensitisation is facilitated in the case of allergens having proteolytic activity, a characteristic which allows them to degrade extracellular matrix proteins and cross the airway epithelium more readily (11). The low water solubility of trichloramine also explains why it mainly increases the serum levels of pneumoproteins associated with the deep lung (SP-A, SP-B, SP-D), and much less that of CC16 predominantly produced in the terminal bronchioles (12).

10. Effects in animals and in vitro studies

Important studies are summarised in Tables 4–6.

10.1 Irritation and sensitisation

10.1.1 Monochloramine

Clear conjunctival irritation was observed when the eyes of rabbits (5–6 animals/group) were constantly wetted with a monochloramine solution corresponding to 4 mg/l of Cl_2 for 1 hour, whereas a 2-mg/l solution did not produce eye irritation. Monochloramine was considerably more irritating than free chlorine (33). Female SENCAR mice submerged (except head) in monochloramine solutions in concentrations up to 1 000 mg/l for 10 min for 4 consecutive days did not display epidermal hyperplasia like mice exposed to e.g. hypochlorous acid did (110).

10.1.2 Dichloramine

No data were located.

10.1.3 Trichloramine

Bradypnoea (slow breathing), indicative of upper airway irritation in mice, was evaluated during a 60-min oronasal exposure to increasing concentrations of chlorine (5.1–44 mg/m^3) or trichloramine (4.5–25 mg/m^3). The airborne concentration causing a 50% decrease in respiratory frequency (RD_{50}) in mice was calculated for each chemical. Chlorine and trichloramine showed different time-courses in their responses. While the maximal response of trichloramine was

reached in 10 min, the maximal response of chlorine was reached after 45–60 min of exposure. The RD_{50} values of chlorine and trichloramine were 17.5 and 12.5 mg/m^3, respectively. The authors concluded that trichloramine appeared to be a strong sensory irritant (43).

10.2 Effects of single exposure

10.2.1 Monochloramine

No inhalation data were found.

Male Sprague Dawley rats (4/group) were given a single dose of 3 ml of water with a monochloramine concentration of 0, 10, 20 or 40 mg/l by gavage (corresponding to ~ 0.19, 0.38 and 0.75 mg/kg bw). Blood was sampled 15, 30, 60 and 120 min after the administration for analysis of glutathione (GSH) and osmotic fragility. The GSH level was significantly increased 15 min after administration of 20 or 40 mg/l and after 30 and 60 min in all dose groups. After 2 hours, the GSH level returned to normal. The authors suggested that the increase of GSH is explained by an increase in the activity of glutathione reductase to compensate for the oxidative stress of monochloramine during the first hour after exposure. Osmotic fragility was without any change in all dose groups (2).

10.2.2 Dichloramine

No data were located.

10.2.3 Trichloramine

Sprague Dawley rats (5/sex/group) were exposed to clean air or average air concentrations of 290, 560, 570, 620 or 785 mg/m^3 of trichloramine in a glass exposure chamber during 1 hour. Of the animals exposed to 785 mg/m^3, 8 out of 10 died during the exposure and the remaining 2 within 23 min after termination of exposure. In the groups exposed to 560–620 mg/m^3, the mortality rate was 40–80%. All animals survived exposure at 290 mg/m^3. During the 4-hour post-exposure period, laboured breathing and yellowish stains of the anogenital region were frequently noted. Additional observations were grasping, rapid breathing, mucoid or red nasal discharge, excessive salivation and lacrimation, shedding of red tears, reduced activity and convulsive movements. The surviving animals were observed during 14 days after exposure, and dry rales, red or mucoid nasal discharge, rapid or laboured breathing and soft stool were noted. All animals that died exhibited red mottling of the lung and clear fluid in the trachea or the lungs. Many showed distension of the gastrointestinal tract at and below the level of the stomach. According to the authors the respiratory tract appears to be a primary site of damage in rats exposed to trichloramine. All animals that died showed pulmonary oedema. The lethal concentration for 50% of the exposed animals at single inhalation exposure (LC_{50}) was estimated to be 560 mg/m^3, 95% confidence interval (CI) 535–585 mg/m^3 (7).

In an experiment performed by Carbonelle *et al*., 2-month-old female C57Bl/6 mice were exposed to trichloramine in an inhalation exposure chamber. In a first

experiment, groups of 9 mice were exposed to clean air or to 11.9 mg/m^3 of trichloramine during 1, 2, 4 or 8 hours and sacrificed immediately after exposure. Blood was collected by cardiac puncture and bronchoalveolar lavage (BAL) was performed. Latex immunoassay techniques were used to determine albumin levels in BAL fluid (BALF) and CC16 levels in both serum and BALF. Total protein and lactate dehydrogenase (LDH) levels were determined in BALF. Serum CC16 levels increased significantly during exposure, peaking after 4 hours at levels on average 2.5 times the pre-exposure level. CC16 levels in BALF decreased with a maximal reduction of about 80% after 8 hours of exposure. Statistically significant elevations of both albumin and total protein levels in BALF after 8 hours were observed. According to the authors, the lung epithelium hyperpermeability caused by trichloramine was not associated with cell cytotoxicity, since the LDH levels in BALF remained normal throughout the experiment. No evidence of lung toxicity was seen at light microscopy. In a parallel experiment, groups of 10 mice were exposed for 4 hours either to filtered air or to 0.53, 0.8, 3.45 and 13.1 mg/m^3 of trichloramine. The observations in the previous experiment were reproduced when mice were exposed to 13.1 mg/m^3 but were not found at 0.53–3.45 mg/m^3 (21).

To determine the *in vitro* toxicity of trichloramine, human alveolar cancer cells (A-549) were exposed to 0.1–40 mg/m^3 of the substance by passing test atmospheres over the cells in a continuous-flow-module during 1 hour. Nitrogen dioxide and synthetic or clean air were used as positive and negative control, respectively. Cell viability and inflammatory response manifested as interleukin (IL)-6 or IL-8 release were investigated 2, 24 and 48 hours post-exposure. A decreasing cell viability with increasing trichloramine concentration was observed. Increased IL-8 and IL-6 levels were demonstrated >10 mg/m^3 and at 20–30 mg/m^3, respectively. Exposure >30 mg/m^3 inhibited the release of both IL-6 and IL-8 due to cytotoxicity. Corresponding investigations with indoor swimming pool air showed similar inflammatory effects in the lung cells at doses <0.2 mg/m^3 trichloramine. The authors concluded that there are additional substances present in the indoor pool air that contribute to the inflammatory response (116).

10.3 Effects of short-term exposure (up to 90 days)

10.3.1 Monochloramine

No inhalation data were found.

Adult African Green monkeys (5 males and 7 females) were administered drinking water containing 100 mg/l of monochloramine daily during 6 weeks giving a total dose of 10 mg/kg bw/day. Blood samples were analysed for different haematological and clinicochemical parameters (red cell count, cell indices, reticulocytes, methaemoglobin and haemoglobin, white cell and differential counts, red cell GSH content, creatinine and blood urea nitrogen (BUN), total bilirubin, total protein, albumin, alkaline phosphatase, LDH and aspartate and alanine aminotransferases) and serum thyroxine (T4). No effects were seen in any of these parameters or on body weight. Each animal served as its own control (8).

Monochloramine was given in drinking water at 2.5–200 mg/l (~ 0.44–35 mg/kg bw/day) to A/J mice (12 males/group) for 30 days. With the exception of body weight loss and increased haematocrit at doses ≥ 50 mg/l, all indicators of prehaemolytic or haemolytic stress (i.e. 10 haematological parameters including osmotic fragility and GSH levels) failed to show any significant exposure-related changes. In the case of haematocrit, which indicates anaemia if it is lowered, values actually increased (89).

Body weight gain and haematological parameters in rats exposed 45 days to drinking water containing 10, 50 or 100 mg/ml (~ 1.2, 6.0, 12 mg/kg bw/day) of monochloramine did not differ from those in control animals. The only significant finding was a decrease in methaemoglobin in blood, the opposite of what was expected (19).

Young male Sprague Dawley rats (12/group) were daily given drinking water containing 0, 9, 19 or 38 mg/l (~ 0.8, 1.7, 3.4 mg/kg bw/day) of monochloramine *ad libitum* during 9 weeks. The water consumption and estimated daily doses were not given. Parameters of immunity measured were spleen and thymus weights, antibody production, delayed-type hypersensitivity reactions, natural killer cell cytotoxicity, oxidative metabolism response and phagocytosis by macrophages, and production of two immunoregulatory cytokines (IL-2 and prostaglandin E_2). Rats had reduced relative spleen weight (38 mg/l), decreased serum immuno-globulin G (IgG) antibody production (9 and 19 mg/l) and augmented prostaglandin E_2 production by adherent resident peritoneal cells (19 and 38 mg/l). The authors concluded that monochloramine is not a particularly strong immunodepressant as the effects were observed at relatively high doses (35).

Immunotoxic effects were examined in groups of 8 female B6C3F1 mice administered monochloramine via drinking water at 2–200 mg/l (~ 0.38–38 mg/kg bw/day) for 28 days. No significant differences in drinking water consumption, body weight, body weight gain, organ weights or haematological parameters were noted and some minimal immunological effects (mixed-leukocyte response and activity of natural killer cells) were judged to be biologically insignificant (50).

Miller *et al*. studied drinking water collected at a pilot-scale drinking water plant using monochloramine for disinfection. The residual monochloramine level was 2.1 mg/l. The samples were concentrated by reverse osmosis (100 and 400 times) before administered to CD-1 mice (10/sex) as drinking water for 30 days. There were some significant differences in relative organ weights but no consistent pattern was observed (87).

10.3.2 Dichloramine and trichloramine

No data were found.

10.4 Genotoxicity

10.4.1 Monochloramine

10.4.1.1 In vitro studies

Monochloramine mutagenesis was tested using different strains of *Bacillus subtilis*. Prepared early stationary phase cells were diluted 10 times into monochloramine solutions (0, 18, 37, 56, 74 and 92 µM) and treated for 30 min at 37 °C. The reaction was stopped by adding one volume of 0.02 M sodium thiosulphate. Viable cell counts were scored by averaging the colonies at two plates (amino acid media) after incubation at 37 °C for 2 days. The minimum number of colonies per plate was 161 ± 8%. The authors concluded that monochloramine is a weak mutagen in the *trpC* locus, when reversion of *trpC* to trp^+ in *B. subtilis* is used as an assay (121).

Thomas *et al.* tested the mutagenic activity of monochloramine in *Salmonella typhimurium* TA100. Bacteria was incubated with 40 µM monochloramine for 1 hour at 37 °C. Duplicate samples were added to top-agar with histidine and biotin. Negative control (no mutagen) values were 140 ± 40 colonies and positive control values with sodium azide was 2 800 ± 700 colonies. Monochloramine showed a low or no mutagenic activity. The authors concluded that monochloramine is highly reactive thus unlikely to penetrate deeply into body tissues when in contact with skin and mucous membranes (130).

A study was designed to examine whether monochloramine could damage the DNA of gastric cells. Rabbit gastric mucosal cells (RGMC) or human gastric carcinoma cells (KATO III) were cultured and suspended. Cell suspensions were exposed to 0.1 mM hypochlorite, ammonia or monochloramine for 15 min, respectively. Monochloramine significantly induced DNA double strand breaks as well as chromatin condensation evoked by DNA fragmentation in the RGMC and KATO III cells ($P < 0.05$). Ammonia or hypochlorite had no such effects on these cell types. Monochloramine, but not ammonia or hypochlorite enhanced the levels of DNA injury, suggesting the possible involvement in the carcinogenesis of the gastric mucosa (125).

Shibata *et al*. treated plasmid pUC18 DNA with 3 mM monochloramine, which induced double strand DNA breaks (120).

10.4.1.2 In vivo studies

Meier *et al.* performed a series of assays evaluating the induction of chromosomal aberrations (4/sex/group) and micronuclei (5/sex/group) in the bone marrow of Swiss CD-1 mice. The animals were dosed with 1 ml of a test solution containing 0, 40, 100 or 200 mg/l (1.6, 4 or 8 mg/kg bw) of monochloramine by oral gavage for 5 consecutive days and were sacrificed after the final exposure. An acute exposure test administration was also done for the bone marrow aberration test by giving the animals 1 ml of each test solution. The animals were killed 6, 24 and 48 hours after dosing. The authors concluded that there was no evidence of any effect caused by exposure to monochloramine in any of the test performed (86).

Monochloramine was also negative in the sperm-head abnormality assay (described further in Section 10.6.1).

Gauthier and coworkers evaluated the clastogenicity of water treated with sodium hypochlorite or monochloramine (0.05, 0.1 or 0.15 µg/ml) using a micronucleus test in newt larvae (*Pleurodeles waltl*) reared for 12 days. Frequencies of micronucleated red blood cells were evaluated per 1 000 cells. The level of micronuclei increased with increasing concentration of monochloramine. Only the 0.15-µg/ml concentration gave a statistically significant response. The authors concluded that monochloramine is responsible for the clastogenic effect in newt larvae (45).

10.4.1.3 Conclusion on monochloramine

Monochloramine was a weak mutagen in *B. subtilis* and *S. typhimurium*, and induced double-strand breaks in plasmid DNA, as well as DNA fragmentation, double strand DNA breakage and chromatin condensation in gastric mucosa cells. Monochloramine did not induce chromosomal aberrations, micronuclei or sperm abnormality in mice but induced micronuclei in newt larvae. Thus, limited data indicate that monochloramine is weakly mutagenic *in vitro* but not genotoxic *in vivo*.

10.4.2 Dichloramine and trichloramine

No data were located.

10.4.3 Drinking water and swimming pool water

More than 600 disinfection by-products have been identified in drinking water, many of which are genotoxic and carcinogenic (e.g. several trihalomethanes and haloacetic acids). A large number of studies have examined the mutagenicity of drinking water extracts or concentrates disinfected by chlorination. The few studies available on drinking water prepared by alternative disinfection methods (including chloramination) all showed that such drinking water was considerably less mutagenic than chlorinated drinking water. Although the chloramination reduce the formation of trihalomethanes and haloacetic acids, it may cause increased levels of other disinfection by-products, e.g. nitrosamines, several of which are carcinogenic (109).

Swimming pools constitute environments with high levels of disinfectant by-products in water and air due to continuous disinfection and constant organic load from bathers. Only a few studies have investigated the mutagenicity of swimming pool water (108). In a recent comprehensive study, water and air samples were collected from a public chlorinated swimming pool and the concentrations of free chlorine, inorganic chloramines and trihalomethanes were determined. Monochloramine and dichloramine, but not trichloramine, could be detected in the pool water. However, a mean air level of 0.29 mg/m^3 indicated that trichloramine had evaporated from the pool water. In addition, approximately one hundred other disinfection by-products were identified in the pool water. Two water samples extracted using a XAD resin process were subjected to a standard plate incorporation Ames *Salmonella* mutagenicity assay (without metabolic activation) in

the base-substitution strain TA100 or in the strain RSJ100, which expresses the rat glutathione *S*-transferase theta 1 (*GSTT1*) gene, and its control strain TPT100. Extracts were tested up to 100 µl/plate over a dose range of 0.01–0.3 litre-equivalents (L-eq) based on doses used for mutagenicity tests for drinking water. One sample was mutagenic in TA100, whereas the other sample showed cytotoxicity based on a reduction of revertants/plate in TA100 at the highest doses. It was suggested that the 30% higher concentration of chloroform in the latter sample may have masked the mutagenic activity due to cytotoxicity. The limited data indicated that the dose range over which the pool waters were mutagenic was approximately 0.1–0.3 L-eq/plate. In comparison, the typical dose range for drinking water mutagenicity is 0.3–1.5 L-eq/plate (108).

The large number of identified disinfection by-products demonstrate the chemical complexity of the chlorinated/chloraminated water and the difficulty to identify individual mutagenic substances in the water.

10.5 Effects of long-term exposure and carcinogenicity

No inhalation studies were located.

10.5.1 Monochloramine

Male Sprague Dawley rats (4/group) were exposed via drinking water containing 0, 1, 10 or 100 mg/l (~ 0.05, 0.5, 5.2 mg/kg bw/day) of monochloramine daily for 12 months. Blood samples were collected for analysis of blood GSH and osmotic fragility every 2nd month and for haematological parameters every month. [^{3}H]Thymidine incorporation (a measure of cell proliferation) into the nuclei of the liver, kidney, testes, small-intestinal mucosa and spleen was determined after 3 months only. The GSH content in blood was significantly decreased at some time-points during exposure in all dose groups, which according to the authors could be related to the oxidative stress of monochloramine and the protective role of GSH against damage caused by oxidants. Increased osmotic fragility was observed in the 10- and 100-mg/l groups, and significantly at a few time-points during exposure. Significant changes in a few haematological parameters were observed at 10- and 100 mg/l at 3 and 10 months, but were not observed at any other time-points. Monochloramine administered for 3 months increased [^{3}H]thymidine incorporation in the kidney, spleen, liver and testes in all dose groups, but without a clear dose-response pattern. The authors concluded that this indicates that exposure to monochloramine increases the DNA synthesis in these organs. The body weight decrease in the 100-mg/l group at 3 months persisted throughout the dosing period (2).

In a subchronic study, monochloramine was administered in drinking water at concentrations of 0, 25, 50, 100 and 200 mg/l for 90 days to groups of Sprague Dawley rats (10/sex). Reductions in final body weight (at 200 mg/l both sexes) and body weight gain ($\geq$ 50 mg/l in males; 200 mg/l in females) along with a dose-related decrease in water consumption (in both sexes at all concentrations) were noted. At 200 mg/ml, reduction in organ weights (absolute, relative or both) was

observed in both males and females, liver and spleen weights decreased in both sexes. In addition, decreased liver and lung weights were noted in males at 100 and 50 mg/ml, respectively. Subsequent histopathological examination did not reveal any exposure-related changes. A few alterations in parameters of haematology and clinical chemistry were noted but were considered not biologically significant, not dosage-related, or within the normal range for rats of this age and strain. The 100-mg/ml concentration (5.8–7.7 mg/kg bw/day) was considered to be a no observed adverse effect level (NOAEL) (28).

In a similar study by the same team, B6C3F1 mice (10/sex/group) were given 0, 12.5, 25, 50, 100 and 200 mg/l of monochloramine in drinking water for 90 days. Final body weight was significantly decreased at doses ≥ 100 mg/l in both sexes and body weight gain at doses ≥ 50 mg/l in males and ≥ 100 mg/l in females. In parallel, dose-related decreases in water and food consumption were observed in both sexes. A variety of changes in parameters of haematology and clinical chemistry were noted with no consistent exposure-related pattern. Numerous significant reductions in absolute and/or relative organ weights were evident at doses ≥ 100 mg/l but no exposure-related histopathology was observed. Decreased liver, heart and lung weights (males) and liver, heart and spleen weights (females) were seen at 100 mg/l, along with decreased body weight gain, reduced water and food consumption. The 50 mg/l concentration (8.6–9.2 mg/kg bw/day) was considered to be the NOAEL (29).

Sprague Dawley rats (10 males) were exposed to 200 mg/l (21.6 mg/kg/day) of monochloramine in drinking water for 13 weeks to resolve whether such exposure could cause reduced body weight gain and other changes observed in earlier studies. Two control groups were included; one group was given water *ad libitum* and the other was given the same volume of water as that consumed by the exposed animals. The authors concluded that reduced body weight gain and the minor biochemical, haematological, immunological and histopathological changes in exposed rats were largely related to reduced water and food consumption and not a direct effect of monochloramine (104).

In a carcinogenicity study by the National Toxicology Program (NTP), drinking water containing 0, 50, 100 or 200 mg/l of monochloramine was provided to male and female F344/N rats or B6C3F1 mice (70 animals in each group) daily for up to 2 years. Doses were calculated to be 0, 5.0, 8.9 and 15.9 mg/kg bw/day for male mice and 0, 4.8, 9.0 and 17.2 mg/kg bw/day for female mice. The corresponding figures for male rats were 0, 2.1, 4.8 and 8.7 mg/kg bw/day and 0, 2.8, 5.3 and 9.5 mg/kg bw/day for female rats. The animals were evaluated at 14, 66 or 155 weeks. Mean body weights of high-dosed rats and dosed mice were lower than those of their respective controls. Decreases in absolute and/or relative organ weights were observed in the high-dose groups of rats and mice at some time-points. There was a dose-related decrease in water consumption in both species. Mononuclear cell leukaemia occurred with marginally increased incidence in the mid- and high-dose female rats receiving chloraminated water (control 8/50, low dose 11/50, mid-dose 15/50 and high dose 16/50). The marginal increase in leukaemia incidence in female

rats was considered equivocal evidence of carcinogenic activity. There were no neoplasms or non-neoplastic lesions in male rats or in male and female mice that were associated with the consumption of chloraminated water (99).

In a study carried out by Herren-Freund *et al*., 9 male rats (strain not given) were administered 14.75 mg/kg bw of monochloramine 24 hours after 2/3 partial hepatectomy. Seven days after the initiation, promotion by 500 mg/l of phenobarbital in the drinking water was begun. After 10 weeks, the exposure to the promoter was ceased and 1 week later the rats were killed. Samples of the liver tissue were stained for the incidence of γ-glutamyltranspeptidase-positive foci (GGT foci) as an indicator of carcinogenicity. Diethylnitrosamine (DENA) was used as a positive initiator control. Exposure to monochloramine did not initiate GGT foci and the authors concluded that monochloramine is not capable of initiating carcinogenesis (62).

In a rat liver foci study, the carcinogenic activity of drinking water treated with monochloramine and concentrated up to 4 000 times by the XAD resin procedure was evaluated. Around 10 rats per group were used for the test samples, vehicle control (2% Emulphor) and positive control (50 mg/kg bw of DENA). All rats were hepatectomised on day 0 and dosed orally 24 hours later with the test solutions or the control solutions. A week later, the rats including controls received 500 mg/l of sodium phenobarbital in drinking water for 56 days. Liver samples were tested for histochemical detection and quantification of GGT foci. No statistical significant differences between monochloramine exposed rats and vehicle control animals were detected. The authors concluded that there was no effect on the rat liver assay following exposure to monochloramine (87).

10.5.2 Dichloramine

Male and female Sprague Dawley rats were each randomly divided into 6 groups each containing 10 animals. The dichloramine solution was prepared in 0.1 M acetate buffer and 2 control groups were used (reagent-grade water and 0.1 M acetate buffer). The rats were exposed to dichloramine in drinking water for 13 weeks at doses of 0.025, 0.26, 2.5 or 24 mg/kg bw/day for females and 0.019, 0.19, 1.9 or 18 mg/kg bw/day for males. No significant changes were detected in xenobiotic metabolising enzyme activities or in haematological and biochemical parameters. Dichloramine induced minimal to mild adaptive histopathological changes in thyroid and kidneys in both sexes (no statistical analysis for individual dose levels). Dichloramine was associated with minimal histological changes in the gastric cardia (epithelial hyperplasia) at concentrations ≥ 0.19 mg/kg bw/day in males and ≥ 2.5 mg/kg bw/day in females. Body weight gains were not significantly different from controls (92).

No carcinogenicity studies were located.

10.5.3 Trichloramine

In an experiment parallel to the one described above for dichloramine, Sprague Dawley rats were exposed to trichloramine in drinking water for 13 weeks at doses

of 0.020, 0.23, 1.1 or 9.6 mg/kg bw/day for males and 0.028, 0.29, 1.3 or 13 mg/kg bw/day for females. The trichloramine solution was prepared in 0.1 M phosphate buffer and contained an average of 20 mg/l residual free chlorine, therefore the following control groups were used: reagent-grade water and 0.1 M phosphate buffer containing 19 mg/l chlorine. Increases in hepatic glutathione *S*-transferase and uridine diphosphate glucuronosyltransferase activities were detected in females receiving 13 mg/kg bw/day. No significant changes were detected in other xenobiotic metabolising enzyme activities or haematological and biochemical parameters. Trichloramine induced minimal to mild adaptive histopathological changes in thyroid and kidneys in both sexes. Relative kidney weights were increased in both sexes at the highest dose. Males in the high-dose group had minimal changes in kidneys consisting of glomerular adhesions and protein casts in the tubules of the inner cortex. Females in all dose groups displayed minimal tubular mineralisation in the outer cortex of the kidneys but with no clear dose-response over the range examined. The authors concluded that trichloramine produced mild histological effects at doses > 0.23 mg/kg bw/day in males and > 0.29 mg/kg bw/day in females (92). It is unclear how these effect levels were derived from the results presented in the paper.

No carcinogenicity studies were found.

10.6 Reproductive and developmental effects

10.6.1 Monochloramine

No inhalation data were found.

Reproductive effects were studied in female (24/group) and male (12/group) Long-Evans rats administered 0, 2.5, 5.0 or 10.0 mg/kg bw of monochloramine by oral gavage. Males were dosed 56 days prior to breeding and throughout the 10-day breeding period. Following breeding, the males were necropsied and evaluated for sperm parameters and reproductive tract histopathology. Females were dosed 14 days prior to breeding and throughout the 10-day breeding period, during gestation and lactation until the pups were weaned at day 21 after birth. Adult females and some pups were necropsied at weaning on postnatal day 21. Other pups were dosed post-weaning until 28 or 40 days of age. These pups were evaluated for the day of vaginal patency and thyroid hormone levels. No differences were observed between control rats and rats exposed up to 10 mg/kg/day of monochloramine when fertility, viability, litter size, day of eye opening or day of vaginal patency were evaluated. No alterations in sperm count, sperm direct progressive movement, percent motility or sperm morphology were observed among adult males. In addition, male and female reproductive organ weights were comparable to their respective control groups, and no significant histopathological changes were observed in the reproductive tract of exposed males and females (23).

Meier *et al.* administered B6C3F1 mice (10 males/group) 1.6, 4 or 8 mg/kg bw of monochloramine by oral gavage for 5 consecutive days and evaluated sperm-

head abnormality at 1, 3 and 5 weeks after the last dose. Monochloramine was judged to be negative in the assay (86).

In a developmental study, mature virgin Sprague Dawley rats (6 females/group) were given 0, 1, 10 or 100 mg/l (~ 0.09, 0.9, 9.3 mg/kg bw/day) of monochloramine in drinking water *ad libitum* daily for 2.5 months prior to and throughout gestation. On day 20 of gestation, the rats were killed and the foetuses (34 controls, 26–28 exposed) were examined. Monochloramine did not produce any significant changes regarding foetal weight, type of skeletal anomaly, skeletal or soft-tissue defects at any dose level. The authors concluded that monochloramine in drinking water at the concentration noted is relatively harmless when fed to pregnant rats (1).

To conclude, limited data indicate that monochloramine does not induce reproductive or developmental effects.

10.6.2 Dichloramine and trichloramine

No data were located.

Table 4. Effects in animals after exposure to monochloramine.

Exposure level	Exposure route and duration	Species, no. and sex	Effect	Reference
Single/short-term studies				
3 ml of 0, 10, 20, 40 mg/l (0.19, 0.38, 0.75 mg/kw bw) [a]	Oral gavage, single dose	Rat, Sprague Dawley 4 males/group	Increased blood GSH level after 15 min at 20 or 40 mg/l and after 30 and 60 min in all dose groups. The GSH levels had returned to normal after 2 h. No effect on blood osmotic fragility.	(2)
10 mg/kg bw/day	Oral (drinking water), 6 wk	Monkey, African green 5 males, 7 females	No effect on haematological and clinicochemical parameters in blood, serum thyroxine (T4) levels or body weight.	(8)
0, 2.5, 25, 50, 100, 200 mg/l (0.44, 4.4, 8.7, 17, 35 mg/kg bw/day) [b]	Oral (drinking water), 30 d	Mouse, A/J 12 males/group	Body weight loss and slightly increased haematocrit at doses ≥50 mg/l whereas other haematological parameters (including osmotic fragility and GSH) were unaffected.	(89)
0, 10, 50, 100 mg/ml (1.2, 6.0, 12 mg/kg bw/day) [b]	Oral (drinking water), 45 d	Rat (strain, no. and sex not given)	No effect on body weight gain. The only significant haematological finding was a decrease in methaemoglobin in blood at 100 mg/l, the opposite of what was expected.	(19)
0, 9, 19, 38 mg/l (0.8, 1.7, 3.4 mg/kg bw/day) [b]	Oral (drinking water), 9 wk	Rat, Sprague Dawley 12 males/group	Altered immune function: decreased serum IgG antibody production at 9 and 19 mg/l, increased prostaglandin E_2 production at 19 and 38 mg/l, and reduced relative spleen weight at 38 mg/l. No effects on other parameters of immunity.	(35)
0, 2, 10, 20, 100, 200 mg/l (0.38, 1.9, 3.8, 19, 38 mg/kg bw/day) [b]	Oral (drinking water), 28 d	Mouse, B6C3F1 8 females/group	No significant differences in water consumption, body weight, body weight gain, organ weights, haematological parameters but some minimal immunological effects that were judged to be biologically insignificant.	(50)

Table 4. Effects in animals after exposure to monochloramine.

Exposure level	Exposure route and duration	Species, no. and sex	Effect	Reference
Long-term and carcinogenicity studies				
0, 1, 10, 100 mg/l (0.05, 0.5, 5.2 mg/kg bw/day) [b]	Oral (drinking water), up to 12 mo	Rat, Sprague Dawley 4 males/group	GSH content in blood significantly decreased at some time-points in all dose groups. Increased osmotic fragility in the 10- and 100-mg/l groups, significantly at a few time-points. Significant changes in a few haematological parameters at 10- and 100 mg/l at 3 and 10 mo, but not at any other time-points. Increased [^{3}H]thymidine incorporation in the kidney, spleen, liver and testes in all dose groups after 3 mo, but without a clear dose-response pattern. Decreased body weight in the 100-mg/l group at 3–12 mo.	(2)
0, 2.1, 4.8, 8.7 mg/kg bw/day (males) 0, 2.8, 5.3, 9.5 mg/kg bw/day (females)	Oral (drinking water), 2 y	Rat, F344/N 70/sex/group	No carcinogenic effect in males. A marginal increase in mononuclear cell leukaemia incidence in females was considered equivocal evidence of carcinogenic activity (control 8/50, low 11/50, mid 15/50 and high dose 16/50). Decreased mean body weights in exposed. Decreases in absolute and/or relative organ weights in the high-dose groups at some time-points. Dose-related decrease in water consumption.	(99)
0, 5.0, 8.9, 15.9 mg/kg bw/day (males) 0, 4.8, 9.0, 17.2 mg/kg bw/day (females)	Oral (drinking water), 2 y	Mouse, B6C3F1 70/sex/group	No carcinogenic effect. Decreased mean body weights in the high-dose groups. Decreases in absolute and/or relative organ weights in the high-dose groups at some time-points. Dose-related decrease in water consumption.	(99)

Table 4. Effects in animals after exposure to monochloramine.

Exposure level	Exposure route and duration	Species, no. and sex	Effect	Reference
0, 25, 50, 100, 200 mg/l (1.8, 3.4, 5.8, 9.0 mg/kg bw/day, males) (2.6, 4.3, 7.7, 12.1 mg/kg bw/day, females)	Oral (drinking water), 90 d	Rat, Crl:CDBR Sprague Dawley 10/sex/group	Reduced final body weights at 200 mg/ml in both sexes and in body weight gain at doses ≥ 50 mg/ml in males and at 200 mg/ml in females. Dose-related decrease in water consumption in both sexes. Some organ weights (absolute, relative or both) were decreased in males at doses ≥ 50 mg/ml and in females at 200 mg/l, but subsequent histopathological examination did not reveal any exposure-related changes. Alterations in parameters of haematology and clinical chemistry were considered not biologically significant, not dose-related or within the normal range for rats of this age and strain. The 100-mg/l concentration was considered a NOAEL.	(28)
0, 12.5, 25, 50, 100, 200 mg/l (2.5, 5.0, 8.6, 11.1, 15.6 mg/kg bw/day, males) (2.8, 4.3, 5.3, 9.2, 12.9, 15.8 mg/kg bw/day, females)	Oral (drinking water), 90 d	Mouse, B6C3F1 10/sex/group	Reduced body weight at doses ≥ 100 mg/l in both sexes and body weight gain at ≥ 50 mg/l in males and at ≥ 100 mg/l in females. Dose-related decreases in water and food consumption in both sexes. Reductions in absolute and/or relative organ weights at doses ≥ 100 mg/l but no exposure-related histopathology. A variety of changes in parameters of haematology and clinical chemistry were noted with no consistent exposure-related pattern. The 50-mg/l concentration was considered to be a NOAEL.	(29)
0, 0, 200 mg/l (21.6 mg/kg bw/day) 2 control groups (see text)	Oral (drinking water), 13 wk	Rat, Sprague Dawley 10 males/group	Reduced body weight gain and minor biochemical, haematological, immunological and histopathological changes were largely related to reduced water and food consumption and not directly caused by monochloramine.	(104)

Table 4. Effects in animals after exposure to monochloramine.

Exposure level	Exposure route and duration	Species, no. and sex	Effect	Reference
14.75 mg/kg bw	Single dose (route not given)	Rat (strain not given) 9 males	Monochloramine did not initiate GGT foci and the authors concluded that monochloramine is not capable of initiating carcinogenesis.	(62)
Reproductive and developmental studies				
0, 1.6, 4, 8 mg/kg bw/day	Oral gavage, 5 consecutive d	Mouse, B6C3F1 10 males/group	No sperm-head abnormalities 1, 3 or 5 wk after the last dose at any exposure level.	(86)
0, 2.5, 5, 10 mg/kg bw/day	Oral gavage, Males: 56 d prior to breeding + 10 d breeding cycle (66 d). Females: 14 d prior to breeding until weaning d 21 (up to 73 d). Some pups dosed post-weaning until 28 or 40 d of age.	Rat, Long-Evans 12 males/group 24 females/group	No effect on sperm count, sperm movement or sperm morphology. No effect on fertility, viability, litter size, day of eye opening or day of vaginal patency or foetal weight. No histopathological changes on reproductive organs in either sex.	(23)
0, 1, 10, 100 mg/l (0.09, 0.9, 9.3 mg/kg bw/day) [b]	Oral (drinking water, *ad libitum*), 2.5 mo prior to and throughout gestation.	Rat, Virgin Sprague Dawley 6 females/group	No effects on foetuses (i.e. no skeletal or soft-tissue defects, no effects on foetal weight).	(1)

[a] Calculated by NEG assuming a body weight of 160 g (in the paper, the body weight is given as 150–170 g).
[b] Calculated by NEG according to the recommendations by the European Food Safety Authority (EFSA) (32).
GGT: γ-glutamyltranspeptidase, GSH: glutathione, IgG: immunoglobulin G, NOAEL: no observed adverse effect level.

Table 5. Effects in animals after exposure to dichloramine.

Exposure level	Exposure route and duration	Species, no. and sex	Effect	Reference
0, 0, 0.019, 0.19, 1.9, 18 mg/kg bw/day (males) 0, 0, 0.025, 0.26, 2.5, 24 mg/kg bw/day (females) (2 control groups, see text)	Oral (drinking water), 13 wk	Rat, Sprague Dawley 10/sex/group	Minimal histopathological changes in the gastric cardia (epithelial hyperplasia) at doses ≥0.19 mg/kg bw and ≥2.5 mg/kg bw in males and females, respectively, and minimal to mild adaptive changes in thyroid and kidneys in both sexes. No significant changes in xenobiotic metabolising enzyme activities, haematological and biochemical parameters or in body weight gains.	(92)

Table 6. Effects in animals after exposure to trichloramine.

Exposure level	Exposure route and duration	Species, no. and sex	Effect	Reference
Single/short-term studies				
4.5–25 mg/m^3	Inhalation, 1 h	Mouse, OF_1 8 males/group	RD_{50}: 12.5 mg/m^3.	(43)
0, 11.9 mg/m^3	Inhalation, 1–8 h	Mouse, C57BL/6 9 females/group	At 11.9 mg/m^3, lung epithelium hyperpermeability: in serum, CC16, levels increased during exposure, peaking after 4 h exposure. In BALF, decreased CC16 levels and increased albumin and total protein levels (all after 8 h exposure), but no effect on LDH levels.	(21)
0, 0.53, 0.8, 3.45, 13.1 mg/m^3	4 h	10 females/group	The results were reproduced at 13.1 mg/m^3 but were not observed at 0.53–3.45 mg/m^3.	
290–785 mg/m^3	Inhalation, 1 h	Rat, Sprague Dawley 5/sex/group	LC_{50}: 560 mg/m^3. Cause of death: oedema in the lungs.	(7)
Long-term studies				
0, 0, 0.020, 0.23, 1.1, 9.6 mg/kg bw/day (males) 0, 0, 0.028, 0.29, 1.3, 13 mg/kg bw/day (females) (2 control groups, see text)	Oral (drinking water), 13 wk	Rat, Sprague Dawley 10/sex/group	Minimal to mild adaptive changes in thyroid and kidneys in both sexes. Females in all dose groups displayed minimal tubular mineralisation in the outer cortex of the kidneys but with no clear dose-response. At 9.6 mg/kg bw, minimal changes in kidneys in males. Increased relative kidney weights in both sexes at 9.6 and 13 mg/kg bw. Increased hepatic GST and UDP-GT activities in females at 13 mg/kg bw. No significant changes in other xenobiotic metabolising enzyme activities or in haematological and biochemical parameters. The authors concluded that mild histological effects occurred at doses >0.23 mg/kg bw/day in males and >0.29 mg/kg bw/day in females. It is unclear how these effect levels were derived from the results presented.	(92)

BALF: bronchoalveolar lavage fluid, CC16: club cell protein 16 kDa, GST: glutathione *S*-transferase, GT: glucuronosyltransferase, LC_{50}: lethal concentration for 50% of the exposed animals at single inhalation exposure, LDH: lactate dehydrogenase, RD_{50}: concentration causing a 50% decrease in respiratory frequency, UDP: uridine diphosphate.

11. Observations in man

11.1 Irritation and sensitisation

Several studies have investigated eye and respiratory tract irritation among workers occupationally exposed to inorganic chloramines in indoor swimming pool facilities and in cleaning and disinfection in the food processing industry as well as among competitive and recreational swimmers, as described below and summarised in Table 7 (effects predominantly evaluated against measurements of trichloramine levels).

Data on irritation from accidental exposure and on asthma-related symptoms and effects are presented in Sections 11.2.1 and 11.3.1, respectively. No studies on dermal sensitisation were found.

11.1.1 Swimming pool workers

Chu *et al*. investigated the prevalence of work-related irritation in eyes and airways among pool workers in 10 indoor swimming pools in Taiwan of which 6 had spa pools located in the same buildings. The exposed group consisted of 61 lifeguards and swimming instructors (36 men, 25 women). The reference group consisted of 43 employees (15 men, 28 women) working at the same swimming facilities, but their exposure was considered negligible. Exposure classification on an individual basis was not performed. Airborne levels of trichloramine were determined using stationary sampling, performed from April through October 2010. The overall average concentration of trichloramine was 0.035 (0.017–0.15) mg/m^3 in swimming pools and 0.059 ± 0.042 (SD) mg/m^3 in spa pools. Corresponding soluble chlorine concentrations were 0.072 (0.005–0.21) mg/m^3 and 0.085 ± 0.056 mg/m^3. Questionnaires were given to the pool workers during the same time as the air samplings were performed and comprised questions about ocular and respiratory symptoms. Symptoms were considered work-related if present during or after a work shift. The prevalence of various symptoms was compared on a group level; in general, exposed workers reported more symptoms from eyes and airways than non-exposed subjects did. Exposed workers had significantly more [odds ratio (OR), 95% CI] throat irritation (11.3, 1.4–88] and phlegm (4.2, 1.2–15) than non-exposed subjects, but there were no significant differences for ocular and nose irritation (25).

Dang *et al.* investigated work-related symptoms via questionnaire among 143 exposed and unexposed pool workers at an indoor waterpark in the United States (US). Stationary measurements of airborne trichloramine were performed during two high-occupancy days and one low-occupancy day. The average concentration for the first high-occupancy day was 0.44 mg/m^3. Only 20% of all samples collected during the second high-occupancy day were quantifiable, but the highest concentration (1.06 mg/m^3) was found this day. Lifeguards (37 men, 32 women) reported significantly more work-related irritation [prevalence ratio (PR), 95% CI] in throat (12, 2.9–48), nose (3.5, 1.9–6.6) and eyes (9.0, 4.1–20) than unexposed employees working outside the pool area (24 men, 50 women). In addition, the lifeguards completed a daily symptom questionnaire during the high-occupancy

days (n = 43) and low-occupancy day (n = 27). Work-related symptoms were significantly more common during the high-occupancy days than the low-occupancy day (PR, 95% CI), such as eye irritation (2.0, 1.2–3.2) and cough (2.2, 1.1–4.5) (adjusted for smoking habits, subjects with asthma not included) (27).

The prevalence of ocular and respiratory symptoms was assessed via questionnaire in 128 pool workers in an Italian study. Lifeguards and swimming instructors (40 men, 41 women) comprised the exposed group and the other employees were considered non-exposed (21 men, 26 women). Measurements of airborne trichloramine using stationary sampling showed an average concentration of 0.65 mg/m^3. Exposed pool workers reported ocular and upper respiratory symptoms (sometimes or often) more frequently than the unexposed. Five levels of exposure to airborne trichloramine were defined: ≤ 0.5, > 0.5, > 0.6, > 0.7 and > 0.8 mg/m^3. A strong dose-response relationship between trichloramine air levels and self-reported irritation in eyes and upper airways was demonstrated. Pool workers exposed to airborne trichloramine levels > 0.5 mg/m^3 had significantly higher risk (OR, 95% CI) for experiencing runny nose (2.9, 1.2–6.9), voice loss (3.6, 1.6–7.9), red eyes (3.2, 1.5–6.8) and itchy eyes (2.2, 1.04–4.8) than non-exposed subjects (36).

Work-related respiratory symptoms were investigated via interview of 146 pool workers (58 men, 88 women) employed at 46 swimming pool facilities in Sweden. In total, 17% of the pool workers reported work-related respiratory symptoms; there were no significant gender differences. The prevalence was relatively high among workers employed 1–3 year (31%) and lower among those employed 4–7 years (6%), indicating a possible healthy worker effect (in this case a selection bias meaning that employees who experience health problems at work tend to quit, and that those who continue to work have better health). However, the prevalence of symptoms was 22% in those employed > 7 years. Most pool workers with airway symptoms (64%) came from 6/46 swimming pool facilities. Five indoor swimming pools with high prevalence of reported airway irritation and four swimming pools without reported airway irritation among the employees were selected for measurements of airborne trichloramine via stationary sampling. The average concentration of airborne trichloramine was 0.20 mg/m^3. The 39 pool workers were evaluated by questionnaire. No association between self-reported work-related airway symptoms and levels of airborne trichloramine was found. Protein profiling of nasal lavage fluid in 9 pool workers and 4 control subjects showed altered distribution of three innate immunity proteins (α-1-antitrypsin, lactoferrin and S100-A8) in pool workers, and more pronounced in subjects with airway irritation (42).

Héry *et al.* measured indoor airborne levels of trichloramine in 7 standard swimming pools and 5 recreational swimming pools in France using stationary sampling. The aim was to assess the exposure of swimming instructors who had complained of irritative symptoms during work. The sampling devices were placed at different spots that were chosen to be as representative as possible of the swimming instructors' exposure. Trichloramine concentrations as ranges of AMs were 0.15–0.39 mg/m^3 at the swimming pools and 0.23–1.25 mg/m^3 at the

recreational centres. Swimming instructors were requested to report at the onset of irritative symptoms during sampling. The onset of irritation in eyes and upper respiratory tract began at concentrations around 0.5 mg/m^3 and all questioned complained of irritation when the concentration reached 0.7 mg/m^3 (64). Information regarding number, age and gender of participating subjects, and how they were selected for the study was lacking.

A questionnaire was sent to 1 066 pool workers from 38 swimming pool facilities in the Netherlands. The response rate was 59% and thus questionnaires from 624 exposed and unexposed pool workers (240 men, 384 women) remained for analysis. Work-related and general respiratory symptoms as well as symptoms indicative of allergy were asked for. Measurements of airborne trichloramine were performed using stationary sampling in 6 different swimming facilities; the overall mean was 0.56 mg/m^3. Swimming instructors (n = 121) reported more work-related symptoms (OR, 95% CI), mainly from upper airways such as sinusitis (2.4, 1.2–4.9), chronic cold (3.4, 1.2–10.1), sore throat (2.4, 1.2–4.5), blocked nose (2.0, > 1.0–3.8) and sneezing (2.0, 1.1–3.6) than 282 reception, catering and management employees. ORs (95% CIs) for runny nose and irritation in eyes were 1.2 (0.8–2) and 1.5 (0.8–2.6), respectively. The 142 employees who combined the jobs of pool attendant and swimming instructor also reported more work-related symptoms in the upper airways (OR, 95% CI) such as chronic cold (3.5, 1.2–10), sore throat (3.2, 1.7–5.9), blocked nose (3.7, 1.9–7.3), runny nose (2.2, 1.3–3.5), sneezing (2.3, 1.2–4.4) and irritation in the eyes (3.0, 1.7–5.3). The OR for sinusitis was 2.3 (1.0–5.6). No association between estimated long-term levels of airborne trichloramine (AM 0.66 mg/m^3) and symptoms was found, but 1-week cumulative exposures (trichloramine levels of each pool multiplied by the quantity of working hours per week for each individual) were significantly associated with upper respiratory symptoms (73).

Löfstedt *et al*. investigated the prevalence of ocular and respiratory symptoms among 52 pool workers (16 men, 36 women) from 8 indoor swimming pool facilities in Sweden. The reference group consisted of 50 office workers (15 men, 35 women). The prevalence of ocular and respiratory symptoms during the last week, as well as during the last 3 months was assessed via questionnaire. The concentration of airborne trichloramine was measured by personal sampling, and the AM was 0.071 mg/m^3. Stationary sampling was performed in parallel to personal sampling and showed an AM of 0.18 mg/m^3 (138). Exposed workers reported more often itchy eyes (36% vs 14%), at least one ocular symptom (62% vs 37%) and blocked nose (55% vs 32%) than referents during the last week. After adjusting for smoking, asthma and sensitisation to inhaled allergens, exposed workers reported more often (OR, 95% CI) at least one ocular symptom such as itchy, smarting, dry, running and red eyes, gravel sensation or swollen eyelids (2.4, 1.0–5.7) and one nasal symptom such as blocked, dripping or itchy nose, and sneezing (2.3, 1.0–5.6) during the last week compared with the referents. The OR (95% CI) for respiratory (tracheobronchial) symptoms was 1.6 (0.7–3.9). Exposed workers reported more often ocular, nasal and/or respiratory symptoms during the

last 3 months than referents (data not shown in paper). No associations were shown between exposure levels and studied health effects (82).

Massin *et al*. assessed irritant eye and upper airway symptoms at work by questionnaire in 334 lifeguards (256 men, 78 women) recruited from 46 public swimming pools and 17 adventure swimming pools in France. There was no reference group. Stationary measurements showed that the average airborne concentrations of trichloramine were 0.24 mg/m^3 in the swimming pools and 0.67 mg/m^3 in the adventure swimming pools. The lifeguards were divided in four subgroups due to measured trichloramine concentrations in air: < 0.14, 0.14–0.22, 0.22–0.50 and > 0.50 mg/m^3. The prevalence rates of eye irritation in the groups were 50%, 56%, 63% and 86%, respectively. Corresponding numbers for nose irritation were 12%, 20%, 28% and 61%. For sore throat and dry cough, the rates were 16%, 15%, 27% and 29%, and 9%, 12%, 21% and 42%, respectively. These concentration-response relationships were all significant. In addition, a cumulative exposure index was calculated for each lifeguard by multiplying the average trichloramine level by the number of working years (mg/m^3-years). The lifeguards were divided in four subgroups: < 0.58, 0.58–1.6, 1.6–3.12 and > 3.12 mg/m^3-years. The prevalence rates of eye irritation in the groups were 51%, 67%, 64% and 75%, respectively. The corresponding numbers for nose irritation were 22%, 27%, 35% and 39%. For sore throat and dry cough, the rates were 15%, 24%, 23% and 25%, and 15%, 26%, 24% and 22%, respectively. Significant concentration-response relationships were found between cumulative exposure index and irritant eye and nose symptoms. No such relations were shown between cumulative exposure and sore throat and dry cough. ORs were not reported (84).

Parrat *et al.* investigated the occurrence of ocular and respiratory symptoms in 178 swimming pool workers (117 men, 61 women) in a Swiss study. Self-reported symptoms that had been present during and before the last 12 months, respectively, were collected by questionnaire. The reference group consisted of 71 office workers (38 men, 33 women). Stationary sampling was used to determine airborne trichloramine levels; the average concentration was 0.11 mg/m^3. Irritative symptoms (sum of symptoms that appeared before, and during the last 12 months, hereafter referred to as "ever") in eyes (53% vs 22%), throat (79% vs 7%), nose (38% vs 7%) and skin (61% vs 8%) due to the working conditions were significantly more common among pool workers than among referents. Pool workers exposed to airborne trichloramine levels > 0.29 mg/m^3 (AM 0.36 mg/m^3, range 0.30–0.52 mg/m^3) had significantly higher prevalences of irritation (OR, 95% CI) in eyes (5.6, 1.3–23.7) and nose (4.2, 1.4–13) during the last 12 months, and "ever" in nose (4.3, 1.5–13) than referents. No increased symptom prevalences were found in pool workers exposed to 0.1–0.29 (AM 0.15) mg/m^3. Employees were divided in five groups according to a 1-week cumulative exposure index (combining the ratio of professional activity, the time spent working in potentially trichloramine-contaminated areas and the measured trichloramine concentration). The group with highest exposure index had increased prevalences of eye and nose irritation, and the second highest index group had increased eye irritation (101).

Westerlund *et al.* investigated irritant symptoms among 23 pool workers (3 men, 20 women) from 10 habilitation and rehabilitation swimming pool facilities in Sweden. The reference group consisted of 50 office workers (15 men, 35 women). Concentrations of airborne trichloramine measured by personal and stationary sampling were 0.001–0.076 (AM 0.019) mg/m^3 and 0.001–0.140 (AM 0.023) mg/m^3, respectively. Data concerning ocular, nasal and respiratory symptoms during the last week, as well as during the last 3 and 12 months were collected via questionnaire. There was no significant difference in prevalences of irritation between exposed and referents at any time-point. The only significant finding was a higher prevalence of having at least 1 out of 6 ocular symptoms (itchy, smarting, dry, running and red eyes, and swollen eyelids) during the last week among those exposed to trichloramine above the median of 0.020 mg/m^3 than in those exposed below the median (relative risk 1.2, 95% CI 1.1–1.4) (adjustment for age and smoking) (137). The finding of eye irritation from exposure to trichloramine levels as low as 0.020–0.076 mg/m^3, seems unlikely, in view of the lack of significant differences between exposed and referents and the results from other studies (described above) suggesting effects only at higher levels.

Demange and coworkers investigated 39 French lifeguards (29 men, 10 women) and reported a high prevalence of work-related symptoms, such as irritation in eyes (72% in men, 70% in women), nose (52%, 50%) and throat (48%, 30%) (30). There was no reference group for comparison and no measurements of airborne trichloramine were performed.

The occurrence of allergic rhinitis was evaluated in 27 pool workers (13 men, 14 women) in Turkey by clinical examination, a skin prick test and a nasal smear. The prevalence of positive skin prick test was 30% compared to 18% in the reference group consisting of 49 office workers (22 men, 27 women); the difference was not statistically significant. Pool workers had significantly more eosinophils in nasal smear than non-exposed workers, indicating allergic inflammation, likely due to exposure to chlorine derivatives in the indoor air, according to the authors (34). No measurements of airborne trichloramine were performed.

A questionnaire was sent to 1 741 individuals who indicated in the Swedish Census of Population and Housing 1990 that they worked at indoor swimming pools. Ocular and respiratory symptoms related to work were asked for, as well as number of years hired as a pool worker and time spent in the pool area. The response rate was 63% and 1 102 respondents (513 men, 589 women) remained for analysis. Measurements of airborne trichloramine were not performed, but exposure was classified in 3 different categories based on the average time during a workday each participant spent in the pool area. Exposure category 0 consisted of those who did not spend any time in the pool area, category 1 occasionally spent some time and category 2 spent most of the workday in the pool area. Irritative symptoms were common among all pool workers, i.e. irritation in eyes (37%), nose (29%), throat (24%) and coughing (23%). A statistically significant association was found between the average number of hours per day spent in the pool environment and the

percentage of workers reporting acute work-related irritant symptoms ($P < 0.01$ logistic regression) (98).

11.1.2 Competitive and recreational swimmers

Gomà *et al*. evaluated health complaints in 320 recreational swimmers (63% men, mean age 36 years) and 53 competitive swimmers including 34 water polo swimmers (84% men, mean age 22 years) before and 8 weeks after introducing a new disinfection method (details in Table 3) in a swimming pool in Spain. Self-reported symptoms related to swimming, such as irritation of the eyes, respiratory tract and skin, were collected by questionnaire. Symptoms were graded from 1 (no symptoms) to 4 (severe). In addition, leukotriene B4 (LTB4) and cysteinyl leukotrienes (CysLTs) (surrogate markers of neutrophilic and eosinophilic inflammation, respectively) were measured in exhaled breath condensate collected from the competitive swimmers 30 min before and 30 min after swimming. Stationary measurements were performed at a sampling point determined as the "worst" point based on levels of total oxidants and subjective information from the pool workers. The sampling point was situated 5 cm over the water surface level and 20 cm from the lateral edge, just over the perimeter drain. The new disinfection method resulted in a 75% reduction of total oxidants and a 39% reduction of trichloramine. Thus, the average airborne concentration of trichloramine fell from 0.62 mg/m^3 using conventional chlorination to 0.38 mg/m^3 using the new disinfection method. The symptom prevalences were higher in competitive swimmers than in recreational swimmers, the most common symptoms in both groups being eye and nose irritation. Competitive swimmers experienced decreased irritation in eyes (48% vs 19%; significant), nose (42% vs 28%; non-significant) and skin (30% vs 24%; non-significant) after shifting from the old to the new disinfection method. Also recreational swimmers had significantly lower prevalences regarding irritation in eyes (17% vs 6.7%), nose (12% vs 2.2%) and skin (11% vs 4.5%), and cough (5.8% vs 0%) after shifting methods. Participants with asthma did not differ from non-asthmatics in symptom prevalences. The baseline level of CysLTs in exhaled breath condensate was significantly reduced when the new method was used, whereas the LTB4 baseline level was not affected (47).

Lévesque *et al*. compared the prevalence of respiratory symptoms in 305 competitive swimmers (101 boys, 204 girls) with that of 499 indoor soccer players (297 boys, 202 girls) in the Québec City region of Canada via questionnaire, and evaluated the relationship between trichloramine concentrations and the athletes' respiratory symptoms. The competitive swimmers reported significantly more symptoms (OR, 95% CI) from upper airways (3.7, 2.4–5.8), irritation in nose (7.2, 4–13), throat (2.1, 1.3–3.5) and eyes (11.9, 6.7–21) (ORs adjusted for gender, age and number of training sessions per week). No significant difference between the groups was observed for skin problems. Respiratory symptoms were also assessed during five training sessions in 72 competitive swimmers, 8–22 years of age and 73 soccer players, 11–17 years of age. The concentration of trichloramine

in air was measured in 7 swimming pool facilities and the AM was 0.34 mg/m^3 (median 0.37 mg/m^3) with a range of 0.26–0.41 mg/m^3. The swimmers experienced more symptoms (OR, 95% CI) from upper airways (3.1, 1.8–5.4) and irritation in eyes (5.7, 1.1–28) during the five training sessions than the soccer players. Swimmers with high exposure to airborne levels of trichloramine (> 0.37 mg/m^3) had significantly more symptoms (OR, 95% CI) from upper airways (2.2, 1.0–4.8) and irritation in eyes (4.9, 1.9–12) compared to swimmers with an exposure < 0.37 mg/m^3 (78).

Seys *et al.* initiated a study after complaints of respiratory symptoms among members of a swimming club when attending a municipal indoor swimming pool in Belgium. Competitive swimmers (n = 39) and coaches (n = 10) were invited to a medical evaluation. Of them, 22 swimmers aged 9–17 years (10 boys, 12 girls) and 6 coaches aged 18–60 years (3 men, 3 women) were evaluated by interview. Repeated measurements of airborne trichloramine were performed by stationary sampling and the concentration ranged from 0.20 to 1.30 mg/m^3. Most commonly reported symptoms were cough (57%), dyspnoea (46%), red tearing eyes (37%) and blocked or runny nose (21%). A glue containing polyamines used to repair a pipework was suspected to contribute to an excessive production of trichloramine. After removal of the glue, the concentration of airborne trichloramine decreased to a concentration below 0.5 mg/m^3. At follow up one year later, including 13/28 subjects from the first evaluation, most subjects reported improvement but some symptoms remained. Some swimmers reported a recent recurrence of symptoms; the intake of outside air to the swimming pool had presently been reduced because of low outside temperature, resulting in rising air levels of trichloramine (0.66 mg/m^3) (118).

11.1.3 Food industry workers

King *et al.* investigated eye and respiratory symptoms among workers in a US poultry processing facility and administered a screening questionnaire to 109 employees. Answers from 68 employees at the evisceration department (39 men, 29 women) and 41 workers in the dark meat department (18 men, 23 women) were available for analysis. The evisceration workers were chosen because of the extensive use of super-chlorinated water in their department, in contrast to the dark meat workers (reference group). Work-related nose irritation, such as sneezing (OR 4.9, 95% CI 1.8–14) (but not itchy, running or stuffy nose), burning or stinging (OR 3.3, 95% CI 1.3–9.2) or watery eyes (OR 7.0, 95% CI 2.4–24) were significantly more common in evisceration workers than in dark meat workers; ORs adjusted for smoking status. The prevalence of work-related sore throat was also higher in evisceration workers, but did not reach statistical significance. A second survey was performed a year later comprising 18 evisceration workers and 16 dark meat workers. Measurements were performed by personal sampling. Levels of trichloramine were significantly higher in the evisceration area (GM 0.0051 mg/m^3) than in the dark meat area (GM 0.0012 mg/m^3). Soluble chlorine was also present in the indoor air of the premises; the concentration was significantly higher in the

evisceration area (GM 0.0635 mg/m^3) than in the dark meat area (GM 0.0094 mg/m^3). Thus, soluble chlorine predominated in the indoor air. Exposure levels of trichloramine were significantly higher for employees reporting burning and stinging eyes (12/34, 35%) compared to those who did not report such symptoms. Further, exposure levels of soluble chlorine were higher for subjects reporting burning or stinging eyes (10/32, 31%), itchy or stuffy nose (9/32, 28%), frequent sneezing (5/32, 16%) and cough (8/32, 25%), compared to those who did not report such symptoms. Aerosolisation of the chlorinated water resulting in high air levels of soluble chlorine makes it difficult to separate effects from exposure to trichloramine from those of soluble chlorine (76).

Massin *et al.* recruited 175 cleaning and disinfecting workers from the food industry (149 men, 26 women) and 70 non-exposed workers (52 men, 18 women). Irritant symptoms were evaluated by questionnaire. The personal inhalation exposure was given as the sum of trichloramine and soluble chlorine (range of AMs 0.33–0.49 mg/m^3). In addition, glutaraldehyde and formaldehyde was used as disinfection agents, but air levels were not reported. A total exposure index including all irritants was calculated for each worker. Three subgroups were constituted; a non-exposed group and two groups with lower and higher exposure index. The prevalence of irritant symptoms was higher among subjects with highest exposure index than in non-exposed; irritation in eyes (48% vs 5.7%), nose (39% vs 1.4%), sore throat (27% vs 2.9%) and dry cough (27% vs 1.4%). Significant concentration-response relationships between irritant eye, nose and throat symptoms and exposure to irritants were found. In addition, the workers were divided in three subgroups taking exposure duration into account; non-exposed group, exposure duration ≤ 6 years and exposure duration > 6 years. The prevalence rates for the groups with exposure duration > 6 years and < 6 years were 51% and 30% (eye irritation), 41% and 20% (nose irritation), 34% and 15% (sore throat) and 27% and 16% (dry cough), respectively. Significant concentration-response relationships between all symptoms and number of working years were found (85).

11.1.4 Conclusion

In summary, inorganic chloramines are strong mucous membrane irritants, and several cross-sectional studies have shown higher prevalences of self-reported ocular and/or upper airway irritation among workers occupationally exposed to inorganic chloramines and competitive swimmers compared to an unexposed reference group (25, 27, 36, 73, 76, 78, 82, 85, 101). Food industry workers (76, 85) and competitive swimmers (78) are to a higher degree co-exposed to soluble chlorine from aerosols or the chlorinated water itself than swimming pool workers. Studies on these categories are therefore of limited value in the risk assessment of irritant effects of airborne trichloramine.

Several studies have demonstrated significantly more ocular and upper airway irritation in pool workers than in referents (25, 27, 36, 73, 82) and exposure-response relationships have been shown in a few studies (36, 84, 101). Stationary

sampling was used in most of these studies. The temporal link between exposure and symptoms was sometimes weak.

Despite the amount of human irritation data on trichloramine, it is difficult to draw a firm conclusion regarding a no observed adverse effect concentration (NOAEC). In the study by Parrat *et al*., irritation symptoms were more frequent in pool workers exposed to 0.30–0.52 mg/m^3 (AM 0.36 mg/m^3) than in referents (101). The study suggests a lowest observed adverse effect concentration (LOAEC) for irritation around 0.4 mg/m^3. This value is supported by several other studies on pool workers which show irritation at approximately 0.5 mg/m^3 (36, 64, 84).

Duration of exposure was taken into account in some studies, and an association between the prevalence of irritation in upper airways or eyes and cumulative trichloramine exposure was observed (73, 84, 101). The cumulative exposures were calculated in different ways and are difficult to interpret in terms of exposure concentration. These data are therefore not suited for identifying NOAECs and LOAECs.

Table 7. Irritation in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Swimming pool workers					
Cross-sectional, Sweden	23 pool workers (20 women, 3 men; mean age 50 y) 50 office workers (35 women, 15 men; mean age 39 y)	0.023 AM 0.009 GM 0.001–0.140 Personal sampling: 0.019 AM 0.008 GM 0.001–0.076	Questionnaire	No significant difference in prevalences of ocular, nasal and respiratory symptoms between exposed workers and referents. After adjusting for age and smoking, workers exposed to trichloramine above the median of 0.020 mg/m^3 reported significantly more often at least one ocular symptom (itchy, smarting, dry, running and red eyes, and swollen eyelids) during the last week than those exposed below the median (RR 1.2, 95% CI 1.1–1.4).	(137)
Cross-sectional, Taiwan	61 lifeguards and swimming instructors (36 men, 25 women) 43 reception and management employees (15 men, 28 women)	Swimming pools AM: 0.035 (0.017–0.15) Spa pools AM ± SD: 0.059 ± 0.042 Soluble chlorine: Swimming pools AM: 0.072 (0.005–0.21) Spa pools AM ± SD: 0.085 ± 0.056	Questionnaire	Exposed subjects reported more symptoms than non-exposed in the same facilities. Exposed workers had more throat irritation (26% vs 2.3%) (OR 11.3, 95% CI 1.4–88) and phlegm (29.5% vs 6.9%) (OR 4.2, 95% CI 1.2–15.4) than referents. No significant differences for eye and nose irritation.	(25)
Cross-sectional, Switzerland	178 pool workers (117 men, 61 women) 71 referents (38 men, 33 women)	0.11 AM Sub-groups (current exposure): < 0.1 (0.05 AM, n = 102) 0.1–0.29 (0.15 AM, n = 61) 0.30–0.52 (0.36 AM, n = 20)	Questionnaire	Irritative symptoms (ever) in eyes (53% vs 22%), throat (79% vs 7%), nose (38% vs 7%) and skin (61% vs 8%) related to work were significantly more common among pool workers than among referents.	(101)

Table 7. Irritation in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
				Pool workers exposed to mean air levels of 0.36 mg/m^3 had higher prevalences of irritation (OR, 95% CI) in eyes (5.6, 1.3–24) and nose (4.2, 1.4–13) during the last 12 months, and ever in nose (4.3, 1.5–13) than referents.	
		Employees divided in 5 groups according to a 1-wk cumulative exposure index.		The highest cumulative exposure index group had increased prevalences of eye and nose irritation; the 2nd highest index group had eye irritation.	
Cross-sectional, Sweden	52 pool workers (36 women, 16 men; mean age 36.9 y) 50 office workers (35 women, 15 men; mean age 39.1 y)	0.18 AM 0.10 GM 0.001–0.64 Personal sampling: 0.071 AM 0.036 GM <0.001–0.24	Questionnaire	Exposed workers reported more often itchy eyes (36% vs 14%), at least one ocular symptom (62% vs 37%), blocked nose (55% vs 32%) and at least one nasal symptom (60% vs 47%; non-significant) than referents during the last wk. After adjusting for smoking, asthma/allergy and Phadiatop, exposed workers reported more often (OR, 95% CI) at least one ocular symptom such as itchy, smarting, dry, running and red eyes, gravel sensation or swollen eyelids (2.4, 1.0–5.7) and one nasal symptom such as blocked, dripping or itchy nose or sneezing (2.3, 1.0–5.6) during the last wk than referents. No significant differences were found for tracheobronchial symptoms. Exposed workers reported more often ocular, nasal and/or respiratory symptoms during the last 3 mo than referents (data not shown). No associations between exposure levels and health effects.	(82, 138)

Table 7. Irritation in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-sectional, Sweden	39 pool workers No referents (except 4 controls in the nasal lavage study)	0.20 AM 0.04–0.36	Questionnaire; Nasal lavage fluid (in 13 subjects)	No association between self-reported work-related airway symptoms and air levels. Protein profiling of nasal lavage fluid in 9 pool workers and 4 control subjects showed altered distribution of three innate immunity proteins (α-1-antitrypsin, lactoferrin and S100-A8) in pool workers, and more pronounced in subjects with airway irritation.	(42)
Cross-sectional, France	334 lifeguards (256 men, 78 women) No referents	Swimming pools: 0.24 AM Leisure swimming pools: 0.67 AM Sub-groups (current exposure): <0.14 (n=86) 0.14–0.22 (n=82) 0.22–0.50 (n=75) >0.50 (n=91)	Questionnaire	The prevalence rates of irritant symptoms at work were (from the lowest to the highest exposed sub-group): Eye symptoms (%): 50, 56, 63, 86 Nose symptoms (%): 12, 20, 28, 61 Throat symptoms (%): 16, 15, 27, 29 Dry cough (%): 9, 12, 21, 42 Significant relationships between current air levels and irritation in eyes, nose and throat, and dry cough, and between cumulative exposure (taking number of working years into account) and eye and nose irritation.	(84)
Cross-sectional, France	Swimming instructors (no. and gender not given) No referents	Swimming pools: 0.15–0.39 AMs Recreational centres: 0.23–1.25 AMs	Interview at workplace	Swimming instructors were requested to report at onset of symptoms while air levels of trichloramine were monitored. Onset of irritation in eyes and upper respiratory tract began at around 0.5 mg/m^3, and all questioned complained of irritative symptoms at 0.7 mg/m^3.	(64)

Table 7. Irritation in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-sectional, United States	69 lifeguards (37 men, 32 women) 74 hotel employees (24 men, 50 women)	High-occupancy days: 0.44 AM (day 1) ND–1.06 ND–0.25 (soluble chlorine) Low-occupancy day: ND–trace ND (soluble chlorine)	Questionnaire	Lifeguards reported more work-related irritation (PR, 95% CI) in throat (11.8, 2.9–48), nose (3.5, 1.9–6.6) and eyes (9.0, 4.1–20) than referents. Work-related symptoms were significantly more common during the high-occupancy days than during the low-occupancy day, such as eye irritation (2.0, 1.2–3.2) and cough (2.2, 1.1–4.5) (adjusted for smoking habits, subjects with asthma not included).	(27)
Cross-sectional, Netherlands	342 exposed pool workers (127 men, 215 women) 282 unexposed reception, catering and management employees (113 men, 169 women)	Current exposure: 0.56 AM 0.13–1.34 Estimated long-term exposure: 0.66 AM 0.38–1.10	Questionnaire	Swimming instructors (n = 121) reported more work-related symptoms (OR, 95% CI) than referents from upper airways such as sinusitis (2.4, 1.2–4.9), chronic cold (3.4, 1.2–10), sore throat (2.4, 1.2–4.5), blocked nose (2.0, > 1.0–3.8) and sneezing (2.0, 1.1–3.6). No significant differences were shown for runny nose and irritation in eyes. Employees who combined the jobs of pool attendant and swimming instructor (n = 142) also reported more work-related symptoms than referents in upper airways (OR, 95% CI) such as chronic cold (3.5, 1.2–10), sore throat (3.2, 1.7–5.9), blocked nose (3.7, 1.9–7.3), runny nose (2.2, 1.3–3.5), sneezing (2.3, 1.2–4.4) and itchy watery eyes (3.0, 1.7–5.3). No significant difference was shown for sinusitis. No association between estimated long-term levels of airborne trichloramine and symptoms, but 1-wk cumulative exposures were significantly associated with upper respiratory symptoms.	(73)

Table 7. Irritation in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-sectional, Italy	81 lifeguards and swimming instructors (40 men, 41 women) 47 other employees (21 men, 26 women)	0.65 AM 0.20–1.02 5 exposure levels defined: ≤ 0.5 (n = 10) > 0.5 (n = 71) > 0.6 (n = 50) > 0.7 (n = 39) > 0.8 (n = 30)	Questionnaire	Pool workers reported more frequently ocular and upper respiratory symptoms. Strong exposure-response relationships were demonstrated. Pool workers exposed to air levels > 0.5 mg/m^3 had higher risk (OR, 95% CI) for experiencing runny nose (2.9, 1.2–6.9), voice loss (3.6, 1.6–7.9), red eyes (3.2, 1.5–6.8) and itchy eyes (2.2, 1.04–4.8) than non-exposed subjects.	(36)
Cross-sectional, France	39 lifeguards (29 men, 10 women) No referents	–	Questionnaire	High prevalence of work-related symptoms such as irritation in eyes (72% in males, 70% in females), nose (52%, 50%) and throat (48%, 30%).	(30)
Cross-sectional, Sweden	1 102 pool workers (513 men, 589 women) No referents	–	Questionnaire	Irritative symptoms were common among pool workers, such as irritation in eyes (37%), nose (29%), throat (24%) and coughing (23%). A significant association was found between number of hours spent in the swimming pool environment during an average day and the percentage of workers reporting work-related symptoms ($P < 0.01$).	(98)
Cross-sectional, Turkey	27 pool workers (13 men, 14 women) 49 office workers (22 men, 27 women)	–	Nasal smear; Skin prick test	The prevalence of positive skin prick test was 30% in pool workers compared to 18% in the referents; the difference was not statistically significant. Exposed workers had significantly more eosinophils in nasal smear, indicating allergic inflammation.	(34)

Table 7. Irritation in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Competitive and recreational swimmers					
Cross-sectional, Canada	*Part 1:* 305 competitive swimmers (101 boys, 204 girls) 499 indoor soccer players (297 boys, 202 girls)	*Part 1:* No data	Questionnaire	*Part 1:* Swimmers reported more symptoms (OR, 95% CI) from upper airways (3.7, 2.4–5.8), irritation in nose (7.2, 4–13), throat (2.1, 1.3–3.5) and eyes (12, 6.7–21) than soccer players; ORs adjusted for gender, age and number of training sessions per week.	(78)
	Part 2 (sub-group): 72 competitive swimmers (8–22 y) 73 indoor soccer players (11–17 y)	*Part 2:* 0.34 AM 0.26–0.41 0.37 (median)	Questionnaire	*Part 2:* Swimmers experienced more symptoms from upper airways (51% vs 28%) (OR 3.1, 95% CI 1.8–5.4) and irritation in eyes (15% vs 4%) (OR 5.7, 95% CI 1.1–28) during the training sessions than soccer players. Swimmers exposed to levels > 0.37 mg/m^3 had more symptoms from upper airways (62% vs 39%) (OR 2.2, 95% CI 1.0–4.8) and irritation in eyes (24% vs 3.4%) (OR 4.9, 95% CI 1.9–12) than swimmers exposed to levels < 0.37 mg/m^3.	
Cross-sectional, Belgium	22 competitive swimmers (10 boys, 12 girls; 9–17 y) 10 coaches (3 men, 3 women) No referents	0.20–1.30	Medical interview	The most commonly reported symptoms were cough (57%), dyspnoea (46%), red tearing eyes (37%) and blocked or runny nose (21%).	(118)

Table 7. Irritation in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-over, Spain	320 recreational swimmers (202 men, 118 women; mean age 36 y) 53 competitive swimmers (45 men, 8 women; mean age 22 y)	0.62 AM (standard method for water disinfection) 0.38 AM (new method for water disinfection, based on NaClO and CO_2 followed by a phase combining saline electrolysis plus UV radiation added after filtering)	Questionnaire; LTB4 and CysLTs in exhaled breath condensate (surrogate markers of neutrophilic and eosinophilic airway inflammation). Measurements 30 min before and 30 min after swimming in both conditions.	Prevalence of symptoms was higher in competitive swimmers than in recreational swimmers, the most common symptoms in both groups were eye and nose irritation. Fewer recreational swimmers experienced irritation in the eyes (6.7% vs 17%), nose (2.2% vs 12%) and skin (4.5% vs 11%), and cough (0 vs 5.8%) during use of the new disinfection method (all significant). Fewer competitive swimmers experienced irritation in the eyes (19% vs 48%; significant) and nose (28% vs 42%; non-significant) during use of the new disinfection method. The baseline level of CysLTs was significantly lower in both groups when the new disinfection method was used compared to the standard method. The LTB4 baseline level was not affected.	(47)
Food industry workers					
Cross-sectional	Poultry processing *1st survey:* 68 evisceration workers (39 men, 29 women) Referents: 41 dark meat workers (18 men, 23 women)	*1st survey:* No data	Questionnaire	*1st survey:* Evisceration workers experienced more work-related (OR, 95% CI) sneezing (4.9, 1.8–14) (but not itchy, runny or stuffy nose), burning or stinging (3.3, 1.3–9.2) or watery eyes (7.0, 2.4–23) than dark meat workers; ORs adjusted for smoking status.	(76)

Table 7. Irritation in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
	2nd survey: 18 evisceration workers 16 dark meat workers	*2nd survey:* Personal sampling GM: 0.0051 0.0012 Soluble chlorine: 0.063 0.009		*2nd survey:* Trichloramine levels were significantly higher for employees reporting burning and stinging eyes (35%), but not for other symptoms. Soluble chlorine levels were significantly higher in employees reporting burning or stinging eyes (31%), itchy or stuffy nose (28%) and frequent sneezing (16%).	
Cross-sectional, France	175 exposed workers (149 men, 26 women) 70 non-exposed workers (52 men, 18 women)	Personal sampling AMs: 0.33–0.49 (sum of soluble chlorine and trichloramine) [a] Co-exposure to glutaraldehyde and formaldehyde Exposed workers were given a total exposure index (for all irritants) taking exposure duration into account and were divided in a low and high total exposure index group.	Questionnaire	The prevalence of irritant symptoms was higher among exposed subjects than among non-exposed referents. The prevalence rates of irritant symptoms for the non-exposed group, low and high total exposure index groups were: Eye symptoms (%): 5.7, 33, 48 Nose symptoms (%): 1.4, 22, 39 Throat symptoms (%): 2.9, 21, 27 Dry cough (%): 1.4, 16, 27 Significant concentration-response relationships between irritant eye, nose and throat symptoms and exposure expressed as total exposure index and exposure duration (years), respectively.	(85)

[a] Unclear if expressed as trichloramine, or chlorine, equivalents.

AM: arithmetic mean, CI: confidence interval, CysLT: cysteinyl leukotriene, GM: geometric mean, LTB4: leukotriene B4, ND: non-detectable, OR: odds ratio, PR: prevalence ratio, RR: relative risk, S100-A8: S100 calcium binding protein A8 (also called calgranulin A), SD: standard deviation, UV: ultraviolet.

11.2 Effects of single and short-term exposure

11.2.1 Accidental exposure

Mixing solutions of ammonia and sodium hypochlorite results in acrid chloramine fumes (49). Gapany-Gapanavicius *et al.* reported the case of a healthy 27-year-old woman who mixed ammonia and sodium hypochlorite in a small and poorly ventilated bathroom. The vapours from the mixture caused burning sensations in the eyes and throat, dyspnoea, coughing, nausea and vomiting. Pneumonitis developed, but pulmonary function had returned to normal after 9 days (44).

A healthy 53-year-old woman was cleaning a walk-in-freezer using a mixture of ammonia and sodium hypochlorite which caused formation and release of inorganic chloramines into the air. The door was closed and there was no air exchange in the freezer. After approximately 30 min she noted shortness of breath. Over the next 3 hours she had increased tightness of the throat and lost her voice. The symptoms worsened. Emergency tracheostomy was performed. Radiologic evidence of pneumonitis developed over the next 4 hours and she received supportive care. The tracheal tube was removed within 5 days and she was fully recovered within 7 days (127).

As the vapours in these 2 cases probably contained also ammonia, which may produce similar health effects as inorganic chloramines, the responsible agent cannot be identified.

Bowen *et al.* investigated outbreaks of acute ocular and respiratory symptoms associated with indoor swimming pool exposure among patrons of two hotels. In one of the hotels, the ventilation system malfunctioned during the outbreak. Out of 77 registered guests who stayed at the first hotel within 2 days of onset of outbreak, 47 (67%) were interviewed by telephone with a standardised questionnaire containing questions about exposure to the swimming pool area, general and respiratory and ocular symptoms. Among the 31 guests who visited the indoor pool area, 22 (71%) developed acute ocular symptoms such as burning and watery eyes, and 15 (48%) reported acute respiratory symptoms such as cough and sore throat. At the second hotel, 30 out of 77 registered guests and 59 companions completed the questionnaire. Among those 69 exposed to the indoor pool area, 41 (59%) developed acute ocular symptoms, and 28 (41%) acute respiratory symptoms. In total, all cases with ocular symptoms and 42/43 with respiratory symptoms had visited the pool area. Symptoms occurred within minutes of exposure to the indoor pool area and lasted up to 14 days, 4 persons sought medical care. Children were predominantly affected, but there was no association with gender. Environmental health investigations were performed. Appropriate water and air samples were not available for laboratory analysis. According to the authors, chloramines likely contributed to the illness; symptoms were consistent with trichloramine exposure and were sometimes severe (17).

Sanderson *et al*. investigated outbreaks of work-related acute eye and upper respiratory irritation and other symptoms such as nausea and headache in 6 poultry processing plants. A questionnaire was administered to all 170 workers at one of these plants. Over 80% of the inspectors, evisceration/reprocessing and clean-up

crew reported eye and nasal irritation, but only about one-third of the packers. Potential causes of the outbreaks were explored; air samples were collected at all 6 plants for chlorine gas and at 4 plants for ammonia, but concentrations of these gases were low. No measurements of airborne trichloramine were performed, but the outbreaks all had temporal association with problems or changes in the plant's water chlorination and super-chlorination processes. The complaints were eliminated after technical changes, such as construction of a new water supply system and ventilation changes, suggesting a causal relationship between the reported complaints and exposure to trichloramine (113).

11.2.2 Effects on lung function and pneumoproteins

Studies investigating effects on lung function and pneumoproteins among workers and swimmers exposed to inorganic chloramines (effects predominantly evaluated against measurements of trichloramine levels) are described below and summarised in Table 8.

11.2.2.1 Swimming pool workers and swimmers

Löfstedt *et al*. measured lung function and FENO before and after work in 52 pool workers and 50 office workers (for details, see Section 11.1.1). The average airborne trichloramine concentrations measured by stationary and personal sampling were 0.18 and 0.071 mg/m^3, respectively. No changes in lung function were found over the work shift and there was no difference between the groups. Regarding FENO, there was a significant difference between the groups in that FENO decreased (as expected) over the work shift among referents but increased in pool workers, suggesting an inflammatory effect on the airways. The increase was more pronounced in non-smoking pool workers (82).

A similar study by the same research group included 23 pool workers and 50 office workers (for details, see Section 11.1.1). The average airborne trichloramine concentrations measured by stationary and personal sampling were 0.023 mg/m^3 and 0.019 mg/m^3, respectively. No changes in lung function were found over the work shift and there was no difference between the groups. Mean FENO values differed between groups before shift (18 ppb vs 16.1 ppb in referents) and decreased over work shift in both groups (17.9 ppb vs 14.3 ppb), but significantly more in referents than in pool workers. Personal trichloramine concentrations were not associated with lung function or FENO (137).

Nordberg *et al*. investigated lung function [forced expiratory volume in the first second (FEV_1) and $FEV_{\%}$ (FEV_1/forced vital capacity × 100) as well as biomarkers of pulmonary epithelial integrity (CC16 and SP-D) in volunteers before and after exposure to indoor pool air. Two groups of volunteers were studied; 37 previously non-exposed healthy persons (20 men and 17 women, mean age 24.5 years) and 14 pool workers (5 men and 9 women, mean age 39.9 years) who performed bicycle exercise for 2 hours in an indoor pool environment. Trichloramine in air was measured by personal sampling during pool exposures. All participants were also exposed to filtered air in a separate exposure chamber, which was used as control

condition. In previously non-exposed volunteers, marginal but statistically significant decreases in both FEV_1 and $FEV_{\%}$ ($P = 0.01$ and 0.05, respectively) were found after exposure to pool air (0.23 mg/m^3 of trichloramine). The individual differences in changes between exposure conditions in FEV_1 and $FEV_{\%}$ were significant with P-values of 0.01 and 0.004, respectively. In pool workers, a statistically significant decrease (marginal effect) was found, but only in $FEV_{\%}$ ($P = 0.003$) after exposure to pool air (0.15 mg/m^3 of trichloramine). The individual differences in changes between exposure conditions in FEV_1 and $FEV_{\%}$ were, however, non-significant. There were no statistically significant exposure-related changes in serum concentrations of CC16 and SP-D after exposure to pool air for 2 hours. According to the authors, the lack of exposure-related changes in biomarker levels could be explained by the relatively short exposure duration and the low exposure level of trichloramine (98).

Bernard *et al*. investigated short-term effects of trichloramine on the pulmonary epithelium of pool attendees. Three lung-specific proteins, the alveolar SP-A and SP-B and the bronchiolar CC16, were measured in serum of 16 children (mean age 9.6 years) and 13 adults (mean age 36.9 years), before and after attending an indoor swimming pool for 2 hours. Children could have free activities while the adults were asked to stay at the poolside for 1 hour and then could swim freely. Stationary sampling of trichloramine in air was performed and the mean concentration was 0.49 mg/m^3. There was a significant increase in serum levels of SP-A and SP-B, and the SP-B/CC16 ratio in both children and adults; in adults already after 1 hour without swimming. CC16 levels decreased significantly after 1 hour and reversed towards normal 1 hour later in adults, but did not show any distinct pattern in children (11).

Carbonelle *et al*. investigated the effect of trichloramine on the pulmonary epithelium of pool attendees. Three lung-specific proteins (SP-A, SP-B and CC16) were measured in serum of 29 recreational swimmers, among them 16 children aged 5–14 years (10 girls, 6 boys) and 13 adults aged 26–49 years (7 women, 6 men) before and after attending a chlorinated pool with a mean airborne trichloramine concentration of 0.49 mg/m^3. These pneumoproteins were also measured in 14 trained swimmers aged 18–23 years (6 women, 8 men) before, immediately after, and 11 hours after performing an intensive 45-min standardised swimming session in a chlorinated pool with a mean airborne trichloramine concentration of 0.36 mg/m^3, and in a non-chlorinated pool sanitised by the copper/silver method. Pulmonary function was evaluated by spirometry at the same time as the blood sampling was done, both in recreational and trained swimmers. Stationary sampling of trichloramine in air was performed at the poolside 20 cm above the pool's water surface to assess exposure during swimming. Serum levels of SP-A and SP-B were significantly increased in a time-dependent manner in recreational and trained swimmers attending the chlorinated pool, but were unaffected by strenuous exercise in the non-chlorinated pool. No significant decrements in lung function were found. Serum CC16 levels increased immediately after strenuous exercise in trained swimmers, both in the non-chlorinated and chlorinated pools, but were not

increased in recreational swimmers. According to the authors, the latter finding is probably due to mechanical stress on the epithelial barrier caused by over-inflation and/or hyperventilation during intense exercise (21).

In a similar study, Carbonelle *et al*. investigated possible effects on the pulmonary epithelium and lung function in adults exposed to lower airborne concentrations of trichloramine. Serum levels of SP-A, SP-B, CC16 and Krebs von den Lungen-6 protein (KL-6) were measured in 11 healthy volunteers (7 women, 4 men) before and after performing an intensive 45-min standardised swimming session in a non-chlorinated pool. After 1 week, the subjects performed a similar swimming session in a chlorinated pool. All tests were repeated 3 hours after exercise had ceased in both conditions. Measurements of airborne trichloramine were performed by stationary sampling on the poolside 20 cm above the pool's water surface and ranged from 0.16 to 0.28 mg/m^3. Lung function was evaluated by spirometry and possible airway inflammation was assessed using measurements of FENO. Serum levels of the pneumoproteins were unaffected after exercise in the chlorinated pool, and no decrements in lung function were found. FENO increased by 34% after exercise in the non-chlorinated pool but remained unchanged in the chlorinated pool. The authors concluded that exercise performed in a pool having an indoor air trichloramine concentration < 0.3 mg/m^3, did not induce any short-term changes in lung function or epithelial permeability (20).

Font-Ribera *et al*. measured lung function, biomarkers of airway inflammation (FENO, 8 cytokines and vascular endothelial growth factor) and oxidative stress (8-isoprostane) in exhaled breath condensate in 48 healthy adult non-smokers, before and after swimming for 40 min in a chlorinated indoor swimming pool. In addition, serum levels of the pneumoproteins SP-D and CC16, *CC16* genotype, energy expenditure during swimming, and atopy were determined. Air measurements of trichloramine were done for a comparison with swimming pools in other countries but were not used for personal exposure estimates; the mean air concentration was 0.29 mg/m^3. Most participants were women (65%), the mean age was 30 years, and 30% had a positive Phadiatop test (allergy screening test). Trihalomethanes in exhaled breath was measured as a marker of individual exposure to disinfection by-products. There was a slight increase in serum CC16 levels (3.3%) after swimming. According to the authors, both exercise and different markers of disinfection by-products exposure, such as change in trihalomethanes concentration in exhaled breath after swimming, explained this association. No significant changes in lung function tests or markers of airway inflammation or oxidative stress were found (38).

Llana-Belloch *et al*. evaluated the effects on markers of lung epithelium permeability and oxidative stress in 20 healthy volunteers (all men, mean age 22 years) before and after swimming for 40 min in three chlorinated indoor pools with different characteristics. Blood samples were collected and analysed for pneumoproteins SP-A, SP-B, markers of oxidative stress (plasma malondialdehyde and protein carbonyls, GSH and oxidised GSH) and lactate before and after exercise. Total air chlorine concentrations were measured in all swimming pools

and were 0.1–1.0 mg/m^3. The authors suggested that trichloramine was the major part of total chlorine in the air samples but the concentration of trichloramine in air was not reported. No increase in blood lactate was found after the swimming session, confirming that the exercise was performed at a moderate level. Concentrations of chlorine in water and air were not associated with changes in markers of lung epithelium integrity and oxidative damage. The authors concluded that short-term moderate exercise and exposure to chlorinated disinfection by-products will not affect markers of lung epithelial damage and oxidative stress (80).

11.2.2.2 Food industry workers

King *et al*. investigated respiratory symptoms in 34 poultry processing workers (for details, see Section 11.1.3). The workers were evaluated with spirometry before and after shift, and 3/34 subjects had significant cross-shift declines in FEV_1 (> 10%). The airborne trichloramine exposure (personal sampling) of these subjects were significantly higher (GM 0.022 mg/m^3) compared to those without significant cross-shift declines in FEV_1 (GM 0.0021 mg/m^3). The GM concentration of soluble chlorine in air was also higher in those with significant cross-shift declines in FEV_1, however, not significantly (0.071 mg/m^3 vs 0.022 mg/m^3). Concurrent exposure to trichloramine and soluble chlorine, the latter due to aerosolisation of the chlorinated water, makes it difficult to identify the responsible agent (76).

11.2.2.3 Conclusion

Short-term changes in pneumoproteins have been shown at mean airborne trichloramine concentrations ≥ 0.29 mg/m^3 (11, 21, 38) but not at lower exposure levels (20, 98). Marginal effects on lung function were demonstrated in one study with personal trichloramine exposure levels of 0.15 mg/m^3 and 0.23 mg/m^3 (98). In contrast, no effects on lung function were demonstrated in studies with exposure levels of 0.023 mg/m^3 (137), 0.18 mg/m^3 (personal exposure 0.071 mg/m^3) (82), 0.16–0.28 mg/m^3 (20), 0.29 mg/m^3 (38), and 0.36 and 0.49 mg/m^3 (21). FENO has been measured in some studies as a possible marker of airway inflammation, with mostly negative results. However, Löfstedt *et al*. found an increase in FENO over work shift in pool workers exposed to 0.18 mg/m^3 of trichloramine (82).

11.2.3 Other effects

Wones *et al*. investigated whether a 4-week consumption of 1.5 l/day of distilled water containing monochloramine under controlled conditions would alter parameters of lipid or thyroid metabolism in healthy men. The 48 subjects drank distilled water during a 4-week dietary stabilisation period. Following this period they were divided into three dose groups (16/group). One group drank 1.5 l of distilled water, the second group drank 1.5 l distilled water containing 2 mg/l of monochloramine (0.043 mg/kg bw/day assuming a body weight of 70 kg) and the third group drank 1.5 l distilled water with a concentration of 15 mg/l of monochloramine (0.32 mg/kg bw/day) each day during 4 consecutive weeks. The study diet was designed individually to be isocaloric. Blood was collected at the beginning of the study, during 4 consecutive days at the end of the stabilisation

period and at the end of the monochloramine exposure. Total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol (calculated), apolipoproteins A1, A2 and B, thyroxine (T4), triiodothyronine (T3), T3 resin uptake and thyroid stimulating hormone (TSH) were analysed. The consumption of water containing 2 mg/l of monochloramine did not affect the parameters studied, whereas 15 mg/l was associated with an increase in the plasma level of apolipoprotein B (142). The authors did not discuss a possible toxic effect as a consequence of this finding.

Monochloramine was given in drinking water to 10 healthy male volunteers every 3rd day at totally 6 occasions at concentrations increasing from 0.01 mg/l at day 1 to 2.4 mg/l at day 16. The 10 control subjects received untreated water. At each occasion the subjects drank two 500-ml portions, the second one administered 4 hours after the first. Assuming a body weight of 70 kg, the highest dose corresponds to 0.034 mg/kg bw/day. In a second experiment, healthy male volunteers (10/group) were administered 0 or 5 mg/l monochloramine in a volume of 500 ml of water daily for 12 weeks (corresponding to 0.036 mg/kg bw/day). An extensive battery of measures including serum chemistry, blood count, urine analysis and physical examination were conducted before, during and following the experiments. The authors concluded that no definitive finding of detrimental physiological impact was identified in any of the experiments (81).

Table 8. Effects on pneumoproteins and lung function in humans after short-term exposure to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Swimming pool workers and swimmers					
Cross-sectional, Sweden	23 pool workers (20 women, 3 men; mean age 50 y) 50 office workers (35 women, 15 men; mean age 39 y)	0.023 AM 0.009 GM 0.001–0.140 Personal sampling: 0.019 AM 0.008 GM 0.001–0.076	Spirometry (in 21 exposed and all referents); FENO. Measurements before and after work shift.	No changes in lung function over work shift and no difference between groups. FENO decreased over work shift in both groups, but significantly more in referents than in pool workers. Personal trichloramine concentrations were not associated with lung function or FENO.	(137)
Cross-sectional, Sweden	52 pool workers (36 women, 16 men; mean age 36.9 y) 50 office workers (35 women, 15 men; mean age 39.1 y)	0.18 AM 0.10 GM 0.001–0.64 Personal sampling: 0.071 AM 0.036 GM <0.001–0.24	Spirometry; FENO. Measurements before and after work shift.	No changes in lung function over work shift and no difference between groups. FENO decreased over work shift in referents and increased in pool workers ($P < 0.05$). The increase was more pronounced in non-smoking pool workers.	(82)
Cross-over, Sweden	14 pool workers (9 women, 5 men; mean age 39.9 y) 37 previously non-exposed healthy volunteers (17 women, 20 men; mean age 24.5 y)	Personal sampling: 0.15 AM Personal sampling: 0.23 AM	Spirometry; CC16 and SP-D in serum. Measurements before and after exposure to pool air and filtered air, respectively, during bicycle exercise for 2 h.	A marginal but significant decrease in $FEV_{\%}$ in pool workers. The individual difference in changes between exposure conditions in FEV_1 and $FEV_{\%}$ was, however, non-significant. Marginal but significant decreases in both FEV_1 and $FEV_{\%}$ in volunteers. The individual difference in changes between exposure conditions in FEV_1 and $FEV_{\%}$ was significant. No significant changes in levels of CC16 and SP-D in either group.	(98)

Table 8. Effects on pneumoproteins and lung function in humans after short-term exposure to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-over, Belgium	11 healthy adults (7 women; mean age 22.0 y, 4 men; mean age 24.5 y)	0.16–0.28 45-min swimming sessions in a non-chlorinated and a chlorinated pool	Spirometry; FENO; SP-A, SP-B, CC16 and KL-6 in serum. Measurements before and after swimming sessions, and 3 h after exercise had ceased.	No decrements in lung function. FENO increased by 34% after exercise in the non-chlorinated but remained unchanged in the chlorinated pool. Levels of pneumoproteins were unchanged after exercise in the chlorinated pool.	(20)
Cross-sectional, Spain	48 healthy adult non-smokers (65% women; mean age 30 y)	0.29 AM 40-min swimming session in a chlorinated pool	Spirometry; FENO; Biomarkers of airway inflammation (8 cytokines, VEGF) and of oxidative stress (8-isoprostane) in exhaled breath condensate; SP-D, CC16 in serum and *CC16* genotype. Measurements before and after swimming session.	No significant changes in lung function tests or markers of airway inflammation or oxidative stress, but a slight increase in CC16 levels (3.3%).	(38)
Cross-over, Belgium	14 trained swimmers (6 women, 8 men; aged 18–23 y)	0.36 AM, 45-min intensive standardised swimming session in a chlorinated pool and in a non-chlorinated pool	Spirometry; SP-A, SP-B and CC16 in serum. Measurements before and after swimming sessions, and 11 h after exercise had ceased (trained swimmers) and before, after 1- and 2-h pool attendance (recreational swimmers).	No significant decrements in lung function in any group. SP-A and SP-B levels were significantly increased in a time-dependent manner in recreational and trained swimmers attending the chlorinated pool, but not in the non-chlorinated pool. CC16 levels increased immediately after exercise in trained swimmers, both in the non-chlorinated and chlorinated pools, but not in recreational swimmers.	(21)
	29 recreational swimmers: 16 children (10 girls, 6 boys; aged 5–14 y) and 13 adults (7 women, 6 men; aged 26–49 y)	0.49 AM, 2-h attendance in a chlorinated pool			

Table 8. Effects on pneumoproteins and lung function in humans after short-term exposure to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-sectional, Belgium	32 recreational swimmers: 16 children (mean age 9.6 y) 16 adults (mean age 36.9 y)	0.49 AM 2-h attendance in a chlorinated pool	SP-A, SP-B and CC16 in serum. Measurements before and after pool attendance.	Significant increases in SP-A and SP-B levels and the SP-B/CC16 ratio in both children and adults after attending the pool area for 2 h, in adults already after 1 h without swimming. CC16 levels decreased significantly after 1 h and reversed towards normal 1 h later in adults, but did not show any distinct pattern in children.	(11)
Food industry workers					
Cross-sectional, United States	Poultry processing: 18 evisceration workers 16 dark meat workers	Personal sampling GM: 0.005 0.0012 Soluble chlorine: 0.063 0.009	Spirometry before and after shift.	3/34 subjects had significant cross-shift declines in FEV_1 (> 10%). For these, trichloramine exposure was significantly higher (GM 0.022 mg/m^3) than for those without significant cross-shift declines in FEV_1 (GM 0.0021 mg/m^3). The GM concentration of soluble chlorine was also higher in those with significant cross-shift declines in FEV_1, however, not significant (0.071 mg/m^3 vs 0.022 mg/m^3). Concurrent exposure to trichloramine and soluble chlorine makes it difficult to identify the responsible agent.	(76)

AM: arithmetic mean, CC16: club cell protein 16 kDa, FENO: fraction of exhaled nitric oxide, $FEV_{\%}$: $FEV_1/FVC \times 100$, FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity, GM: geometric mean, KL-6: Krebs von den Lungen-6 protein, SP: surfactant-associated protein, VEGF: vascular endothelial growth factor.

11.3 Effects of long-term exposure

11.3.1 Asthma-related symptoms

Asthma is characterised by reversible obstruction in the airways, airway hyperresponsiveness and chronic airway inflammation. Common symptoms are shortness of breath, wheezing, chest tightness and coughing (46).

Spirometry is a standard test for measuring pulmonary function, and to diagnose asthma. Bronchial challenge test is used to detect airway hyperreactivity. The subject inhales nebulised methacholine or histamine to provoke bronchoconstriction and the degree of narrowing is quantified by spirometry. Chronic airway inflammation is associated with higher levels of nitric oxide and measurements of FENO can help to identify different asthma phenotypes and improving management of asthma (107).

Several studies have investigated chronic respiratory symptoms, indicating asthma, among workers with occupational exposure to inorganic chloramines in indoor swimming pool facilities, in cleaning and disinfection in the food industry and among swimmers, as described below and summarised in Table 9. In most studies questionnaires were used for assessment of chronic respiratory symptoms, and in several studies objective clinical tests were also used. Effects were predominantly evaluated against measurements of trichloramine levels.

11.3.1.1 Swimming pool workers

Chu *et al.* investigated the prevalence of asthma-related symptoms among 61 pool workers in 10 indoor swimming pools in Taiwan of which 6 had spa pools located in the same buildings. The reference group consisted of 43 management employees (for details, see Section 11.1.1). The overall average air concentration of trichloramine was 0.035 (0.017–0.15) mg/m^3 in the swimming pools and 0.059 ± 0.042 (SD) mg/m^3 in the spa pools. Corresponding soluble chlorine concentrations were 0.072 (0.005–0.21) mg/m^3 and 0.085 ± 0.056 mg/m^3. Symptoms were considered work-related if present during or after a work shift. Exposed workers had significantly more phlegm (OR 4.2, 95% CI 1.2–15) than non-exposed subjects, but there were no significant differences for asthma-related symptoms (OR, 95% CI) such as shortness of breath (0.5, 0.1–2.5), cough (1.3, 0.5–3.5), chest tightness (2.3, 0.7–7.6) and wheezing (0.3, 0.03–4) (25).

Dang *et al.* investigated work-related respiratory symptoms among 143 exposed and unexposed pool workers at an indoor waterpark and performed measurements of airborne trichloramine during two high-occupancy days and one low-occupancy day (for details, see Section 11.1.1). Lifeguards (n = 69; 37 men) reported significantly more work-related respiratory symptoms (PR, 95% CI) such as coughing (10.2, 4.3–24), wheezing (9.7, 2.4–40), shortness of breath (6.7, 2.5–18) and chest tightness (6.7, 2.1–21) (adjusted for smoking habits and asthma) compared to unexposed employees working outside the pool area (n = 74; 24 men). All 6 lifeguards with existing asthma in the exposed group reported worsening of asthma symptoms at work, but none of the 7 employees with asthma in the unexposed group (27).

Fantuzzi *et al.* investigated the prevalence of asthma-related respiratory symptoms in 81 lifeguards and swimming instructors (for details, see Section 11.1.1). The average air concentration of trichloramine was 0.65 mg/m^3. No significant association between reported asthma symptoms and airborne trichloramine levels was shown, but the number of subjects with asthma was low (36).

In the study by Fornander *et al.*, possible airway inflammation was evaluated in 39 pool workers by measuring FENO (for details, see Section 11.1). The average level of trichloramine was 0.20 mg/m^3. In most pool workers, FENO was within the normal range (mean value 15 ± 13 ppb). Prevalence of airway irritation was not associated with FENO or air trichloramine levels (42).

Jacobs *et al.* investigated the prevalence of asthma-related symptoms, physician-diagnosed asthma and use of asthma medication in 342 exposed pool workers (for details, see Section 11.1.1). Measurements of airborne trichloramine were performed in 6 different swimming facilities and the overall mean was 0.56 mg/m^3. Pool workers reported significantly more asthma-related symptoms (OR, 95% CI) such as phlegm (1.8, 1.3–2.4) and chest tightness (1.4, > 1.0–1.8) during the last 12 months, physician-diagnosed asthma (2.1, 1.5–3.0), asthma attacks (2.6, 1.5–4.6) and use of asthma medication (3.6, 2.4–5.3) compared to a randomly selected reference group from the general population (n = 2 711) (73).

Massin *et al.* used spirometry and methacholine bronchial challenge test to assess pulmonary function and airway hyperresponsiveness in 334 lifeguards recruited from 46 public swimming pools and 17 adventure swimming pools in France (for details, see Section 11.1.1). The average concentrations of trichloramine were 0.24 mg/m^3 in the public swimming pools and 0.67 mg/m^3 in the adventure swimming pools. In general, the prevalence of chronic respiratory symptoms was low, and no association was found with current or cumulative trichloramine exposure. Measured values of pulmonary function exceeded the predicted values for all variables in both men and women. The prevalence of positive methacholine bronchial challenge test was twice as common in women as in men. No association was found between trichloramine exposure and airway hyperresponsiveness (84).

Thickett *et al.* reported 3 pool workers with suspected work-related asthma following exposure to trichloramine, 2 of which had previous asthma and allergy. The investigation included spirometry, peak expiratory flow (PEF) measurements and bronchial challenge tests to methacholine, as well as trichloramine measurements. Two pool workers had PEF measurements showing significant work-related changes, as well as a positive specific challenge test (immediate asthmatic reactions) to trichloramine at 0.5 mg/m^3. The third pool worker had a positive workplace challenge test, i.e. spirometry (FEV_1) was first performed at baseline, and then after three 10-min exposures at the poolside. Measurements of trichloramine in the indoor swimming pool showed air levels of 0.1–0.57 mg/m^3. The authors concluded that trichloramine might be a cause of occupational asthma (129).

In the study by Demange *et al.*, 39 lifeguards were given a health questionnaire, and spirometry, measurement of FENO and a methacholine bronchial challenge test were performed (for details, see Section 11.1.1). Overall, pulmonary function

values exceeded the predicted ones for FEV_1, both among men and women. The prevalence of positive methacholine bronchial challenge test among lifeguards was relatively high (38%), but there was no reference group for comparison. The median FENO was higher among those with positive methacholine bronchial challenge test (18.9 ppb) compared to the rest (12.5 ppb), but the values were within the upper reference range (30). Measurements of airborne trichloramine were not performed.

Nordberg *et al.* investigated the prevalence of self-reported asthma in a cohort of 1 102 pool workers by questionnaire (for details, see Section 11.1.1). Exposure was classified in 3 different categories based on the average time during a workday each participant spent in the pool area. Exposure category 0 was given to those who did not spend any time in the pool area, category 1 did occasionally spend some time and category 2 spent most of the workday in the pool area. "Self-reported asthma" was defined as having a positive answer to the following question: "Do you suffer from asthma or have you suffered from asthma?". In a nested case-control study within the cohort, 44 cases of self-reported asthma that occurred after beginning as pool worker were compared with 128 age- and sex-matched controls without asthma. Subjects who spent most of the workday in the pool area (category 2) reported asthma more (non-significantly) often, after correction for heredity (OR 2.3, 95% CI 0.8–6.7). There was a tendency to a reduced risk of developing asthma in relation to the number of years of work in swimming pool environments among individuals who had worked more than 1 year, however not significant ($P = 0.07$), indicating a possible healthy worker effect (98). Measurements of airborne trichloramine were not performed.

Rosenman *et al.* investigated the occurrence of swimming pool workers with confirmed work-related asthma using data from the state surveillance systems in California, Michigan and New Jersey. In total, 44 confirmed cases of work-related asthma were identified; 17 cases 1994–2011 in California, 15 cases 1991–2012 in Michigan and 12 cases 1990–2011 in New Jersey. A majority (52%) of the cases were new onset; 32% secondary to an acute exposure incident and 20% to repeated exposure. Maintenance workers (35%) and lifeguards (32%) were the most common occupations. The authors concluded that the pool environment either might be a trigger of pre-existing asthma or associated with new onset of work-related asthma (112). Airborne concentrations of trichloramine were not reported.

11.3.1.2 Food industry workers

King *et al.* investigated asthma symptoms related to work in 109 poultry processing workers, of which 68 (39 men, 29 women) worked in the evisceration department and 41 (18 men, 23 women) in the dark meat department (for details, see Section 11.1.3). Evisceration workers reported more work-related wheezing (OR 5.9, 95% CI 1.4–40) and coughing (OR 6.2, 95% CI 2.1–21) than dark meat workers, ORs adjusted for smoking status. The prevalence of work-related asthma symptoms was also higher among evisceration workers, but did not reach statistical significance. A second survey was performed a year later comprising 34 workers (18 evisceration workers and 16 dark meat workers). Personal airborne levels of trichloramine were

significantly higher in the evisceration area (GM 0.0051 mg/m^3) than in the dark meat area (GM 0.0012 mg/m^3). However, workers (both groups) reporting current asthma symptoms (wheezing or two of the following symptoms: chest tightness, shortness of breath and cough) did not have significantly higher exposure levels of trichloramine than those without symptoms. Instead, workers reporting current asthma symptoms had higher exposure to soluble chlorine than those without such symptoms (GMs 0.048 mg/m^3 vs 0.019 mg/m^3), but the relationship was no longer significant after adjustment for smoking (76).

Massin and coworkers administered a symptom questionnaire to 175 cleaning and disinfecting workers in the food industry (149 men, 26 women) and 70 non-exposed workers (52 men, 18 women) (for details, see Section 11.1.3). Lung function and bronchial responsiveness were evaluated by spirometry and an abbreviated version of the methacholine bronchial challenge test. The sum of airborne soluble chlorine and trichloramine was measured by personal samplers for each step in the production process. Glutaraldehyde and formaldehyde was also used as disinfection agents, but air levels were not reported. A total exposure index for all irritants was calculated for each exposed worker. Three subgroups were constituted; a non-exposed group and two groups with lower and higher exposure. The workers were also divided in three subgroups with respect to cumulative exposure, taking number of working years into account. Overall, the prevalence of chronic respiratory symptoms was rather low and no relation to exposure levels or exposure duration was found. Baseline levels of pulmonary function were normal and not related to exposure. No associations between bronchial responsiveness and exposure levels or exposure duration were found (85).

11.3.1.3 Competitive swimmers

Exercise may increase ventilation up to 200 l/min in endurance athletes such as swimmers, and exercise alone increases bronchial responsiveness to methacholine in patients with asthma. Competitive swimmers, with up to 30 hours per week of training, inhale large amounts of air that floats above the water surface. In addition, they may microaspirate water in the airways. A high prevalence of asthma and use of asthma medication has been reported among competitive athletes participating in the Summer Olympic Games and particularly among endurance athletes, such as cycling, rowing and swimming (54).

Goodman and Hays found a higher prevalence of asthma among competitive swimmers compared to other competitive athletes (OR 2.6, 95% CI 1.9–3.5) in a meta-analysis including 6 studies (48). Mountjoy *et al.* reported a significantly higher prevalence of airway hyperresponsiveness/asthma in competitive swimmers compared to other aquatic disciplines (90).

Other studies have shown higher prevalences of asthma symptoms in competitive swimmers than in the general population (106, 111). However, the direction of the association is not clear and both exposure to chemicals and preference to swimming among asthmatics may be responsible for the association.

Helenius *et al.* investigated respiratory symptoms, bronchial responsiveness and signs of airway inflammation in 29 professional swimmers (12 men and 17 women, mean age 19 years) from the Finnish national team and 19 healthy control subjects (14 men and 5 women, mean age 24.4 years). Respiratory symptoms were evaluated via questionnaire, lung function was assessed using spirometry, and bronchial responsiveness by a histamine challenge test. Induced sputum samples were also collected and a skin prick test was performed. Of the swimmers, 8 (28%), including 4 of 6 with asthma previously diagnosed by a physician, had a history of exercise-induced bronchial symptoms. Spirometry values were within normal limits for all the swimmers. Fourteen (48%) of the swimmers and three (16%) of the controls showed increased bronchial responsiveness. Fifteen (52%) of the swimmers and seven (39%) of the control subjects had positive skin prick tests. Sputum from swimmers had significantly higher differential cell counts of eosinophils (mean 2.7% vs 0.2%) and neutrophils (54.7% vs 29.9%) than sputum from control subjects ($P < 0.01$). Eosinophilia (sputum differential eosinophil count > 4%) was observed in 6 (21%) of the swimmers and in none of the controls ($P < 0.05$). The 8 swimmers with a history of exercise induced bronchial symptoms had significantly higher sputum eosinophil differential cell counts than symptom-free swimmers ($P < 0.01$). No association was found between the sputum eosinophil counts and increased bronchial responsiveness. Atopic and non-atopic swimmers had similar amounts of sputum eosinophils and neutrophils. The authors concluded that long-term and repeated exposure to chlorine compounds in swimming pools during training and competition may contribute to the increased occurrence of bronchial hyperresponsiveness and airway inflammation in swimmers (56). Exposure data were not reported.

In another study, Helenius *et al.* followed 42 professional swimmers, most of them from the Finnish national team, for 5 years. All swimmers were evaluated with spirometry, histamine challenge test, skin prick test and questionnaire at baseline and at follow-up. Sputum samples were collected from 29 swimmers at both occasions. Sixteen (38%) swimmers were still active competitive swimmers at follow-up while 26 (62%) had stopped competing. Bronchial responsiveness was increased in 7 (44%) of the 16 active swimmers at baseline and in 8 (50%) of the active swimmers at follow-up, but only in 8/26 (31%) of the past swimmers at baseline and 3/26 (12%) at follow-up. The difference in change in bronchial hyperresponsiveness between groups was significant ($P = 0.023$). There was also a significant difference in the change in current asthma between the groups; it occurred in 31% of active swimmers at baseline and in 44% at follow-up, the corresponding numbers in past swimmers was 31% at baseline and 12% at follow-up ($P = 0.004$). Mild eosinophilic airway inflammation was aggravated over time in active swimmers as reflected in the sputum eosinophil counts. The authors concluded that the athletes' asthma is partly reversible and may develop during and decline after an active sports career (55). Exposure data were not reported.

Lévesque *et al.* compared the prevalence of respiratory symptoms in 305 competitive swimmers with that of 499 indoor soccer players in the Québec City

region of Canada via questionnaire, and evaluated the relationship between trichloramine concentrations and the athletes' respiratory symptoms (for details, see Section 11.1.2). There were no differences between the groups regarding wheezing or previous or current asthma diagnosis. The competitive swimmers reported significantly more symptoms (OR, 95% CI) from the lower airways (1.5, 1.0–2.2), such as cough (1.2, 1.1–2.7) (ORs adjusted for gender, age and number of training sessions per week). In a second part of the study, respiratory symptoms were assessed during five training sessions in 72 competitive swimmers and 73 soccer players. The mean concentration of trichloramine in air was 0.34 mg/m^3. The swimmers experienced significantly more symptoms from lower airways (adjusted OR 3.5, 95% CI 2.0–6.0). The swimmers were divided in two groups based on the median exposure level (0.37 mg/m^3). Swimmers with high exposure did not have more symptoms from lower airways than those with lower exposure (78).

Pedersen *et al.* investigated airway responsiveness and airway inflammation among 33 adolescent competitive swimmers (15 girls, 18 boys; mean age 14 years) and in two control groups consisting of 35 unselected adolescents (19 girls, 16 boys; mean age 14 years) and 32 asthmatics (13 girls, 19 boys; mean age 14 years). The swimmers and controls were evaluated via questionnaire, spirometry, methacholine challenge test, FENO and induced sputum. No differences in FENO, cellular sputum composition or prevalence of airway hyperresponsiveness were found between the groups, and the swimmers did not differ in the prevalence of respiratory symptoms from the unselected adolescents. The authors concluded that adolescent competitive swimmers that had been involved in competitive swimming for only a few years had no significant signs of airway damage (102).

Seys *et al.* evaluated members of a swimming club who had complained of respiratory symptoms associated with attending a municipal indoor swimming pool in Belgium (for details, see Section 11.1.2). Competitive swimmers and coaches were invited to a medical evaluation, and of them, 22 adolescent swimmers and 6 adult coaches were investigated by clinical interview and spirometry, measurement of FENO and a methacholine bronchial challenge test. Repeated measurements of airborne trichloramine by stationary sampling showed levels of 0.20–1.30 mg/m^3. Common reported symptoms from lower airways were cough (57%) and dyspnoea (46%). Mean FEV_1 % predicted was 109.1%. Mean FENO level was 19.7 ppb; the cut-off value of 25 ppb was exceeded in 3 subjects. Airway hyperreactivity was detected in 22/28 swimmers (85%). After removal of a glue containing polyamines, used to repair a pipework, the concentration of trichloramine in air decreased to below 0.5 mg/m^3. At follow-up 1 year later including 13/28 subjects from the first evaluation, the hyperreactivity was less pronounced in 6/12 subjects, more pronounced in 5/12 subjects and was unchanged in 1 subject. However, the air levels of trichloramine had presently risen due to reduced intake of outside air because of low outside temperature (118).

11.3.1.4 Children/adolescents

In general, children's exposure to indoor swimming pool air during leisure time and school time is limited compared to that of pool workers and competitive swimmers. Studies conducted in Belgium have demonstrated an increased risk of asthma symptoms among children with atopy associated with cumulative indoor swimming pool attendance (9, 11, 15).

Bernard *et al.* investigated prevalence of asthma in relation to pool attendance among 1 881 children aged 7–14 years in Belgium by retrospectively analysing data from an earlier asthma survey conducted 1996–1999. Data on health status, respiratory symptoms and environmental and lifestyle variables were obtained via questionnaire, completed by their parents. Asthma was defined as a positive exercise induced bronchoconstriction (EIB) test, i.e. a reduction in PEF of ≥ 10% at 5 or 10 min after exercise. In addition, children with medication for asthma were included (total asthma). School directors gave information on pool attendance. Cumulative pool attendance was estimated by multiplying the time spent in pool water by the weekly frequency of attendance, and the number of years attending the school pool. The prevalence of respiratory symptoms, i.e. wheezing, was not associated with positive EIB test or total asthma. Positive EIB test and total asthma prevalence were significantly associated with cumulative attendance. The associations remained significant after adjustment for the height of the pool hall, pets and passive smoking, and were strongest among the youngest children ($P < 0.001$) (11). Measurements of airborne trichloramine were not performed.

The authors also studied effects on the lung epithelium in relation to pool attendance. Lung-specific proteins (SP-A, SP-B and CC16) and immunoglobulin E (IgE) were measured in serum of 226 children (116 boys and 110 girls), mean age 10 years. Children with asthma were not included. The school directors provided information on pool attendance; measurements of airborne trichloramine were not performed. A significant dose-effect association between cumulative pool attendance and proteins SP-A and SP-B was demonstrated (11).

Bernard *et al.* also investigated respiratory symptoms among 341 children aged 10–13 years who all visited the same indoor swimming pool facility in Belgium. The concentrations of trichloramine in air were 0.25–0.54 mg/m^3. The parents completed a questionnaire concerning their children's health status, respiratory symptoms and current and previous swimming pool attendance. Total and allergen-specific IgE were measured in serum, and an EIB test was performed. The test was defined as positive if a reduction of 20% or more in FEV_1 was seen after exercise. All children performed a FENO test and it was considered elevated if nitric oxide was > 30 ppb. Asthma was defined as having a positive EIB test or a physician-diagnosed asthma (total asthma). Cumulative pool attendance was associated with elevated FENO (OR 1.3, 95% CI 1.1–1.4) and total asthma but only in children with IgE > 100 kIU/l (OR 1.8, 95% CI 1.1–2.7). There was a dose-response effect and the strongest effect was found with pool attendance before the age of 6–7 years (9).

In a later study, Bernard *et al*. examined 847 school children, aged 13–18 years who had attended outdoor or indoor chlorinated pools, 114 of them had mainly

attended a copper-silver pool (referents). Data on pool attendance and the child's health status were collected via parental questionnaire. The students were interviewed about respiratory symptoms, and total and allergen-specific IgE were measured in serum, and an EIB test was performed. The test was defined as positive if a reduction of ≥ 10% in FEV_1 after exercise was found. Ever asthma was defined as asthma diagnosed at any time by a physician, and current asthma was defined as physician-diagnosed asthma presently treated with medication and/or a positive EIB test. The concentration of trichloramine in air was in the range 0.3–0.5 mg/m^3 in the indoor swimming pools the children attended. In those with a cumulative pool attendance > 1 000 hours, ORs (95% CIs) for ever and current asthma was 3.7 (1.4–9.9) and 8.1 (1.7–37), respectively, compared to referents. Atopic children (i.e. those with total IgE > 30 kIU/l) had a significantly higher risk for asthma symptoms and for ever or current asthma related to total numbers of hours spent in chlorinated pools; among those with cumulative pool attendance > 1 000 hours, the ORs (95% CI) for ever and current asthma were 7.8 (2.1–29) and 15 (1.8–120), respectively, compared to atopics with cumulative pool attendance < 100 hours (15).

The information on the exposure assessments of trichloramine in these three Belgian studies (9, 11, 15) is very sparse regarding sampling time, where measurements were performed and number of samples. This makes it difficult to relate the exposure of trichloramine to the effects reported.

Studies in other European countries such as Spain (39, 40), the United Kingdom (41) and the Netherlands (72) found no association between cumulative swimming pool attendance and respiratory symptoms among children. These studies were population-based and had larger sample sizes.

In the Spanish study, Font-Ribera *et al.* investigated the prevalence of asthma in children related to early pool attendance. A questionnaire was sent to the parents of 3 223 children aged 9–12 years. Data was collected concerning the children's pool attendance and respiratory symptoms the last 12 months. The children attended different swimming pools; most of them were chlorinated (median air trichloramine concentration 0.16 mg/m^3). Swimming pool attendance during the last 12 months was associated with a slightly lower prevalence (OR, 95% CI) of current asthma (0.5, 0.2–0.8) compared to those children who never attended pools. A similar (non-significant) finding was shown for ever asthma (0.7, 0.4–1.1) (39).

A prospective longitudinal study was performed in a population-based British cohort comprising 5 738 children (50.7% boys) followed by questionnaires up to 10 years of age. Data on swimming were collected at 0.5–6.7 years of age, and data on respiratory symptoms, allergies, asthma and asthma medication at 7 and 10 years. Spirometry and a skin prick test were performed at 7–8 years. No increased risk of asthma or any respiratory symptoms associated to swimming pool attendance was found either in all or in atopic children. Children with high cumulative swimming pool attendance from birth to 7 years had an OR (95% CI) of 0.9 (0.6–1.4) and 0.5 (0.3–0.9), for ever and current asthma, respectively, at 7 years, and a 0.2 (95% CI 0.02–0.4) standard deviation increase in midexpiratory flow, compared to those with low cumulative exposure. Children with asthma and

high cumulative swimming pool attendance had lower prevalence of current asthma at 10 years (OR 0.3, 95% CI 0.14–0.8) than those with low cumulative swimming pool attendance. The authors concluded that swimming was associated with increased lung function and a lower prevalence of asthma symptoms, especially among children with pre-existing respiratory conditions (41). Air levels of trichloramine were not reported.

Font-Ribera *et al*. performed a cross-sectional survey among 2 758 children aged 6–12 years in Spain. Data on previous and current swimming pool attendance, health status and respiratory symptoms the last 12 months was collected via parental questionnaire. Current regular swimming in indoor pools was not associated with symptoms in the last 12 months. Regular indoor pool attendance before 2 years of age was not associated with ever had or having asthma or wheezing (40). Air levels of trichloramine were not reported.

The study by Jacobs *et al*. included 2 359 Dutch children aged 6–13 years, of which 419 children were tested for allergen sensitisation and CC16 levels in serum. The parents were given a questionnaire concerning swimming pool attendance, upper and lower respiratory symptoms, allergy and eczema. Measurements of airborne trichloramine were performed by stationary sampling in 9 swimming pool facilities visited on a regular basis by 77% of the study population. The average concentration of airborne trichloramine was 0.21 mg/m^3. CC16 levels were associated with sensitisation to house dust mites and common allergens but not with respiratory symptoms. Reported swimming pool attendance and trichloramine exposure were not associated with asthma, wheezing or CC16 levels (72).

Bernard *et al.* measured CC16, SP-D, total and allergen-specific IgE in 835 school children (470 girls, 365 boys; mean age 15.4 years). Data on pool attendance, general and respiratory health were collected via parental questionnaire. The CC16/SP-D ratio was calculated and was believed to integrate changes in permeability (SP-D) and secretory function (CC16) of the airway epithelium. Children with the highest pool attendance (total or before the age of 7 years) had significantly lower serum levels of CC16 and CC16/SP-D ratios than other children. CC16 levels were not associated with any sensitisation (pollen, house mite or pets) or prevalence of asthma, hay fever and rhinitis. Among boys, a low CC16/SP-D ratio was associated with a higher prevalence of house dust mite sensitisation, of allergic rhinitis in those sensitised to house dust mite and of asthma in those sensitised to any aeroallergen (OR 3.4, 95% CI 1.2–11), house dust mite (OR 5.2, 95% CI 1.4–24) or pollen (OR 5.8, 95% CI 1.5–27). Among girls, a low CC16/SP-D ratio was associated with pet sensitisation and with hay fever in those sensitised to pollen, but not with asthma (14). Air levels of trichloramine were not reported.

In a recent study, Andersson *et al.* investigated the prevalence of physician-diagnosed asthma and respiratory symptoms among 1 866 Swedish school children aged 11–12 years (boys 51%) by questionnaire. Of them, 1 652 also participated in skin prick testing. Current swimming pool attendance was reported as ≥ 1/week or < 1/week in the last 12 months. The prevalence of current asthma was 8.9% (boys 10%, girls 7.9%). Stratified analyses for allergic sensitisation adjusted for

gender, parental smoking, parental asthma and damp housing showed statistically significant associations (OR, 95% CI) between physician-diagnosed asthma (1.9, 1.1–3.3) and current asthma (1.9, 1.1–3.3) and pool attendance among atopic children (5). Air levels of trichloramine were not reported.

11.3.1.5 Conclusion

Exposure to trichloramine in the workplace air may aggravate asthma symptoms in individuals with existing asthma (27, 129). Some studies have shown higher prevalences of self-reported asthma-related symptoms (27, 73), physician-diagnosed asthma, asthma attacks and use of asthma medication (73) in exposed workers compared to an unexposed reference group. The overall mean concentration of airborne trichloramine in the study by Jacobs *et al*. was 0.56 (0.13–1.34) mg/m^3 (73). No significant associations between self-reported asthma-related symptoms and trichloramine exposure were found in other studies (42, 76, 85), even at higher mean exposure levels (36).

Young competitive swimmers reported significantly more symptoms from lower airways in general and during training sessions (trichloramine air levels: 0.26–0.41 mg/m^3) than referents, but there was no association between trichloramine levels and symptoms (78).

A high prevalence of airway hyperreactivity has been found in pool workers (30) as well as in competitive swimmers (56, 118). There are, however, indications that the increased hyperreactivity is partially reversible when exposure cease or decrease (55, 118). There were no associations between exposure to trichloramine and objective clinical tests of airway hyperreactivity (84) and airway inflammation (42).

A high prevalence of work-related asthma among lifeguards (112) as well as in competitive swimmers (48, 90) has been reported, and two studies indicated that occupational exposure to trichloramine may contribute to development of asthma in individuals without previous respiratory diseases (98, 129). Some cross-sectional studies indicate an association between cumulative attendance in chlorinated pools and an increased risk of asthma among atopic school children (5, 9, 11, 15). These findings are, however, contradicted by results from other large population-based studies in children (39-41, 72).

11.3.2 Other effects

In a study by Zierler *et al*., the cancer mortality in 43 communities in Massachusetts using either chlorine or monochloramine for disinfection of drinking water was investigated. Residents exposed to chloraminated water were used as controls assuming less exposure to chlorination-by-products (trihalomethanes). In general, cancer mortality was not associated with type of disinfectant used, except a slight association for chlorine use and bladder cancer. A small increase in mortality from influenza and pneumonia was noted in chloraminated communities (144). In a later case-control study, the relationship between residence in communities using chlorine for disinfection and mortality in bladder cancer remained (145). Again, exposure to chloraminated drinking water was used as control, and the results from

these studies can not be used to evaluate adverse health effects from exposure to inorganic chloramines.

11.4 Genotoxic effects

No data were located.

11.5 Carcinogenic effects

No data were located.

11.6 Reproductive and developmental effects

No data were located.

Table 9. Asthma-related symptoms/effects in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Swimming pool workers					
Cross-sectional, Taiwan	61 lifeguards and swimming instructors (36 men, 25 women) 43 reception and management employees (15 men, 28 women	Swimming pools AM: 0.035 (0.017–0.15) Spa pools AM ± SD: 0.059 ± 0.042 Soluble chlorine: Swimming pools AM: 0.072 (0.005–0.21) Spa pools AM ± SD: 0.085 ± 0.056	Questionnaire	Exposed workers had more phlegm (30% vs 6.9%) (OR 4.2, 95% CI 1.2–15) than non-exposed subjects, but there were no significant differences for asthma-related symptoms such as shortness of breath, cough, chest tightness and wheezing.	(25)
Cross-sectional, Sweden	39 pool workers (gender not given) No referents	0.20 AM 0.04–0.36	Questionnaire; FENO	FENO was within the normal range (mean 15 ± 13 ppb) in pool workers. Prevalence of airway irritation was not associated with FENO or exposure levels.	(42)
Cross-sectional, France	334 lifeguards (256 men, 78 women) No referents	Swimming pools: 0.24 AM Leisure swimming pools: 0.67 AM	Questionnaire; Spirometry; Methacholine bronchial challenge test	No associations between exposure levels and airway hyperresponsiveness.	(84)
Cross-sectional, United States	69 lifeguards (37 men, 32 women) 74 hotel employees (24 men, 50 women)	0.44 AM (high-occupancy day)	Questionnaire	Lifeguards reported more work-related respiratory symptoms (PR, 95% CI) such as coughing (10, 4.3–24), wheezing (9.7, 2.4–40), shortness of breath (6.7, 2.5–18) and chest tightness (6.7, 2.1–21) (adjusted for smoking habits and asthma) compared to unexposed employees. All 6 lifeguards with asthma reported worsening of asthma symptoms at work, but none of the 7 controls with asthma.	(27)

Table 9. Asthma-related symptoms/effects in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Case report, United Kingdom	2 lifeguards (1 man, 1 woman) and 1 swimming instructor (woman) No referents	0.1–0.57	Spirometry (PEF); Provocation tests	2 pool workers had PEF measurements showing significant work-related changes as well as a positive specific challenge test to trichloramine at 0.5 mg/m^3. The 3rd pool worker had a positive workplace challenge test.	(129)
Cross-sectional, Netherlands	342 exposed pool workers (127 men, 215 women) 2 711 subjects randomly selected from the general Dutch population	0.56 AM 0.66 AM (estimated long-term exposure)	Questionnaire	Pool workers reported more asthma-related symptoms (OR, 95% CI) such as phlegm (1.8, 1.3–2.4) and chest tightness (1.4, > 1.0–1.8) during the last 12 mo, physician-diagnosed asthma (2.1, 1.5–3.0), asthma attacks (2.6, 1.5–4.6) and use of asthma medication (3.6, 2.4–5.3) than referents.	(73)
Cross-sectional, Italy	81 lifeguards and swimming instructors (40 men, 41 women) 47 other employees (21 men, 26 women)	0.65 AM	Questionnaire	No significant association between reported asthma symptoms and airborne trichloramine levels. The number of subjects with asthma was low.	(36)
Cross-sectional, France	39 lifeguards (29 men, 10 women) No referents	–	Questionnaire; Spirometry; Methacholine bronchial challenge test; FENO	Pulmonary function values exceeded the predicted ones for FEV_1. The prevalence of positive challenge test among lifeguards was relatively high (38.5%). The median FENO was higher among those with positive challenge test (18.9 ppb) compared to the others (12.5 ppb); values were within the upper reference range.	(30)

Table 9. Asthma-related symptoms/effects in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Nested case-control, Sweden	44 cases of self-reported asthma that occurred after they began working as a pool worker 128 age- and sex-matched controls without asthma	–	Questionnaire	Increased prevalence of asthma (OR 2.3, 95% CI 0.8–6.7) (after correction for heredity) among pool workers in the highest exposure category (2) compared to categories 0 and 1 (no and low exposure) (non-significant). Association between numbers of hours, during an average day, spent in the swimming pool environment and the percentage of workers reporting work-related symptoms such as dyspnoea and coughing ($P < 0.01$).	(98)
Cross-sectional, Sweden	1 102 pool workers (513 men, 589 women)				
Food industry workers					
Cross-sectional, United States	Poultry processing workers *1st survey:* 68 evisceration workers (18 men, 29 women) Referents: 41 dark meat workers (18 men, 23 women) *2nd survey:* 18 evisceration workers 16 dark meat workers	*1st survey:* No data *2nd survey:* Personal sampling GM: 0.005 evisceration 0.0012 dark meat Soluble chlorine GM: 0.063 evisceration 0.009 dark meat	Questionnaire; Spirometry	*1st survey:* Evisceration workers reported more (OR, 95% CI) work-related wheezing (5.9, 1.4–40) and coughing (6.2, 2.1–21) than dark meat workers, ORs adjusted for smoking status. The prevalence of work-related asthma symptoms was also higher in evisceration workers (non-significant). *2nd survey:* Workers (both groups) reporting current asthma symptoms did not have higher exposure to trichloramine than those without symptoms. No association between exposure to trichloramine and asthma symptoms (adjusted for smoking habits) was found. Instead, an association between soluble chlorine and current asthma symptoms was reported.	(76)

Table 9. Asthma-related symptoms/effects in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-sectional, France	175 workers in the food industry (149 men, 26 women) 70 non-exposed workers (52 men, 18 women)	Personal sampling: 0.33–0.49 AMs (sum of soluble chlorine and trichloramine) [a] Co-exposure to glutaraldehyde and formaldehyde	Questionnaire; Spirometry; Methacholine bronchial challenge test	Overall, the prevalence of chronic respiratory symptoms was rather low and no relation to exposure levels or exposure duration (years) was found. Baseline levels of pulmonary function were normal and not related to total exposure. No association between bronchial responsiveness and exposure expressed as total exposure index and exposure duration, respectively, was found.	(85)
Competitive swimmers					
Cross-sectional, Canada	*Part 1:* 305 competitive swimmers (101 boys, 204 girls) 499 indoor soccer players (297 boys, 202 girls)	*Part 1:* No data	Questionnaire (respiratory symptoms)	*Part 1:* Swimmers reported more symptoms (OR, 95% CI) from lower airways (1.5, 1.0–2.2) such as cough (1.2, 1.1–2.7) than soccer players (ORs adjusted for sex, age and number of training sessions per week).	(78)
	Part 2: 72 competitive swimmers 73 indoor soccer players	*Part 2:* 0.34 AM 0.37 median 0.26–0.41	Questionnaire (respiratory symptoms during training sessions)	*Part 2:* Swimmers reported more symptoms from lower airways (OR 3.5, 95% CI 2.0–6.0) than soccer players. Swimmers exposed to trichloramine levels > 0.37 mg/m^3 did not report more symptoms from lower airways than swimmers exposed to < 0.37 mg/m^3.	
Cross-sectional, Belgium	22 competitive swimmers (10 boys, 12 girls) and 10 coaches (3 men, 3 women) No referents	0.20–1.30	Clinical interview; Spirometry; Methacholine bronchial challenge test; FENO	Common symptoms from lower airways were cough (57%) and dyspnoea (46%). Mean FEV_1% predicted was 109%. Mean FENO level was 19.7 ppb; the cut off value of 25 ppb was exceeded in 3 subjects. Airway hyperreactivity was detected in 22/28 swimmers (85%).	(118)

Table 9. Asthma-related symptoms/effects in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-sectional, Finland	29 competitive swimmers (12 men, 17 women) 19 healthy non-exposed subjects	–	Questionnaire; Spirometry; Histamine bronchial challenge test; Induced sputum test	*Spirometry:* Values were within normal limits for all swimmers. 14 (48%) of the swimmers and 3 (16%) of the controls showed increased bronchial responsiveness. *Sputum differential cell counts:* Swimmers had higher cell counts of eosinophils (mean 2.7% vs 0.2%) and neutrophils (55% vs 30%) than controls ($P < 0.01$). Eosinophilia (eosinophil count of > 4%) was observed in 6 (21%) swimmers and in none of the controls ($P < 0.05$). The 8 swimmers with a history of exercise induced bronchial symptoms had higher eosinophil cell counts than symptom-free swimmers ($P < 0.01$). No association was found between eosinophil counts and increased bronchial responsiveness.	(56)
Follow-up, Finland	42 competitive swimmers (16 active and 26 past swimmers) No referents	–	Questionnaire; Spirometry; Histamine bronchial challenge test; Skin prick test; Induced sputum test	Bronchial responsiveness was increased in 7 (44%) and 8 (50%) of the active swimmers at baseline and at follow-up, but only in 8 (31%) of the past swimmers at baseline and 3 (12%) at follow-up. The difference in change in bronchial hyperresponsiveness between groups was significant ($P = 0.023$). There was a significant difference in the change in current asthma between the groups; it occurred in 31% of active swimmers at baseline and in 44% at follow-up, corresponding numbers in past swimmers were 31% at baseline and 12% at follow-up ($P = 0.004$). Mild eosinophilic airway inflammation was aggravated over time in active swimmers as reflected in the sputum eosinophil counts.	(55)

Table 9. Asthma-related symptoms/effects in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-sectional, Finland	33 competitive swimmers (15 girls, 18 boys; mean age 14.3 y) 2 control groups: 35 unselected adolescents (19 girls, 16 boys; mean age 14.4 y) 32 asthmatics (13 girls, 19 boys; mean age 14.1 y)	–	Questionnaire; Spirometry; Histamine bronchial challenge test; FENO; Induced sputum test	No differences in FENO, cellular sputum composition or prevalence of airway hyperresponsiveness between the groups. The swimmers did not differ in the prevalence of respiratory symptoms compared to the unselected adolescents.	(102)
Children/adolescents					
Cross-sectional, Spain	3 223 children aged 9–12 y No referents	0.16 AM	Parental questionnaire (respiratory symptoms last 12 mo)	Swimming pool attendance during the last 12 mo was associated with a slightly lower prevalence of current asthma (OR 0.5, 95% CI 0.2–0.8) compared to children who never attended pools; a similar (non-significant) finding was shown for ever asthma (OR 0.7, 95% CI 0.4–1.1).	(39)
Cross-sectional, Netherlands	2 369 children aged 6–13 y No referents	0.21 AM	Parental questionnaire (respiratory symptoms, allergy and pool attendance); CC16 in serum; Aeroallergen-specific IgE	CC16 levels were associated with sensitisation to house dust mites and common allergens but not with respiratory symptoms. Reported swimming pool attendance and trichloramine exposure were not associated with asthma, wheezing or CC16 levels.	(72)

Table 9. Asthma-related symptoms/effects in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-sectional, Belgium	341 children aged 10–13 y No referents	0.25–0.54	Parental questionnaire (respiratory symptoms and pool attendance); EIB test; FENO; CC16 in serum; Total and allergen-specific IgE	Cumulative pool attendance was associated with elevated FENO (OR 1.3, 95% CI 1.1–1.4) and total asthma but only in children with IgE > 100 kIU/l (OR 1.8, 95% CI 1.1–2.7). There was an exposure-response effect and the strongest effect was found with pool attendance before the age of 6–7 y.	(9)
Cross-sectional, Belgium	847 school children aged 13–18 y, of which: 733 exposed (attending outdoor or indoor chlorinated pools, 114 non-exposed (mainly attending copper-silver pools)	0.30–0.50	Parental questionnaire (respiratory symptoms and pool attendance); EIB test; Total and allergen-specific IgE	In children with a cumulative pool attendance > 1 000 h, OR (95% CI) for ever asthma was 3.7 (1.4–9.9) and for current asthma 8.1 (1.7–37) compared to referents. Atopic children had higher risk for asthma symptoms, and for ever or current asthma related to total numbers of hours spent in chlorinated pools; among atopics with cumulative pool attendance > 1 000 h, ORs (95% CIs) for ever and current asthma were 7.8 (7.8–29) and 15 (1.8–120), respectively, compared to those with cumulative pool attendance < 100 h.	(15)
Cross-sectional, Sweden	1 866 school children aged 11–12 y (boys 51%) No referents	–	Parental questionnaire (respiratory symptoms and pool attendance); Skin prick test; Total and allergen-specific IgE	Current swimming pool attendance was reported as ≥ 1/wk or < 1/wk in the last 12 mo. The prevalence of current asthma was 8.9% (boys 10%, girls 7.9%). Stratified analyses for allergic sensitisation adjusted for gender, parental smoking, parental asthma and damp housing showed a significant association (OR, 95% CI) for physician-diagnosed asthma (1.9, 1.1–3.3) and current asthma (1.9, 1.1–3.3) and pool attendance but only among atopic children.	(5)

Table 9. Asthma-related symptoms/effects in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-sectional, Belgium	1 881 children aged 7–14 y No referents	–	Parental questionnaire (health status, respiratory symptoms); School directors reported pool attendance; EIB test	Prevalence of respiratory symptoms was not associated with positive EIB test or total asthma (positive EIB test and/or medication for asthma). Positive EIB test and total asthma prevalence were significantly associated with cumulative pool attendance. The associations remained significant after adjustment for pool height, pets and passive smoking, and were strongest among the youngest children ($P < 0.001$).	(11)
Cross-sectional, Belgium	835 school children (470 girls, 365 boys; mean age 15.4 y) No referents	–	Parental questionnaire (health status, respiratory symptoms and pool attendance); CC16 and SP-D in serum; Total and allergen-specific IgE	Children with the highest pool attendance (total or before the age of 7 y) had significantly lower levels of CC16 and CC16/SP-D ratio than other children. CC16 was not associated with any sensitisation or prevalence of asthma, hay fever or rhinitis. Among boys, a low CC16/SP-D ratio was associated with a higher prevalence (OR, 95% CI) of house dust mite sensitisation, of allergic rhinitis in subjects sensitised to house dust mite and asthma in those sensitised to any aeroallergen (3.4, 0.1–0.8), house dust mite (5.2, 1.4–24) or pollen (5.8, 1.5–27). Among girls, a low CC16/SP-D ratio was associated with pet sensitisation and with hay fever in those sensitised to pollen, but not with asthma.	(14)

Table 9. Asthma-related symptoms/effects in humans exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Study design/ country	Study group	Exposure level, mg/m^3	Method	Effects	Reference
Cross-sectional, Spain	2 758 children aged 6–12 y No referents	–	Parental questionnaire (health status, respiratory symptoms last 12 mo and previous and current pool attendance)	Current regular swimming in indoor pools was not associated with symptoms in the last 12 mo. Regular indoor pool attendance before 2 y of age was not associated with ever had or having asthma or wheezing.	(40)
Prospective longitudinal, United Kingdom	5 738 children (boys 51%) No referents	–	Parental questionnaire (health status, respiratory symptoms at 7 and 10 y) and pool attendance at 0.5–6.7 y); Spirometry and skin prick test at 7–8 y	No increased risk of asthma or any respiratory symptoms associated with pool attendance was found either in all or atopic children. Children with high cumulative pool attendance from birth to 7 y had ORs (95% CIs) of 0.9 (0.6–1.4) and 0.5 (0.3–0.8) at 7 y for ever and current asthma, respectively, and a 0.2 (95% CI 0.02–0.4) SD increase in midexpiratory flow, compared to those with low cumulative exposure. Children with asthma and high cumulative pool attendance had lower prevalence for current asthma at 10 y (OR 0.3, 95% CI 0.14–0.8) than those with low cumulative pool attendance.	(41)

[a] Unclear if expressed as trichloramine, or chlorine, equivalents.

AM: arithmetic mean, CC16: club cell protein 16 kDa, CI: confidence interval, EIB: exercise induced bronchoconstriction, FENO: fraction of exhaled nitric oxide, FEV_1: forced expiratory volume in the first second, GM: geometric mean, IgE: immunoglobulin E, OR: odds ratio, PEF: peak expiratory flow, PR: prevalence ratio, SD: standard deviation, SP: surfactant-associated protein.

12. Dose-effect and dose-response relationships

12.1 Monochloramine

No inhalation data were located.

12.1.1 Human studies

Daily consumption of drinking water containing monochloramine corresponding to 0.043 mg/kg bw/day (assuming a body weight of 70 kg) for 4 weeks did not alter parameters of lipid and thyroid metabolism in 16 healthy men, whereas 0.32 mg/kg bw/day was associated with an increase in the plasma level of apolipoprotein B (142).

No effects were shown in 10 healthy male volunteers administered monochloramine in water daily for 12 weeks (corresponding to 0.036 mg/kg bw/day assuming a body weight of 70 kg) or every 3rd day for 13 days at increasing concentrations corresponding to ≤ 0.034 mg/kg bw/day as evaluated by an extensive battery of measures including serum chemistry, blood count, urine analysis and physical examination (81).

No relevant studies on long-term exposure were located.

12.1.2 Animal studies

Animal studies on monochloramine are summarised in Table 4 (Chapter 10). Clear conjunctival irritation was observed in rabbits after 1 hour of exposure to a solution containing monochloramine (corresponding to 4 mg/l Cl_2). Monochloramine was considerably more irritating than free chlorine (33).

Transiently increased GSH levels in rats were reported after single oral gavage doses of 0.19–0.75 mg/kg bw of monochloramine (2).

Some short-term drinking water studies have been performed. After 9-week exposures of rats to 0.8–3.4 mg/kg bw/day of monochloramine, some alterations in immune function were observed (35). In mice, administration for 28 days at dose levels of 0.38–38 mg/kg bw/day resulted in some minimal immunological effects that were judged to be biologically insignificant. No effects were observed in haematological parameters, organ weights, body weight, body weight gain or water consumption (50). No effects on body weight gain or haematological parameters were observed in rats exposed 45 days at 1.2–12 mg/kg bw/day, except a decrease in methaemoglobin, opposite to what was expected (19). In mice, reduced body weight and slightly increased haematocrit were seen at doses ≥ 8.7 mg/kg bw/day, whereas other haematological parameters (including GSH levels) were unaffected following administration during 30 days at doses of 0.44–35 mg/kg bw/day (89). Exposure of monkeys for 6 weeks (10 mg/kg bw/day) had no effect on haematological and clinicochemical parameters in blood, on serum thyroxine (T4) levels or body weight (8).

Some long-term drinking water studies were located. Following administration of 0.05–5.2 mg/kg bw/day of monochloramine to male rats (4/group) for up to 12

months, an indication of increased DNA synthesis (thymidine incorporation) in kidney, spleen, liver and testes, and decreased blood GSH levels, were seen at all doses (2).

Male and female rats and mice were administered monochloramine in drinking water (2.1–17.2 mg/kg bw/day) for up to 2 years. No carcinogenic effects were seen in mice and male rats. A marginal, dose-related increase in mononuclear cell leukaemia incidence among female rats was considered as equivocal evidence of carcinogenic activity (99).

Reduced body weight gain and minor biochemical, haematological, immunological and histopathological changes were observed in rats exposed to 21.6 mg/kg bw/day of monochloramine for 13 weeks in drinking water. The effects were largely related to reduced water and food consumption (104). Similar effects were reported also in other long-term studies in rats and mice at daily doses of 5–17 mg/kg bw/day (2, 28, 29, 99).

A few oral studies on reproductive or developmental toxicity were found. After administration of 1.6–8 mg/kg bw/day of monochloramine by oral gavage for 5 consecutive days to mice, no sperm-head abnormalities were observed 1, 3 and 5 weeks after the last dose (86). No histological changes or effects on reproductive organs were noted in male and female rats administered monochloramine (2.5–10 mg/kg bw/day) by oral gavage for up to 73 days. Sperm quality and foetuses were unaffected (23). Neither were any effects on foetuses shown after exposure of Virgin rats to monochloramine via drinking water (0.09–9.3 mg/kg bw/day) 2.5 months prior to and throughout gestation (1).

12.2 Dichloramine

In the only study located, male and female rats were administered dichloramine in drinking water (0.019–24 mg/kg bw/day) for 13 weeks. Minimal to mild histological effects in thyroid, kidneys or gastric cardia were observed from 0.19 mg/kg bw/day in males and from 2.5 mg/kg bw/day in females, respectively (Table 5, Chapter 10) (92).

12.3 Trichloramine

12.3.1 Human studies

12.3.1.1 Ocular and airway irritation

Several cross-sectional studies have shown higher prevalences of self-reported ocular and/or upper airway irritation among pool workers exposed to trichloramine compared to unexposed reference groups (Table 10). Pool workers are mainly exposed to trichloramine in air, whereas food industry workers and competitive swimmers to a higher degree are exposed also to soluble chlorine, in aerosols and/or the chlorinated water itself. Only swimming pool workers are therefore included in the following compilation of irritant effects of airborne trichloramine.

Chu *et al*. reported significantly more irritation ("during or after work shift") in the throat (but not in the eyes and nose) in pool workers exposed to trichloramine concentrations of 0.017–0.15 mg/m^3 (co-exposure to soluble chlorine) compared to unexposed referents, however, no concentration-response data were presented (25).

Löfstedt *et al*. reported significantly more ocular and nasal symptoms during the last week in pool workers with stationary and personal measurements of trichloramine being in the range 0.001–0.64 mg/m^3 and < 0.001–0.24 mg/m^3 (AMs 0.18 and 0.071 mg/m^3), respectively, compared to referents, but there was a lack of concentration-response relationships among exposed (82). Also some other studies did not find any concentration-response relationships between airborne trichloramine levels and self-reported irritation (42, 73).

In contrast, concentration-response relationships were demonstrated in some studies. Significantly higher prevalences of irritative symptoms in eyes and nose were reported in pool workers in one study at 0.36 (0.30–0.52) mg/m^3 of trichloramine (101) and in three other studies with pool workers from around 0.5 mg/m^3 (36, 64, 84). In addition, significant concentration-response trends for eye, nose and throat irritation over the whole exposure range (4 sub-groups) were reported for lifeguards (84).

An association between the prevalence of irritation in upper airways or eyes and cumulative trichloramine exposure was observed in some studies (73, 84, 101). However, the cumulative exposures were calculated in different ways and are difficult to interpret in terms of exposure concentration. NOAECs and LOAECs can therefore not be identified from the cumulative exposure data.

12.3.1.2 Effects on pneumoproteins and lung function

Respiratory effects after short-term exposure are summarised in Table 11. Effects on pneumoproteins were shown at trichloramine concentrations ≥ 0.29 mg/m^3 (11, 21, 38) but not at lower exposure levels (20, 98).

Marginal but significant effects on lung function were demonstrated in one study with trichloramine concentrations of 0.15 and 0.23 mg/m^3 (personal exposure) (98). In contrast, no effects on lung function were demonstrated in studies with exposure levels of 0.023 mg/m^3 (137), 0.18 mg/m^3 (personal exposure 0.071 mg/m^3) (82), 0.16–0.28 mg/m^3 (20), 0.29 mg/m^3 (38) and 0.36 and 0.49 mg/m^3 (21).

An increase in FENO over work shift was observed in pool workers exposed to 0.18 mg/m^3 of trichloramine, suggesting an inflammatory effect on the airways (82).

12.3.1.3 Asthma

Exposure to trichloramine in the workplace air may aggravate asthma symptoms in individuals with existing asthma (27, 129). The average concentration of trichloramine reported in the study by Dang *et al.* was 0.44 mg/m^3 (27). In the case report by Thickett *et al.*, 2 pool workers with occupational asthma had a positive specific challenge test to trichloramine at 0.5 mg/m^3, and the 3rd pool worker had a

positive workplace challenge test to indoor pool air with trichloramine levels of 0.1–0.57 mg/m^3 (129).

Some studies showed higher prevalences of self-reported asthma-related symptoms in exposed pool workers and competitive swimmers compared to unexposed referents (27, 73, 78). The overall mean concentration of trichloramine in the study by Jacobs *et al*. was 0.56 (0.13–1.34) mg/m^3 (73); the air levels in the study by Lévesque *et al*. were 0.26–0.41 mg/m^3 (78). A high prevalence of airway hyperreactivity has been found in pool workers (30), as well as in competitive swimmers (56, 118). No significant associations have been found between levels or duration of trichloramine exposure and self-reported asthma symptom, pulmonary function, airway hyperreactivity and airway inflammation.

12.3.2 Animal studies

Animal studies on trichloramine are summarised in Table 6 (Chapter 10). In female mice, lung epithelium hyperpermeability (expressed as changes in concentrations of albumin and total proteins in BALF, and of CC16 in BALF and serum) was observed after single inhalation exposures at 11.9 and 13.1 mg/m^3 up to 8 hours. No effects were seen at 0.53–3.45 mg/m^3 (21).

An RD_{50} value of 12.5 mg/m^3 in mice was reported following a 1-hour inhalation exposure to trichloramine (43).

In rats, an LC_{50} value of 560 mg/m^3 following 1 hour of exposure was determined. The cause of death was lung oedema (7).

In the only long-term study located, male and female rats were administered trichloramine in drinking water (0.020–13 mg/kg bw/day) for 13 weeks. Minimal to mild histological effects in thyroid and kidneys were observed at doses > 0.23 mg/kg bw/day in males and > 0.29 mg/kg bw/day in females, respectively. Increased hepatic enzyme activities were observed among females only (13 mg/kg bw day) (92). It is unclear how these effect levels were derived from the results presented in the paper.

Table 10. Ocular and airway irritation in swimming pool workers occupationally exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise) as reported by questionnaires.

Exposure level, mg/m^3 (AM)	Study group	Effects: OR (95% CI); prevalence (%)	Reference
Swimming pools: 0.035 (0.017–0.15) Spa pools: 0.059 ± 0.42 (SD) Soluble chlorine: Swimming pools: 0.072 (0.005–0.21) Spa pools: 0.085 ± 0.056 (SD)	61 pool workers 43 referents	*Symptoms occurring during or after work shift:* Throat irritation: 11.3 (1.4–88); 26% vs 2.3% Phlegm: 4.2 (1.2–15); 30% vs 6.9% Eye irritation: 1.7 (0.6–4.6); 28% vs 16% Cough: 1.3 (0.5–3.4); 25% vs 19 % No further concentration-response data presented.	(25)
0.11	178 pool workers 71 referents	Eye irritation ever, work-related: 53% vs 22% Throat irritation ever, work-related: 79% vs 7% Nose irritation ever, work-related: 38% vs 7%	(101)
3 exposure groups: < 0.1 (0.05) 0.1–0.29 (0.15) 0.30–0.52 (0.36)	No. of exposed/group: 102 61 20	*Exposed to 0.36 (0.30–0.52) mg/m^3:* Eye irritation last 12 mo: 5.6 (1.3–23.7) Nose irritation last 12 mo: 4.2 (1.4–13.1) Nose irritation ever: 4.3 (1.5–12.6)	
0.18 (0.10 GM) 0.001–0.64 Personal sampling: 0.071 (0.036 GM) < 0.001–0.24	50 pool workers 49 referents	*Symptoms during the last week:* Ocular symptom: 2.4 (1.0–5.7); 62% vs 37% Nasal symptom: 2.3 (1.0–5.6); 60% vs 47% No concentration-response relationship among exposed.	(82)

Table 10. Ocular and airway irritation in swimming pool workers occupationally exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise) as reported by questionnaires.

Exposure level, mg/m^3 (AM)	Study group	Effects: OR (95% CI); prevalence (%)				Reference
0.24 swimming pools 0.67 leisure pools	334 pool workers No referents	Significant concentration-response relationships between airborne levels and symptoms (ever at work). *Prevalences in the 4 exposure groups (%):*				(84)
4 exposure groups:	No. of exposed/group:	Eye irritation	Nose irritation	Throat irritation	Dry cough	
< 0.14	86	50	12	16	9	
0.14–0.22	82	56	20	15	12	
0.22–0.50	75	63	28	27	21	
> 0.50	91	87	61	29	42	
0.27 swimming pools 0.57 recreational centres	Swimming instructors (no. and gender not given) No referents	Swimming instructors were requested to report at onset of symptoms while exposure levels were monitored. Onset of irritation in eyes and upper respiratory tract began at around 0.5 mg/m^3, and all questioned complained of irritative symptoms at 0.7 mg/m^3.				(64)
0.56 (0.13–1.34)	342 pool workers 282 referents	*Swimming instructors:* Sinusitis: 2.4 (1.2–4.9) Chronic cold: 3.4 (1.2–10.1) Sore throat: 2.4 (1.2–4.5) Blocked nose: 2.0 (> 1.0–3.8) Sneezing: 2.0 (1.1–3.6) *Combining jobs as pool attendant and swimming instructor:* Chronic cold: 3.5 (1.2–10.2) Sore throat: 3.2 (1.7–5.9) Blocked nose: 3.7 (1.9–7.3) Runny nose: 2.2 (1.3–3.5) Sneezing: 2.3 (1.2–4.4) Itchy watery eyes: 3.0 (1.7–5.3) No association between levels of trichloramine and symptoms.				(73)

Table 10. Ocular and airway irritation in swimming pool workers occupationally exposed to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise) as reported by questionnaires.

Exposure level, mg/m^3 (AM)	Study group	Effects: OR (95% CI); prevalence (%)	Reference
0.65	81 lifeguards and swimming instructors 47 referents	A strong concentration-response relationship between exposure levels and self-reported irritation in eyes and upper airways (symptoms reported as never, sometimes or often).	(36)
5 exposure groups:	No. of exposed/group:	*Exposed > 0.5 mg/m^3:*	
≤0.5	10	Runny nose: 2.9 (1.2–6.9)	
>0.5	71	Voice loss: 3.6 (1.6–8.0)	
>0.6	50	Red eyes: 3.2 (1.5–6.8)	
>0.7	39	Itchy eyes: 2.2 (1.04–4.8)	
>0.8	30		

AM: arithmetic mean, CI: confidence interval, GM: geometric mean, OR: odds ratio, SD: standard deviation.

Table 11. Respiratory effects in humans following short-term exposure to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Exposure level, mg/m^3 (AM)	Study group	Exposure duration	Effects	Reference
0.023 (0.009 GM) 0.001–0.140 Personal sampling: 0.019 (0.009 GM) 0.001–0.076	23 pool workers 50 office workers	Work shift	No changes in lung function over work shift and no difference between groups. FENO decreased over work shift in both groups, significantly more in referents than in pool workers.	(137)
0.18 (0.10 GM) 0.001–0.64 Personal sampling: 0.071 (0.036 GM) < 0.001–0.24	52 pool workers 50 office workers	Work shift	No changes in lung function over work shift and no difference between groups. FENO decreased over work shift in referents and increased in pool workers ($P < 0.05$). The increase was more pronounced in non-smoking pool workers.	(82)
Personal sampling: 0.15 0.23	14 pool workers 37 healthy volunteers (all non-smokers)	2-h bicycle exercise in a chlorinated pool environment and in an exposure chamber with filtered air	Marginal but significantly decreased $FEV_{\%}$ in pool workers exposed to 0.15 mg/m^3. Marginal but significantly decreased FEV_1 and $FEV_{\%}$ in volunteers exposed to 0.23 mg/m^3. No significant changes in serum levels of CC16 and SP-D after exposure to pool air.	(98)
0.16–0.28	11 healthy adults	45-min swimming sessions in a non-chlorinated and a chlorinated pool	No decrements in lung function. FENO increased by 34% after exercise in the non-chlorinated pool but remained unchanged in the chlorinated pool. No change in serum levels of pneumoproteins (SP-A, SP-B, CC16 and KL-6) after exercise in the chlorinated pool.	(20)

Table 11. Respiratory effects in humans following short-term exposure to airborne trichloramine (exposure levels refer to stationary sampling if not stated otherwise).

Exposure level, mg/m^3 (AM)	Study group	Exposure duration	Effects	Reference
0.29 (0.17–0.43)	48 healthy adult non-smokers	40-min swimming session in a chlorinated pool	No significant changes in lung function (spirometry) or markers of airway inflammation (FENO, 8 cytokines, VEGF) or of oxidative stress (8-isoprostane) before and after swimming session. Slight increase in serum CC16 levels (3.3%). The CC16 change was not different among *CC16* genotypes. No change in serum SP-D.	(38)
0.36	14 trained swimmers (6 women, 8 men, aged 18–23 y)	45-min intensive swimming sessions in a chlorinated pool and in a non-chlorinated pool	No significant decrements in lung function. Serum SP-A and SP-B levels increased significantly in a time-dependent manner in recreational and trained swimmers attending the chlorinated pool, but not in the non-chlorinated pool. Serum CC16 levels increased immediately after exercise in trained swimmers, both pools, but not in recreational swimmers. Measurements performed before and after swimming sessions, and 11 h after exercise had ceased (trained swimmers) and before, after 1 and 2 h pool attendance (recreational swimmers).	(21)
0.49	29 recreational swimmers; 16 children (aged 5–14 y) and 13 adults	2-h attendance in a chlorinated pool		
0.49	32 recreational swimmers; 16 children (mean age 9.6 y) and 16 adults	2-h attendance in a chlorinated pool	Significant increases in serum SP-A and SP-B levels and in the SP-B/CC16 ratio in both children and adults after attending the swimming pool area, in adults already after 1 h without swimming. CC16 levels decreased significantly after 1 h and reversed towards normal 1 h later in adults, but did not show any distinct pattern in children.	(11)

AM: arithmetic mean, CC16: club cell protein 16 kDa, FENO: fraction of exhaled nitric oxide, FEV_1: forced expiratory volume in the first second, $FEV_{\%}$: $FEV_1/FVC \times 100$, FVC: forced vital capacity, GM: geometric mean, KL-6: Krebs von den Lungen-6 protein, SP: surfactant-associated protein, VEGF: vascular endothelial growth factor.

13. Previous evaluations by national and international bodies

Some previous evaluations regarding inorganic chloramines have been performed with the main focus on monochloramine in drinking water. A few bodies have evaluated the health effects of trichloramine following inhalation exposure.

13.1 Chloramines/monochloramine

US Environmental Protection Agency (US EPA) 1994, Chloramines
US EPA concluded that several short-term studies on monochloramine showed no observed adverse haematological effects in mice, rats and monkeys. EPA further concluded that studies regarding mutagenicity of chloramines were inconclusive and stated that equivocal evidence of carcinogenic activity was found in female rats because of a slightly increased incidence of mononuclear cell leukaemia. There was no evidence of carcinogenic activity in male rats, female or male mice. As regards human health, it was noted that no epidemiologic studies had been designed to address specifically the potential adverse health effects of exposure to chloramines. The EPA Carcinogenic Risk Assessment Verification Endeavour (CRAVE) Work group verified (12/02/92) a classification for monochloramine of group D, not classifiable as to human carcinogenicity, meaning that there is inadequate human and animal evidence of carcinogenicity (132).

Government of Canada. Healthy Canadians 1996, Monochloramine
Monochloramine was considered weekly mutagenic *in vitro*. No treatment-related developmental or reproductive effects had been observed in rats exposed to monochloramine in drinking water. Some possible immunological effects were noted, but the biological significance of these effects were considered not clear. An administered dose of 3.8 mg/kg bw had been reported to cause a reduction in spleen weight and augmented production of prostaglandin E_2 in male rats. The available epidemiologic studies were regarded inadequate for the assessment of carcinogenicity of monochloramine in humans. There were some clinical evidence of neoplastic responses in rats and mice following chronic exposure to monochloramine in drinking water. The evidence for the carcinogenicity of monochloramine was considered to be limited and the compound was classified as being possibly carcinogenic to humans (inadequate evidence in humans, some evidence in animals).

A tolerable daily intake was estimated to 0.048 mg/kg bw per day and a maximum acceptable concentration (MAC) for monochloramine in drinking water of 1.8 mg/l was derived (53).

International Agency for Research on Cancer (IARC) 2004, Chloramines
No human carcinogenicity data specifically on chloramine were available to the Working Group. Chloraminated drinking-water (predominantly in the form of monochloramine) tested for carcinogenicity by oral administration in female and

male mice and rats did not demonstrate clear evidence of carcinogenic activity. Ingestion of monochloramine produced no clinical abnormalities in male volunteers at a concentration of 15 mg/l. No reproductive or developmental effects had been associated with monochloramine. Monochloramine induced single-strand breaks and loss of DNA-transforming activity and was a week mutagen in *B. subtilis*. It was not mutagenic to *S. typhimurium*. *In vitro*, monochloramine caused double-strand breaks and chromatin condensation in rabbit gastric mucosal cells and human stomach cancer cells. *In vivo*, monochloramine did not induce micronuclei, chromosomal aberration, aneuploidy or sperm abnormality in mice, but induced the formation of micronuclei in erythrocytes of newt larvae.

IARC concluded that there was *inadequate evidence* in humans for carcinogenicity of chloramine and *inadequate evidence* in experimental animals for the carcinogenicity of monochloramine. The overall evaluation was that chloramine was not classifiable as to its carcinogenicity to humans (Group 3) (68).

World Health Organization (WHO) 2011, Monochloramine

WHO concluded that although monochloramine had been shown to be mutagenic in some *in vitro* studies, it had not been found to be genotoxic *in vivo*.

A tolerable daily intake (TDI) of 94 µg/kg bw was calculated based on the highest dose administered to male rats in a 2-year drinking water study by NTP (99). An additional uncertainty factor for possible carcinogenicity was not applied because equivocal cancer effects reported in the NTP study in only one species and in only one sex were within the range observed in historical controls. No other increases in tumour incidence were observed (140).

13.2 Trichloramine

World Health Organization (WHO) 2006

WHO based its recommendations on the study by Héry *et al*. (64) in which onset of irritative symptoms in the eyes and throat were reported at an air level of 0.5 mg/m^3 of trichloramine; at 0.7 mg/m^3 all of the staff reported irritative symptoms. WHO thus recommended a maximum trichloramine level of 0.5 mg/m^3 in indoor swimming pool air as a comfort value, in order to protect the visitors from possible health effects (139).

German Working Group on Indoor Guide Values of the Federal Environment Agency and the States' Health Authorities 2011

In its risk assessment of trichloramine in the air of indoor swimming pools, the Working Group noted that few human and animal studies were available (no repeated exposure studies in animals). A valid lowest observed adverse effect level (LOAEL) could therefore not be derived from the current studies and no toxicologically based indoor air guide value established. Instead, the Swiss technical standard of 0.2 mg/m^3 of trichloramine (122) was adopted to protect the public against irritation from air in indoor swimming pools. As toxicological and epidemiological support, it was referred to the absence of irritation in recreational

swimmers following a few hours of exposure to 0.5 mg/m^3 of trichloramine (21), whereas irritation occurred in competitive swimmers and lifeguards after repeated exposure near 0.4 mg/m^3 (preliminary data by Parrat *et al.* 2009) (143).

Ministry of Social Affairs and Health, Finland 2012
In the evaluation of data on trichloramine, respiratory irritation was identified as the critical effect for the setting of an OEL. It was recognised that such effects had been observed at exposure levels starting from 0.5 mg/m^3 (64, 73). On the basis of these findings, an 8-hour OEL of 0.5 mg/m^3 was set in 2012 (88).

14. Evaluation of human health risks

14.1 Assessment of health risks

Inorganic chloramines are not commercially available, but monochloramine is produced *in situ* for disinfection or for use in chemical synthesis. Mono, di- and trichloramine are also formed when free chlorine reacts with nitrogen containing substances present in e.g. chlorinated water sources.

Monochloramine and dichloramine are water-soluble but monochloramine is the principal chloramine in chlorine disinfected water. Trichloramine is immiscible with water and evaporates rapidly into the air and is the predominant inorganic chloramine in the indoor air of swimming pool facilities. In contrast, in the food processing industry, a significant amount of the inorganic chlorine species in the air is soluble. The primary occupational exposure route for the inorganic chloramines is inhalation. Drinking water studies are therefore considered to be of low relevance in the occupational setting.

Air monitoring has mostly been performed as stationary sampling. The results may deviate from results obtained by personal sampling. Linear regression analyses based on data from parallel 8-hour samplings of trichloramine in pool air suggested a relation between personal and stationary sampling of approximately 1:2 (137, 138).

14.1.1 Monochloramine
The data base is scarce and no inhalation data were located.

No clinical effects were seen among male healthy volunteers ingesting monochloramine in drinking water daily during 4 or 12 weeks in doses corresponding to 0.043 mg/kg bw/day (142) or 0.034 mg/kg bw/day (81), respectively.

Monochloramine was regarded considerably more eye irritating than free chlorine in a study on rabbits (33). Minor immunological and haematological effects after short-term oral exposure (0.8–38 mg/kg bw/day) were reported in some studies in rodents (19, 35, 50, 89). No haematological or clinicochemical effects were seen in monkeys after 6 weeks of oral exposure to 10 mg/kg bw/day (8). A transient increase in GSH production was observed in rats after single oral gavage doses of approximately 0.19–0.75 mg/kg bw (2).

In long-term drinking water studies, reduced body weight gain and minor biochemical, haematological, immunological and histopathological changes were observed in rats exposed to 21.6 mg/kg/day for 13 weeks. The effects were largely related to reduced water and food consumption (104). Similar effects were reported also in other long-term studies in rats and mice at daily doses of 5–17 mg/kg bw/day (2, 28, 29, 99).

No carcinogenic effects were seen in mice or male rats administered monochloramine in drinking water for up to 2 years. A marginal increase in mononuclear cell leukaemia incidence among female rats was considered as equivocal evidence of carcinogenic activity (99). Limited data indicate that monochloramine is weakly mutagenic *in vitro* but not genotoxic *in vivo*.

No reproductive or developmental effects were shown in the few animal studies located.

14.1.2 Dichloramine

No human data were located.

In the only animal study located, mild histopathological effects in kidneys, thyroid and gastric cardia were observed among male and female rats administered dichloramine in drinking water for 13 weeks (92).

14.1.3 Trichloramine

The animal database is meagre and comprise to our knowledge three single inhalation studies and a 13-week drinking water study. However, there were no indications of adverse systemic effects from trichloramine exposure, even after acute inhalation exposure at lethal concentrations. Human studies have mainly focused on ocular and airway irritation and pulmonary effects.

14.1.3.1 Irritation

Trichloramine is a strong sensory irritant and accidental high short-term airborne exposure may cause acute irritative symptoms in humans, mainly in the upper airways and eyes (17, 113). Several cross-sectional studies have shown higher prevalences of self-reported ocular and upper airway irritation among competitive swimmers and workers with occupational exposure to trichloramine compared to unexposed reference groups. In these studies, men and women as well as adolescents and children were included, but results regarding health effects were generally not presented separately for the different groups. Pool workers are mainly exposed to trichloramine in air, whereas food industry workers and competitive swimmers to a higher degree are exposed also to soluble chlorine, in aerosols and/or the chlorinated water itself. Only swimming pool workers are therefore included in the assessment of airborne trichloramine.

Irritative symptoms in eyes and upper respiratory tract are evident at airborne trichloramine levels of 0.5 mg/m^3 (36, 64, 84). In another study, irritation symptoms were more frequent among pool workers exposed to 0.36 (0.30–0.52) mg/m^3 than among referents (101).

Irritation below 0.5 mg/m^3 has been reported in some additional studies (25, 82). However, due to lack of exposure-response relationships, these studies were considered less suited to form the basis for a health-based OEL. Nevertheless, they provide additional support for irritation as the critical effect.

It should be noted that the measurements were performed by stationary sampling in these studies.

Duration of exposure seems to be of importance; an association between the prevalence of irritative symptoms in exposed pool workers and cumulative trichloramine exposure has been shown (73, 84, 98, 101). However, the data are not presented in a way that allows the cumulative exposure estimates to be used as basis for a health-based OEL.

The human irritation data are supported by animal data. Depressed breathing was shown in rats at a single exposure (60 min) to trichloramine at 4.5–25.0 mg/m^3 giving an estimated RD_{50} value of 12.5 mg/m^3 (43).

Overall, irritation is considered to be the critical effect of trichloramine. However, despite a large amount of human data it is difficult to draw a firm conclusion regarding a NOAEC. The study by Parrat *et al.* (101) suggests a LOAEC around 0.36 mg/m^3, rounded to 0.4 mg/m^3.

14.1.3.2 Pneumoproteins and lung function

A marginal but significant decrement in lung function was demonstrated in one study after exposure to airborne trichloramine levels of 0.15 mg/m^3 and 0.23 mg/m^3 (both personal sampling) (98). In contrast, no effects on lung function were demonstrated in other studies with average exposure levels of 0.02–0.49 mg/m^3 (stationary sampling) (20, 21, 38, 82, 137). Transient changes in serum pneumoproteins associated with changes in lung epithelium permeability were seen in some studies at airborne trichloramine concentrations ≥ 0.3 mg/m^3 (11, 21, 38), whereas no such effects were observed in studies at lower mean exposure levels (20, 98).

One animal study supports an effect on pneumoproteins. Mice inhalation exposed to 12 mg/m^3 of trichloramine for 1–8 hours showed an increased bidirectional leakage of proteins across the pulmonary epithelium. These effects were not seen at 0.53–3.45 mg/m^3 (21).

The results on lung function are inconsistent and the interpretation and clinical relevance of changes in pneumoproteins is uncertain at present, therefore these studies cannot be used to derive a recommendation for a health-based OEL.

14.1.3.3 Asthma

Exposure to trichloramine in the workplace air may aggravate asthma symptoms in individuals with existing asthma (27, 129).

Some studies showed higher prevalences of self-reported asthma-related symptoms in exposed pool workers (work-related) (27, 73) and competitive swimmers (during training) (78) compared to unexposed reference groups or other competitive athletes or athletes in other aquatic disciplines (48, 90).

A high prevalence of airway hyperreactivity has been found in pool workers (30) as well as in competitive swimmers (56, 118).

Limited data indicate that occupational exposure to trichloramine may contribute to the development of asthma in individuals without previous respiratory diseases (98, 129). Some cross-sectional studies indicate an association between cumulative attendance in chlorinated pools and an increased risk of asthma among atopic school children (5, 9, 11, 15), but these findings are contradicted by results from other large population-based studies in children (39-41, 72).

No significant associations have been found between levels or duration of trichloramine exposure and self-reported asthma symptom, pulmonary function, airway hyperreactivity and airway inflammation (36, 42, 76, 78, 84, 85).

In conclusion, the risk of developing asthma following long-term exposure to trichloramine cannot be evaluated at present.

14.1.3.4 Other data

Data on genotoxicity, carcinogenicity and reproductive and developmental toxicity are lacking.

14.2 Groups at extra risk

Inorganic chloramines are regarded as irritants. Asthmatics and atopic individuals who are hyperreactive to other respiratory irritants are expected to be more sensitive to these substances.

14.3 Scientific basis for an occupational exposure limit

There are insufficient toxicological data to recommend health-based OELs for monochloramine and dichloramine.

The major effect after trichloramine inhalation is self-reported irritation of the eyes and upper respiratory tract. Irritation is considered to be the critical effect and has been reported in many studies on pool workers. Several of these studies reported irritation at approximately 0.5 mg/m^3 of trichloramine (36, 64, 84). One study showed irritation at slightly lower trichloramine levels, 0.36 (0.30–0.52) mg/m^3 (101). Therefore, 0.4 mg/m^3 is regarded as the LOAEC and is used to derive a recommended health-based OEL.

Considering that there are no indications of adverse systemic effects from trichloramine exposure, the sharpness of the concentration-effect curve for irritation and that a LOAEC is used as point of departure, an assessment factor of 2 is applied, to account for extrapolation from LOAEC to NOAEC (95). As the irritation data are collected from various field studies with occupationally exposed subjects, no assessment factor for interindividual variability is needed. The studies on pool workers reviewed in this document used stationary sampling to determine the trichloramine concentrations. Two studies with stationary and personal sampling carried out in parallel suggest that the stationary method may overestimate the true

personal exposure in swimming pool facilities (Section 14.1) (137, 138). This motivates an additional assessment factor of 2 when personal monitoring is applied.

The resulting recommended health-based OEL is 0.1 mg/m^3 (0.4/2/2) as an 8-hour time-weighted average. This corresponds to 0.2 mg/m^3 for stationary measurements in swimming pool facilities.

No short-term exposure limit (STEL) is recommended as currently available analytical methods require longer sampling times.

No measurement difficulties are foreseen at the recommended health-based OEL.

15. Research needs

Air sampling and analysis

The air sampling method and the chemical analytical methods used today are relatively unspecific. Methods for analysis and identification of monochloramine, dichloramine or trichloramine in air samples should be developed.

Today pumped sampling is used and the equipment is relatively heavy to wear; a diffusive sampler for the inorganic chloramines should be developed.

Health effects

Long-term animal studies are needed to establish a NOAEC for inhalation exposure.

Data on human toxicokinetics and on mechanisms of toxicity are lacking. More studies regarding short-term effects of the inorganic chloramines in humans should be performed, preferably in an exposure chamber under controlled conditions to establish human NOAECs. For future occupational studies, exposure should be assessed by personal sampling in parallel to a standardised validated questionnaire regarding human health effects. In addition to studying self-reported symptoms for evaluation of health effects following exposure to inorganic chloramines, more studies should be performed using objective measurements including effect markers such as FENO, inflammatory markers or eye and nose irritation tests. Possible gender differences in exposure and health effects should be evaluated. Larger longitudinal studies with sufficient statistical power are needed to evaluate the possible risk of developing asthma following long-term exposure to the inorganic chloramines, especially in adolescents and children with atopy. Data are lacking regarding possible persistent health effects after cessation of exposure.

16. Summary

Wastensson G, Eriksson K. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. *152. Inorganic chloramines*. Arbete och Hälsa 2019;53(2):1–110.

Inorganic chloramines are not commercially available, but monochloramine is produced *in situ* for disinfection or for use in chemical synthesis. Inorganic chloramines are also formed when free chlorine reacts with nitrogen containing substances, e.g. ammonia and urea, present in chlorinated water sources. Occupational exposure may therefore occur in e.g. swimming pool facilities and the food processing industry.

Monochloramine is soluble and stable in water and the dominating inorganic chloramine in chlorinated water sources. No clinical effects were seen in healthy volunteers given monochloramine in drinking water during 4 or 12 weeks in doses of 0.043 or 0.034 mg/kg bw/day, respectively. Limited data indicate that monochloramine is weakly mutagenic *in vitro* but not genotoxic *in vivo*. One drinking water study indicated equivocal evidence of carcinogenicity in female rats but not in male rats and mice. No reproductive or developmental effects were shown in rodents in the few studies located.

Dichloramine is soluble but unstable in water. In the only study located, mild histological effects in kidneys, thyroid and gastric cardia were observed in rats administered dichloramine in drinking water for 13 weeks.

Trichloramine is immiscible with water and evaporates easily from water into air. Therefore, the primary exposure route of concern in the occupational setting is inhalation. Occupational exposure to trichloramine has been demonstrated in indoor swimming pool facilities and in the food processing industry where chlorinated water is used for disinfection. Exposure-response relationships between airborne levels and self-reported ocular and upper airway irritation have been shown in several studies. Exposure to trichloramine may aggravate asthma symptoms in individuals with existing asthma. The risk of developing asthma following long-term exposure to trichloramine cannot be evaluated at present. No data on genotoxic, carcinogenic, reproductive or developmental effects were located.

Conclusions: The toxicological data for mono- and dichloramine are insufficient to recommend health-based occupational exposure limits (OELs).

As regards trichloramine, the critical effect is judged to be irritation observed in several studies on pool workers, starting at approximately 0.4 mg/m^3 (stationary sampling). Based on these data, a health-based OEL of 0.1 mg/m^3 (8-hour time-weighted average) is recommended. This corresponds to 0.2 mg/m^3 for stationary measurements in swimming pool facilities. No short-term exposure limit (STEL) is recommended.

Key words: asthma, dichloramine, health-based occupational exposure limit, irritation, monochloramine, review, risk assessment, toxicity, trichloramine.

17. Summary in Swedish

Wastensson G, Eriksson K. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. *152. Inorganic chloramines.* Arbete och Hälsa 2019;53(2):1–110.

Oorganiska kloraminer tillverkas inte kommersiellt men monokloramin produceras *in situ* för desinfektion eller för användning som synteskemikalie. Oorganiska kloraminer bildas även när fritt klor reagerar med kväveinnehållande föreningar, såsom urea och ammoniak, som finns i klorerat vatten. Yrkesmässig exponering förekommer därför tex. i badhus och i livsmedelsindustrin.

Monokloramin är lösligt och stabilt i vatten och den dominerade oorganiska kloraminen i klorerat vatten. Inga kliniska effekter observerades bland friska individer som fick dricksvatten med 0,043 eller 0,034 mg monokloramin/kg kroppsvikt under 4 eller 12 veckor. Ett begränsat antal studier antyder att monokloramin är svagt mutagent *in vitro* men inte genotoxiskt *in vivo*. En dricksvattenstudie antydde en carcinogen effekt på honråttor men inte på hanråttor och möss. Inga effekter på reproduktion hos gnagare eller deras avkomma sågs i de få studier som hittades.

Dikloramin är lösligt men instabilt i vatten. Den enda studie som påträffades visade på milda vävnadsförändringar i njurarna, sköldkörteln och övre magmunnen hos råttor efter intag av dikloramin i dricksvatten under 13 veckor.

Trikloramin är inte blandbart med vatten och avdunstar lätt från vatten. Den huvudsakliga exponeringsvägen i arbetsmiljön är därför via inandning. Yrkesmässig exponering för trikloramin har påvisats i badhus och i livsmedelsindustrin där klorerat vatten används för desinfektion. Ett samband mellan lufthalter och självrapporterad irritation i ögon och övre luftvägar har påvisats i ett flertal studier. Exponering för trikloramin kan förvärra astmasymtom bland personer med befintlig astma. Risken att utveckla astma efter långvarig exponering för trikloramin kan i dagsläget inte utvärderas. Inga uppgifter hittades om genotoxicitet, carcinogenicitet eller effekter på reproduktion eller avkomma.

Slutsatser: Det går inte att rekommendera hälsobaserade gränsvärden för mono- och dikloramin på grund av otillräckligt vetenskapligt underlag.

För trikloramin bedöms den kritiska effekten vara irritation vilket observerats i ett flertal studier på badhusanställda, från cirka 0,4 mg/m^3 (stationär provtagning). Med detta som utgångspunkt rekommenderas ett hälsobaserat nivågränsvärde på 0,1 mg/m^3 (tidsvägt medelvärde, 8 timmar). Detta motsvarar 0,2 mg/m^3 vid stationär provtagning i badhusmiljö. Inget korttidsgränsvärde rekommenderas.

Nyckelord: astma, dikloramin, hygieniskt gränsvärde, irritation, monokloramin, riskbedömning, toxicitet, trikloramin, översikt.

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19. Data bases used in search of literature

In the search for literature the following data bases were used:

Arbline
Chemical Abstracts
HSELINE
Medline EBSCO
Medline OVID
NIOSHTIC
PubMed
Toxline

Last complete search was performed in February 2017.

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Appendix 1. Exposure limits for trichloramine in air

Country	8-hour TWA, mg/m^3	Reference
Occupational exposure limits		
Canada, Ontario	–	1
Denmark	–	2
European Union	–	3
Finland	0.5	4
Germany, AGS, DFG	–	5, 6
Norway	–	7
Sweden	–	8
United Kingdom	–	9
United States, OSHA	–	10
Recommended values		
Canada, Workers Compensation Board	< 0.35	11
France, ANSES/AFFSET	0.3	12
Germany, Environment Agency	0.2	13
Switzerland, SIA	0.2	14
WHO	0.5	15

AFFSET: Agence française de sécurité sanitaire de l'environnement et du travail (Agency for environmental and occupational health safety), AGS: Ausschuss für Gefahrstoffe (Committee for Hazardous Substances), ANSES: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (Agency for food, environmental and occupational health safety), DFG: Deutsche Forschungsgemeinschaft (German Research Foundation), OSHA: Occupational Safety and Health Administration, SIA: Schweizerischer Ingenieur- und Architektenverein (Swiss Society of Engineers and Architects), TWA: time-weighted average, WHO: World Health Organization.

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Appendix 2. Previous NEG criteria documents

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Acetonitrile	1989:22, 1989:37*
Acid aerosols, inorganic	1992:33, 1993:1*
Acrylonitrile	1985:4
Allyl alcohol	1986:8
Aluminium and aluminium compounds	1992:45, 1993:1*, 2011;45(7)*D
Ammonia	1986:31, 2005:13*
Antimony	1998:11*
Arsenic, inorganic	1981:22, 1991:9, 1991:50*
Arsine	1986:41
Asbestos	1982:29
Benomyl	1984:28
Benzene	1981:11
1,2,3-Benzotriazole	2000:24*D
Boric acid, Borax	1980:13
1,3-Butadiene	1994:36*, 1994:42
1-Butanol	1980:20
γ-Butyrolactone	2004:7*D
Cadmium	1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	1990:2*D
Carbon monoxide	1980:8, 2012;46(7)*
Carbon nanotubes	2013;47(5)*
Ceramic Fibres, Refractory	1996:30*, 1998:20
Chlorine, Chlorine dioxide	1980:6
Chloromequat chloride	1984:36
4-Chloro-2-methylphenoxy acetic acid	1981:14
Chlorophenols	1984:46
Chlorotrimethylsilane	2002:2
Chromium	1979:33
Cobalt	1982:16, 1994:39*, 1994:42
Copper	1980:21
Creosote	1988:13, 1988:33*
Cyanoacrylates	1995:25*, 1995:27
Cyclic acid anhydrides	2004:15*D
Cyclohexanone, Cyclopentanone	1985:42
n-Decane	1987:25, 1987:40*
Deodorized kerosene	1985:24
Diacetone alcohol	1989:4, 1989:37*
Dichlorobenzenes	1998:4*, 1998:20
Diesel engine exhaust	2016;49(6)*D
Diesel exhaust	1993:34, 1993:35*

NEG documents published in the scientific serial Arbete och Hälsa (Work and Health).

Substance/Agent	Arbete och Hälsa issue
Diethylamine	1994:23*, 1994:42
2-Diethylaminoethanol	1994:25*N
Diethylenetriamine	1994:23*, 1994:42
Diisocyanates	1979:34, 1985:19
Dimethylamine	1994:23*, 1994:42
Dimethyldithiocarbamates	1990:26, 1991:2*
Dimethylethylamine	1991:26, 1991:50*
Dimethylformamide	1983:28
Dimethylsulfoxide	1991:37, 1991:50*
Dioxane	1982:6
Endotoxins	2011;45(4)*D
Enzymes, industrial	1994:28*, 1994:42
Epichlorohydrin	1981:10
Ethyl acetate	1990:35*
Ethylbenzene	1986:19
Ethylenediamine	1994:23*, 1994:42
Ethylenebisdithiocarbamates and Ethylenethiourea	1993:24, 1993:35*
Ethylene glycol	1980:14
Ethylene glycol monoalkyl ethers	1985:34
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*: in English, remaining documents are in a Scandinavian language.
D: collaboration with the Dutch Expert Committee on Occupational Safety (DECOS).
N: collaboration with the US National Institute for Occupational Safety and Health (NIOSH).

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