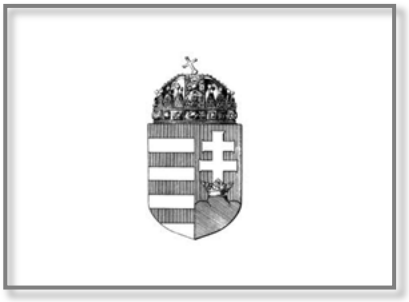

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Sodium chlorite

EC No. 231-836-6

CAS RN 7758-19-2

Evaluating Member State(s): Hungary

Dated: 3 July 2023

Evaluating Member State Competent Authority

National Public Health Centre
Albert Flórián út 2-6.
H-1097 Budapest
Hungary
Tel: +36-1-476-1100
Email: reach.ca@nnk.gov.hu

Year of evaluation in CoRAP: 2019

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation conducted by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Sodium chlorite (EC 231-836-6), i.e., the Substance, was originally selected for substance evaluation to clarify concerns about:

- suspected mutagenicity (M) and reproductive toxicity (R)
- wide dispersive use
- exposure of workers.

During the evaluation, the following additional concerns were identified:

- acute toxicity
- skin corrosion/irritation
- eye damage/irritation
- repeated dose toxicity

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

In 2019, ECHA initiated a dossier evaluation (compliance check – CCH) and identified data gaps. These included information requirements for mutagenicity and reproductive toxicity. In the resulting CCH decision[2], the addressees of the decision were requested to submit the missing information. However, some of the requested information was within the scope of the initial concerns and could have an impact on the substance evaluation. Consequently, the substance evaluation process was suspended until the data requested under CCH became available.

As regards the mutagenicity concern, despite some ambiguity, the result of the comet assay is regarded as positive because all criteria for a positive result are met. Consequently, an *in vivo* follow-up with a germ cell test is needed. However, the compliance check process is appropriate to request the follow-up study. Therefore, ECHA is recommended to open a new CCH for the Substance to require the above follow-up information.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the Substance has led the evaluating Member State to the following conclusions, as summarised in Table 1.

[2] https://echa.europa.eu/documents/10162/0a4086da-1bf9-c54c-6b8c-2f2a1b3abb27

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	x
Harmonised Classification and Labelling	x
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level; a compliance check needed instead to clarify identified concerns.	

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

Based on the available information, harmonised classification and labelling of the Substance is deemed warranted for acute toxicity (Acute Tox. 3, H301 and Acute Tox. 2, H310), skin corrosion (Skin Corr. 1B, H314), eye damage (Eye Dam. 1, H318), repeated dose toxicity (STOT RE 2, H373) and mutagenicity (Muta 2, H341). Although the Registrant has already self-classified the Substance as Acute Tox. 3 (H301), Acute Tox. 2 (H310), Skin Corr. 1B (H314) and STOT RE 2 (H373, spleen), the evaluating Member State considers harmonised classification and labelling as warranted due to divergence in the notified self–classifications.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Not applicable.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

As indicated in section 4, harmonised classification and labelling of the Substance is deemed warranted.

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a CLP Annex VI dossier should be made via the Registry of Intentions.

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
CLP Annex VII dossier	2024	HU

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

The Substance was originally selected for substance evaluation to clarify concerns about:

- Suspected mutagenicity (M) and reproductive toxicity (R)
- wide dispersive use
- exposure of workers.

During the evaluation, the following additional concerns were identified:

- acute toxicity
- skin corrosion/irritation
- eye damage/irritation
- repeated dose toxicity

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Acute toxicity	**Concern confirmed**: Harmonised classification and labelling is warranted (Acute Tox. 3, H301 and Acute Tox. 2, H310).
Skin corrosion	**Concern confirmed**: Harmonised classification and labelling is warranted (Skin Corr. 1B, H314).
Eye damage	**Concern confirmed**: Harmonised classification and labelling is warranted (Eye Dam. 1, H318).
Repeated dose toxicity	**Concern confirmed**: Harmonised classification and labelling is warranted (STOT RE 2, H373).
Mutagenicity	**Concern confirmed**: Harmonised classification and labelling is warranted (Muta 2, H341).
Reproductive toxicity	**Concern removed** based on the available data.
Exposure of workers	**Concern confirmed**: However, there are no risks identified if appropriate risk management measures are followed.
Additional endpoint evaluated	**Outcome / conclusion**
Sensitisation	Based on the available data, the Substance does not cause skin sensitisation. Respiratory sensitisation is not expected due to the low vapour pressure of the substance.
Carcinogenicity	Based on the available data, the Substance has no carcinogenic effects.

7.2. Procedure

The Substance has been selected for substance evaluation according to Article 44 of REACH Regulation for 2019, based upon the Justification Document prepared by the evaluating Member State. The Justification Document identified the above listed initial concerns which warranted a substance evaluation.

During the substance evaluation process, ECHA initiated a dossier evaluation (compliance check) and identified certain data gaps. CCH decision was adopted in 2020[3] and the addressees of the decision were requested to submit the missing information by 7 January 2022.

Since some of the identified data gaps were on the area of the initial concerns, it was appropriate to suspend the substance evaluation process until the new data become available from the requested *in vivo* mammalian alkaline comet assay according to OECD TG 489 and the pre-natal developmental toxicity study according to OECD TG 414, in rat (second species).

The registrants updated their registration dossier in December 2021.

After ECHA completed the follow-up evaluation of the requested information under CCH, the evaluating Member State re-started substance evaluation in September 2022.

The result of the comet assay is regarded as positive because all three criteria for a positive result are fulfilled. Therefore, the concern for mutagenicity is confirmed.

The PNDT study requested under CCH clarified the concern for reproductive toxicity: no relevant effects on the foetuses were observed. The initial concern for reproductive toxicity was therefore removed.

7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Sodium chlorite
EC number:	231-836-6
CAS number:	7758-19-2
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	ClHO2.Na
Molecular weight range:	90.442 g/mol
Synonyms:	*Chlorous acid, sodium salt*

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

[3] https://echa.europa.eu/documents/10162/0a4086da-1bf9-c54c-6b8c-2f2a1b3abb27

Structural formula:

7.4. Physico-chemical properties

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Solid
Vapour pressure	1.1 x 1E-7 Pa at 25°C
Water solubility	551 - 593 g/L at 20°C (pH >= 5)
Partition coefficient n-octanol/water (Log Pow)	< -2.7
Flammability	Non flammable
Explosive properties	Non-explosive
Oxidising properties	Sodium chlorite (solid) is a strong oxidising agent
Granulometry	31.3 µm ± 4.2
Melting point	Sodium chlorite decomposes at 180–200 °C.
Dissociation constant	141

7.5. Manufacture and uses

7.5.1. Quantities

According to ECHA's dissemination site[4], sodium chlorite is manufactured in and/or imported to the European Economic Area in ≥ 1 000 - < 10 000 tonnes per year.

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

[4] 07/03/2023

7.5.2. Overview of uses

Sodium chlorite is used by consumers, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing.

Table 7

USES	
Uses as intermediate	Used in synthesis as TII under SCC.
Formulation	Used in formulation stage.
Uses at industrial sites	Used as industrial oxidant, in industrial bleaching for textiles, as industrial laboratory reagent, in industrial paper pulp bleaching, bioethanol production, as refractory binder for lining of blast furnaces and other applications, in industrial and cooling water treatment, as paper process aid staying in process water, Paper Machine Foam Cleaner and supplied as 31% solution.
Uses by professional workers	Used in professional bleaching and market sector cleaners, including textiles, formulation of cleaning products, brushing application (end-use stage), cleaning outdoors (end-use stage).
Consumer Uses	Used in consumer end-use stage: for cleaning outdoors and indoors.
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

There are no harmonised classifications for the Substance and the evaluating Member State has no information about any proposal for harmonised classification regarding the Substance.

7.6.2. Self-classification

- In the registration(s):
  - Ox. Solid 1 (H271)
  - Acute Tox. 2 (H310)
  - Acute Tox. 3 (H301)
  - Skin Corr. 1B (H314)
  - STOT RE 2 (H373)
  - Aquatic Acute 1 (H400)
  - Aquatic Chronic 2 (H412)

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:
  - Ox. Solid 2 (H272)
  - Eye Dam. 1 (H318)
  - Eye Irrit. 2 (H319)
  - Aquatic Chronic 3 (H412)
  - Acute Tox. 3 (H311)
  - Acute Tox. 2 (H330)

- Acute Tox. 3 (H331)
- Acute Tox. 4 (H302)
- Acute Tox. 4 (H332)
- STOT SE 3 (H335)
- Skin Corr. 1C (H314)
- STOT SE 3 (H371)
- STOT RE 1 (H373)
- Skin Irrit. 2 (H315)
- Carc. 1B (H350)
- Not Classified

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

Oral

Three toxicokinetic studies are available in the registration dossier, all conducted by Abdel-Rahman et al. (1982).

In the first and second study radiolabelled chlorine dioxide, the Substance, sodium chlorate and hypochlorous acid was given to four groups of four male Sprague-Dawley rats via oral gavage in a single administration. The administered dose was 1.5 mg/kg bw, 0.15 mg/kg bw, 0.065 mg/kg bw and 3.26 mg/kg bw, respectively. Blood samples were collected at 5, 10, 20, 30 and 60 minutes, and 2, 4, 8, 24 and 48 hours. 72 hours after administration the animals were euthanized and tissue samples were collected and prepared from stomach, testes, lung, kidney, duodenum, ileum, spleen, liver, bone marrow, carcass, and skin.

The rate constant for absorption was highest to chlorine dioxide and the lowest for hypochlorous acid. For elimination from plasma the highest rate constant was for chlorite and the lowest for hypochlorous acid. The distribution of chlorine dioxide was highest in the kidney, plasma, stomach, ileum, liver, duodenum, spleen, and bone marrow. The distribution of sodium chlorite was the highest in plasma, followed by stomach, testes, skin, lung, duodenum, kidney, carcass, spleen, ileum, bone marrow and liver.

After 72 hours the following metabolites were found in the urine: chloride ion (Cl^-), chlorite ion (ClO_2^-) and chlorate ion (ClO_3^-) (for chlorine dioxide and chlorate ion), and chloride ion and chlorite ion (for chlorite ion). Chloride ion was the major metabolite in all cases. For sodium chlorite 87 and 13% of the initial dose was found in urine and faeces, respectively.

In the third experiment male Sprague-Dawley rats were administered with 10 or 100 mg/L chlorine dioxide, the Substance or sodium chlorate 20 h/day, 7 days/week, for 12 months. After one year, samples from different tissues were collected. A concentration of 100 mg/L chlorine dioxide caused an increase in chloroform levels in blood, liver, testes, and brain. A concentration of 10 mg/L chlorine dioxide increased chloroform levels in rat testes, while levels in blood, liver, kidney, spleen, and brain remained unchanged. A concentration of 100 mg/L chlorite elevated the level of chloroform levels in the liver and

brain (blood was not affected). A concentration of 100 mg/L chlorate increased the liver but not the blood chloroform concentration.

According to the results of these studies, no bioaccumulation is expected regarding the Substance.

Read-across:

In the registration dossier, read-across between the Substance and chlorine dioxide has been proposed for repeated dose toxicity, mutagenicity and toxicity for reproduction endpoints.

Chlorine dioxide is a gas that is used as bleach at pulp mills and as a disinfectant at water treatment facilities. To produce chlorine dioxide gas, hydrochloric acid (HCl) or chlorine gas (Cl_2) is brought together with the Substance:

$NaClO_2 + 1/2\ Cl_2 \rightarrow ClO_2 + NaCl$

On this basis, in acidic conditions (such as in the stomach containing gastric acid), chlorine dioxide would be formed from the Substance after oral administration. Moreover, after rapidly reacting with water, the primary degradation product for both chlorine dioxide and the Substance is chlorite ion.

According to the toxicokinetic studies by Abdel-Rahman et al. (1982), the metabolism of chlorine dioxide and the Substance is similar; chlorite ion and chlorate ion also appeared in the urine after oral administration of chlorine dioxide and the Substance.

Considering all the information regarding the toxicokinetics of chlorine dioxide and the Substance, the evaluating Member State accepts the read-across approach by the Registrant for repeated dose toxicity, mutagenicity, and toxicity for reproduction endpoints.

Dermal

One dermal absorption *in vivo*/*ex vivo* study is available in the registration dossier.

In a dermal absorption *in vitro*/*ex vivo* study (unpublished study report, 2008, OECD 428, GLP) rat and human dermatomed skin (prepared by a special dermatomisation technique, contains: epidermis and some dermis, thickness: 200-400 µm) samples were treated with a single application of a high (390 g/L, 30.8%) and a low (44 g/L, 3.5%) concentration of the Substance. The human skin samples were obtained from human donors' post-mortem. Rat dermatomed skin was from Sprague-Dawley rats' dorsal region. Seven static glass diffusion cells were applied at each dose level. The receptor chamber was filled with receptor fluid. Control cells and procedural recovery cells were also used. The skin samples were exposed to the test material for 8 hours, the remaining dose was washed off from the skin with a mild detergent solution by a swabbing procedure. Samples of receptor fluid were collected at 0, 2, 4, 8 and 24 hours after dosing. At the end of the experiment, the skin membranes were tape stripped to get residual surface dose and stratum corneum.

Mass of the test substance recovered in the surface washings, the skin swabs, the surface tape strips and that remaining in the donor chamber of the diffusion cell was considered the non-absorbed dose, and that recovered in the receptor fluid was considered the absorbed dose. According to the visual examination, the skin membranes were disrupted/damaged post dosing due to the corrosive nature of the Substance. Greater damage was observed on the rat skin membranes, which led to higher absorption results. The maximum absorbed dose trough human skin was 9.7 % with the high concentration solution. This dose was 7-fold less than the dose absorbed through rat skin membrane. The maximum absorbed dose through human skin was 5.1 % with the

low concentration solution. This was approximately 5-fold less than the dose absorbed through rat skin membrane. However, the total absorbed dose, due to the higher absorption rate via damaged or disrupted skin membranes, was likely to be overestimated. The mean method recoveries were less than 90 %. The proportion of the dose that was degraded over the 24-hour exposure period was approximately 80 % for both the rat and human skin groups.

Based on this study, rat skin is more permeable than human skin. In addition, the absorbed dose was overestimated in both rat and human due to the higher penetration rate of the corrosive test solutions through damaged skin membranes. Greater absorbed dose at higher test solution concentration is observed, due to the more significant skin membranes disruption.

7.9.2. Acute toxicity and Corrosion / Irritation

Oral

Three reliable oral acute toxicity study reports are available with the Substance in rats in the registration dossier.

In one of these study (unpublished study report, 1984a, OECD TG 401, GLP) Sprague-Dawley rats were exposed to a 25% aqueous solution of the Substance via gavage. The doses were 150, 200, 250, 400, 450 and 500 mg/kg bw. At doses of 250, 400, 450 and 500 mg/kg bw, mortality appeared on days 0-3. No effects were seen at 150 mg/kg bw, body weight loss occurred at 200 mg/kg bw, brown discolouration of the organs of the abdominal and thoracic cavity appeared above 200 mg/kg bw. The LD50 was 284 mg/kg bw for the Substance and 212 mg/kg bw for chlorite.

In another study 10 adult albino Sprague-Dawley rats were exposed to a 31% aqueous solution of the Substance (unpublished study report, 1985a, EPA 1978 guideline). The doses were 250 and 500 mg/kg bw. The animals were observed for 14 days. At 500 and 250 mg/kg bw 70% and 10% of the rats died, respectively. Several signs of toxicity were observed in different organs (lung, stomach, intestines), and the LD50 was 390 mg/kg bw.

An acute oral toxicity study (unpublished study report, 2017a, OECD TG 420, GLP) was conducted with female Sprague-Dawley rats. The doses were 300 (5 animals) and 2000 mg/kg bw (1 animal). After one single oral administration the animals were observed for 14 days. The animal treated at 2000 mg/kg bw was found dead at day 5. A decrease of body weight was noted on day 2. The mortality was preceded by an absence or a decrease in spontaneous activity, muscle tone, Preyer's and righting reflex, associated with bradypnea, eyes partly closed, piloerection, hypothermia, myosis and dark yellow to brown colouration of urines. Macroscopic observations on day 5 revealed a thinning of forestomach and a greenish corpus. In addition, lysis of the main organs was recorded. At 300 mg/kg bw no clinical signs and no mortality were observed. The LD50 was between 300 and 2000 mg/kg bw. The study was scored Klimisch 1, although only two doses were applied but, considering that, at 300 mg/kg bw, no signs of toxicity were observed, the results are acceptable.

Dermal

Two study reports are available for the dermal acute toxicity of the Substance in the registration dossier.

In one of the studies, which can be considered the key study (unpublished study report, 1984, EPA OPP 81-2, GLP), New Zealand White rabbit’s skin (5/sex/dose) were treated with the test substance (purity: 80%) for 24 hours. The doses were 50, 100, 150 and 300 mg/kg bw. The Substance caused death of seven out of ten rabbits at dermal dose of 150 mg/kg bw, on days 1-4, and ten out of ten rabbits at dose of 300 mg/kg bw, on

days 1-3. Depression was noted in all groups, a cyanotic appearance was noted in two males at 150 mg/kg bw. All survivors appeared normal by termination and did not show any gross visible lesion. Dermal LD50 was 134 mg/kg bw for the Substance and 100 mg/kg bw for chlorite.

The second study (unpublished study report, 1985b, EPA 8/22/78) was conducted on New Zealand rabbits. The rabbits' (10/sex/dose) skin was exposed to 31 % aqueous solution of the Substance for 24 hours. A dose of 1.68 ml (2.0 g liquid/kg bw) was used. There were no deaths. In one male rabbit ascites in the abdominal cavity appeared and in one female rabbit scattered petechiae throughout all lobes of lung was observed, but these symptoms were not related to the treatment. The dermal LD50 was greater than 620 mg/kg bw for the Substance.

These studies were not published, and no other information is available. The Registrant classified the Substance according to the abovementioned test results, for acute oral toxicity category 3 and acute dermal toxicity category 2. The evaluating Member State found this classification appropriate. Corresponding harmonised classification will be proposed due to the divergence among notifiers in their self–classifications.

Eye damage/irritation

Four study reports are available for the eye irritation of the Substance in the registration dossier. Three out of the four studies were considered as key studies.

One in vitro eye irritation study (unpublished study report, 2017b, OECD TG 438, GLP) was conducted on isolated chicken eyes (ICE). In the study, 9 % aqueous solution of the test substance was applied on three enucleated chicken eyes for 10 seconds. Before the application of the test solution, the enucleated eyes were examined with a slit-lamp microscope to ensure that no damage occurred during the dissection procedure. The ocular reactions (corneal opacity, fluorescein retention, corneal swelling) caused by the test substance were assessed by a scoring system at 30, 75, 120, 180, and 240 minutes after treatment only on the approved eyes. Positive and negative controls were also used. The mean maximum corneal opacity was 2.0 (easily discernible translucent area; details of the iris are slightly obscured), which led to ICE class III. The mean fluorescein retention after 30 minutes was 2.0 (focal or confluent dense single cell staining), which also corresponded to ICE class III. The highest mean corneal swelling was 5 %, which led to ICE class I. According to the OECD guideline, no prediction can be made based on these results.

In one eye irritation in vivo study (unpublished study, 2017c, OECD TG 405, GLP) three New Zealand white rabbit's eyes were treated with one dose (0.1 ml) of 9 % aqueous solution of the Substance. Ocular examination was performed 1-, 24-, 48- and 72-hours following treatment on both eyes. The ocular reactions were moderate and reversible in all animals. All tested animals had corneal opacity greater than 1 by the scoring system.

In another study (unpublished study report, 1985c), 31 % solution of the Substance was tested by single administration in New Zealand White rabbits (9 rabbits/group) to investigate the eye irritating effects of the Substance. The observation period was 14 days. According to the results, 6 out of 9 animals had corneal opacity that was not fully reversible within 21 days. Iritis and conjunctiva redness/chemosis were also observed in some cases. Rinsing for 30 seconds after treatment did not alleviate the irritation response. The study was conducted according to Guideline for Hazardous Evaluation for Humans and Domestic Animals (Federal Register, Vol. 43), GLP was not used.

Despite the fact, that the GLP-compliant studies showed only moderate irritating effects of the Substance, in these studies the concentration of the Substance was only 9%, and in the non-GLP study, where more severe effects were observed and they were not fully reversible, the concentration was 31%. Moreover, the Substance has strong oxidising

properties, and it is corrosive to the skin, therefore it is considered that it has serious eye damage properties as well.

Therefore, the evaluating Member State considers that the classification of the Substance for Eye Dam. Category 1 is warranted and will propose a harmonised classification for this hazard class.

Skin irritation/corrosion

Four study reports are available for the skin irritation/corrosion of the Substance in the registration dossier. Three out of the four studies were key studies.

In one of the studies (unpublished study report, 1994), 34.5% aqueous solution of the Substance was used in New Zealand White rabbits by cutaneous route according to the OECD 404 guideline. The study was GLP-compliant. Two sequential exposures were conducted in one rabbit. The results were then confirmed on two additional rabbits. Two out of three rabbits did not receive any test substance on the left flank, the untreated skin areas served as control. A dose of 0.5 ml was applied to the test site. The dermal reactions were evaluated for each animal 1, 24, 48 and 72 hours after patch removal and then daily until day 10. No cutaneous reactions (erythema, oedema) were observed during the study in two animals after 4 hours treatment. Very slight reversible erythema of the skin was recorded in one animal within nine days following four hours treatment. No necrosis or ulceration was observed. In summary, 34.5 % aqueous solution of the Substance was non-irritant by cutaneous route in rabbits.

The Substance is self-classified by the Registrant as Skin Corrosion Category 1B based on a study similar to OECD guideline 404 conducted with New Zealand White rabbits (3 males, 3 females) with 0,5 g of the Substance (80% purity) (unpublished study report, 1984b). The treatment period was 4 hours, and dermal responses were graded and scored at 30-60 minutes, 24, 48, and 72 hours and on days 4, 7, 14, and 21. Erythema was observed in all sites at 30-60 minutes and 24 hours and lasted for 7 days in two animals. Oedema occurred in one site at 30-60 minutes and in two sites at 48 hours. The erythema score was 0.83 of max. 2, the oedema score was 0.11 of max. 1. Other dermal effects (blanching, thickening, sloughing) and necrosis was observed in two animals.

In a study (unpublished study report, 1985d), 31 % aqueous solution of the Substance was used in New Zealand White rabbits (5 males, 5 females) by cutaneous route according to 8/22/78 EPA guidelines. The study was not GLP-compliant. A dose of 1.67 ml (2.0 g of liquid/kg bw) was applied. The dermal reactions (erythema, oedema) were evaluated for each animal 24, 48 and 72 hours after application. The erythema score was 1.7 of max. 2, the oedema score was 0.9 of max. 1. No other dermal effects were recorded. 31 % aqueous solution of the Substance was non-irritant by cutaneous application in rabbits.

Since necrosis occurred in two animals in one of the studies (unpublished study report, 1984b), in which the Substance with 80% purity was applied, and as not all notifiers self-classified the substance as Skin Corr. 1B, the evaluating Member State considers that a harmonised classification is warranted.

7.9.3. Sensitisation

One sensitisation study is available in the registration dossier. It was performed according to OECD TG 406 with the Substance (unpublished study report, 2002). The study was conducted under GLP conditions. In this study, 10 guinea pigs were treated with a 31 % solution of the Substance in 0.9% NaCl. In the induction phase, 6 injections were made into the dermis, and 3 into the interscapular region. On day 8 a pad of filter paper loaded with 1.55% of the Substance was applied on the interscapular region and the pad was removed after 48 hours. In the challenge phase, the animals were treated with 0.31% of the Substance for 24 hours. The sensitizer substance

mercaptobenzothiazole was used as positive control. During the study, no delayed contact hypersensitivity was observed. Based on the available data, the evaluating Member State concluded that the Substance is not a skin sensitiser.

7.9.4. Repeated dose toxicity

Table 8. Summary of repeated dose toxicity studies via oral route.

Method, guideline, deviations if any, species, strain, sex, No/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
Range-finding study for a 90-day oral toxicity study in rats Equivalent to EPA OPP 82-1 GLP compliance CD rats 5/sex/dose group key study	The Substance (Purity: 80.9%) 0, 25, 50, 100, 200 mg/kg bw/day vehicle: water oral gavage 14-day exposure period	200 mg/kg bw/day: 3 animals died Necropsy: brown coloured blood and blood-stained fur around the urethral opening 100 mg/kg bw/day: ↓bodyweight gain ↓red blood cell count, haemoglobin concentration, packed cell volume ↑total leucocyte count, neutrophil count, and methaemoglobin levels Gross or moderate red blood cell polychromasia and anisocytosis, Howell-Jolly bodies and punctate basophilia was observed. 50 mg/kg bw/day: ↓male bodyweight gain ↓packed cell volume 25 mg/kg bw/day: ↑packed cell volume	Harrington et al., 1995a

90-day oral toxicity study in rats Equivalent to EPA OPP 82-1 OECD 408 GLP compliance CD rats 15/sex/group key study	The Substance (Purity: 80.9%) 0, 10, 25, 80 mg/kg bw/day vehicle: water oral gavage 13-week duration	80 mg/kg bw/day: 4 animals died salivation observed in all animals 3/15 hunched posture Blood morphology: polychromasia, anisocytosis, poikilocytosis, Howell-Jolly bodies, normoblasts, macrocytosis and neutrophilia (2M and 3F) ↓mean erythrocyte count (M/F) ↓ haematocrit and haemoglobin (M) ↑methaemoglobin, neutrophil (M) ↓total protein level (M/F) ↑aspartate aminotransferase, bilirubin (2M/1F) ↑adrenal weight/body weight (M/F) ↑spleen weight/body weight (M/F) squamous hyperplasia with hyperkeratosis and ulceration, chronic inflammation, and oedema (7M and 8F) ↑extramedullary haematopoiesis (EMH) in the spleen (2M/2F) ↑urine volume (4F) 25 mg/kg bw/day: 1 accidental death salivation in two males ↓erythrocyte counts (M/F) ↑adrenal weight/body weight (F) ↑spleen weight/body weight (F) EMH (1 animal) ulceration, chronic inflammation, and oedema (2M) 10 mg/kg bw/day: ↓erythrocyte counts (M/F) EMH (1 animal) NOAEL 10 mg/kg bw/day	Harrington et al., 1995a

The effect of chlorine dioxide and the Substance on erythrocytes of A/J and C57LJ mice No guideline stated No GLP A/J and C57L/J mice (63/4 groups and 59/4 groups) supportive study	The Substance (No information on purity) 0 mg/L, 0.75 mg/L, 7.5 mg/L, 75 mg/L (equivalent to 0, 0.19, 1.9 and 19 mg/kg bw/day respectively) via drinking water 30-day duration	19 mg/kg bw/day: ↑glucose-6-phosphate dehydrogenase (G6PD) activity, mean Corpuscular Volume (MCV), osmotic fragility NOAEL: 1.9 mg/kg bw/day	Moore GS and Calabrese EJ, 1980
Sub chronic toxicity of chlorine dioxide and related compounds in drinking water in the nonhuman primate No guideline stated No GLP African Green monkeys 5 males and 7 females/group supportive study	The Substance (Analytical grade) 25 mg/L, 50 mg/L, 100 mg/L, 200 mg/L, 400 mg/L (equivalent to 3, 6, 12, 23, 46 mg/kg bw/day, respectively) by drinking water 30/60-day duration	↓red cell count and cell indices, serum thyroxine (T4), haemoglobin ↑serum glutamate–pyruvate transaminase (SGPT), reticulocyte, methaemoglobin	Bercz JP et al., 1982

Oxidative damage to the erythrocyte induced by the Substance, in vivo No guideline stated No GLP CD rats (6 males/group) supportive study	The Substance (No information on purity) 0 mg/L, 10 mg/L, 50 mg/L, 100 mg/L, 250 mg/L, 500 mg/L (equivalent to 0, 1, 5, 10, 25, 50 mg/kg bw/day, respectively) by drinking water 30/60/90-day duration	after 30 days: 10, 25, 50 mg/kg bw/day: ↓haemoglobin, red blood cell, haematocrit 5, 10 mg/kg bw/day ↓GSH level after 60 days: 50 mg/kg bw/day: ↑relative kidney weights 10 mg/kg bw/day: ↓haemoglobin, red blood cell, haematocrit ↓GSH level after 90 days: 10 mg/kg bw/day: ↑haemoglobin, red blood cell, haematocrit 25 and 50 mg/kg bw/day: haemoglobin, red blood cell, haematocrit returned to normal level ↓GSH level NOAEL: 1 mg/kg bw/day	Heffernan et al., 1979

Evaluation of the immunomodulatory effects of the disinfection by product, the Substance, in female B6C3F1 mice: A drinking water study No guideline stated No GLP B6C3F1 mice/ no data on no. of animals/sex/ dose supportive study	The Substance (No information on purity) 0, 0.1, 1, 5, 15, 30 mg/L by drinking water 28-day duration	↑blood reticulocyte, relative spleen weight 30 mg/L: ↑splenic CD8+ cells (26%) 0.1 mg/L: ↓augmented natural killer cell activity (42%)	Karrow et al., 2001
The renal effect of the Substance in the drinking water of C57L/J male mice No guideline stated No GLP C57L/J mice (11 males/group) supportive study	The Substance (No information on purity) 0 mg/L, 3 mg/L, 15 mg/L, 75 mg/L by drinking water 30/90/180-day duration	No significant alterations in body weight gain, absolute and relative kidney weight, water consumption or kidney histology. NOAEL: >75 mg/L	Connor et al., 1985

Toxicity of chlorine dioxide in drinking water No guideline stated No GLP Sprague-Dawley rats (no data on the number of animals) supportive study	Chlorine dioxide, ClO_2^- and ClO_3^- 0 mg/L, 10 mg/L, 100 mg/L by drinking water 1-year duration	All groups: ↓osmotic fragility of the red blood cells, red blood cell counts, haematocrit, haemoglobin (after 9 months) ↓body weight (after 10 and 11 weeks) ClO_2^- and ClO_3^-: ↓blood glutathione	Abdel-Rahman et al., 1985

In the key study (Harrington et al., 1995a, EPA OPP 82-1, equivalent to OECD TG 408, GLP) blood and urine samples were collected during the 13-week treatment period (See Table 8.). Complete haematology analysis was conducted on the blood. Ocular examination on both eyes of all animals, clinical chemistry and biochemistry examinations were also conducted. Organ weights and gross pathological findings were examined, and samples were collected and fixed from several tissues for histopathological examination. The doses were selected based on the results of a dose selection study (Harrington et al., 1995a), where at 100 mg/kg bw/day, bodyweight gain was reduced, certain haematological parameters were changed (red blood cell count, haemoglobin concentration and packed cell volume decreased, total leucocyte count, neutrophil count and methaemoglobin levels increased, gross or moderate red blood cell polychromasia and anisocytosis, Howell-Jolly bodies and punctate basophilia were observed) and urine volume was increased.

At the highest dose level of 80 mg/kg bw/day treatment-related mortalities were observed. Mostly in male rats, based on the haematological examination, several haematological parameters were significantly changed. Morphological changes of erythrocytes, statistically significant differences in the spleen and adrenals weight on body weight related basis, extramedullary haematopoiesis and elevated serum bilirubin levels were reported in both sexes. Urine volume was increased with reduced specific urinary gravity in four females at 80 mg/kg bw/day, but these changes were not associated with histopathological changes in the kidneys.

At dose level of 25 mg/kg bw/day slight reduction of erythrocyte count in both sexes (not statistically significant), and statistically significant increase in spleen and adrenal weight on bodyweight-related basis in females were observed. At this dose level, the histopathological examination revealed extramedullary haematopoiesis in one animal, which was a spontaneous incidence. At the higher dose levels, the above alterations were indicative of treatment-related haemolytic anaemia. In the highest dose group, the Substance caused irritation of gastric mucosa. Symptoms linked to the stomach irritation occurred at a lower frequency at dose of 25 mg/kg bw/day.

The most important adverse effects observed at 80 mg/kg bw/day were significant changes in haematological parameters (mean erythrocyte count, haemoglobin, haematocrit, methaemoglobin level, neutrophil count), spleen and adrenal weight/body weight and irritation of the gastric mucosa. At 25 mg/kg bw/day, significantly increased spleen and adrenal weight/body weight and non-significant decrease in erythrocyte counts were observed. Although some effects (such as erythrocyte count non-significantly reduced in males, spleen weight on absolute basis significantly increased without dose-dependency in females and spontaneous extramedullary haemopoiesis occurred in one animal) were observed at 10 mg/kg bw/day, these were not considered

treatment-related. Consequently, it was concluded that the NOAEL was 10 mg/kg bw/day.

Supporting studies:

In the study by Moore and Calabrese (1980), no treatment-related effects on body weight and no differences in water consumption were observed in the treated groups compared to the respective control. The haematological effects were all statistically significant at the highest dose level (See Table 8.). Despite the strain-specific difference in the level of G6PD activity (as in the control groups the A/J strain mice exhibited a G6PD activity about three-fold than the C57L/J strain), the two mice strains showed no obvious differences in their response to the treatment and no other alterations in hematologic parameters were noted. At the lowest dose level, no treatment-related effects were observed.

These results suggest that the primary effect was a disruption of the erythrocyte cell membrane. However, the erythrocyte glutathione level was not affected and there were no associated signs of haemolytic anaemia suggesting that the slight increase in G6PD activity acted as a sufficient compensatory mechanism to limit the oxidative stress. Based on these haematological effects, a NOAEL was 1.9 mg/kg bw/day; however, due to several uncertainties and deficiencies (no guideline stated, no GLP-compliance specified, very large dose-intervals used) this value cannot be used for the final conclusion.

Sub chronic toxicity of the Substance was also studied in African Green monkeys (Cercopithecus aethiops) by Bercz et al. (1982). Blood samples were taken at each dose changeover, then biweekly. Standard haematology tests were conducted for each blood sample.

The Substance, at most of the tested doses, induced a self-compensating oxidative stress in the monkey haematopoiesis. About midway through exposure, a rebound effect occurred for haemoglobin and red cell synthesis. A dose-dependent rise in alanine aminotransferase (ALT) was detected, which may indicate accelerated hepatic activity during the transient oxidative haemolytic period. Due to poor presentation of the data no NOAEL could be identified (See Table 8.).

In the study by Heffernan et al. (1979), where groups of 6 male CD rats were given oral doses of the Substance in their drinking water for 30 to 90 days, the rats were observed to have slightly depressed haemoglobin concentration, red blood cell (RBC) counts and haematocrit after 30 days of exposure. These signs of slight haemolytic anaemia were of a lower magnitude after 60 days. The haematological parameters returned to near normal levels by 90 days of treatment suggesting that compensatory physiological mechanisms occurred. After 30 and 90 days of exposure at 5 and 10 mg/kg bw/day, a decrease in erythrocyte glutathione levels was reported and based on this a NOAEL of 1 mg/kg bw/day was identified (See Table 8.).

In the study by Karrow et al. (2001), increases in the percentages of blood reticulocytes and increases in the relative spleen weights were observed, occurring at different exposure levels and without dose-dependency (See Table 8.). An increase in the number of spleen antibody-forming cells was observed across the range of dose groups, but none were statistically significant at any treatment level, and it was not reflected by changes in serum IgM levels. Splenic mixed leukocyte response and peritoneal macrophage activity were unaffected and so was natural killer cell activity.

In a sub-chronic study (Connor et al., 1985), no significant alterations in body weight gain, absolute and relative kidney weight, water consumption or kidney histology were observed at any dose and exposure period, and the NOAEL was identified as >75 mg/L drinking water (See Table 8.).

The study by Abdel-Rahman et al. (1985) investigated the oral toxicity of chlorine dioxide (ClO_2) and its metabolites, ClO_2^- and ClO_3^- in rats. ClO_2, ClO_2^- and ClO_3^- administered chronically in drinking water for 3 months inhibited the incorporation of 3H-thymidine into nuclei of rat testes. Also, this inhibition was observed in the liver of ClO_2^- groups and in the kidney of 100 mg/L ClO_2^- treatment. The incorporation in small intestinal nuclei increased at both 10 and 100 mg/L ClO_2 and at 10 mg/L ClO_2^-. The data do not provide enough basis to draw a conclusion about the NOAEL (See Table 8.).

Human information:

To assess the relative safety of chronically administered chlorine water disinfectants in humans, a controlled study was undertaken by Lubbers et al. (1982). The clinical evaluation was conducted in the three phases common to investigational drug studies. Physiological impact was assessed by evaluation of a battery of qualitative and quantitative tests. For Phase I and II, healthy adult male volunteers were selected, where normal methaemoglobin levels, thyroid function, and glutathione levels were mandatory. For Phase III, volunteers were defined as glucose-6-phosphate dehydrogenase (G6PD)-deficient based on a haemoglobin G6PD level of less than 5.0 IU/GM haemoglobin in the pre-study screening but were normal in all other parameters.

In general, freshly prepared stock solutions of the Substance were assayed by the colorimetric techniques of Palin, and then diluted in organic-free demineralised deionised water to appropriate concentrations. In Phase I, which was a rising dose tolerance investigation, the acute effects of progressively increasing single doses of chlorine disinfectants were examined, with treatment concentrations of 0.01, 0.1, 0.5, 1.0, 1.8 and 2.4 mg/L. In Phases II and III, the concentration of the Substance ingested was 5 mg/L and each subject received 500 ml daily for 12 consecutive weeks. The control groups received untreated water in all phases. The treatment sequence included physical examination and collection of blood and urine samples for laboratory assays.

Haemoglobin electrophoresis results indicated that, in Phase II, a small number of the subjects yielded abnormal haemoglobin distributions, but these individuals were randomly distributed in both treatment groups and in the control group. Examination of electrocardiograms revealed no abnormalities. The compiled vital signs examined provided no evidence of consistent response to the treatment. There were no obvious undesirable clinical sequelae noted. In several cases, statistically significant trends in certain biochemical or physiological parameters were associated with the treatment but none of these trends was judged to have physiological consequence. However, the possibility that over a longer treatment period these trends might achieve proportions of clinical importance cannot be ruled out.

Dermal

Only one, non-reliable study is available for repeated dose toxicity of the Substance via dermal route in the registration dossier.

In this study (Scatina et al., 1984), the dermal toxicity of antimicrobial Alcide gel was assessed in New Zealand White rabbits (4 animals/sex/group). The gel contained the Substance in the Base part, and lactic acid in the Activator part. After mixing the two parts, a solution was formed consisting of short-lived chlorous acid (it was stable up to 15 minutes) and its oxychlorine products. This solution should be prepared immediately before application and used within 3 hours (based on summary product characteristics of Alcide gel).

The product was applied on the back of rabbits for three months (5 days/week) with doses of 0.5 g/kg, 1 g/kg, and 2 g/kg. No further information on the application of the gel was given. The animals in the placebo group received 2.0 g/kg of a gel, which contained only gel-forming material. Another control group did not receive any treatment. Any test material remaining on the skin following the daily exposure was

washed off prior to the new application. Food consumption was measured daily, body weight was recorded bimonthly. Three months after the start of the study, blood was collected from all animals, and haematology and clinical chemistry examination was conducted. No mortality was observed. No effects on body weight and on food consumption were observed. Treatment-related haematological and clinical biochemistry findings were recorded. Glutathione concentrations in blood were decreased in the high dose group and in the placebo gel group. According to the authors, this observation suggested that the vehicle was responsible for decrease of glutathione level. Adrenal cortical hyperplasia, which was observed in the treated and in the control animals, was related to animal stress. As several crucial information are not presented in the study (guideline, gel composition and its application) its results bear reduced significance.

Summary:

In the key study (Harrington et al., 1995b), a treatment with the Substance elicited toxicity at doses of 80 and 25 mg/kg bw/day. At these doses, evidence of irritation in gastric mucosa was observed and treatment-related haemolytic anaemia occurred. At the lowest treatment dose (10 mg/kg bw/day), the haematological and histological effects and the difference in the organ weight were considered not to be treatment related. The supporting oral and dermal studies, due to several uncertainties (no guideline stated, no GLP-compliance specified, one sex used, no data on number of animals were provided, very large dose-intervals used, not recommended species used, no complete examination was performed), were non-reliable studies. In the human clinical investigation, none of the trends observed in certain biochemical or physiological parameters were considered to have physiological consequences.

Considering these observations, the evaluating Member State concluded that the concern for target organ toxicity after repeated exposure of the Substance was confirmed. Based on the result of the key study the NOAEL is_10 mg/kg bw/day. The target organs were the stomach and spleen. The evaluating Member State considers that the classification of the Substance for STOT RE Category 2 is warranted and will propose a harmonised classification for this hazard class.

7.9.5. Mutagenicity

Mutagenicity *in vitro*

In the registration dossier, four *in vitro* studies are available, three of which gave positive results. Four *in vitro* studies are available in the registration dossier regarding the Substance or chlorine dioxide.

Table 9. Summary table of *in vitro* genotoxicity studies

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
Mammalian cell gene mutation assay Similar to OECD 476 no GLP mouse lymphoma L5178Y +/-S9	Chlorine dioxide	+S9: 6.73, 14.9, 18.5, 30.9, 36.9, 48.3 and 65.2 µg/mL -S9:1.32, 3.2, 6.73, 11.1, 14.9, 24.3 and 36.9 µg/mL	Positive +/-S9	Unpublished study report (1986)
Chromosome aberration test Similar to OECD 473 no GLP Chinese hamster lung fibroblast cells (V79) -S9	The Substance	Maximum concentration: 0.02 mg/mL	Positive -S9	Ishidate et al., 1984a
Bacterial reverse mutation assay in Salmonella typhimurium Similar to OECD 471 no GLP in TA100 +S9 in TA 92, TA 1535, TA 1537, TA 94, and TA 98 +/-S9	The Substance	Maximum dose: 0.3 mg/plate	Positive in TA 100 +S9 Negative in TA 92, TA 1535, TA 1537, TA 94, TA 98 +/-S9	Ishidate et al., 1984b
Bacterial reverse	The	0, 0.001, 0.005, 0.01,	Negative in TA 97 and TA 102	Fujita et al.,

Method, guideline, deviations if any	Test substance	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
mutation assay in Salmonella typhimurium No guideline stated No GLP in TA 97, TA 102 +/-S9	Substance	0.05, 0.1 mg/plate	+/-S9	1987

In a mammalian cell gene mutation assay equivalent or similar to OECD Guideline 476 (In Vitro Mammalian Cell Gene Mutation Test), chlorine dioxide was positive in mouse lymphoma L5178Y cells with and without metabolic activation (unpublished study report, 1986). Ethylmethanesulphonate and 3-methylcholanthrene were applied as positive controls. Without metabolic activation mutation frequency increased from 3.2 to 24.3 µg/ml. With metabolic activation a 2.7-fold increase in the mutant frequency was induced at 48.3 µg/mL.

The Substance was positive in a chromosome aberration test without metabolic activation in Chinese hamster fibroblast cell line (Ishidate et al., 1984a). No data on positive controls were provided. The cells were exposed to three different doses for 24 and 48 hr. Untreated cells and solvent-treated cells served as negative controls, in which the incidence of aberrations was usually less than 3.0%. The results were considered negative if the incidence was less than 4.9%, equivocal if it was between 5.0 and 9.9%, and positive if it was more than 10.0%. For a quantitative evaluation of the clastogenic potential of the positive samples, the D20 was calculated, which is the dose (mg/mL) at which structural aberrations (including gaps) were detected in 20% of the metaphases observed. In addition, the translocation (TR) value was calculated, which indicates the frequency of cells with exchange-type aberrations per unit dose (mg/mL). At 0.02 mg/mL (D20) the number of structural aberrations were 26% after 24h and 18% at 48h. The TR value was 500 per dose unit (mg/mL).

The Substance was positive in Salmonella typhimurium TA100 in a bacterial reverse mutation assay with metabolic activation at 0.3 mg/plate concentration. In TA 92, TA 1535, TA 1537, TA 94, and TA 98 strains the result was negative in the same assay with and without metabolic activation (Ishidate et al., 1984b).

The Substance gave negative result in Salmonella typhimurium TA 97 and TA 102 strains by preincubation procedure in a bacterial reverse mutation assay with and without metabolic activation (Fujita et al., 1987). The Substance was preincubated with S9 mix or phosphate buffer (pH=7.4) for 20 minutes. Only two strains were used, and there were no data on the number of replicates.

The positive results of the above-mentioned *in vitro* studies, although there are several uncertainties, raised the concern for gene mutation and chromosome aberration potential of the Substance.

Mutagenicity *in vivo*

Nine *in vivo* studies were available in the registration dossier regarding the Substance or chlorine dioxide. Six out of the nine studies were considered acceptable. The *in vivo* Mammalian Alkaline Comet Assay was conducted and submitted, as required in ECHA's compliance check decision, to follow up the positive *in vitro* result for gene mutation and chromosomal aberration.

Table 10. Summary table of genotoxicity in vivo studies

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Micronucleus assay in mice Similar to OECD 474 no GLP Six ddY male mice per group	The Substance and chlorine dioxide	Doses: the Substance: 7.5, 15, 30, 60 mg/kg bw/day by ip. injection × 1 chlorine dioxide: 3.2, 6.3, 12.5 and 25 mg/kg bw/day by ip. injection × 1 positive control: mitomycin C	Positive	Hayashi et al., 1988
Micronucleus assay in mice Similar to OECD 474 One dose tested no GLP six ddY male mice	The Substance	Dose: 15 mg/kg bw/day by ip. injection × 4 positive control: mitomycin C	Negative	Hayashi et al., 1988
Micronucleus assay in mice Equivalent to OECD 474 no GLP ddY male mice	The Substance	Doses: 37.5, 75, 150, 300 mg/kg bw/day by oral gavage positive control: mitomycin C	Negative	Hayashi et al., 1988
Micronucleus assay in mice Similar to OECD 474	The Substance	10, 25, 50 mg/kg bw/day by oral gavage 5 days positive control: TEM	Negative	Meier et al., 1985a

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No GLP CD-1 mice		by ip. injection		
Chromosome aberration assay in mice Similar to OECD 475 No GLP CD-1 mice	The Substance	10, 25, 50 mg/kg bw/day by oral gavage 5 days positive control: TEM by ip. injection	Negative	Meier et al., 1985b
In vivo comet assay OECD 489 GLP Wistar rats	The Substance	25, 50, 100 mg/kg bw/day by oral gavage positive control: ethyl methanesulfonate	Positive	Unpublished study report (2022)

In an *in vivo* micronucleus assay (Hayashi et al., 1988) that gave positive results, eight-week-old male ddY mice were used to test the mutagenicity of several food additives including the Substance and chlorine dioxide (4% solution). The highest score for micro nucleated polychromatic erythrocytes (MNPCE) was at 12.5 mg/kg for chlorine dioxide (1.13%) and at 30 mg/kg for the Substance (1.05%). The MNPCE number in the vehicle control was 0.28% and 0.18% for chlorine dioxide and the Substance, respectively. In the same study, after four intraperitoneal injections at a dose level of 15 mg/kg bw and when the Substance was administered via oral gavage, the results were negative.

According to two studies by Meier et al. (1985a, 1985b), the Substance was negative in a chromosome aberration assay and a micronucleus assay. In the chromosome aberration assay fewer animals/sex/group were tested. Triethylenemelamine (TEM) was administered as positive control via intraperitoneal injection. TEM increased significantly both structural and numerical chromosomal aberrations compared to the negative control and induced a significant number of micronuclei for both sexes.

In a follow-up *in vivo* comet assay (unpublished study report, 2022) requested by ECHA under compliance check, enabling to determine whether the substance is mutagenic, Wistar rats were exposed to 31.7 % aqueous solution of the Substance via single gavage by two consecutive days to assess DNA damage in glandular stomach, liver, and duodenum mucosa. The administered doses were 25 (low dose-LD), 50 (mid dose-MD) and 100 (high dose-HD) mg/kg bw, and 5, 5 and 7 rats were dosed, respectively. The highest dose was selected based on the outcome of a dose range finding study. The dose selection was justified by the fact that there were no deaths and severe suffering at this dose level, therefore euthanasia was not necessary for animal welfare reasons in the rats administered (3/sex). At higher dose levels (2000, 1000, 500, 250, 120 mg/kg bw) rapidly occurring deaths or severe, prolonged clinical signs requiring euthanasia were observed.

The sampling time was 4 h after the last treatment for all dose groups. Tissue samples were collected from the glandular stomach, duodenum, and liver.

Rats in the MD and the LD groups showed no clinical signs of toxicity. Animals treated with the high dose showed slight to moderate clinical signs (e.g., reduced spontaneous activity, prone position, piloerection, half eyelid closure, hunched posture), which were disappeared within 24 hours after the 2nd treatment. The body weight variation was below 20 % during the study in all dosed groups.

The Substance induced statistically significant increases in the mean %-tail intensity compared to the negative control in the high dose and the mid dose groups for glandular stomach mucosa. These results were above the negative historical control data. No statistically significant increase in mean % tail intensity was observed in the low dose group compared to the negative control, and the result was within the negative historical control range. No statistically significant increases were recorded in mean % tail intensities for liver and duodenum at all dose levels compared to the negative control, and the results were within the negative control range (Table 11).

Table 11. Summary of mean tail intensities (%) in *in vivo* comet assay with the Substance.

Dose group	Mean tail intensity % in liver	Mean tail intensity % in glandular stomach	Main tail intensity % in duodenum
PC	7.77*	12.36*	8.02*
NC	1.08	1.90	1.55
LD (25 mg/kg bw)	1.96	4.12	2.85
MD (50 mg/kg bw)	1.47	6.01*	2.78
HD (100 mg/kg bw)	1.42	7.44*	3.81
Historical control ranges	negative control: 0.07-3.82% positive control: 2.81-28.08%	negative control: 1.30-5.46% positive control: 5.99-34.62%	negative control: 0.82-4.06% positive control: 1.77-30.75%

* Statistically significantly increased (One-way ANOVA with Dunnett's test after normality test by Kolmogorov-Smirnov) compared to negative control

NC: Negative Control (Aqua ad iniectabilia), PC: Positive Control (Ethyl methanesulfonate: 230 mg/kg bw, LD: Low Dose, MD: Mid Dose, HD: High Dose

According to the histopathological analysis the Substance caused degenerative inflammatory, degenerative, and reactive lesions in several dosed rats via irritation in the stomach mucosa. Correlation between the severity of the gastric changes and the DNA damage was observed in the high dose group. The severity of the histopathological abnormalities in the MD group was less significant compared to the HD group and was similar to the LD group. These observations were not supported by detailed description of the histopathological findings in the dossier. Similar histopathological findings and correlations for glandular stomach were reported in a range finding prenatal developmental toxicity study (unpublished study report, 2021.) detailed in Section 7.9.7.

The test substance showed more prominent cytotoxic effect in glandular stomach mucosa of rats at the highest dose level. At lower doses (in the LD and MD groups), where increase in DNA migration was also observed, the cytotoxic effect was less significant or not reported.

The above correlations suggested that the DNA strand breaks are not purely due to cytotoxic effect of the Substance.

In summary:

In the *in vivo* comet assay, DNA strand breaks were induced in glandular stomach mucosa of rats after oral administration of the Substance (31.7% aqueous solution) for two days. Two out of the three test doses (MD and HD) caused statistically significant increases in the mean tail intensity % compared to the concurrent negative control. These increases were dose-related when evaluated with an appropriate trend test. In addition, two of the main tail intensity results (in the MD and HD groups) were outside the distribution of the historical negative control data. Based on this, the Substance fulfilled all three criteria for positive comet assay according to OECD TG 489. However, further *in vivo* follow-up is needed to investigate the mutagenicity effect of the Substance in germ cells.

The evaluating Member State considers that the classification of the Substance for Mutagen Category 2 is justified, and harmonised classification is warranted.

7.9.6. Carcinogenicity

Six carcinogenicity studies are available for the Substance in the registration dossier. All of them were experimental studies, and no information is available about the GLP compliance or similarity to any the test guideline. Four of them were conducted via oral route in mice and rats, the remaining two were conducted by topical application in mice.

In the study by Kurokawa et al. (1986), the Substance was given to male and female Fisher 344 rats at concentrations of 600 ppm (equivalent to 40.9 mg/kg bw/day in males, 32.1 mg/kg bw/day in females) or 300 ppm (equivalent to 28.3 mg/kg bw/day in males, 18.0 mg/kg bw/day in females) in drinking water for 85 weeks. At necropsy pneumonia was found in all animals. Increase of body weight was observed in a dose-dependent manner in both males and females. Drinking water intake in treated animals was slightly lower than in control animals of both sexes. No statistically significant differences in the tumour incidences or in the rates of tumour development in any organs were observed between treatment and control groups of either sex. NOEL was ≥32.1 mg/kg bw/day for females and ≥40.9 mg/kg bw/day for males (Kurokawa et al., 1986a).

Kurokawa et al. (1986) performed a carcinogenicity study also in B6C3F1 mice (50 males and 50 females). In this study, the Substance was administered at concentrations of 250 ppm and 500 ppm in drinking water for 85 weeks. The animals were observed daily. No mortality was observed. Increase of body weight was comparable among all groups of either sex. In males, the combined incidences of hyperplastic nodules and hepatocellular carcinomas of the liver in the low-dose group, and adenomas and adenocarcinomas of the lung in the high-dose group were marginally increased compared to controls. These incidences in treated males were within the range of values of historical control data. According to the authors, the results for mice were inconclusive.

In a study similar to OECD 451 guideline Fisher 344 rats (50 males and 50 females) were treated with the Substance at concentrations of 0.06% (equivalent to 41 mg/kg bw/day in males, 32 mg/kg bw/day in females) and 0.03% (equivalent to 28 mg/kg bw/day in males, 18 mg/kg bw/day in females) in drinking water for 85 weeks (Shimoyama et al., 1985). Treatment related mortality was observed. The body weight of males and females in the treated groups were lower than of control rats, but no significant differences were recorded in the three groups. Drinking water intake was reduced in males and in females. Haematological examinations, laboratory examinations of the serum and urine, and measurements of organ weights showed no significant differences between the groups in week 85. Tumours developed in the testis, uterus, pituitary gland, thyroid gland and adrenal gland of both treatment and control rats, but the incidences of tumours and non-neoplastic lesions in the three groups were not statistically significantly different. NOEL was ≥32 mg/kg bw/day for females and ≥41 mg/kg bw/day for males. No evidence was obtained that the Substance had a carcinogenic effect in rats.

In a study by Yokose et al. (1987), B6C3F1 mice were given the Substance at concentrations of 0.025 and 0.05% in drinking water for 80 weeks, and then just distilled water for 5 weeks. The animals were observed daily for abnormalities. Individual body weights were recorded weekly for the first 13 weeks and every other week thereafter. Water consumption was measured over the 1-day period before each weighing. The NOEL was ≥83 mg/kg bw/day for males and ≥58 mg/kg bw/day for females. The incidence of pulmonary adenomas in the male high dose group was significantly higher than in the control group. However, the increase was not dose dependent.

Unreliable studies (Klimisch 3):

The Substance was tested for tumour-promoting activity in skin carcinogenesis in female Sencar mice (unpublished study report, 1984c). The test substance was dissolved in acetone and a dose of 0.2 ml was applied. Thus, 20 mg/ml (equivalent to 57.14 mg/kg bw/day, for 20 g body weight) of test solution was used twice a week for 51 weeks after DMBA (dimethylbenzanthracene) initiation on the dorsal skin of rats. 20 female mice were in the treated group and the positive control group, 15 females in the vehicle control group, respectively. TPA (tetradecanoylphorbolacetate) was the positive control. No mortality and no effects were observed in body weights. The numbers and diameters of all skin tumours were recorded weekly and body weights were measured monthly. 30 % of the mice treated with the Substance developed skin tumours and 5 out of these 6 mice had squamous cell carcinomas. In this group, the first skin tumour appeared in week 17, the tumour incidences did not show statistically significant difference to the vehicle control group. All the mice treated with TPA after initiation with DMBA developed squamous cell carcinomas within 39 weeks. Control mice applied with acetone after DMBA-initiation had no skin tumours. The high incidences of adenocarcinomas of the mammary gland and adenomas of the lung and the uterus were observed in all groups. There were no historical control data.

The previous study (unpublished study report, 1984c) was repeated with the same parameters but without initiation (unpublished study report, 1984d). Positive control group was not used. The number and diameter of all skin tumours were recorded weekly and body weight was measured monthly. No mortality and no effects were observed in body weights. No skin tumours developed in either the treated mice or the vehicle group.

In summary, increase in tumour incidences was observed in five out of six studies. These incidences did not show any statistical significance in three cases. In one study, statistically significant change in tumour incidence was reported, but no dose dependency was observed, the study was not GLP-compliant and only two doses were tested. In another case, the incidence values, which were statistically significantly different from the control, fell within the historical control range. In the light of these observations, the evaluating Member State concludes that no concern for the carcinogenic potential of the Substance was raised.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Four fertility studies were available in the registration dossier regarding the Substance or chlorine dioxide. One of the four fertility studies was reliable, while the remaining three had reduced relevance.

Table 12. Summary table of animal studies on adverse effect on sexual function and fertility.

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Two generation reproduction and developmental neurotoxicity study EPA-OPP 870.3800, GLP-compliant Sprague-Dawley rats (30/sex/group)	The Substance 35, 70 and 300 ppm (equivalent to 4, 8 and 30 mg/kg bw/day for males, and 5, 10 and 39 mg/kg bw/day for females via drinking water 10 weeks study Exposure: 10 weeks before mating, during mating, gestation, parturition During lactation, the doses were reduced to 50%.	<u>Parental (P0)</u> ↓ water consumption (M at 70, 300 ppm, and occasionally at 35 ppm, F at 70, 300 ppm) <u>F1 (P1)</u> ↓ body weight (M/F at 300 ppm) ↓ food consumption (M at 300 ppm) preputial separation and delayed vaginal opening at 300 ppm ↓ absolute brain weight (at 70 ppm) altered liver weight (iat70 ppm) ↓ amplitude of auditory startle response (at 70, 300 ppm) ↓ RBC, HCT, MCV, MCH, MCHC (M/F in 300 ppm) ↓ WBC (M/F at 70, 300 ppm) ↑ MetHb (M at 300 ppm, F at 35, 70, 300 ppm) <u>F2</u> ↓ body weight (M/F at 300 ppm) ↓ absolute brain weight (at 70 ppm) altered liver weight (at 70 ppm) NOEL: 4 mg/kg bw/day in males and 5 mg/kg bw/day in females	Unpublished study report (2000)
Reproductive toxicity study in rats No guideline No GLP Long-Even male rats (12/sex/group)	The Substance 0, 1, 10, 100, 500 ppm via drinking water no data on exposure time	Significant increase in abnormal sperm form at 100 and 500 ppm	Carlton and Smith, 1985
Reproductive toxicity study in rats No guideline No GLP	The Substance 200 mg/kg bw ×1 1-day treatment	No changes in testis and epididymis	Linder et al., 1992

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Sprague-Dawley male rats (4 to 6 rats/group)	100 mg/kg bw ×5 5-day treatment oral gavage		
One-generation reproductive toxicity study No guideline No GLP Long-Evans rats (12 males and 24 females/group)	Chlorine dioxide 0, 2.5, 5.0 or 10 mg/kg bw via drinking water 56 day-exposure for males for females: 14 days prior to breeding, 10-day breeding period until lactation day 21	<u>Parental</u> ↓ T4 (M at 10 mg/kg bw/day) <u>F1</u> ↑T4 (M at 10 mg/kg bw/day) ↓ vaginal weight (F at 10 mg/kg bw/day) NOEL parental: 10 mg/kg bw/day NOEL F1 female:5 mg/kg bw/day	Carlton, 1991

In a two-generation reproductive toxicity study (unpublished study report, 2000), male and female rats were exposed to the Substance (30 animals/sex/dose). 25 F1 weanlings of each gender per group were selected randomly as parents for the F2 generation. Selected F1 weanlings were given the same treatment as their parents. Several fertility and developmental parameters were measured. A group of F1 animals were chosen for neurohistopathological examination, and another for neurotoxicological endpoints at all dose levels (See Table 12.).

There were no treatment-related clinical signs of toxicity or mortality in F0 or F1 parental animals, and no changes in body weight or food consumption in F0 parental animals were observed. Water consumption decreased in males in all treatment groups and in females in the 70 and 300 ppm treatment groups. Body weight and food consumption were significantly decreased in F1 males in the 300 ppm group. The parallel decrease in food and water consumption is not unusual, however, in the F0 generation this association did not occur, therefore, it could be treatment-related in F1.

There were no treatment-related changes in oestrous cyclicity, sperm motility and morphology, in mating fertility or gestational indices in the F0 or F1 generations and microscopic changes in reproductive tissues in male and female parental animals. The preputial separation and vaginal opening delayed in F1 pups at 300 ppm, but sexual maturation is usually in association with decreased body weight.

There were no treatment-related changes in the number of pups born, the pup gender ratio, live birth index or pup survival indices, nor were there differences in anogenital distance or gross external alterations in the pups. Treatment-related decreases in body weight were observed in male and female pups in the 300 ppm treatment group from the

F1 and F2 generations. The absolute brain weight was decreased in the F1 and F2 generations and altered liver weights were observed in two generations.

No blood samples were taken from F0 animals in the two-generation study. For F1 (13-week-old) adults, changes in blood parameters were examined at concentration of 300 ppm. Thyroid hormone levels were not affected by the treatment. No treatment-related changes occurred in the total serum concentrations of the thyroid hormones T3 or T4 for F1 PND 25 or F1 13-week-old animals.

Effects on the nervous system were limited to small decrease in amplitude of auditory startle response in the 70 and 300 ppm groups of F1 PND 25 animals. Based on this the NOEL was 35 ppm (4 mg/kg bw/day in males and 5 mg/kg bw/day in females).

Based on the two repeated dose toxicity studies described in Section 7.9.4. (Harrington et al., 1995 and Bertz et al., 1982) it can be assumed that changes in blood parameters were not developmental toxicity effects as the repeated dose toxicity studies also reported changes in blood parameters in rats and non-primate monkeys.

In an experimental study (Carlton and Smith, 1985) sperm count was unaltered, but significant increase in abnormal sperm form was observed in 100 to 500 ppm dose groups after the treatment in male rats. No other effect of the Substance was recorded.

In another experimental study (Linder et al., 1992), spermatotoxicity of the Substance was examined in male rats by oral gavage. Animals were dosed on day 0 with a single dose of 200 mg/kg bw/day. In case of negative or questionable positive result, additional groups of animals given five daily doses of 100 mg/kg bw/day. No changes were recorded in the testis and epididymis after either 1-day or 5-day exposure.

In a one-generation reproductive toxicity study (Carlton, 1991) Long-Evans rats were dosed with chlorine dioxide via drinking water. Changes in T4 thyroid hormone levels were observed in parent and F1 generation males in the highest dose group compared to the control. The author considered that these findings are not test item related. No other treatment-related clinical signs were observed in parental animals in any dose groups. Post-mortem examination (histopathology, organ weights) of parental animals did not show any abnormalities, also no defects on reproductive functions (oestrous cycle, sperm parameters) were observed. During post-mortem examination of the offspring only the F1 females in the highest group showed some treatment-related change (reduction in vaginal weight). The parental NOEL was 10 mg/kg bw/day, and 5 mg/kg bw/day in F1 female generation.

As the last three studies were not GLP-compliant, the methods did not follow any guidelines, and the reporting of the results lacked detailed information, therefore the eMSCA does not consider these studies acceptable.

Developmental toxicity studies:

Nine developmental toxicity studies were available in the registration dossier regarding the Substance or chlorine dioxide. Four of these studies were not considered acceptable, due to significant methodological or other deficiencies.

Table 13. Summary table of developmental toxicity studies.

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Developmental toxicity study in rats No guideline No GLP Sprague-Dawley rats (8 males/litter)	Chlorine dioxide Direct exposure: 14 mg/kg bw PND 5-20 by oral gavage Indirect exposure: via drinking water at concentration of 100 ppm from 14 days prior to breeding until PND 21	No data on maternal toxicity Foetal: Direct exposure: ↓ body weight on PND 21 ↓ exploratory behaviour on PND 60 ↓ locomotor activity on PND 18-19 ↓ DNA content of cerebellum and forebrain on PND 11 Indirect exposure: ↓ exploratory behaviour on PND 28 ↓ DNA content of cerebellum on PND 21 no data on thyroid functions	Taylor et al. 1985
Developmental toxicity study in rats No guideline No GLP Long-Evans rats (4 animals/sex)	Chlorine dioxide 14 mg/kg bw/day by oral intubation on PND 1-20	No data on maternal toxicity Foetal: ↓ body weight on PND 11, 21, 35 ↓ absolute forebrain weight and protein content on PND 21, 35 ↓ DNA content of forebrain on PND 35	Toth et al., 1990
Developmental toxicity study in rats EPA OPP 83-3 guideline GLP New Zealand rabbits (16 or 17 dams/group)	The Substance (80.58 %) 0, 200, 600 and 1200 mg/l (0, 12.2, 36.6 and 58.7 mg/kg bw/day) 7-19 days during pregnancy via drinking water	Maternal: ↓ water consumption at 600, 1200 ppm ↓ food consumption at 600, 1200 ppm Foetal: ↓ mean foetal weight at 600, 1200 ppm ↑ foetal skeletal malformations NOEL maternal: 200 ppm NOEL foetal: 200 ppm	Harrington et al., 1995b
Prenatal developmental toxicity range finding study	The Substance 0, 25, 50 and 75/100 mg/kg bw/day	75/100 mg/kg bw/day Maternal: 2 deaths, 2 euthanized dams	Unpublished study report, 2021a

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
OECD TG 414 No GLP Wistar rats (8 dams/group)	oral gavage gestation days 5-19	salivation, piloerection reduced spontaneous activity, abnormal breathing, half eyelid closure, hunched posture ↓ mean body weight and mean body weight change ↓ mean food consumption lung adhesion, abnormal colour/surface/consistency of stomach, enlarged stomach, abnormal colour of kidneys, abnormal colour of thymus, small thymus, enlarged spleen abnormalities in oesophagus, stomach, kidneys, and the liver, EMH in liver, aspiration/regurgitation in nasal cavity, larynx, lungs, forestomach hyperkeratosis associated squamous epithelial hyperplasia, glandular stomach mucosa inflammation and degeneration No developmental toxicity 50 mg/kg bw/day Maternal: 1 death, 1 euthanized dam heart adhesion, fluid filled lung, abnormal colour of stomach, liver, thymus, kidneys, enlarged liver, spleen, adrenals abnormalities in oesophagus, stomach, kidneys, and the liver, EMH in liver, forestomach hyperkeratosis squamous epithelial hyperplasia, aspiration/regurgitation in nasal cavity, larynx, lungs, glandular stomach mucosa inflammation and degeneration No developmental toxicity 25 mg/kg bw/day Maternal: 1 euthanized dam abnormal colour of lung and thymus EMH in liver, forestomach hyperkeratosis, aspiration/regurgitation in nasal cavity, larynx, lungs No developmental toxicity	
Prenatal developmental toxicity study	The Substance5, 12.5 and 25 (mg/kg	25 mg/kg bw/day Maternal:	Unpublished study report,

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
OECD TG 414 GLP Wistar rats (23 dams/group)	bw/day oral gavage gestation days 5-19	2 euthanised dams reduced activity, moving the bedding, slight wasp waist, piloerection ↓ mean RBC, haemoglobin, mean reticulocyte Foetal: ↑ mean foetal weight (M) ↓ foetal incidences of large thymus ↑ litter incidences of liver lobe supernumerary ↓ litter incidences of malpositioned umbilical artery ↑ litter incidences of abdominal internal haemorrhage ↑ litter incidences of malpositioned testis ↑ litter incidences of 14th (B) rudimentary ↑ litter incidences for incomplete ossification findings ↑ litter incidences for ossification deficiencies ↑ litter incidences for increased ossification ↑ litter incidences in wavy ribs ↑ litter incidences for head subcutaneous space increase <u>12.5 mg/kg bw/day</u> Foetal: ↓ foetal incidences of large thymus ↑ litter incidences of liver lobe supernumerary ↓ litter incidences of malpositioned umbilical artery ↑ litter incidences of 14th rib (B), rudimentary ↑ litter incidences in wavy ribs ↑ litter incidences for head subcutaneous space increase ↑ litter incidences for head subcutaneous space increase ↑ litter incidences for head subcutaneous space increase	2021b

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		5 mg/kg bw/day Foetal: ↓ foetal incidences of large thymus ↑ litter incidences of liver lobe supernumerary ↓ litter incidences of malpositioned umbilical artery ↑ litter incidences of abdominal internal haemorrhage ↑ litter incidences of malpositioned testis ↑ litter incidences in wavy ribs ↑ litter incidences for head subcutaneous space increase ↑ litter incidences for head subcutaneous space increase NOEL maternal < 5 mg/kg bw/day NOEL developmental: 25 mg/kg bw/day	

In a developmental toxicity study the effects of chlorine dioxide on neurobehavioral development was investigated by Taylor et al. (1985) with direct and indirect exposure of the pups. 8 pups/litter from unexposed dams were dosed directly daily with 14 mg/kg bw chlorine dioxide by oral gavage from postnatal day (PND) 5 to 20. In indirect exposure, dams were exposed to chlorine dioxide via drinking water at concentration of 100 ppm from 14 days prior to breeding until the pups reached 21 days of age. In the pups, locomotor activity was examined and after decapitation cerebellum and forebrain were weighed and DNA was extracted.

The direct exposure resulted in significant reduction in pup's body weight, exploratory behaviour, locomotor activity and the total DNA content of the cerebellum and the forebrain. As a result of the indirect exposure, no body weight reduction and no significant effect on locomotor activity were observed. The exploratory behaviour and the total DNA content of the cerebella were decreased. These data indicate that rat pups exposed to chlorine dioxide pre-, and postnatally showed behavioural deficits and depressed brain growth. According to the authors, these treatment-related effects were consistent with effects produced by depressed thyroid function.

In a developmental toxicity study (Toth et al., 1990) Long-Evans rat pups were exposed to chlorine dioxide by oral intubation during PND 1 to 20. Forebrain weight and protein content were decreased on PND 21 and 35, as were the DNA content on day 35. Histopathological examinations revealed no gross lesions in the brain. On PND 11, 21 and 35 the level of T3 and T4 thyroid hormones were measured, but no change was observed.

In a prenatal developmental study (Harrington et al., 1995b) New Zealand rabbits were exposed to the Substance via drinking water. Besides the decrease in maternal water and food consumption and body weight gain at 36.6 and 58.7 mg/kg bw/day, only a slight,

not dose-related increase in foetal skeletal abnormalities was observed, which was related to maternal toxicity. A NOEL of 200 ppm (12.2 mg/kg bw/day) was identified for maternal and developmental toxicity.

In a prenatal developmental range-finding toxicity study (unpublished study report, 2021a), Wistar rats were exposed to 31.7 % aqueous solution of the Substance via oral gavage during gestation days 5-19. The administered doses were 0 (control), 25 (LD), 50 (MD) and 75/100 (HD) mg/kg bw/day. As two dams were found dead and two were euthanized at a dose of 100 mg/kg bw/day (days 7-9), the treatment of the four survivors was continued at a reduced dose (75 mg/kg bw/day).

In HD and MD groups aspiration/regurgitation, stomach/intestine irritation and renal failure were recorded as the cause of morbidity. In the LD group, one dam was euthanized in a moribund condition due to aspiration/regurgitation of the Substance. Clinical signs i.e., salivation, piloerection, reduced spontaneous activity, abnormal breathing, half eyelid closure, hunched posture occurred with higher frequency in the HD group.

Lower mean body weight, mean body weight change and mean food consumption were observed mostly in the HD group compared to the control group.

The most notable macroscopic abnormalities are shown in Table 14:

Table 14. Summary table of macroscopic findings in the dosed groups of the prenatal developmental toxicity range finding study with the Substance (unpublished study report, 2021a).

Organ	Finding	Dose (mg/kg bw/day)	Incidence (out of 8 animals)
Lung	fluid filled	50	3
	adhesion	100/75	4
Stomach	abnormal colour	100/75	2
	abnormal consistency	100/75	2
Thymus	abnormal colour	50	2
Spleen	enlarged	50	3

Histologically, treatment-related findings were observed in the oesophagus, stomach, kidneys, and the liver mostly in the MD and HD groups. Extramedullary hemopoiesis in the liver occurred in all treated groups. Histological changes, because of aspiration/regurgitation, were also reported in the nasal cavity, larynx, and the lungs in almost all dosed groups. The histopathological findings in the stomach mucosa are shown in Table 15.

Table 15. Histopathological findings in stomach mucosa in the prenatal developmental toxicity range finding toxicity with the Substance (unpublished study report, 2021a).

Dose (mg/kg bw/day)	0	25	50	75/100
Total of Females	8	8	8	8
	Affected / Mean Severity*	Affected / Mean Severity*	Affected / Mean Severity*	Affected / Mean Severity*
Hyperkeratosis	1/1.0	2/1.5	3/1.3	6/1.5
Hyperplasia, squamous, forestomach	0	5/1.4	5/2.6	7/2.1
Acanthosis, forestomach	0	0	1/2.0	2/2.0
Ulceration, forestomach	0	0	3/2.3	5/3.4
Inflammation, forestomach	0	1/2.0	3/3.0	6/2.3
Inflammation, glandular stomach	0	0	0	2/1.5
Degeneration, glandular mucosa	0	0	0	2/2.5

* The numbers indicate the incidence of affected animals and its mean severity degree Grade 0 = No finding; Grade 1 = Minimal; Grade 2 = Slight; Grade 3 = Moderate; Grade 4 = Marked; Grade 5 = Massive

Slight decrease in mean male/female foetus weights was observed in the MD and LD groups, but as there was no difference at the top dose, these foetal effects were not considered test-item related. No test-item related effects were recorded for mean total number and sex ratio of foetuses per pregnant female, and no signs of external foetal anomalies were observed.

Based on findings of the range-finding study, 25 mg/kg bw/day was selected as the highest dose for the main study.

In the main prenatal developmental toxicity study (unpublished study report, 2021b), Wistar rats were exposed to 31.7 % aqueous solution of the Substance via oral gavage during gestation days 5-19. Four experimental groups (23 dams/group) were included in the study: the vehicle only (C), 5 (LD), 12.5 (MD) and 25 (HD) mg/kg bw/day.

Maternal toxicity

At the top dose, slight to moderate clinical signs were observed in 5 out of 23 animals. No test substance-related effects on mean body weight gain and food consumption were observed in any of the treated animals during the study.

For haematology examinations, blood samples were collected from all dams in all groups at termination. T3, T4 and TSH hormone levels were comparable to the control. Statistically significant decrease in mean RBC count (mean reticulocyte %) were observed in the HD group. The haemoglobin level was slightly lowered compared to control in the HD group but did not show statistical significance.

Macroscopic findings in heart, lungs, stomach/intestine, liver, kidneys, spleen, and adrenals occurred with higher frequency in the HD group, but some of them (spleen, adrenals) were also observed in the MD group. In the LD group macroscopic abnormalities were observed in the heart, liver, kidneys, spleen, and the head with one incidence per organ. However, these findings occurred only in 1-3 animals, except the enlargement of the spleen, which occurrence increased in a dose-related matter (C: 0, LD: 1, MD: 4, HD: 8).

Prenatal/litter data

There were no treatment-related effects on prenatal parameters including terminal body weight, carcass weight, uterine weight, number of corpora lutea, implantation sites and late resorptions. No dead foetuses were noted in any of the groups. In the HD group, male mean foetal weight was above the control without statistical significance, and it was also within the historical control range.

Foetal variations and malformations

No treatment-related external abnormalities were observed in all dosed groups.

The visceral findings are listed in Table 16.

Table 16 Foetal (f) and litter (l) incidences of foetal visceral findings in prenatal developmental toxicity study with the Substance (unpublished study report, 2021b).

Findings	Control 0 mg/kg bw	LD 5 mg/kg bw	MD 12.5 mg/kg bw	HD 25 mg/kg bw
large thymus (f)**	29.39%*	6.80 %	8.32 %	1.47 %
liver lobe supernumerary (l)	20%	35%	29.4%	41.2% *
malpositioned umbilical artery (l)	55%	45%	35.3%	52.9%

*Incidence not within the historical control range
** statistically significant change

Slightly higher litter incidences without statistical significance of abdominal internal haemorrhage (88.2% compared to 80% in the control) and malpositioned testis (40% compared to 25% in the control) were observed in the HD and LD group, respectively. In these cases, no historical control data were found in the dossier.

Since there was no dose-dependency in any of the above-mentioned cases, the observed visceral findings were not treatment-related.

Skeletal findings:

The statistical analysis showed significantly higher litter incidence value of 14th rib rudimentary in the MD group without dose dependency. For this finding, the incidence values were within the historical control range in all dosed and the control group. Moreover, several, not statistically significant higher or lower litter incidences were observed for the following ossification-related findings.

Litter incidences of skeletal findings are listed in Table 17.

Table 17. Litter incidences of skeletal findings in prenatal developmental toxicity study with the Substance (unpublished study report, 2021b).

Findings	Control 0 mg/kg bw	LD 5 mg/kg bw	MD 12.5 mg/kg bw	HD 25 mg/kg bw	Historical control range
Rib(14th) (B) rudimentary	50.0%	75.0%	89.5%	83.3%	0.00-95.00%
Incomplete ossification: hindlimb femur	35%	35%	31.6 %	50%	0.00-12.5%
ossification deficiencies: vertebra caudal arch(es)	5.0%	5.0%	10.5%	11.1%	0.00-5.00%
Increased ossification: skull supraoccipital with small hole	75%	80.0%	78.9%,	88.9%	0.00-20.0%
head subcutaneous space increase	0%	20%	29.4%	29.4%	0.00-15.00%
subdural haematoma in midbrain	5%	30%	17.6%	23.5 %	0.00-15.79%

Wavy ribs were observed in all the treated groups, without dose dependency.

Since there was no dose-dependent correlation in any of the above-mentioned cases, the observed findings were not related to the treatment.

In summary:

Two dams were euthanized in the HD group due to clinical signs of toxicity. No mortality or clinical signs of toxicity were recorded in the LD and the MD groups. Macroscopic findings typically occurred in the HD group dams, but some of these abnormalities were also observed in the MD and LD groups at a lower frequency. There were no treatment-related effects on prenatal parameters and litter data. No external malformations were evident in the litters in any dose group. The visceral findings were either minor variations and/or without dose dependency. Most of foetal bones were affected by incomplete, irregular, unossified or increased ossification in the treated groups, but no dose-dependency was observed in any of cases. In addition, the skeletal abnormalities were minor variations. For craniofacial findings, no dose dependency or statistical significance was observed. Most of the incidence values in the foetal findings were within the historical control ranges. In three parameters (for large thymus, hindlimb femur, skull supraoccipital with small hole), the control values were outside the historical control range without any explanation. No historical control data were found in the dossier for two findings (abdominal internal haemorrhage, malpositioned testis). The NOAEL was less than 5 mg/kg bw/day for maternal toxicity and 25 mg/kg bw/day for developmental toxicity.

Considering the above data, the evaluating Member State concluded that the Substance is not a reproductive toxicant and the concern for reproductive toxicity was removed in this substance evaluation.

7.9.8. Hazard assessment of physico-chemical properties

The Substance is a strong oxidising agent and, according to the relevant studies, corrosive to the skin, therefore, it should be classified for Skin Corrosion Category 1B. According to the CSR, corrosivity was tested in GLP studies (UN test C.1.), and the 34.5

%, 20 %, 15 % 5% solutions of the Substance were corrosive to metals. Even though this physico-chemical property of the Substance is not relevant under substance evaluation, the evaluating Member State considers including this endpoint in the proposed harmonised classification.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The Registrant selected a two-generation study (unpublished study report, 2000) for starting point to DNEL calculation (NOAEL: 4 mg/kg bw/day). It is based on the decreased auditory startle response in males and females in F1 and F2 generations. The evaluating Member State agreed with the selected value and the calculated DNELs made by the Registrant.

Table 18. DNELs/DMELs for workers.

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s)**	**DNEL/ DMEL**	**Justification/ Remarks**
acute dermal toxicity	acute systemic effects (dermal)	unpublished study report (2000)	NOAEL	0.8 mg/kg bw/day	AF=50
acute inhalation toxicity	acute systemic effects (inhalation)	unpublished study report (2000)	NOAEL	0.28 mg/m^3	AF=12.5
repeated dose dermal toxicity	long-term systemic effects (dermal)	unpublished study report (2000)	NOAEL	0.8 mg/kg bw/day	AF=50
repeated dose inhalation toxicity	long-term systemic effects (inhalation)	unpublished study report (2000)	NOAEL	0.28 mg/m^3	AF=12.5

Table 19. DNELs/DMELs for consumers.

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s)**	**DNEL/ DMEL**	**Justification/ Remarks**
acute oral toxicity	acute systemic effects (oral)	unpublished study report (2000)	NOAEL	0.04 mg/kg bw/day	AF=100
acute dermal toxicity	acute systemic effects (dermal)	unpublished study report (2000)	NOAEL	0.4 mg/kg bw/day	AF=100
acute inhalation toxicity	acute systemic effects (inhalation)	unpublished study report (2000)	NOAEL	0.07 mg/m^3	AF=25
repeated dose oral toxicity	long-term systemic effects (oral)	unpublished study report (2000)	NOAEL	0.04 mg/kg bw/day	AF=100
repeated dose dermal toxicity	long-term systemic effects (dermal)	unpublished study report (2000)	NOAEL	0.4 mg/kg bw/day	AF=100
repeated dose inhalation toxicity	long-term systemic effects (inhalation)	unpublished study report (2000)	NOAEL	0.07 mg/m^3	AF=25

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

The evaluating Member State has come to the following conclusions based on the available data:

Acute toxicity

The evaluating Member State considers the derived acute oral toxicity LD50 value of 284 mg/kg bw/day and of acute dermal toxicity LD50 value of 134 mg/kg bw/day for human health assessment acceptable. Based on these values, the evaluating Member State concludes that a harmonised classification is warranted for the substance as Acute Tox. 3 (H301:" Toxic if swallowed") and as Acute Tox. 2. (H310:" Fatal in contact with skin") due to the divergence among notifiers in their self–classifications.

Toxicity via inhalation is unlikely to occur, considering the low vapour pressure of the Substance, and the evaluating Member State is not aware of any spraying applications.

Skin irritation/corrosion

In a study similar to OECD guideline 404, skin corrosivity was observed in New Zealand White rabbits (unpublished study report, 1984b). Based on the positive result, the evaluating Member State concludes that harmonised classification for Skin Corrosion Category 1B (H314:" Causes severe skin burns and eye damage") is needed due to the divergence among notifiers in their self–classifications.

Eye irritation

In a study investigating eye irritation in rabbits (Unpublished study report, 1985c), the Substance caused eye irritation, which was not fully reversible within 21 days. Moreover, the substance is a strong oxidiser and corrosive to the skin, therefore the evaluating Member State concludes that a harmonised classification is warranted as Eye Damage Category 1.

Sensitisation

Based on the available study performed according to OECD TG 406 (unpublished study report, 2002), the Substance does not cause skin sensitisation. Respiratory sensitisation is not expected due to the low vapour pressure of the substance.

Repeated dose toxicity

Several studies (repeated dose toxicity studies and a two-generation reproductive toxicity study) confirmed that prolonged exposure to the Substance could change the blood parameters in a negative way. Therefore, the evaluating Member State concludes that harmonised classification for STOT RE Category 2 is warranted due to the divergence among notifiers in their self–classifications.

Mutagenicity

Several *in vivo* and *in vitro* studies were conducted on the Substance, and some of them gave positive results including an *in vivo* mammalian alkaline comet assay requested under CCH. Based on the results, the evaluating Member State considers that, as the criteria for positive result for mutagenicity are fulfilled, harmonised classification for Mutagenicity Category 2 is warranted for the Substance.

Carcinogenicity

In the available studies, the Substance caused tumours in different organs, but the incidences did not increase statistically significantly nor were dose-dependent, or similar tumours were observed also in control animals. According to the available data, the evaluating Member State concludes that the substance has no carcinogenic effects.

Reproductive toxicity

Based on the available data, including a prenatal developmental toxicity study in a second species (rat) requested under CCH, the evaluating Member State concludes that the Substance is not a reproductive toxicant and the concern for reproductive toxicity is removed.

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and VPVB assessment

Not evaluated.

7.12. Exposure assessment

7.12.1. Human health

As the vapour pressure of the Substance is very low (1.1 x 1E-7 Pa at 25°C) and the evaluating Member State is not aware of any spraying applications of the Substance, exposure via inhalation is unlikely. Therefore, based on the available data, the evaluating Member State concludes that there are two main exposure routes for the Substance, i.e., oral, and dermal routes.

The Registrant used CHESAR 1.1.1., AISE REACH Exposure Assessment Consumer Tool and HERA Guidance document for the assessment of exposure scenarios for manufacture, professional, industrial and consumer uses. According to the CSR and the registration dossier the evaluating Member State considers that the applied risk management measures are appropriate.

Moreover, based on the available data, the estimated exposure values are below the derived DNEL(s) and all the RCRs are below 1.

7.12.1.1. Worker

Manufacture and industrial use of the Substance (in water treatment, paper pulp bleaching, textile bleaching and starch industry) occur in closed systems, therefore, there is no significant human exposure. As the Substance is self-classified as skin corrosive, adequate risk management measures should be applied, including ventilation, personal protection equipment and training.

7.12.1.2. Consumer

As consumers use the Substance as diluted solutions, the exposure is negligible based on the exposure scenarios.

7.12.2. Environment

Not evaluated.

7.12.3. Combined exposure assessment

Not evaluated.

7.13. Risk characterisation

Human Health

Based on the calculated values of risk characterisation ratios (<1.0 at every identified operation) there is no concern posed by the exposure of workers to the Substance when all specified risk management measures and operational conditions are in place and followed. The highest calculated risk characterisation ratio is given for acute and long-term dermal exposure (both below 0.5).

The estimated exposure concentrations and risk characterisation ratios for consumers are lower than that for workers since consumers use the Substance as a very dilute solution. Based on the findings, indirect exposure of humans via the environment can be excluded.

The evaluating Member State concludes that there is no overall concern regarding workers' and consumers' exposure and the risk management measures indicated in the CSR by the Registrant are appropriate.

Environment

Not evaluated.

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7.15. Abbreviations

ALT	Alanine aminotransferase
CA	Competent Authority
CAS	Chemical Abstracts Service
CCH	Compliance check
CLP	Classification, labelling and packaging
CMR	Carcinogenic, Mutagenic or Toxic for Reproduction
CoRAP	Community Rolling Action Plan
CSR	Chemical Safety Report
D20	The D20 value is the estimated dosage of the test substance that is necessary to induce an aberration in 20% of metaphase cells.
DMEL	Derived Minimal Effect Level
DNA	Deoxyribonucleic acid
DNEL	Derived No Effect Level
ECHA	European Chemicals Agency
ED	Endocrine disruptor
EPA OPP	Environmental Protection Agency Office of Pesticide Programs
ERC	Environmental Release Category
GLP	Good Laboratory Practice

G6PD	Glucose-6-phosphate dehydrogenase
LD50	Median lethal dose
MNPCE	Number of polychromatic (immature) erythrocytes (PCE) with micronuclei
MCV	Mean corpuscular volume
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
OECD TG	Organisation for Economic Co-operation and Development Test Guideline
PBT	Persistent Bioaccumulative and Toxic
PC	Product category
PND	Postnatal day
ppm	Part per million
PROC	Process category
RCR	Risk characterisation ratio
SCC	Strictly controlled conditions
SGPT	Serum glutamate–pyruvate transaminase
SEV	Substance Evaluation
STOT	Specific Target Organ Toxicity
STOT RE	Specific target organ toxicity — repeated exposure
STOT SE	Specific target organ toxicity — single exposure
SVHC	Substance of Very High Concern
T4	Serum thyroxine
TII	Transported isolated intermediate
TR	Translation Ratio
vPvB	Very Persistent and Very Bioaccumulative