Toxicological assessment of hypochlorite as cleaning agent for re-usable urethral catheters

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Prepared for Coloplast A/S

The expert in WATER ENVIRONMENTS

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Abbreviations

E: released amount of hypochlorite to the STP per day

EC10: concentration at which the studied effect is observed for 10% of the test species during the test period

EC50: concentration at which the studied effect is observed for 50% of the test species during the test period

LC50: concentration at which 50% of the test species died during the test period

LD50: estimated exposure level for 50% mortality in acute toxicity test

LOAEC: lowest observed adverse effect concentration

LOEC: lowest observed effect concentration

MOS: margin of safety

NOAEC: no observed adverse effect concentration

NOEC: no effect concentration

PEC: predicted environmental concentration

PNEC: predicted no effect concentration: highest concentration in the environment at which no unacceptable effects on the organism is expected

QSAR: Quantitative structure–activity relationship

STP: Sewage Treatment Plant

TE: tolerable exposure

W: daily amount of treated water in the STP

Executive summary

Coloplast A/S has from DHI A/S requested a safety assessment of the use of hypochlorite solutions as cleaning and disinfection solutions for reusable urinary catheters. The safety assessment is to cover human health as well as the environment.

Safety assessment, human health

For the human health assessment relevant exposure of the catheter users to the hypochlorite solution was assumed to be exposure to:

- the fingertips when handling the catheter during cleaning and disinfection

and

- exposure to the mucous membrane of the urethra from residual amounts of hypochlorite solutions mixed into the lubricating gel used before insertion of the catheters.

When assessing the toxicological data on hypochlorite in relation to exposure to fingers and mucous membranes local irritation/ cytotoxicity is considered the most critical effect of the substance at the site of contact. Hypochlorite is not considered to have a potential for systemic toxicity due to lack of systemic absorption of the reactive substance.

The safety assessments for women as well as for men were conducted based of use of either 0.012% or 0.6% hypochlorite solution as cleaning and disinfectant solutions.

The safety assessment of the fingertips for both women and men were based on direct exposure to either of the specific concentrations, i.e. 0.012% or 0.6% hypochlorite solution

Safety assessments of the female and male urethra were based on the assumptions that a residual layer of 0.1 mm of the hypochlorite solutions would remain on the catheter before the application of the lubricant gel. Based on the surface areas of the catheters and the amount of gel used the hypochlorite exposure concentration in the gel was calculated to 0.001% hypochlorite for the female urethra and 0.0009% hypochlorite for the male urethra when using the 0.012% hypochlorite solution for cleaning and disinfection.

When using the 0.6% hypochlorite solution the corresponding exposure concentrations were calculated to 0.5% and 0.46% hypochlorite for women and men, respectively.

Based on the toxicological data a tolerable exposure level (TE) for skin contact to the fingers of 0.1% hypochlorite was estimated (considering up to six times daily exposures for long-term use of the hypochlorite solvents).

Based on the toxicological data a tolerable exposure level (TE) of 0.005% hypochlorite was estimated for mucous membrane contact (considering up to six times daily exposure for long-term use of the hypochlorite solvents.

Based on this the following safety assessments were made by calculation of the Margin of Safety values (MoS-values):

$$MoS = TE / Exposure$$

MoS calculations	
Use of 0.012% hypochlorite solution (scenario 1)	
Women	MoS (urethra) = 0.005% / 0.001% = 5 * MoS (urethra) = 0.005% / 0.012% =0.42
	MoS (fingertips) = 0.1% / 0.012% = 8.3
Men	MoS (urethra) = 0.005% / 0.0009% = 5.6 * MoS (urethra) = 0.005% / 0.012% = 0.42
	MoS (fingertips) = 0.1% / 0.012% = 8.3
Use of 0.6% hypochlorite solution (scenario 2)	
Women	MoS (urethra) = 0.005% / 0.05% = 0.10 * MoS (urethra) = 0.005% / 0.6% = 0.008
	MoS (fingertips) = 0.1% / 0.6% = 0.17
Men	MoS (urethra) = 0.005% / 0.046% = 0.11 * MoS (urethra) = 0.005% / 0.6% = 0.008
	MoS (fingertips) = 0.1% / 0.6% = 0.17

**alternative scenarios if no lubricant gel is applied on the catheter and urethra exposure is directly to the hypochlorite solution*

As all the calculated MoS values for use of a 0.012% sodium hypochlorite solution are considerable above 1 the female and male exposure scenarios for urethra and fingers can be considered safe.

As all the calculated MoS values for use of a 0.6% sodium hypochlorite solution are considerable below 1 the female and male exposure scenarios for urethra and fingers cannot be considered safe. However, this conclusion is considered rather uncertain due to the conservative exposure estimate that may overestimate the actual exposure – maybe even more than with a factor of 10 (it was assumed – using a default value from exposure models - that a residual layer of 0.1 mm hypochlorite solution may still remain over the entire surface on the catheter when using the catheter). In order to make a more precise safety assessment it is recommended to make an experimental determination of residual solvent volume remaining on the catheter after the cleaning and disinfection procedure.

However, in alternative scenarios risk will apply for both men and women for urethra exposure if no lubricant gel is applied before use of the catheter and the urethra of both women and men may be exposed to drops with the initial concentration of the hypochlorite solution, i.e. for scenario 1 a concentration of 0.012% and scenario 2 a concentration of 0.6% hypochlorite.

Safety assessment, environment

An environmental safety assessment of the discharge of used hypochlorite from the catheter cases to the sewer has been carried out. Both hypochlorite and its major degradation/transformation products were included in the environmental assessments.

The assessments were based on the calculation of the PEC/PNEC ratio:

PEC: is the Predicted Environmental Concentration

PNEC: is the Predicted No Effect Concentration which can be interpreted as the highest concentration in the environment, where you do not expect unacceptable effects

Unacceptable effects to the environment cannot be excluded, if the PEC/PNEC ratio exceeds 1. The following assumptions were made in the assessments (see the report for the background of these assumptions):

- Concentration of hypochlorite in the disinfection agent: 0.0125% - 0.6%
- Content of in each catheter case: 0.04 L
- Frequency of changing disinfection agent: 1 time per day
- Number of inhabitants around a public sewage treatment plant: 10,000
- Number of catheter users connected to a public sewage treatment plant: 62. In addition, it is assumed that all catheter users will use reusable urethral catheters.
- All hypochlorite is assumed to be degraded/transformed before release to the fresh water
- The maximum observed transformation of chlorine into halogenated organic compounds is 5%
- Each of the considered halogenated organic compound are assumed to constitute 100% of the formed AOX
- Chlorate is a likely impurity in the disinfection agent, and it is not expected – contrary to hypochlorite – to be readily degraded/transformed in the sewer treatment plan (STP). All hypochlorite is assumed to be transformed into chlorate before release to the sewer.

The PECs and PEC/PNEC ratios are presented below

Substance	PEC (STP) (mg/L)	PEC (Surface water) (µg/L)	PEC/PNEC (STP)	PEC/PNEC (Surface water)
Hypochlorite	1.5E-05 - 5.1E-03		4.7E-06 - 1.6E-03	
Chlorate	8.3E-06 - 2.8E-03	8.3E-04 - 0.28	1.1E-07 - 3.5E-05	5.0E-03 - 1.7
Trichloroacetic acid	8.1E-07 - 2.7E-04	8.1E-05 - 2.7E-02	8.1E-09 - 2.7E-06	4.8E-04 - 0.16
Chloroform	5.9E-07 - 2.0E-04	5.9E-05 - 2.0E-02	1.2E-06 - 4.1E-04	4.1E-07 - 1.4E-04
Trichloroacetonitrile	7.2E-07 - 2.4E-04	7.2E-05 - 2.4E-02	-	3.6E-03 - 1.2
Trichloroacetaldehyde	7.3E-07 - 2.5E-04	7.3E-05 - 2.5E-02	-	3.9E-07 - 1.3E-04
Trichloracetamide	8.1E-07 - 2.7E-04	8.1E-05 - 2.7E-02	-	6.1E-07 - 2.1E-04
Dichlorophenol (2,3-, 2,4-, 2,5-)	1.2E-06 - 4.1E-04	1.2E-04 - 4.1E-02	-	2.2E-05 - 7.5E-03

The PEC/PNEC in the lower end of the PEC/PNEC range are all well below 1 – both for the STP and the surface water. The PEC/PNEC ratios in the higher end of the PEC/PNEC range were found to be slightly above 1 (1.7 respectively 1.2) for chlorate respectively trichloroacetonitrile.

Overall, the current assessments do not indicate a high risk to the environment due to the use of hypochlorite in reusable urethral catheters. Chlorate may be the degradation product which will exhibit the highest risk to environment. As the formation of chlorate from hypochlorite is a quite slow – far below the retention time in the sewer and the STP (time frame hours) – then the formation of chlorate will primarily take place during the storage of the hypochlorite solution prior to use.

1 Introduction

Coloplast has asked DHI to perform a safety assessment of a hypochlorite solution used for cleaning and disinfection of reusable urethral catheters. The assessment is prepared according to the assessment methodologies described in the ISO-10093 series concerning biological evaluation of medical devices.

2 Scope

According to the agreed Statement of Work (SOW; dated 7 January 2022) the work will cover the following:

- Investigating the biocidal product Milton which is used for disinfection of reusable catheters (e.g., the catheter Cliny; re-used for up to 28 days with disinfection of the catheter before each use)
- Performing a toxicological assessment (human and environment) of the biocidal active substance hypochlorite for the specific use as disinfectant of catheters.

DHI will identify and review relevant data on the hypochlorite product Milton including the data already identified by Coloplast. The information shall provide data on the concentration of the biocidal active substance in the product.

Based on this DHI will perform a hazard and risk assessment of residual hypochlorite on the catheter. The assessment will have special focus on effects in relation to long-term use. The assessment will be based on information in free databases, expert opinions etc. identified by DHI.

Also, the assessment shall further include an evaluation of possible effects to the environment from long-term use of the hypochlorite solution for the disinfection of reusable catheters

3 Methodology

3.1 Regulatory compliance

3.1.1 Human health safety assessment

The human health safety assessment will according to *EU Regulation 2017/745 on medical devices"* be performed according to the methodologies described in the ISO-1003 series on biological evaluation of medical devices. The following ISO standards will be of relevance for the assessment:

- ISO 10993-1: 2020 "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"
- ISO 10993-17: 2009. DS/EN ISO 10993-17:2009. Biological evaluation of medical devices, Part 17: Establishment of allowable limits for leachable substances.
- ISO 10993-18: 2020. Biological evaluation of medical devices, Part 18: Chemical characterisation of medical device materials within a risk management process.

3.1.2 Environmental assessment

The environmental assessment will be performed according to the methodologies given in connection with Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products:

- ECHA (2017). Guidance on the Biocidal Products Regulation Volume IV Environment - Assessment & Evaluation. (Parts B+C). Version 2.0. October 2017.

3.2 Approach

3.2.1 Relevant data for the assessment

The starting point for the assessment are specific pieces of information provided by Coloplast:

- a product sheet from the company *Create Medic CO* on the reusable Cliny catheter for urethral self-catherisation
- an instruction for use (IFU) for a self-catherisation set from the company *Dalian Create Medical products Co.*

and publications by Macaulay et al. (2016) and Wilks et al. (2019) considering cleaning of reusable catheters.

Gathering of further data may be an iterative process depending to which extent specific qualitative and quantitative additional data is needed for exposure estimation and hazard assessment (see below).

3.2.2 Exposure estimation

Based on this, further literature search will be conducted if necessary, in order to conduct relevant exposure scenarios when using a hypochlorite solution for cleaning and disinfection of the catheter in order to estimate the daily exposure to residual hypochlorite.

3.2.3 Hazard assessment

Based on toxicological expert assessments on hypochlorite the critical effects of hypochlorite will be identified in relation to long-term use and contact with the mucous membrane of the urethra. Dose-response relationship for the adverse effects will be given and a tolerable (or safe) exposure level will be identified

3.2.4 Safety assessment

In the safety assessment the exposure estimates for hypochlorite exposure will be compared to the safe exposure level and it will be assessed to which extent the espouse can be considered safe or constitute a risk.

The result will be discussed in relation to uncertainties and limitations (e.g., knowledge gaps) and the validity of the assessment will be evaluated. Critical parameters for which variation may have impact on the conclusion will be identified.

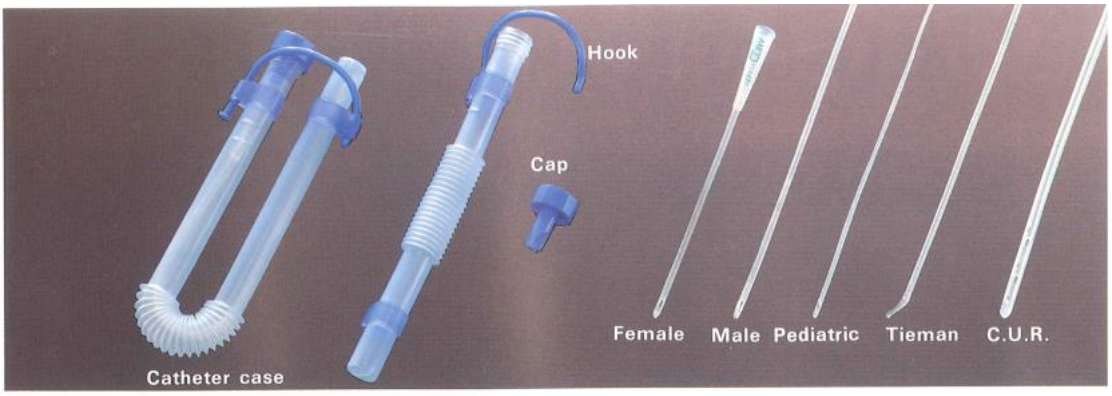
4 Relevant data for the assessment

4.1 Devices in scope

4.1.1 Urethral catheter

As a relevant device for the assessment the reusable urethral self-catherization device *"Cliny"* from the company *Create Medic Co., LTD* has been selected.

A description of the device is given in a product information sheet from the company (*Create Medic Co):*



1. Foldable catheter case
   Since the central part of the catheter case is foldable, it can be folded into a small size.
2. Hooks applicable to multiple purposes
   A hook provided at the case upper end is designed to act as a fixing device when folding the case and as a hook to place the case on a door knob or similar devices while the catheter is in use.
3. Special cap keeps cleanliness
   A cap with special structure does not only seal the case interior from exterior, but also allows sterilizer to freely enter the catheter interior, thereby always keeping the catheter clean.
4. Provided with an external container
   An external container, provided as a standard accessory, is convenient for transporting the catheter case, and protects patient's privacy since the container conceals what is contained.

Self-Catheterization Set

Product No.	Catheter type	Size & Length	Side holes	Content
04-4110	Female	10Fr, L : 165mm	1 hole	Catheter×1 catheter case with hook×1 cap×1
04-4112		12Fr, L : 165mm		
04-4114		14Fr, L : 165mm		
04-4210	Male	10Fr, L : 300mm		
04-4212		12Fr, L : 300mm		
04-4214		14Fr, L : 300mm		
04-4312	Male-L	12Fr, L : 350mm		
800 000 5376		14Fr, L : 385mm	2 hole	
04-4409	Pediatric	9Fr, L : 265mm	1 hole	
04-4512	Tieman	12Fr, L : 300mm	1 hole, w/Tieman Top	
800 000 5375		14Fr, L : 300mm		
04-4614	C. U. R	14Fr, L : 395mm	5 hole, with numeral markings	
04-4616		16Fr, L : 395mm		
04-4618		18Fr, L : 395mm		
04-4620		20Fr, L : 395mm		

Package: NOT sterilized, 5 sets in a box C. U. R.=Continent Urinary Reservoir

All Silicone Self Catheter (for exchange)

Product No.	Type	Size
04-5110	Male	10Fr
04-5112		12Fr
04-5114		14Fr
04-5210	Female	10Fr
04-5212		12Fr
04-5214		14Fr
04-5312	Male-L	12Fr
800 000 5478		14Fr
04-5409	Pediatric	9Fr
04-5512	Tieman	12Fr
800 000 5479		14Fr
04-5614	C. U. R	14Fr
04-5616		16Fr
04-5618		18Fr
04-5620		20Fr

Package: NOT sterilized, 5pcs in a box

4.1.2 Hypochlorite solution

In the “Instruction for use” for the Cliny catheter it is indicated that after use the catheter is to be cleaned with tap water, boiling or other cleaning procedures (DCMP 2018). The catheter is then placed in the catheter case that has been filled with a disinfection solution of either:

Sodium hypochlorite 0.0125 – 0.02% (e.g., by diluting “Milton” 50-80 times with water).

or using a

benzalkonium chloride solution or a benzthonium chloride solution in a concentration range of 0.05-0.1%.

The duration of use of one device is indicated to up to 1 month during which some discoloration may occur depending on disinfectant used.

The catheter case – shown above - contains disinfection agent up to a volume of about 0.04 L. According to the Cliny catheter IFU, the solution must be changed every 24 hours as indicated in Pelvitec (2022a+b).

4.1.3 Intended use of the device

According to Statens Serums Institut´s use instruction for catheterisation a daily frequency of self-catheterisation of 2-6 times per day is indicated for both male and females. Before insertion, the catheter should be lubricated with a water-soluble lubricating gel. At least 10 ml is recommended for men and a volume of 3-5 ml is considered the most common for females (SSI 2019).

4.1.4 Use of catheters in the community

In a Dutch study (Berendsen et al., 2021), the use of indwelling, intermittent and external urinary catheters in neurogenic and non-neurogenic bladder patients in the Netherlands from 1997 to 2018 was mapped.

The identified characteristic of users in the Netherlands are shown in the below table, Table 1.

Table 1 **Characteristics of catheter users in 1997 and 2018. Data retrieved from Berendsen et al., 2021. Users are expressed by users per 100,000 insured people in that specific age and sex category for the total Dutch population**

	Indwelling catheters		Intermittent catheters		External catheters	
	1997	2018	1997	2018	1997	2018
Total users	159	315	92	267	40	28
Sex and age distribution						
Male users	180	396	92	334	85	57
0–25years	11	6	25	39	6	4
25–45years	21	24	41	84	35	14
45–65years	122	159	111	272	73	37
65–75years	493	839	287	952	191	125
75–85years	1564	2464	453	1700	660	312
85+years	4704	8133	719	2040	1544	743
Female users	140	235	91	201		
0–25years	7	5	35	42		
25–45years	26	34	60	113		
45–65years	85	128	102	212		
65–75years	191	355	157	392		
75–85years	603	886	221	589		
85+years	2271	3210	441	724		

Data on the distribution of the population by age and sex can be retrieved from the Eurostat statistics. The data for EU27, the Netherlands and Denmark in 2021 can be seen in the table below.

Table 2 **Distribution of the population by age and sex. Data from Eurostat database (https://ec.europa.eu/eurostat/data/database)**

	European Union – 27 countries	Denmark	Netherlands
Total	447,089,099	5,838,844	17,472,879
Males	218,511,438	2,904,677	8,686,125
Females	228,577,661	2,934,167	8,786,754
Age group (females)			
0–25years	58,917,000	853,521	2,480,526
25–45years	57,850,870	736,950	2,192,340
45–65years	61,668,232	772,169	2,408,601
65–75years	22,855,927	308,719	970,206
75–85years	12,933,221	188,167	499,770
85+years	4,286,188	45,151	134,682
Age group (males)			

	European Union – 27 countries	Denmark	Netherlands
0–25years	55,663,343	812,633	2,370,426
25–45years	56,645,341	716,385	2,154,665
45–65years	63,289,541	772,115	2,411,322
65–75years	26,526,744	328,521	1,004,608
75–85years	17,802,677	223,469	593,413
85+years	8,650,015	81,044	252,320
Age group (females and males)			
0–25years	114,580,343	1,666,154	4,850,952
25–45years	114,496,211	1,453,335	4,347,005
45–65years	124,957,773	1,544,284	4,819,923
65–75years	49,382,671	637,240	1,974,814
75–85years	30,735,898	411,636	1,093,183
85+years	12,936,203	126,195	387,002

It is considered reasonable to assume that the Dutch statistics on catheter use also can be applied to the other EU countries. Therefore, the number of catheter users per 10,000 inhabitants can be estimated combining the Dutch distributions of catheter usage (sex and age group) (Table 1) and the age and sex distribution of the EU population (Table 2).

Table 3 Estimated total number of catheter users per 10,000 inhabitants (indwelling, intermittent and external catheters, 2021)

Estimated total number of catheter users per 10,000 inhabitants	European Union - 27	Denmark	Netherlands
	61.0	60.2	59.1
Sex and age distribution			
Male users	**41.9**	**41.4**	**40.5**
0–25years	0.6	0.7	0.7
25–45years	1.6	1.5	1.5
45–65years	6.5	6.2	6.5
65–75years	9.8	10.1	10.6
75–85years	12.9	14.4	12.8
85+years	10.5	8.4	8.4
Female users	**19.1**	**18.8**	**18.6**
0–25years	0.6	0.7	0.7
25–45years	1.9	1.9	1.8
45–65years	4.7	4.5	4.7
65–75years	3.8	3.9	4.1
75–85years	4.3	4.8	4.2
85+years	3.8	3.0	3.0

4.2 Relevant literature

The publications provided by Coloplast (i.e., Macaulay et al. (2016) and Wilks et al. (2020) are considered sufficient in order to describe the cleaning process of the catheters. Both publication recommends “Milton” sodium hypochlorite solutions as disinfectant, however, at different concentrations.

Further recommendations for use of urethral catheters were obtained from a publication by Statens Serum Institut (SSI 2019).

Macaulay et al. (2016).

Up until about 15 years ago reuse of uncoated PVC catheters for intermittent catheterisation this was standard practice in the UK. Adults and children were taught to wash their catheters with soapy water and store them in a small container between uses. Regulatory changes around 2000 stopped re-use because catheter manufacturers were required to provide tested cleaning instructions or label their catheters ‘single-use’.

For introducing reuse Macaulay et al. (2016) under controlled conditions examined various cleaning and disinfectant procedures among users of catheters. Based on feed-back from the users and microbial testing of the devices the following “flush and soak” procedure was concluded as the preferred method:

First wash the catheter using tap water and soap and rinse inside and out under the running tap. Then use diluted Milton solution (6 ml in 1 litre) to flush trough the catheter using a syringe and then place the catheter in the solution for 15 minutes.

In the publication there is a reference to the Milton product “Milton® Sterilising Fluid” which according to the Material Safety Data Sheet from Milton contain 2% sodium hypochlorite. I.e. the diluted solution contains 2% x 6ml/ 1000ml = 0.012%.

Wilks et al. (2020).

This publication conducted microbial examinations of reusable urethral catheters in relation to different cleaning methods. In conclusion, a similar method using Milton disinfectant was considered the most efficient method for sterilization, however, in this study a dilution of Milton to a concentration of 0.6% sodium hypochlorite was used.

5 Exposure assessment

The exposure assessment is according to ISO 10993-1: 2021 a central part of the biologiasafety assessment and ISO-10993-18: 2020 provide guidance for setting-up worst-case exposure scenarios for chemical substances based on conservative assumptions i.e., realistic maximum values for of each of the parameters below:

- identification of relevant exposure routes
- volume/ amount per use
- concentration of the chemical
- frequency of use (e.g., uses per day)
- duration of use (e.g., exposure only a short period, e.g., few days or up to chronic/ lifetime use)

Below the intended use of sodium hypochlorite solution for cleaning and disinfection of urethral catheters is described and worst-case exposure scenarios are established and the associated exposure levels to sodium hypochlorite are estimated for the relevant exposure routes.

5.1 Use of urinary catheters

In connection with use of sodium hypochlorite disinfection of the urethral catheter there may remain a residual amount of the hypochlorite solution on the catheter before the next use. It can be assumed that the residual amount on the outer surface of the catheter will be mixed into the water soluble lubricant gel used in connection with insertion of the catheter, i.e. the smaller amount of gel used the higher concentration of sodium hypochlorite.

In instructions from Statens Serum Institut (2019) a lubricant gel volume of at least 10 ml is recommended for catheters for men and a volume of 3-5 ml is considered the most common for females. I.e., a volume of 3 ml for females will result in the most concentrated hypochlorite exposure.

5.1.1 Solvent residues on catheters

When considering exposure to aqueous solvents attached to skin the EU exposure guidance used for the assessment of biocides assumes an attachment of an aqueous layer of 0.01 cm (ECHA 2015). As a worst-case scenario this is also assumed for the solvent surface layer residing on the catheter even though this surface is a smooth and non-sticky polymer surface.

Among the Cleany catheters the largest **female** catheter has a width of 5.3 mm and a length of 165 mm. When considering a solvent layer of a height of 0.01 cm on this surface the total volume can be calculated to:

$$Vol = \pi \times D \times L \times H$$

$Vol = 3.14 \times 0.53\ cm \times 16.5\ cm \times 0.01\ cm = 0.27 cm^3$ or 0.27 ml (approx. 5 drops)

Among the Cleany catheters the largest **male** catheter has a width of 6.7 mm and a length of 395 mm. When considering af solvent layer of a hight of 0.01 cm on this surface the total volume can be calculated to:

Vol = π x D x L x H

Vol = 3.14 x 0.67 cm x 39.5 cm x 0.01 cm = 0.83 cm^3 or 0.83 ml (approx. 16 drops)

5.1.2 Solvent residues on fingertips

Handling the catheter by taking it in and out of the hypochlorite solution exposure to the fingertips is to be considered. For each use of the catheters the fingertips (total surface area of 60 cm^2) are exposed to a 0.01 cm solvent layer, giving a total volume of:

Vol = 60 cm^2 x 0.01 cm = 0.6 cm^3 or 0.6 ml (approx. 12 drops)

5.1.3 Relevant exposure metrics

The safety assessment must cover both local effects from local exposure to the mucous membrane in the urethra and systemic effects in relation to the potential uptake and systemic distribution of sodium hypochlorite. Thus, the exposure metric has to be expressed in *"%"* sodium hypochlorite for evaluating potential local effects and *"mg/kg bw/day"* for evaluating potential systemic effects.

5.2 Exposure assessment females

Based on the available information the following parameters are used for calculating worst-case hypochlorite exposure for female users:

Number of self-catheterisations per day:

6 times as highest number indicated

Residual volume of hypochlorite solution on outer surface:

0.27 ml

Concentration of hypochlorite in solution:

Scenario 1: 0.012 % (Macaulay et al. (2016)).

Scenario 2: 0.6 % (Wilks et al. (2019)).

Amount of lubricating gel per use:

3 ml for women´s use

Scenario 1 (0.012% hypochlorite)

Urethra, mucous membranes, scenario 1:

The body weight for a woman is assumed to be 60 kg and the weight of the residual 0.27 ml hypochlorite solution corresponds to 270 mg.

Exposure (%) = 0.012% x (0.27 ml/ (3ml + 0.27 ml)) = **0.0010% sodium hypochlorite**

As exposure occurs up to 6 times daily this may be considered as a constant concentration in the urethra as a worst-case

Exposure (mg/kg bw/day) on mucous membrane, scenario 1 = 270 mg/d x 0.00012 x 6 times/d / 60 kg = **0.0032 mg sodium hypochlorite /kg bw/day**

Fingertips, scenario 1:

The body weight for a woman is assumed to be 60 kg and the weight of the residual 0.60 ml hypochlorite solution exposed to fingertips corresponds to 600 mg.

Exposure (%) = **0.012% sodium hypochlorite**

Exposure occurs up to 6 times daily for an exposure duration of few minutes each time

Exposure (mg/kg bw/day) dermal to fingertips, scenario 1 = 600 mg/d x 0.00012 x 6 times/d / 60 kg = **0.0072 mg sodium hypochlorite /kg bw/day**

Scenario 2 (0.6 % hypochlorite)

Urethra, mucous membranes, scenario 1:

The body weight for a woman is assumed to be 60 kg and the weight of the residual 0.27 ml hypochlorite solution corresponds to 270 mg solution.

Exposure (%) = 0.6% x (0.27 ml/ (3 ml + 0.27 ml)) = **0.050% sodium hypochlorite**

As exposure occurs up to 6 times daily this may be considered as a constant concentration in the urethra as a worst-case

Exposure (mg/kg bw/day) on mucous membrane, scenario 2 = 270 mg/d x 0.006 x 6 times/d / 60 kg = **0.16 mg sodium hypochlorite /kg bw/day**

Fingertips, scenario 2:

The body weight for a woman is assumed to be 60 kg and the weight of the residual 0.60 ml hypochlorite solution corresponds to 600 mg.

Exposure (%) = **0.6% sodium hypochlorite**

Exposure occurs up to 6 times daily for an exposure duration of few minutes each time

Exposure (mg/kg bw/day) dermal on fingertips, scenario 2 = 600 mg/d x 0.006 x 6 times/d / 60 kg = **0.36 mg sodium hypochlorite /kg bw/day**

5.3 Exposure assessment males

Based on the available information the following parameters are used for calculating worst-case hypochlorite exposure for male users:

Number of self-catheterisations per day:

6 times as highest number indicated

Residual volume of hypochlorite solution on outer surface:

0.83 ml

Concentration of hypochlorite in solution:

Scenario 1: 0.012 % (Macaulay et al. (2016)).

Scenario 2: 0.6 % (Wilks et al. (2019)).

Amount of lubricating gel per use:

10 ml for men´s use

Scenario 1 (0.012% hypochlorite)

Urethra, mucous membranes, scenario 1:

The body weight for a man is assumed to be 70 kg and the weight of the residual 0.83 ml hypochlorite solution corresponds to 830 mg.

Exposure (%) = 0.012% x (0.83 ml/ (10ml + 0.83 ml)) = **0.0009 % sodium hypochlorite**

As exposure occurs up to 6 times daily this may be considered as a constant concentration in the urethra as a worst-case

Exposure (mg/kg bw/day) on mucous membrane, scenario 1 = 830 mg/d x 0.00012 x 6 times/d / 70 kg = **0.0085 mg sodium hypochlorite /kg bw/day**

Fingertips, scenario 1:

Data does not allow for a male specific estimation so same exposure level for men as for females is assumed i.e.:

Exposure (%) = **0.012% sodium hypochlorite**

Exposure (mg/kg bw/day) dermal on fingertips, scenario 1 = **0.0072 mg sodium hypochlorite /kg bw/day**

Scenario 2 (0.6 % hypochlorite)

Urethra, mucous membranes, scenario 2:

The body weight for a man is assumed to be 70 kg and the weight of the residual 0.83 ml hypochlorite solution corresponds to 830 mg.

Exposure (%) = 0.6% x (0.83 ml/ (10ml + 0.83 ml)) = **0.046% sodium hypochlorite**

As exposure occurs up to 6 times daily this may be considered as a constant concentration in the urethra as a worst-case

Exposure (mg/kg bw/day) on mucous membrane, scenario 2 = 830 mg/d x 0.006 x 6 times/d / 70 kg = **0.42 mg sodium hypochlorite /kg bw/day**

Fingertips, scenario 2:

Data does not allow for a male specific estimation so same exposure level for men as for females is assumed i.e.:

Exposure (%) = **0.6 % sodium hypochlorite**

Exposure (mg/kg bw/day) dermal on fingertips, scenario 2 = **0.36 mg sodium hypochlorite /kg bw/day**

5.4 Exposure scenarios, alternative scenarios

According to Coloplast A/S urinary catheters may by some patients be used without lubricant gel. In such cases the first part of the urethra of both women and men may be exposed to drops with the initial concentration of the hypochlorite solution, i.e. for scenario 1 a concentration of 0.012% and scenario 2 a concentration of 0.6% hypochlorite

6 Hazard assessment

6.1 Introduction

In literature various terms in relation to the concentration for sodium hypochlorite solutions has been used, e.g.:

- % chlorite (ClO-)
- % sodium hypchlorite (NaClO)
- % “active” “available” chlorine (calculated as % Cl2)

The relation between these terms can be described by the following chemical reactions in aqueous solution:

NaClO + H2O ↔ Na+ + HClO + OH─ (dissociation to ions in water and formation of hypochlorous acid which is considered to be responsible for the biocidal effects)

HClO + H3O+ + Cl─ ↔ Cl2 + 2H2O (redox- process with hypochlorous acid and chloride and formation of chlorine under acidic conditions)

From these equations it can be seen that from one molecule of sodium hypochlorite one molecule of “active” Cl_2 can be generated. As the molecular weights of sodium hypochlorite (74.44 g/mol) and chlorine (70.90 g/mol) are very comparable the % expressed as “active” chlorine is nearly identical to the % expressed as sodium hypochlorite (e.g. 1.0% vs 1.05%).

The ratio of Cl2/HClO/ClO─ is pH and temperature dependent. The pH-dependence is displayed in the following figure 1, where the percentage of the different species at the equilibrium is showed as a function of pH. Hypochlorous acid is predominant in the pH range 3 to 7, whereas the hypochlorite anion predominates at pH >9-10. Chlorine can be present at pH < 4 only.

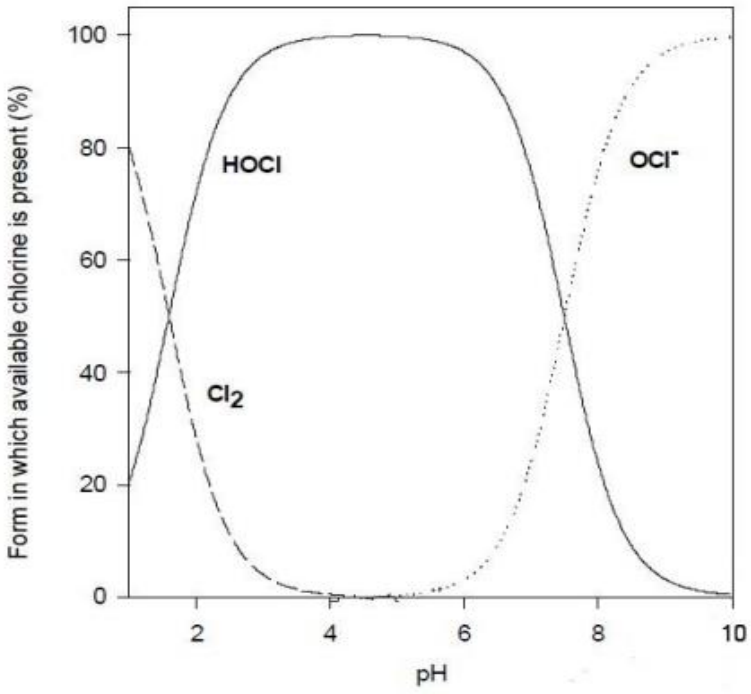


Figure 1 The relative presence of the different chlorine species at various pH values

According to the American Association for Clinical Chemistry, the average value for urine pH is 6.0, but it can range from 4.5 to 8.0. So, hypochlorous acid (and the hypochlorite ion) will be the dominant chemical species in this pH interval in the urethra.

6.2 Toxicological data on sodium hypochlorite

A focused literature search has been conducted for retrieving the most relevant hazard assessments of sodium hypochlorite in order to gather data on toxicity in relation to dermal exposure and exposure to mucous membranes.

In table 1 below the gathered data from the relevant references are presented in a condensed form.

Table 1 General information and toxicological data for sodium hypochlorite

Parameters/ endpoints	Sodium hypochlorite	Reference
CAS No.	7681-52-9	REACH-reg (2021)
Physical state	liquid	REACH-reg (2021)
Molecular weight (g/mol)	74.44	REACH-reg (2021)

Parameters/ endpoints	Sodium hypochlorite	Reference
Molecular Formula	NaClO	REACH-reg (2021)
Structural formula		PubChem (2021)
Melting point (°C)	- 28.9 °C	REACH-reg (2021)
Boiling point (°C)	With increasing temperature crystals are formed	REACH-reg (2021)
Solubility in water (°C)	Miscible in water	REACH Reg. (2021)
Vapour pressure (at 25 °C)	Negligible	REACH Reg. (2021)
Log Pow	-3.42	REACH Reg. (2021)
Stability	The stability of sodium hypochlorite solutions is affected by heat, light pH and presence of heavy metal cations.	REACH Reg. (2021)
	In water sodium hypochlorite degrades to chlorate and chloride. The degradation rate is a function of the active chlorine concentration and of temperature. For a sodium hypochlorite aqueous solution with an active chlorine concentration of 5% w/ w, the half-life is reported to be 5000 days at 15 °C; 790 days at 25 °C; 13.5 days at 60 °C; 0.25 days at 100 °C.	ECHA (2017)
	Chlorite, chlorate and, ultimately, perchlorate ions are formed during the slow decomposition of hypochlorite solutions. Chlorate production is a concern for hypochlorite solutions that are stored at warm temperatures for extended periods of time. This applies to its presence in purchased hypochlorite solutions that are not fresh, as well as hypochlorite solutions stored on site.	WHO (2016)
EU chemicals classification, human health	Skin Corr.1B; H314 (Causes severe skin burns and eye damage) C≥ 5% Eye Dam. 1; H318 (Causes serious eye damage) Aquatic Acute 1: H400 (Very toxic to aquatic life) Aquatic Chronic 1: H410 (Very toxic to aquatic life with long-lasting effects)	CLP Regulation (EC) No. 1272/2008 (REACH reg. 2020).

Parameters/ endpoints	Sodium hypochlorite	Reference
Regulatory information	***Biocides (Regulation (EU) 528/2012):*** Currently approved as a biocidal active substance "Active chlorine released from sodium hypochlorite" for biocidal product type 1,2,3,4,5. ***Cosmetics (Regulation (EC) No 1223/2009):*** Not allowed as preservative in cosmetic products. ***Pharmaceuticals (ICH guidelines):*** No Permitted Daily Exposure limit value has been established. ***Drinking water, Directive (EU) 2020/2184, hypochlorite:*** No limit values indicated for hypochlorite. For both chlorate and chlorite a concentration limit of 0.25 mg/L as parametric value (limit value) is given. A parametric value of 0.70 mg/l shall be applied where a disinfection method that generates chlorate or chlorite is used for drinking water.	
Toxicological information		
Literature used for the toxicological information	The following recent expert assessment was found to contain the most relevant and updated information for the toxicological evaluation of sodium hypochlorite: *ECHA (2017). Assessment Report Active chlorine released from sodium hypochlorite.* Furthermore, data was extracted from the REACH-registration: *REACH Reg. (2021). REACH registration data on sodium hypochlorite* Also, the data below represent the findings from more focused search on cytotoxicity data, whereas additional relevant data on systemic exposure to sodium hypochlorite and urethral mucous membrane exposure was not found.	
Toxicokinetics	Oral absorption is considered as not relevant because chlorine-related toxicity is based on local effects only (with secondary systemic effects at high doses). Regarding dermal exposure, the potential of hypochlorite solutions to penetrate the skin is low given its reactivity to proteinaceous material at the site of first contact. Dermal absorption is considered as not relevant because chlorine-related toxicity is based on local effects only (with secondary systemic effects at high doses).	ECHA (2017)

Parameters/ endpoints	Sodium hypochlorite	Reference
	Once in the body, it reacts directly with organic molecules to form some organochlorinated compounds. Studies with radioactive labelled HO36Cl indicate that the substance is converted and eliminated in the chloride form. Animal data suggest that after exposure via oral route, HOCl is absorbed and excreted mainly through urine as chloride. A lesser extent of HO36Cl-derived radioactivity not necessarily associated with absorption was detectable in the faeces.	REACH Reg. (2021)
Biocidal mechanism	Sodium hypochlorite, as active chlorine releaser, has strong bactericidal, fungicidal, sporicidal and virucidal activity. The chlorination and the oxidation reaction of hypochlorite are unspecific. The active substance is “active chlorine released from sodium hypochlorite”, which is thought to consist of chlorine (Cl2), hypochlorous acid (HClO) and hypochlorite anion (ClO^-) in equilibrium. The predominant species will depend on pH value (chlorine is available only at pH < 4, hypochlorous acid is predominant in the range 3 to 7, whereas only the hypochlorite anion is present at pH >9-10 The term available (or active) chlorine is used for the total amount of reactive chlorine that can be released from the solution. Concentrations in the range of between 3.6 and 3600 mg/L of available chlorine are showing bactericidal, fungicidal, sporicidal and virucidal action.	ECHA (2017)
Cytotoxicity	Cytotoxicity testing (XTT viability assay according to ISO 10993-5) were performed in human skin fibroblasts and human keratinocytes for commercial brands dilutions of sodium hypochlorite solutions and various dilutions of these using incubation durations of 1, 5 and 15 minutes. In general the highest degree of cytotoxicity was seen after 15 minutes of incubation. In keratinocytes at 15 minutes of incubation a NOAEC of 0.01% (0.1 mg/ml) of sodium hypochlorite was found and a LOAEC of 0.025% (0.25 mg/ml) (for the product Veriforte). In fibroblasts at 15 minutes of incubation a NOAEC of 0.018% (0.18 mg/ml) of sodium hypochlorite was found and a LOAEC of 0.036% (0.36 mg/ml)(for the product Lavonox).	Svering et al 2019
	Cytotoxicity testing (XTT viability assay) were performed in human skin fibroblasts with various dilutions of sodium hypochlorite solutions using incubation durations of 2, 4, 8 and 24 hours. At the lowest concentration of 0.0075% (0.075 mg/ml)	Hidalgo et al. (2002)

Parameters/ endpoints	Sodium hypochlorite	Reference
	cytotoxicity was found after 8 hours of incubation but not for the other incubation durations while a concentration of 0.0125% (0.125 mg/ml) resulted in cytotoxic response for all incubation durations.	
Irritation, skin	In rabbits and guinea pigs dermal exposure to a sodium hypochlorite solution at 5.25%, was slightly irritant (old studies from 1975). In humans weak to moderate irritation was observed in 15 of 69 dermatitis patients patch tested (48 h, patch conditions not specified, reported as “covered contact”) with 2% NaOCl. No irritation was observed in 20 persons from the same group after additional patch testing (48 h “covered contact”) with 1% NaOCl.	ECHA (2017)
Irritation, mucous membranes	Two eye irritation studies in rabbits and monkeys are available indicating eye irritating properties for concentrations of 5.25 and 5.5% available Cl respectively.	ECHA (2017)
	Sodium hypochlorite concentrations of 5.25, 0.525, 0.052 and 0.005% were tested in eye irritation tests in rabbits. One drop (~0.05 mL) at the highest concentration resulted in significant eye irritation while the concentration of 0.525% gave a moderate reaction at 2 and 6 h. which was gone within 24 h. No signs of irritation were observed at concentrations of 0.052 and 0.005%. I.e. a NOAEC of 0.052%. In a human case of a single accidental exposure of the eye of a female patient with a commercial sodium hypochlorite solution (0.5% NaOCl) burning discomfort of the affected eye occurred and slight superficial disturbance of the corneal epithelium cleared completely within two days without special treatment. In a human case about 10 ml of a sodium hypochlorite solution containing 0.5% of NaOCl was accidentally infused as a disinfectant in connection with intraperitoneal dialysis. The incidence occurred twice. At both times the patients experienced severe abdominal pain and discomfort remained for up to 10 days. Furthermore, the dialysis was affected as a significant increase in solute transport and a decrease in ultrafiltration were found. These clinical parameters did not return to the pre-infusion values.	REACH-reg. (2021)
Sensitization	Three skin sensitisation studies conducted in guinea pigs with sodium hypochlorite showed no sensitising effects.	ECHA (2017)

Parameters/ endpoints	Sodium hypochlorite	Reference
Acute toxicity	In the acute oral and dermal studies, the LD50 was determined to be greater than 2000 mg available Cl/kg bw	ECHA (2017)
Repeated dose toxicity	*Local effects:* On the shaved skin of the upper dorsum of female guinea pigs a gauze pad was placed and soaked at 8-hour intervals with 0.1 or 0.5% sodium hypochlorite solution freshly prepared each day by dilution of Clorox bleach. Animals were sacrificed on day 1, 4, 7 or 14. A 15% decrease in basal cell viabilities was observed after 2 weeks of treatment with 0.5 % sodium hypochlorite. Morphological changes in cells were observed after 7 and 14 days of treatment with the 0.5% solution and 14 days with the 0.1% solution. It was concluded that a 0.1 % solution of sodium hypochlorite could be used for long-term maintenance of human burn wound due to the relatively low toxicity. In a non-standard study for the effect of sodium hypochlorite solutions on skin, 10 male and 10 female guineapigs per group were exposed to a 0.125% sodium hypochlorite solution on the dorsal side of their ears. This was done daily for 1, 2, 4 and 8 weeks. There were no treatment related effects on the parameters measured (e.g., number of epidermal cells, area of epidermis, area of papillary layer). No inhalation studies with hypochlorite aerosols were reported but in chronic toxicity studies with chlorine vapours at the lowest concentration of 1.2 mg Cl_2/ m^3 resulted in both rats and mice in treatment-induced lesions in the nasal epithelium due to the irritative properties of the vapours. *Systemic effects:* Three subchronic repeated dose toxicity drinking water studies of sodium hypochlorite are available for rats and mice. Data on chronic repeated dose toxicity is available from four chronic toxicity/carcinogenicity drinking water studies in rats and mice. The NOAECs derived lay between >0.0275% and 0.1% avCl. Overall, no systemic effects or morphological changes on microscopic examination could be observed after oral administration of sodium hypochlorite solutions to rats and mice, with the exception of body weight and liver effects. However, these changes were	ECHA (2017)

Parameters/ endpoints	Sodium hypochlorite	Reference
	considered secondary to the local toxicity of sodium hypochlorite.	
Genotoxicity	Hypochlorite solutions show sporadic equivocal/positive results in in vitro assays (three Ames tests, cytogenetic assay in mammalian cells) which is due to the ability to generate reactive oxygen species and to induce DNA damage Standard in vivo studies (two micronucleus tests, bone marrow aberration assay, DNA damage in renal tissue) were negative The negative results in the *in vivo* studies are considered sufficient to reassure about the absence of a mutagenic potential of hypochlorite *in vivo*. Based on the available data, no genotoxic potential of sodium hypochlorite is expected.	ECHA (2017)
Carcinogenicity	Sodium hypochlorite was tested for carcinogenicity by the oral route in several studies. The NOAECs derived lay between 0.0275% and 0.1% available Cl. Based on the available data, no carcinogenic potential of sodium hypochlorite is expected.	ECHA (2017)
Toxicity to reproduction	From a prenatal developmental toxicity study in rats and from a multi-generation study in rats at dose levels up to 100 mg/L hypochlorite in drinking water no adverse effects were observed in relation to development and reproductive toxicity. Limitations apply to these studies due to the low dose levels. However, as sodium hypochlorite is rapidly degraded in the body to physiological metabolites (sodium, chloride and hydroxide ions), it can be predicted that the embryo/foetus will not be exposed due to the fast degradation of sodium hypochlorite in blood and other body fluids before becoming systemically available.	ECHA (2017)
Tolerable exposure levels		
Tolerable oral exposure	A tolerable exposure level in relation to systemic effects from oral exposure was not considered relevant because systemic effects are considered secondary to the local effects of the substance.	ECHA (2017)
Internal (systemic) exposure	No relevant data from systemic exposure is available for derivation of a tolerable systemic exposure level.	DHI evaluation
Tolerable dermal exposure	Based on the human data where skin irritation was seen above concentration levels of 1% and no irritation at 1% in dermatitis patients a tolerable	ECHA (2017)

Parameters/ endpoints	Sodium hypochlorite	Reference
	dermal concentration level of 1% was concluded for professional as well as non-professional users.	
	The tolerable exposure level derived by ECHA (2017) was derived from data in relation to single exposure to humans. In case of dermal exposure several times per day every day during lifetime it is considered relevant also to consider animal data with repeated exposure. One study in guinea pigs indicated histopathological changes (hyperplasia) in the epidermis cell layer after 14 days dermal exposure to a concentration level of 0.5% and to a lesser extent at 0.1%. Based on this it is considered relevant to apply an uncertainty factor of 10 for extrapolation for a tolerable exposure level of 1% for short-term exposure in humans to repeated daily exposure over a long (lifetime) exposure period. Thus, a tolerable exposure level of 0.1% is proposed for long-term dermal exposure to sodium hypochlorite.	DHI evaluation
Tolerable inhalation exposure	Not considered relevant for hypochlorite solutions used for disinfection of catheters as inhalation in relation to aerosol is not considered likely.	DHI evaluation
Tolerable exposure, mucous membrane	In rabbits eye exposure one drop of 0.525% sodium hypochlorite gave a moderate reaction whereas 0.052% as a NOAEC did not cause irritation. Also, in humans 0.5% short-term exposure to 0.5% resulted in mild degree of irritation A NOAEC on 0.052% from the rabbit test is considered relevant for humans as well as this is 10 times lower than the human LOAEC. However, short-term exposure to mucous membranes of the eye may not reflect repeated daily exposure to hypochlorite from use of catheters in relation to everyday over long-term use. Using an uncertainty factor of 10 for extrapolation to a long-term exposure scenario a tolerable concentration level of 0.052% / 10 = 0.005% can be proposed. It can be noted that this level is very close to a LOAEC of 0.0075% (0.075 mg/ml) for cytotoxicity in *in vitro* testing in relation to 8 hours of incubation.	DHI evaluation
References **ECHA (2017).** Evaluation of active substances Assessment Report Active chlorine released from sodium hypochlorite Product-type 2 (Disinfectants and algaecides not		

Parameters/ endpoints	Sodium hypochlorite	Reference
intended for direct application to humans or animals). Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products. **Hidalgo et al. (2002).** Cytotoxicity mechanisms of sodium hypochlorite in cultured human dermal fibroblasts and its bactericidal effectiveness. Chemico-Biological Interactions 139 (2002) 265–282 **REACH reg (2021)**. Data from REACH registration of sodium hypochlorite: Registration Dossier - ECHA (europa.eu) **Severing et al. (2019).** Safety and efficacy profiles of different commercial sodium hypochlorite/ hypochlorous acid solutions (NaClO/HClO): antimicrobial efficacy, cytotoxic impact and physicochemical parameters in vitro. J Antimicrob Chemother 2019; 74: 365–372 doi:10.1093/jac/dky432 **WHO (2016)** -WHO Guidelines for Drinking-water Quality, Chlorine Dioxide, Chlorite and Chlorate in Drinking-water. WHO/FWC/WSH/16.49		

6.3 Derivation of tolerable exposure levels

In the assessment report for active chlorine derived from sodium hypochlorite a tolerable exposure levels for *dermal exposure* as well as for *inhalation* (in relation to spraying of the hypochlorite solution) was derived by ECHA (2017). No tolerable exposure level for oral exposure or systemic exposure were considered relevant. Hypochlorite is considered to react and degrade at the site-of-contact and thereby limiting the systemic bioavailability. Also, it was concluded that effects observed from oral exposure most likely could be considered as secondary effects caused by the irritant properties of the substance.

Based on the data described in section 6.2 tolerable exposure levels for the relevant exposure routes in relation to the use of sodium hypochlorite for cleaning and disinfection of urethra catheters will be derived.

As sodium hypochlorite is used for cleaning and disinfection of a medical device the tolerable exposure levels are derived according to the methodology in ISO 10993-17:2009 “Biological evaluation of medical devices, Part 17: Establishment of allowable limits for leachable substances”.

6.3.1 Tolerable exposure, dermal exposure

ECHA (2017) concluded a tolerable dermal concentration level of 1% sodium hypochlorite based on the human data where skin irritation was seen above concentration levels of 1%, but where no irritation was observed at 1% in dermatitis patients. The tolerable dermal concentration level of 1% was concluded for professional as well as non-professional users.

Hover, the tolerable exposure level derived by ECHA (2017) was derived from data in relation to single exposure to humans. In case of dermal exposure several times per day every day during a longer period (up to lifetime) it is considered relevant also to consider the animal data from repeated dermal exposure.

One study in guinea pigs indicated histopathological changes (hyperplasia) in the epidermis cell layer after 14 days dermal exposure to a sodium hypochlorite concentration level of 0.5% and to a lesser extent at 0.1%. However, in another study no effects were note in relation to repeated dermal exposure to a concentration level of 0.125%.

As these data indicate lower effect levels compared to single exposure and a no-effect-level at about 0.1%, it is considered relevant to apply an uncertainty factor of 10 for extrapolation for a tolerable exposure level of 1% for short-term exposure in humans to repeated daily exposure over a longer exposure period.

Thus, a tolerable exposure level of 0.1% is proposed for long-term dermal exposure to sodium hypochlorite.

6.3.2 Tolerable exposure, mucous membranes

ECHA (2017) did not derive a tolerable level for the mucous membrane exposure route.

In rabbits eye exposure one drop of 0.525% sodium hypochlorite gave a moderate reaction whereas 0.052% as did not cause irritation. Also, in humans 0.5% short-term exposure to 0.5% resulted in mild degree of irritation

A NOAEC of 0.052% from the rabbit test is considered relevant for humans as well as this is 10 times lower than the human LOAEC.

However, *short-term exposure* to mucous membranes of the eye may not reflect repeated daily exposure to hypochlorite to the mucous membranes of the urethra from use of catheters in relation to everyday and long-term use.

Using an uncertainty factor of 10 for extrapolation to a tolerable long-term exposure scenario a tolerable concentration level of 0.052% / 10 = 0.005% can be proposed.

This level can be considered as sufficient protective for the mucous membrane, as this level is very close to a predicted NOAEC for cytotoxicity just below 0.0075% (0.075 mg/ml) as indicated in the *in vitro* testing reported by performed by Hidalgo et al. (2002). Normally for the same substance the cytotoxic no effect level *in vivo* for organ tissue would be much higher than the no effect level in a very sensitive *in vitro* cytotoxicity test.

6.3.3 Tolerable systemic exposure

It is not possible to derive at tolerable exposure level for systemic exposure as no adequate data is available in relation to systemic exposure.

Furthermore, the most critical effects from sodium hypochlorite from any exposure route is considered to be the local effects due to the high reactivity at the site-of-contact. Thus, the systemic bioavailability of the substance can be considered as very limited or absent.

6.3.4 Tolerable exposure level, inhalation

This exposure route is not considered relevant as generation of aerosols from the hypochlorite solution is considered unlikely in connection with the cleaning and disinfection procedures.

7 Safety assessment

For the safety assessment the tolerable exposure levels will be compared to the estimated exposure levels by calculating the Margin of Safety, MoS:

MoS = TE / Exposure

For MoS values above 1 the estimated exposure is below the tolerable exposure level indicating a safe exposure scenario.

For MoS values below 1 the estimated exposure is above the tolerable exposure level indicating that the exposure scenario cannot be considered as safe.

The MoS values will only be calculated in relation to safety assessment of local effects, i.e. using the exposure levels expressed in % sodium hypochlorite solution and the tolerable exposure level expressed in %. A safety assessment for systemic effects will not be performed as the systemic bioavailability of sodium hypochlorite is considered negligible due to the reactiveness of the substance.

7.1 Safety assessment of scenario 1 exposure scenarios

7.1.1 Female exposure

Urethra

MoS = 0.005% / 0.001% = 5

Fingertips

MoS = 0.1% / 0.012% = 8.3

As the calculated MoS values are considerable above 1 the female exposure scenarios for urethra and fingers can be considered safe for use of a 0.012% sodium hypochlorite solution.

7.1.2 Male exposure

Urethra

MoS = 0.005% / 0.0009 % / 0.005% = 5.6

Fingertips

MoS = 0.1% / 0.012% = 8.3

As the calculated MoS values are considerable above 1 the male exposure scenarios for urethra and fingers can be considered safe for use of a 0.012% sodium hypochlorite solution.

7.1.3 Reliability, scenario 1

The reliability of the conclusion of the safety assessment of use of 0.012% hypochlorite solution is considered to be high as even though conservative exposure estimates have been used relatively high MoS values were obtained.

7.2 Safety assessment of scenario 2 exposure scenarios

7.2.1 Female exposure

Urethra

MoS = 0.005% / 0.05% = 0.10

Fingertips

MoS = 0.1% / 0.6% = 0.17

As the calculated MoS values are considerable below 1 the female exposure scenarios for urethra and fingers cannot be considered safe for use of a 0.6% sodium hypochlorite solution.

7.2.2 Male exposure

Urethra

MoS = 0.005% / 0.046 % = 0.11

Fingertips

MoS = 0.1% / 0.6% = 0.17

As the calculated MoS values are considerable below 1 the male exposure scenarios for urethra and fingers cannot be considered safe for use of a 0.6% sodium hypochlorite solution.

7.2.3 Reliability, scenario 2

The reliability of the conclusion of the safety assessment of use of 0.6% hypochlorite solution is considered to be medium - low due to the conservative exposure estimates that may overestimate the actual exposure even with a factor of 10 (it was assumed – using a default value from exposure models - that a residual layer of 0.1 mm hypochlorite solution may still remain over the entire surface on the catheter when using the catheter).

In order to make a more precise safety assessment it is recommended to make an experimental determination of residual solvent volume remaining on the catheter after the cleaning and disinfection procedure.

7.3 Risk assessment of alternative scenario

According to Coloplast A/S urinary catheters may by some patients be used without lubricant gel. In such cases the first part of the urethra of both women and men may be exposed to drops with the initial concentration of the hypochlorite solution, i.e. for scenario 1 a concentration of 0.012% and scenario 2 a concentration of 0.6% hypochlorite.

When making risk assessment of these alternative scenarios the following MoS values can be obtained when comparing to tolerable exposure concentration for the mucous membrane of the urethra at 0.005%:

Scenario 1 (alternative):

$$MoS = 0.005\% / 0.012\% = 0.42$$

Scenario 2 (alternative):

$$MoS = 0.005\% / 0.6\% = 0.008$$

Thus, it can be concluded that when using reusable catheters without using lubricant gel then there is a risk for local effects in the urethra at even the lowest concentration of 0.12% of hypochlorite solution.

7.4 Conclusions on the human health safety assessment

Safety assessments were performed for the use of sodium hypochlorite solutions as cleaning and disinfectant solution for female and male re-usable urinary catheters using sodium hypochlorite concentrations of either 0.012% or 0.6%.

The critical effect in relation to health was concluded to be local dermal irritation of the fingers (by handling the catheter during cleaning and use) and local irritation of the mucous membranes in the urethra. Due to reactivity and rapid degradation of hypochlorite no systemic effects were considered likely.

Considering the dermal exposure to the fingertips it was concluded that repeated and long-term use of 0.012% sodium hypochlorite solution is safe while use of 0.6% may constitute a risk for dermal effects unless gloves or other protective measures avoiding dermal exposure are used.

Considering exposure to the urethra of either females and males it was concluded that repeated and long-term use of 0.012% sodium hypochlorite is safe, whereas use of 0.6% sodium hypochlorite may constitute a risk for irritational effects of the mucous membranes. However, this assessment was based on an exposure model assumption that 0.1 mm of sodium hypochlorite solution would remain on the whole surface on catheter during use before mixed into the lubricant gel. This is considered a conservative assumption that overestimate exposure. If experimental data indicates a significantly less remaining solution volume on the catheter this may alter the conclusion.

However, in alternative scenarios risk will apply for both men and women for urethra exposure if no lubricant gel is applied before use of the catheter and the urethra of both women and men may be exposed to drops with the initial concentration of the hypochlorite solution, i.e. for scenario 1 a concentration of 0.012% and scenario 2 a concentration of 0.6% hypochlorite.

It should be noted that the safety assessment only covers effects related to sodium hypochlorite and *not* potential effects related to degradation products of hypochlorite (e.g. chlorate) or chlorinated reaction products generated during use, as lack of precise data on this would make an assessment very hypothetical.

8 Environmental assessment

8.1 Exposure assessment

8.1.1 Fate in the environment

It is well known that chlorine forms by-products (DBP: Degradation By-Products) – both organics and inorganics – during its degradation into primarily chloride ions. The EU DBP guidance document has pointed out a number of marker substances in relation to swimming pool use (ECHA, 2017).

Hypochlorite is a strong oxidizing agent and a large fraction of the hypochlorite will be readily reduced to chloride ions in the environment. Bromide ions are readily converted into hypobromite by reducing hypochlorite to chloride ions. Hypobromite is an even stronger oxidizing agent than hypochlorite and can form for example brominated organic compounds.

Hypochlorite reacts with organic material – and a fraction of the hypochlorite will be transformed into chlorinated organic compounds e.g., mono-, di- and trichloroacetic acid

ECHA (2017) includes an overview of the reactions of free chlorine with organic matter and other naturally occurring component I the environment:

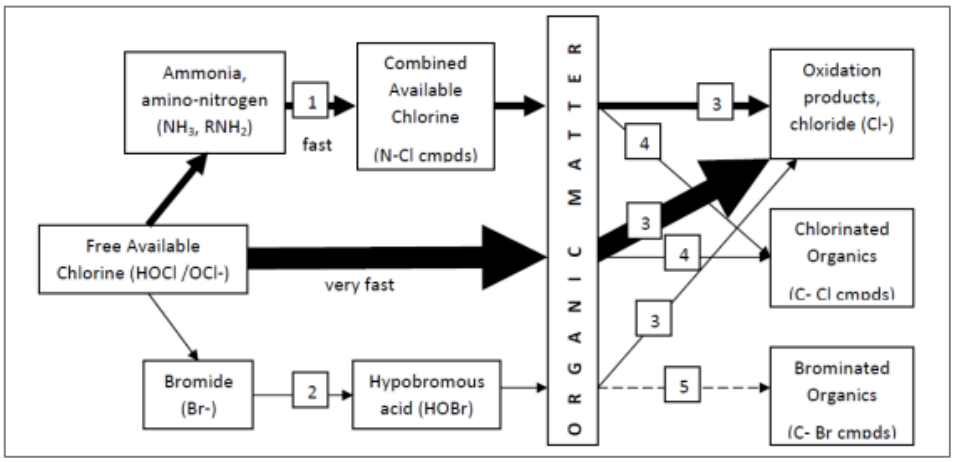


Figure 1 Schematic overview of the reactions of free available chlorine with organic matter and other components. From ECHA (2017).

1) Active chlorine reacts rapidly with amino-nitrogen atoms that are frequently present in proteins or amino acids in natural organic matter, and with ammonia. The products will be N-chloramines, mainly labile, inorganic species that are often collectively referred to as combined available chlorine

2) In the presence of bromide ion, some active chlorine reacts initially to produce hypobromous acid. This reaction is highly relevant in saltwater where bromide is present at a higher level

3) The dominant reaction of active chlorine is oxidation of organics (and also reducible inorganics), generally rapid reactions which result in the chlorine being mineralised as chloride. Active bromine will react in the complete same manner.

4) Active chlorine (and to a lesser extent the intermediate combined chlorine) can chlorinate organic molecules forming carbon-chlorine (or carbon-halogen) bonds to produce halogenated organics

5) Hypobromous acid produces oxidation products releasing the bromide (reaction 3) again with the formation of small quantities of brominated organics

ECHA (2017) lists a number of by-products from active chlorine (DBP):

- Chlorite and chlorate (this reaction is not shown in figure 1): Chlorate may be formed as the resultant of two reactions: a slow one with formation of chlorite and a fast one with formation of chlorate by reaction between chlorite and hypochlorite.
- Trihalomethanes (THMs): chloroform (trichloromethane), bromoform (tribromomethane), dichlorobromomethane and dibromochloromethane. When bromide concentrations are low (freshwater), chloroform is the dominant compound, while in seawater bromoform is dominant (ECHA, 2017)
- Halogenated acetic acids (HAAs): This group consists of nine different chlorinated/brominated acetic acids. The five most common are monochloroacetic acid (MCA), dichloroacetic acid (DCA), trichloroacetic acid (TCA), monobromoacetic acid (MBA) and dibromoacetic acid (DBA).
- Halogenated aldehydes: The most commonly known representative of this group is chloral hydrate (trichloroacetaldehyde), other chloro- and bromo-substituted acetaldehydes (dichloro, bromochloro etc.) are also reported
- Halogenated acetonitriles: The four haloacetonitriles most commonly reported as by-products of active chlorine use are dichloroacetonitrile, trichloroacetonitrile, chlorobromoacetonitrile and dibromoacetonitrile. Brominated compounds are formed in the presence of bromide.
- Halogenated amides: Chlor- and bromacetamides, have been detected in drinking water and swimming pools
- Halogenated ketones: e.g., 1,1-dichloropropanone, 1,1,1-trichloropropanone, and bromopropanone. These substances may be formed by reactions with humic and fulvic acids
- Halogenated phenols: chloro- and bromophenols may be formed by reactions with humic or fulvic acid. After initial addition leading to monochloro- or bromophenol, further addition leads to di- or tri-halogenated phenols.
- Bromate can be formed when high levels of free available chlorine are present in combination with a high pH, and when bromide is present.
- Halogenated amines: These compounds are formed when amines or ammonium is present. They react subsequently and produce the above mentioned DBPs

For the actual assessment, it is assessed that it is not relevant to consider brominated compounds, as the bromide concentration in fresh water – contrary to sea water - and drinking water is quite low, and as hypochlorite is expected to be completely transformed into its degradation by products or chloride.

According to the information provided in the EU DBP guidance document (ECHA, 2017), the maximum observed transformation of chlorine into halogenated organic compounds is 5%. This number is used in the assessment.

8.1.2 Emission calculations

The below emission scenario is defined for the use:

- Concentration of hypochlorite in the disinfection agent: 0.0125% - 0.6% (see sections 0, 4.2)
- Content of in each catheter case: 0.04 L (see section 0)

- Frequency of changing disinfection agent: 1 time per day (1 day^{-1}) (see section 0)
- Number of inhabitants around a public sewage treatment plant: 10,000 (default in the ECHA guidance for environmental risk assessment and ECHA guidance on environmental risk assessment of biocidal products (ECHA, 2016, ECHA, 2017))
- Number of catheter users connected to a public sewage treatment plant: 62 (see Table 3). It is in addition assumed that all catheter users will use reusable urethral catheters.

8.1.3 Tier 0 assessments

The predicted environmental concentration, PEC, is calculated by:

$$PEC_{STP} = \frac{E}{W}$$

$$PEC_{Surface\ water} = \frac{E \cdot (1 - D)}{W \cdot DILUTION}$$

where

E	is the released amount of hypochlorite to the STP per day
D	is the fraction degraded/removed in the STP
W	is the daily amount of treated water = No of inhabitants connected to the STP (10,000)×Water use per inhabitant (200 l/day) = 2000 m^3/d (ECHA (2016), ECHA (2017)))
DILUTION	dilution factor = 10 which is the default value according to the ECHA guidance documents for discharges to fresh water, ECHA (2016), ECHA (2017)

Hypochlorite is readily degraded in the sewer and sewage treatment plant due to the high concentration of organic matter and also due to the anaerobic conditions in the sewer. Therefore, D is set to 1 and there is no need to calculate the PECs for hypochlorite in the fresh water, as it will be negligible. Thus, only the PEC in the STP is calculated for hypochlorite.

At the Tier 0 level, the PECs for the formed halogenated organic compounds is conservatively calculated by assuming that each of the considered halogenated organic compound constitutes 100% of the formed AOX (which is set to 5% of the consumed hypochlorite – see section 8.1.1).

Chlorate is a likely impurity in the disinfection agent, and it is not expected – contrary to hypochlorite – to be readily degraded/transformed in the STP. However, it is assumed that the all hypochlorite is transformed into chlorate before release to the sewer.

The PECs of hypochlorite and the DPBs for the STP and for the surface water are presented in Table 4.

Table 4 PEC range for Sewage Treatment Plants (STP) and surface water.
Min: minimum chlorine concentration (0.0125%), discharge every day
Max: maximum chlorine concentration (0.6%), discharge every day

Substance	PEC (STP (mg/L)	PEC (Surface water) (µg/L)
Hypochlorite	1.1E-04 - 5.1E-03	
Chlorate	5.8E-05 - 2.8E-03	5.8E-03 - 0.28
Trichloroacetic acid	5.7E-06 - 2.7E-04	5.7E-04 - 2.7E-02
Chloroform	4.1E-06 - 2.0E-04	4.1E-04 - 2.0E-02
Trichloroacetonitrile	5.0E-06 - 2.4E-04	5.0E-04 - 2.4E-02
Trichloroacetaldehyde	5.1E-06 - 2.5E-04	5.1E-04 - 2.5E-02
Trichloracetamide	5.6E-06 - 2.7E-04	5.6E-04 - 2.7E-02
Dichlorophenol (2,3-, 2,4-, 2,5-)	8.5E-06 - 4.1E-04	8.5E-04 - 4.1E-02

8.2 Hazard assessment

The below tables (Table 5 - Table 12) give an overview of the inherent toxicity, degradability and potential for bioaccumulation of hypochlorite and its main marker DBP.

The tables also give the PNECs for the STPs and for the surface water. PNEC (Predicted No Effect Concentration) is the highest concentration, where no unacceptable effect on the environment is expected.

8.2.1 Environmental fate of hypochlorite and its main DBPs

Hypochlorite is – as already mentioned – not persistent in the environment. The DBPs are all assessed not to be readily biodegradable in the environment. Only chloroform is found to be volatile in water and is therefore expected to readily evaporate. The other DBPs are found not to be very volatile, so they tend to persist in the water for a long time.

Table 5 Properties of the hypochlorite. Data from the REACH registration dossier for sodium hypochlorite, ECHA (2022)

	Hypochlorite
CAS (sodium salt)	7681-52-9 (sodium salt)
Mw (g/mol)	74.44 (sodium salt)
Mw (g/mol)	51.45 (hypochorite ion)
CLP classification	Aquatic Acute 1, H400 Skin Corr. 1B, H314 Eye Dam. 1, H318 Aquatic Chronic 1, H410 (Har)
(Bio)degradability	Is readily transformed
Henry's constant ($Pa \times m^3/mole$)	-
Environmental toxicity	The environmental toxicity of hypochlorite has been extensively studies, and it has been found that hypochlorite is toxic to the aquatic environment. The most sensitive endpoint for the aquatic compartment is found to be the algal biomass in microcosm experiment. The test revealed a no effect concentration (NOEC) (7 day) of 0.0021 mg/L
PNEC (STP) (mg/l)	3.24 (hypochlorite ion)
PNEC (surface water) (µg/L)	0.15 (hypochlorite ion)
logKow	-
BioConcentrationFactor	-

Table 6 Properties of the chlorate. Data from the REACH registration dossier, ECHA (2022)

	Chlorate
CAS (sodium salt)	7775-09-9
Mw (g/mol)	106.44 (sodium salt)
Mw (g/mol)	83.45 (chlorate ion)
CLP classification	Ox. Sol. 1, H271 Acute Tox. 4, H302 Aquatic Chronic 2, H411 (Har)
(Bio)degradability	Quite stable in the environment. It should be noted that – with a time frame of weeks/months - the formation of chlorate from hypochlorite is not a very fast reaction.
Henry's constant Pa×m^3/mole	-
Environmental toxicity	Short-term tests with fish and invertebrates, freshwater as well as marine species, gave effect concentrations greater than 1000 mg/l. For long-term tests with fish and daphnids NOEC values greater than 500 mg/l were obtained. Algae species (freshwater and marine) were more sensitive, but EC50 values were still greater than 100 mg/l and NOECs were greater than 62.5 mg/l. *Lemna minor* was most sensitive with a NOEC of 10 mg/l. Two other taxonomic groups of marine organisms were tested as well. Molluscs were not sensitive in a short-term test with an EC50 greater than 1000 mg/l. The rotifer *Brachionus plicatilis* was the most sensitive marine species with an EC50 of 596 mg/l and an EC10 of 21 mg/l, both based on reproduction.
PNEC (STP) (mg/l)	78.40
PNEC (surface water) (µg/L)	0.16
logKow	-
BioConcentrationFactor	-

Table 7 Properties of the Trichloroacetic acid. Data from the REACH registration dossier, ECHA (2022)

	Trichloroacetic acid
CAS (sodium salt)	76-03-9
Mw (g/mol)	163.39
Mw (g/mol)	
CLP classification	Skin. Corr. 1A, H314 Aquatic Chronic 1, H410 Aquatic Acute 1, H400 (Har)
(Bio)degradability	Neither readily nor inherently biodegradable.
Henry's constant Pa×m^3/mole	0.0014 (not volatile) (EpiSuite, exp. database)
Environmental toxicity	Data are available for the short-term toxicity of TCA for freshwater organisms within algae, crustaceans and fish including higher plants and insects. Valid data (Klimisch code 2) for algae indicate EC50 values 4.7-4.9 mg/L measured as biomass and NOEC values of 3.0 mg/L for both growth and biomass. Studies of the toxicity of the sodium salt of TCA to higher plants indicate a EC50 value of 50 mg/L for the most sensitive endpoint being root growth. The corresponding NOEC value is 3 mg/L. EC50-values for crustaceans are in the range 110-10 000 mg/L for daphnia and 17 mg/L (larvae of *Thamnocephalus platyurus*). The chronic toxicity data show that algae are the most sensitive organism with the lowest NOEC reported at 0.01 mg/L and the lowest EC50 reported at 0.3 mg/L (14-day study, Na-TCA, green algae of the genus *Chlorella*). In 21-day studies with *Daphnia magna*, a NOEC of 285 mg/L has been determined although the study is considered less valid due to lack of pH control. Data for fish show a LOEC of 7 mg/L determined in a 63-day study. Two brackish water tests with brackish water fish and crustaceans are available in addition to one short-term test with marine algae however the latter is not considered valid. Data from long-term tests in salt water are available for algae but results are not valid due to lack of pH control in the tests.
PNEC (STP) (mg/l)	100
PNEC (surface water) (µg/L)	0.17
logKow	1.33
BioConcentrationFactor	-

Table 8 Properties of the chloroform. Data from the REACH registration dossier, ECHA (2022)

	Chloroform
CAS (sodium salt)	67-66-3
Mw (g/mol)	119.38
Mw (g/mol)	
CLP classification	Carc. 2, H351 Skin Irrit., 2 H315 Acute, Tox. 4, H302 STOT RE 2, H373 Eye Irrit. 2, H319 Repr. 2, H361d STOT RE 1, H372 Acute Tox. 3, H331 (Har)
(Bio)degradability	No significant biodegradation of chloroform in surface waters is observed under aerobic, environmental conditions. Chloroform is only degraded under anaerobic conditions in water. Degradation tests performed with soils indicated that chloroform is only degraded by certain methane-utilising bacteria under special aerobic conditions.
Henry's constant Pa×m^3/mole	372 (volatile) (EpiSuite, exp database)
Environmental toxicity	The available data on the aquatic toxicity of chloroform, three long-term NOECs from species representing three trophic levels have been identified: Fish: NOEC (6 to 9 months. *Oryzias latipes*): 1.463 mg/L NOEC (21 days, *Daphnia magna*): 6.3 mg/L EC10 (72 hours, *Chlamydomonas reinhardii*): 3.61 mg/L The toxicity of chloroform to microorganisms, the lowest effect level has been identified from the study where a NOEC of 0.48 mg/L was found for Nitrosomonas bacteria in the ammonium consumption inhibition test.
PNEC (STP) (mg/L)	0.48
PNEC (surface water) (µg/L)	146
logKow	1.97
BioConcentrationFactor	-

Table 9 Properties of the Trichloroacetonitrile.

	Trichloroacetonitrile
CAS (sodium salt)	545-06-2
Mw (g/mol)	144.39
Mw (g/mol)	
CLP classification	Acute Tox. 3*, H301 Acute Tox. 3*, H311 Acute Tox. 3*, H331 Aquatic Chronic 2, H411 (Har)
(Bio)degradability	No data are available. However, both EpiSuite and LeadScope calculations predict the substance not to be readily biodegradable. It may be biodegradable at anaerobic condition (as chloroform).
Henry's constant Pa×m^3/mole	0.14 (not volatile) (EpiSuite, calc.)
Environmental toxicity	Only very few toxicity data are available for the substance. LC50 (96 hr, *Oryzias latipes*): 0.072 mg/L (NITE data, 2005), EC50 (*Daphnia magna*, 48 hr): 0.044 mg/L. EC50 (*Raphidocelis subcapitata*, 48 hr, growth rate): 0.02 mg/L (US EPA, ecotox)
PNEC (STP) (mg/l)	
PNEC (surface water) (µg/L)	0.02 derived on the basis of the above data applying an assessment factor of 1000
logKow	2.09 (EpiSuite experimental database)
BioConcentrationFactor	-

Table 10 Properties of the Trichloroacetaldehyde

	Trichloroacetaldehyde
CAS (sodium salt)	75-87-6
Mw (g/mol)	147.39
Mw (g/mol)	
CLP classification	Eye Irrit. 2, H319 Skin Irrit. 2, H315 Acute Tox. 4, H302 STOT SE 3, H335 Acute Tox. 1, H330 Acute Tox. 3, H301 STOT RE 2, H373 (CLP in reg. Dossier)
(Bio)degradability	Not readily biodegradable
Henry's constant Pa×m^3/mole	0.0003 (not volatile) (EpiSuite, exp)
Environmental toxicity	The substance is not acute toxic to the environment. EC50(48 hr, Daphnia magna): 112 mg/L (US EPA ecotox), LC50 (96hr, *Oryzias latipes*): 106 mg/L QSAR estimates (REACH reg. dosserier, ECHA 2022): The estimated EC50 values for aquatic green algae after 96 hours was 186.317 mg/l on the basis of growth rate.
PNEC (STP) (mg/l)	-
PNEC (surface water) (µg/L)	186
logKow	0.99
BioConcentrationFactor	Trichloroacetaldehyde

Table 11 Properties of the Trichloracetamide

	Trichloracetamide
CAS (sodium salt)	594-65-0
Mw (g/mol)	162.4
Mw (g/mol)	
CLP classification	Eye Irrit. 2, H319 Skin Irrit. 2, H315 Acute Tox. 4 H302
(Bio)degradability	Not readily biodegradable (DK QSAR database)
Henry's constant Pa×m^3/mole	0.007 (not volatile) (EpiSuite, calc.)
Environmental toxicity	DK QSAR database predictions (Leadscope, SciQSAR): LC50(*Fathead minnow*, 96 hr): 244 mg/L; EC50 (*Daphnia magna*, 48 hr): 178 mg/L; EC50 (*Pseudokirchneriella s*., 72hr): 151 mg/L
PNEC (STP) (mg/l)	-
PNEC (surface water) (µg/L)	151 – derived from the above data using an assessment factor of derived in this report)
logKow	1.04 (EpiSuite exp database)
BioConcentrationFactor	-

Table 12 Properties of the Trichloroacetaldehyde. Data primarily from REACH registration database

	Dichlorophenol (2,3-, 2,4-, 2,5-)
CAS (sodium salt)	576-24-9 120-83-2 583-78-8
Mw (g/mol)	163
Mw (g/mol)	
CLP classification	Acute Tox. 3, H311 Skin Corr. 1B, H314 Aquatic Chronic 2, H411 Acute Tox. 4, H302 (Har)
(Bio)degradability	Dichlorophenol is not biodegradable in the aerobic aqueous environment.
Henry's constant Pa×m^3/mole	0.44 (not volatile) (EpiSuite, exp.)
Environmental toxicity	Data from the NITE exp. Database, 2003: EC50 (*Pseudokirchnerella subcapitata*, 72 hr):4.8 mg/L NOEC (*Pseudokirchnerella subcapitata*, 72 hr):0.67 mg/L EC50 (*Daphnia magna*, 48 hr): 2.2 mg/L EC10 (*Daphnia magna*, 21 d): 0.27 mg/L LC50 (*Oryzias latipes*, 96 hr): 3.4 mg/L
PNEC (STP) (mg/l)	
PNEC (surface water) (µg/L)	5.4 derived on the basis of the above data using an assessment factor of 50
logKow	2.84 (EpiSuite, exp database)
BioConcentrationFactor	

8.3 Safety assessment

Table 13 shows the PEC/PNEC ratios for hypochlorite and the considered DBPs. It is recalled that a risk to the environment cannot be excluded if PEC/PNEC ratio is above 1. On the other hand, If the PEC/PNEC is below 1, then no unacceptable effects on the environment are expected.

8.3.1 Sewage treatment plan

It is seen that the PEC/PNEC ratios for the STP are very well below 1 for all substances, so no unacceptable effects on the microorganism in the STP are expected.

8.3.2 Surface water

It is seen that the PEC/PNEC ratios are below 1 for all substances – except for chlorate and trichloroacetonitrile for which the maximum PEC/PNEC ratios are slightly above 1 (1.7 respectively 1.2). The PEC/PNEC in the lower end of the range are all well below 1.

Due to the very conservative assumptions are made in the calculation of the PEC/PNEC, primarily:

- That all hypochlorite is converted into chlorate, that 5% of the used hypochlorite is transformed into AOX together with that each considered halogenated organic compound constitutes 100% of the formed AOX
- That all catheter users use reusable urethral catheters. .

Overall, the current assessments do not indicate a high risk to the environment due to the use of hypochlorite in reusable urethral catheters. Chlorate may be the degradation product which will exhibit the highest risk to environment. As the formation of chlorate from hypochlorite is a quite slow process (see Table 6) – far below the retention time in the sewer and the STP (time frame hours) – then the formation of chlorate will primarily take place during the storage of the hypochlorite solution prior to use.

Table 13 PEC/PNEC ranges for Sewage Treatment Plants (STP) and surface water.
Min: minimum chlorine concentration (0.0125%), discharge every day
Max: maximum chlorine concentration (0.6%), discharge every day

Substance	PEC/PNEC (STP)	PEC/PNEC (Surface water)
Hypochlorite	3.3E-05 - 1.6E-03	
Chlorate	7.4E-07 - 3.5E-05	3.5E-02 - 1.7
Trichloroacetic acid	5.7E-08 - 2.7E-06	3.3E-03 - 0.16
Chloroform	8.6E-06 - 4.1E-04	2.8E-06 - 1.4E-04
Trichloroacetonitrile	-	2.5E-02 - 1.2
Trichloroacetaldehyde	-	2.7E-06 - 1.3E-04
Trichloracetamide	-	4.3E-06 - 2.1E-04
Dichlorophenol (2,3-, 2,4-, 2,5-)	-	1.6E-04 - 7.5E-03

8.4 Conclusions on the environmental safety assessment

A conservative safety assessment of the use of a hypochlorite solution for cleaning and disinfection of reusable urethral catheters has been prepared. Both hypochlorite and its' main degradation products have been considered.

Overall, the current assessments do not indicate a high risk to the environment due to the use of hypochlorite in reusable urethral catheters. Chlorate may be the degradation product which will exhibit the highest risk to environment. As the formation of chlorate from hypochlorite is a quite slow process (see Table 6) – far below the retention time in the sewer and the STP (time frame hours) – then the formation of chlorate will primarily take place during the storage of the hypochlorite solution prior to use

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