



Australian Government

Department of Health and Aged Care

Australian Industrial Chemicals Introduction Scheme

Chlorendic acid and chlorendic anhydride

Evaluation statement

14 December 2023



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AICIS evaluation statement

Subject of the evaluation

Chlorendic acid and chlorendic anhydride

Chemicals in this evaluation

Name	CAS registry number
[Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid, 1,4,5,6,7,7-hexachloro- (chlorendic acid)	115-28-6
4,7-Methanoisobenzofuran-1,3-dione, 4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro- (chlorendic anhydride)	115-27-5

Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

These chemicals are listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of these chemicals.

These chemicals have been assessed as a group as they are structurally similar and have similar use pattern. Chlorendic anhydride hydrolyses to chlorendic acid in aqueous solution. Therefore, systemic effects are expected to be due to exposure to chlorendic acid.

Summary of evaluation

Summary of introduction, use and end use

There is currently no specific information about the introduction, use and end use of these chemicals in Australia.

Based on international information, the main use of chemicals in this group is as a flame retardant monomer in a variety of products including coatings, polyurethane foams and wool textiles.

Chlorendic acid and chlorendic anhydride are used as reactive flame retardants where they are built into the polymeric backbone of polyester resins and plasticisers for electrical systems and paint.

Human health

Summary of health hazards

The identified health hazards are based on available data for these chemicals. Based on the toxicokinetic studies, these chemicals are rapidly distributed throughout the body and metabolised. Chlorendic anhydride can be metabolically transformed to chlorendic acid due to hydrolysis of anhydride to corresponding acid in aqueous solutions.

The available data suggests that these chemicals:

- have low acute oral, dermal and inhalation toxicity
- are not expected to cause serious systemic health effects following repeated oral, dermal or inhalation exposure
- are not expected to have genotoxic potential.

Based on the available animal and in silico data, chlorendic acid may be irritating to skin and eyes, particularly following repeated exposures. Chlorendic anhydride has existing classifications for skin, eye and respiratory irritation. There are limited data available to evaluate these classifications. Eye and respiratory irritation effects have been observed in available studies in rabbits. The severity of eye irritation effects could not be determined. In the available skin irritation study in rabbits, only slight effects were observed.

Based on the available data, including in vivo data, quantitative structure activity relationship (QSAR) modelling and a human case study chlorendic anhydride is considered to be a skin sensitiser. Positive results were reported in an in vivo skin sensitisation study (guinea pig maximisation test). Positive reactions were observed in 62.5% of animals at 24 hours and in 25% of animals at 48 hours following intradermal induction at 0.9%. The available data suggest that chlorendic acid is not a skin sensitiser.

Respiratory sensitisation are well known effects of occupational exposure to cyclic acid anhydrides. The respiratory sensitisation potential of chlorendic anhydride cannot be ruled out based on QSAR modelling and limited available animal and human data.

Based on the available data, chlorendic acid has sufficient evidence of carcinogenicity in animals based on the observation of benign and malignant tumours in multiple organs and both sexes of rats and in male mice. In rats, neoplastic lesions were found in the liver of both sexes and in the lungs and pancreas of males. Male mice had increased incidences of hepatocellular carcinoma and hepatocellular adenoma. In addition, there was evidence of metastasis of hepatocellular carcinoma to lungs. Alveolar/bronchiolar adenomas and alveolar/bronchiolar adenomas or carcinomas (combined) in female mice occurred with significant positive trends, although statistically significant increases were not noted. The mode of action for carcinogenicity of the chemical is uncertain and the availability of mechanistic data is limited. The available data supports a likely threshold mode of action. As there is no established mechanism for the carcinogenicity of the chemical, the relevance to humans cannot be ruled out.

There are no specific carcinogenicity data for chlorendic anhydride. As chlorendic anhydride is metabolically transformed into chlorendic acid. Both chemicals in this group are considered carcinogens.

There is insufficient data to determine whether exposure to these chemicals affect fertility and developmental toxicity. In a single non-guideline study with chlorendic anhydride, while post implantation losses were reported in two highest dose groups, the magnitude of these increases in individual animals were not reported. In the substance evaluation conclusion document for chlorendic anhydride it was also pointed out that this study may not have been conducted to the limit dose, which could prevent the differentiation of effects between the dams and the offspring.

For further details of the health hazard information see **Supporting information**.

Hazard classifications relevant for worker health and safety

The chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards. The classifications for skin irritation, eye irritation and specific target organ toxicity – single exposure, are current classifications for chlorendic anhydride under the Hazardous Chemical Information System (HCIS) (SWA n.d.).

The classifications for skin, eye and respiratory irritation, and skin sensitisation only applies to chlorendic anhydride (CAS No. 115-27-5). The classification for carcinogenicity applies to both chemicals in the group.

Health hazards	Hazard category	Hazard statement
Skin corrosion/irritation	Skin Irrit. 2	H315: Causes skin irritation
Serious eye damage/eye irritation	Eye Irrit. 2	H320: Causes eye irritation
Specific target organ toxicity (single exposure)	STOT Single Exp. 3	H335: May cause respiratory irritation
Skin sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction
Carcinogenicity	Carc. 1B	H350: May cause cancer

Summary of health risk

Public

Based on the available use information it is unlikely that the public will be exposed to these chemicals. Although the public could come into contact with articles or coated surfaces containing these chemicals it is expected that these chemicals will be bound within articles or coated surfaces and hence will not be bioavailable. Therefore, there are no identified risks to the public that require management.

Workers

During product formulation and packaging, dermal, ocular and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the identified systemic and local health effects and potential for respiratory sensitisation (chlorendic anhydride), these chemicals could pose a risk to workers. Control measures to minimise dermal, ocular and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risks** section).

Control measures implemented due to the proposed carcinogenicity classification are expected to be sufficient to protect workers from any potential reproductive and developmental effects of the chemicals.

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the HCIS to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from oral, dermal, ocular and inhalation exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- using local exhaust ventilation to prevent these chemicals from entering the breathing zone of any worker.
- minimising manual processes and work tasks through automating processes.
- adopting work procedures that minimise splashes and spills.
- cleaning equipment and work areas regularly.
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Measures required to eliminate or manage risk arising from storing, handling and using this hazardous chemical depend on the physical form and how the chemical is used. Guidance within the Interpretation of Workplace Exposure Standards for Airborne Contaminants (Safe Work Australia, 2019) advises that 'exposure to carcinogens should be eliminated or minimised so far as is reasonably practicable'.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to the chemical, if valid techniques are available to monitor the effect on the worker's health.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The Executive Director is satisfied that the identified risks to human health from the introduction and use of the industrial chemicals can be managed.

Note:

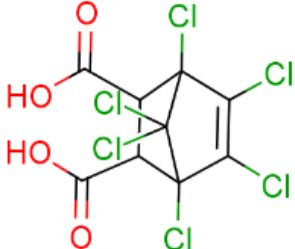
1. Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Supporting information

Grouping rationale

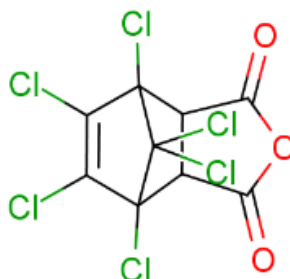
The chemicals in this group are chlorendic acid and chlorendic anhydride. Chlorendic anhydride is expected to hydrolyse to chlorendic acid in contact with water; therefore, systemic effects are expected to be due to exposure to chlorendic acid. Local effects are expected to differ between these two chemicals due to the high reactivity potential for chlorendic anhydride compared to chlorendic acid.

Chemical identity

Chemical name	Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid, 1,4,5,6,7,7-hexachloro-
CAS No.	115-28-6
Synonyms	1,4,5,6,7,7-hexachloro-8,9,10-trinorborn-5-ene-2,3-dicarboxylic acid chlorendic acid HET acid hexachloroendomethylenetetrahydrophthalic acid
Molecular formula	C ₉ H ₄ Cl ₆ O ₄
Molecular weight (g/mol)	388.84
SMILES (canonical)	O=C(O)C1C(C(=O)O)C2(Cl)C(Cl)=C(Cl)C1(Cl)C2(Cl)Cl
Chemical description	-
Structural formula	

Chemical name	4,7-Methanoisobenzofuran-1,3-dione, 4,5,6,7,8,8-hexachloro-3a,4,7,7a-tetrahydro
CAS No.	115-27-5
Synonyms	bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride, 1,4,5,6,7,7-hexachloro chlorendic anhydride HET anhydride hexachloroendomethylene tetrahydrophthalic anhydride

Molecular formula	C ₉ H ₂ Cl ₆ O ₃
Molecular weight (g/mol)	370.83
SMILES (canonical)	O=C1OC(=O)C2C1C3(Cl)C(Cl)=C(Cl)C2(Cl)C3(Cl)Cl
Chemical description	-
Structural formula	



Relevant physical and chemical properties

Chemicals in this group are bridged organochlorine compounds. Chlorendic anhydride hydrolyses to chlorendic acid in aqueous solution. Therefore, determination of partition coefficient on chlorendic anhydride is not relevant. Chlorendic acid loses water when heated in an open system to give anhydride and emits chlorine when heated to decomposition.

Chemical	chlorendic acid	chlorendic anhydride
Physical form	white crystalline powder	white crystalline powder
Melting point	209 °C	239 °C
Water solubility	0.499 g/L at 20 °C	< 2.5 mg/L at 20 °C
pKa	3.6 and 5.6 at 22.8 °C	7.35 (predicted)
log K_{ow}	-1.59 at 25 °C	-

Introduction and use

Australia

There is currently no specific information about the introduction, use and end use of these chemicals in Australia.

International

The following international uses have been identified through International Agency for Research on Cancer (IARC) monograph volume 48, International Programme for Chemical safety Environmental Health Criteria (IPCS EHC) 185, NTP reports (NTP 2021), PubChem, Substances in Preparations in Nordic Countries (SPIN), ECHA FCMs Recycled Plastic & Articles Regulation - Annex I - Authorised Use, Recycled Plastic FCMs - Regulation (EU) 2022/1616 and Chemwatch.

These chemicals have reported commercial uses in:

- flame retardants (in coatings, polyurethane foams and wool textiles)
- adhesives and binding agents
- paints, laquers and varnishes
- plasticisers
- plastic food contact material
- lubricants.

These chemicals have reported site limited uses as a chemical intermediate.

Chlorendic acid and chlorendic anhydride are used as reactive flame retardants where they are built in to the polymeric backbone of polyester resins and plasticizers for electrical systems and paint (Johannes Karl Fink 2000).

Chlorendic acid is likely to be bound covalently to the material when used as a reactive flame retardant or hardening agent, reducing the potential for human exposure (Horrocks AR 1986; NTP 2021).

In 2009, chlorendic acid was produced by two manufacturers in Europe and was available from eleven suppliers worldwide, including five U.S. suppliers. Reports filed in 1986, 1990, and 2002 under the U.S. Environmental Protection Agency's (US EPA) Toxic Substances Control Act (TSCA) Inventory indicated that U.S. production plus imports of chlorendic acid was 500,000 lb to 10 million pounds (NTP 2021). Chlorendic acid is listed as active in TSCA Inventory updates as of February 2023 (US EPA 2023), but is not listed in US EPA, Chemical Data Reporting (CDR) database for 2012, 2016 and 2020 (US EPA 2012; US EPA 2016; US EPA 2020).

US EPA CDR reports for 2016 and 2020 indicate the national aggregated production volume for chlorendic anhydride is 760,000 lbs and 802,483 lbs respectively (US EPA 2016; US EPA 2020).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

Anhydrides and organic acid for use as curing agents for epoxy resins are listed under Schedule 5 in the Therapeutic Goods *Poisons Standard* (SUSMP) except when separately

specified in these Schedules (TGA 2023). This entry covers both chemicals when used as curing agents for epoxy resins.

Schedule 5 chemicals are labelled with 'Caution'. These are “substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label”.

Workers

Chlorendic acid is not listed on the Hazardous Chemical Information System (HCIS) and no specific exposure standards are available in Australia (SWA n.d.).

Chlorendic anhydride is listed on HCIS with following classifications

Health hazards	Hazard category	Hazard statement
Skin corrosion/irritation	Skin Irrit. 2	H315: Causes skin irritation
Serious eye damage/eye irritation	Eye Irrit. 2	H320: Causes eye irritation
Specific target organ toxicity (single exposure)	STOT Single Exp. 3	H335: May cause respiratory irritation

No specific exposure standards are available in Australia.

International regulatory status

Canada

Chlorendic acid is subject to significant new activity provisions (SNAc) of Canadian Environmental Protection Act, 1999. SNAc provisions are applied to the chemical if after chemical assessment, there is a suspicion that new chemical activities may pose a risk to human health and/or environment. (Health Canada n.d.)

European Union

Chlorendic anhydride is considered for identification as a substance for very high concern as per substance evaluation conclusion report (ECHA 2022).

United States of America

Chlorendic acid is listed in the Current Proposition 65 (Safe Drinking Water and Toxic Enforcement Act of 1986) List. This list contains chemicals that are known to cause cancer or birth defects or other reproductive harm (OEHHA 2023). No Significant Risk Level (NSRL) derived from expedited cancer potency for chlorendic acid is 8 µg/day (OEHHA 1992).

Asia

Chlorendic acid is listed as Type II Monitoring Chemical Substances in Japan – suspected to have a long term toxicity to humans.

Health hazard information

Toxicokinetics

Chlorendic anhydride rapidly hydrolyses to chlorendic acid in contact with aqueous media with a half life of approximately one hour. Conversely when chlorendic acid is heated in an open system, chlorendic anhydride can be formed by dehydration (ECHA 2022; IPCS 1996). Because chlorendic anhydride is expected to hydrolyse to chlorendic acid in the body they are expected to have a similar toxicokinetic profile.

Chlorendic acid and chlorendic anhydride are rapidly absorbed after oral administration.

In a study with radio labelled chlorendic acid in rats, the major site of radiolabelled chlorendic acid deposition was the liver, with smaller amounts found in the blood, muscle, skin, intestines and kidneys. Chlorendic acid-derived radioactivity was excreted primarily through the bile and into the faeces (up to 90%). Only 3-6% was excreted in urine. Within one day, more than 75% of the total dose was excreted in the faeces, primarily as a conjugate.

A similar pattern of excretion was found in a rat gavage study with radiolabelled chlorendic anhydride. The primary route of excretion was via faeces and a small amount was excreted via urine. The absorption of chlorendic anhydride followed the two compartment open model, with rapid equilibration in the first compartment (blood and selected tissues) and a slower equilibration in the second compartment (fat). (ECHA 2022; IPCS 1996).

Following intravenous administration of radiolabelled chlorendic acid, more than 50% of the administered radioactivity was found in the liver within 15 min. Biliary excretion was the primary route of removal of radioactivity from the liver, with a half-life of 1.19 hours. The blood contained 20% of the administered radioactivity at 1 hour, and this declined with a half-life of 0.84 hour. Muscle contained 14% of the administered radioactivity at 15 min, and this level fell rapidly, with a half-life of 0.57 hours, with smaller amounts detected in other organs. The major route of excretion was via faeces (IARC 1990).

Acute toxicity

Oral

Based on the available data chemicals in this group have low acute oral toxicity.

In a non-GLP compliant, acute oral toxicity study, male Charles River CD rats (number not reported) were administered single doses of chlorendic acid, as a solution in acetone-peanut oil (1:9), by oral gavage at 1.5, 2, 12, 130, 670, 1000, 1500, 2250, 3400 or 5000 mg/kg body weight (bw). Mortality was observed at doses ≥ 2250 mg/kg bw. Clinical observations included inactivity, irregular respiration, and weight loss. Gross necropsy was not reported (IPCS 1996).

Other reported median lethal dose (LD50) values for chlorendic acid or chlorendic anhydride in rats include:

- 1770 mg/kg bw (chlorendic acid) (IPCS 1996).
- 2480 mg/kg bw (chlorendic anhydride) (IPCS 1996)
- 2336 mg/kg bw (chlorendic anhydride) (REACH n.d.).

Dermal

No data are available for chlorendic acid.

Based on the available data, chlorendic anhydride has low dermal acute toxicity.

In a non-GLP compliant, acute dermal toxicity study similar to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 402, New Zealand white (NZW) rabbits (2/sex/dose) were treated with a single dose of chlorendic anhydride at 10,000 or 20,000 mg/kg bw. No sublethal signs of toxicity were reported. The LD50 was between 10,000 and 20,000 mg/kg bw (REACH n.d.; ECHA 2022).

In another study, the acute dermal LD50 of chlorendic anhydride in albino rabbits was >3000 mg/kg bw. No further study details are available (IPCS 1996).

Inhalation

Based on the available data these chemicals are expected to have low acute inhalation toxicity.

In a non-GLP compliant acute inhalation toxicity study similar to OECD TG 403, Charles River CD rats (5/sex) were exposed to chlorendic acid as dust at 0.79 mg/L of air for 4 hours. The median lethal concentration was >0.79 mg/L. No sublethal signs of toxicity were reported (IPCS 1996).

In a non-GLP compliant, acute inhalation toxicity study similar to OECD TG 433, Charles River CD, rats (5/sex) were exposed to chlorendic anhydride as a dust (whole body) for 1 hour at 203 mg/L in air. Sub-lethal effects included salivation and nasal discharge. A median lethal concentration (LC50) value of >203 mg/L was determined (IPCS 1996, REACH n.d., ECHA 2022).

In another inhalation study, LC50 values for chlorendic anhydride vapour in albino rats was reported as >5.27 mg/L (IPCS 1996). No further study details are available.

Corrosion/Irritation

Skin irritation

Based on the available animal and in silico data, chlorendic acid may be irritating to skin, particularly following repeated exposure. There are insufficient data to warrant hazard classification. Chlorendic anhydride is classified as hazardous in the HCIS (Safe Work Australia) as 'Skin irritation – Category 2'. There is insufficient evidence to amend this classification.

Repeated application of chlorendic acid (as a powder or as a solution in dimethyl phthalate) to the skin of NZW rabbits caused local skin irritation. No further study details are available (IPCS 1996).

In a non-guideline, non-GLP compliant skin irritation study, 6 NZW rabbits (sex not known) were treated with chlorendic anhydride for 4 hours under occluded conditions. Observations were recorded at 24, 48, 72 hours after patch removal. The following mean scores were reported for observations at 72 hours: 0.6 for erythema and 0.19 for oedema respectively (maximum score of 4) (REACH n.d.). No further study details are available.

Chlorendic anhydride was reported to be a 'mild' skin irritant in NZW rabbits. No further study details are available (IPCS 1996).

In silico

QSAR modelling for skin irritation using the OASIS TIMES software indicated that chlorendic acid (89% in domain) and chlorendic anhydride (100% in domain) were positive for skin irritation based on structural alerts (carboxylic acid and alkyl/aryl halides derivatives) (OASIS TIMES). Chlorendic anhydride is reported as one of the chemicals in the training set for this model.

The knowledge based expert system; Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus (version 6.0.1) did not reveal any specific skin irritation structural alerts for chlorendic acid. Chlorendic anhydride had structural alerts (cyclic acid anhydride) for skin irritation (Lhasa Limited).

Eye irritation

Based on the available animal and in silico data, chlorendic acid may be irritating to eyes, particularly following repeated exposure. There is insufficient data to warrant hazard classification. Chlorendic anhydride is classified as hazardous in the HCIS (Safe Work Australia) as 'Eye irritation – Category 2'. The available data is insufficient to determine the severity of the eye irritation. In the absence of more comprehensive information, there is insufficient evidence to amend this classification.

Repeated application of chlorendic acid (as a powder or as a 5, 10 or 20% solution in dimethyl phthalate) beneath the eyelids of NZW rabbits was reported to cause severe eye irritation. No further details of the study are available (IPCS 1996).

In a non-GLP compliant study similar to OECD TG 405, chlorendic anhydride was instilled into 1 eye each of NZW rabbits (n=6). The reported mean irritation score was 16.4. Maximum score was 17.3. No further study details are available (REACH n.d.).

Chlorendic anhydride was reported to be severely irritating to the eyes of albino rabbits. No further study details are available (IPCS 1996)

In silico

The knowledge based expert system, Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus (version 6.0.1) did not reveal any specific eye irritation structural alerts for chlorendic acid. Chlorendic anhydride had structural alerts (cyclic acid anhydride) for eye irritation (Lhasa Limited).

QSAR modelling for eye irritation using the OASIS TIMES software indicated that these chemicals were positive for eye irritation based on structural alerts (carboxylic acid and alkyl/aryl halides derivatives or extrapolation from skin to eye irritation). However, these chemicals were out of the applicability domain of the model used for these predictions, indicating greater uncertainty about the reliability of the results. (OASIS Times)

Respiratory irritation

No data are available for chlorendic acid. Chlorendic anhydride is classified as hazardous in the HCIS (Safe Work Australia) as 'Specific target organ toxicity (single exposure) –

Category 3, H335 (May cause respiratory irritation). The limited available data support this classification.

Acute inhalation exposure of rats to chlorendic anhydride dust resulted in salivation and nasal discharge (See **Acute toxicity inhalation**).

In a repeat dose toxicity study (See **Repeat dose inhalation**), rats displayed dose dependent ocular and nasal irritation and salivation immediately after the 6 hour exposure period. Repeated exposure to chlorendic anhydride resulted in the inflammation of nasal turbinates, trachea and lungs.

Sensitisation

Skin sensitisation

Based on the available data, chlorendic acid is not expected to be a skin sensitiser. Based on the available human, animal and in silico data chlorendic anhydride is considered to be a skin sensitiser.

Chlorendic acid was negative in a skin sensitisation test in albino guinea pigs. No further study details are available (IPCS 1996).

In a non-guideline, guinea pig maximisation test (GPMT) study, intradermal induction was performed on 8 male, albino guinea pigs using 0.9% chlorendic anhydride in sodium chloride solution and topical induction with 0.9% of the chemical. The animals were challenged with 0.9% chlorendic anhydride in sodium chloride solution. After challenge, reactions were reported in 5/8 (62.5%) animals after 24 hours and 2/8 (25%) after 48 hours (REACH n.d.).

In a skin sensitisation study in albino guinea pigs, chlorendic anhydride produced a positive response. No further study details are available (IPCS 1996).

In silico

The knowledge based expert system; Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus (version 6.0.1) did not reveal any specific skin sensitisation structural alerts for chlorendic acid. Chlorendic anhydride had structural alerts (cyclic acid anhydride, azlactone or analogue) for skin sensitisation (Lhasa Limited).

Observation in humans

A welder exposed to welding fumes containing phthalic anhydride and chlorendic anhydride developed contact urticaria. An IgE-mediated allergy was verified with skin prick tests and specific chlorendic anhydride IgE antibodies. An open test with chlorendic anhydride was also positive (Nordic expert group 2004, WHO 2009, ECHA 2022).

Respiratory sensitisation

No data are available for chlorendic acid.

Based on animal data, in silico data and a single human case study, chlorendic anhydride may be a respiratory sensitiser. Further evaluation of data for similar cyclic anhydrides is needed to determine classification for respiratory sensitisation.

Inflammation was observed in respiratory organs after repeated exposure to chlorendic anhydride (see **Repeat dose toxicity: inhalation**).

Allergic respiratory manifestations are well known effects of occupational exposure to cyclic acid anhydrides. The mechanism of respiratory sensitisation is mainly IgE mediated allergy. Specific IgE antibodies for chlorendic anhydride were identified in a single human case study (see **Skin sensitisation**). Asthmatic symptoms were observed in this worker (ECHA 2022, Nordic expert group 2004, WHO 2009).

Modelling based on the mechanistic profiling functionality of the OECD quantitative structure activity relationship (QSAR) Application Toolbox (OECD QSAR Toolbox v4.2) produced no structural alerts for chlorendic acid. However, structural alerts for chlorendic anhydride were identified (Acylation >> Ring opening acylation at a carbonyl >> Anhydrides) (OECD 2018)

The knowledge based expert system, DEREK Nexus (version 6.0.1) indicated specific respiratory sensitisation structural alerts for chlorendic anhydride (cyclic acid anhydride) (Lhasa Limited).

Repeat dose toxicity

Oral

Based on the available data, these chemicals are not expected to cause serious systemic health effects following repeated oral exposure. The observed liver effects occurred at high doses only.

Chlorendic acid

In a repeat dose study conducted in accordance with NTP test guidelines, F344/N rats (n=10/sex/dose) were fed a diet containing 0, 620, 1250, 2500, 5000 or 10,000 ppm (equivalent to 0, 31, 62.5, 125, 250 or 500 mg/kg bw) of chlorendic acid for 13 weeks.

All animals survived the study. The final mean body weight was 10% lower in males at ≥ 125 mg/kg bw/day and in females at ≥ 62.5 mg/kg bw/day. Food consumption was decreased in the 2 highest dose groups during the first half of the study and increased in the highest dose group during the second half of the study. No clinical signs of toxicity were reported. Increased incidences of hepatocytomegaly, mitotic alteration of the liver, and bile duct hyperplasia were observed in the 2 highest dose groups. The bile duct hyperplasia was more severe in females. The no observed adverse effect level (NOAEL) of the study is considered to be 125 mg/kg bw based on liver and bile duct effects at the two highest doses (IPCS 1996, NTP 1987).

In a repeat dose study conducted in accordance with NTP test guidelines, F344/N rats (n=5/sex/dose) were fed a diet containing 0, 3100, 6200, 12,500, 25,000 or 50,000 ppm (equivalent to 0, 155, 310, 625, 1250 or 2500 mg/kg bw/day) of chlorendic acid for 14 days. Mortality was observed at the highest dose. No treatment related gross observations were reported at necropsy. Histological examinations were not performed (NTP 1987).

In a repeat dose study conducted in accordance with NTP test guidelines, B6C3F1/N mice (n=10/sex/dose) were fed a diet containing 0, 1250, 2500, 5000, 10,000 or 20,000 ppm (equivalent to 0, 125, 250, 500, 1,000, 2,000 mg/kg bw/day) of chlorendic acid for 13 weeks. There were no effects on survival or food consumption. Mean body weights of all dosed mice were 7% lower than those of controls. No clinical signs of toxicity were reported. Microscopic

liver changes were observed in both males and females. Centrilobular cytomegaly, mitotic alteration or coagulative necrosis was observed in males at doses ≥ 125 mg/kg bw/day and in females at $\geq 1,500$ mg/kg bw/day (IPCS 1996 NTP 1987).

In a repeat dose study conducted in accordance with National Toxicology Program (NTP) Test Guidelines, B6C3F1/N mice (n=5/sex/dose) were fed a diet containing 0, 3100, 6200, 12 500, 25 000 or 50 000 ppm (equivalent to 0, 310, 620, 1,250, 2,500 or 5,000 mg/kg bw) chlorendic acid for 14 days. Mortality and weight loss was observed at the highest dose. No treatment related gross lesions were observed at necropsy. Histological examinations were not performed (IPCS 1996; NTP 1987).

Chlorendic anhydride

In a non-GLP compliant repeat dose toxicity study, similar to OECD TG 408, Charles River CD rats (15/sex/dose) were fed diets containing 0, 100, 500 or 2500 ppm (equivalent to 0, 5, 25 or 125 mg/kg bw/day) chlorendic anhydride for 90 days. Mortality was observed in females at highest dose only. Weight loss was observed in the two highest dose groups. Food consumption was decreased in males at ≥ 25 mg/kg bw/day and females at 125 mg/kg bw/day. Serum alkaline phosphatase activity was increased in both sexes throughout the study. The mean absolute heart weight was decreased in all treated males. The mean absolute and relative liver weight were decreased in all treated animals. No treatment related gross or microscopic lesions were observed in the highest dose group. Therefore, the NOAEL for the study is considered to be 125 mg/kg bw/day (ECHA 2022; IPCS 1996).

In a non-GLP compliant study similar to OECD TG 407, Crj:CD (SD) rats (5/sex/dose) were fed a diet containing 500, 1000, 2500, 5000, 10000 ppm chlorendic anhydride (purity-93.81%) (equivalent to 53, 108, 282, 529, 1113 mg/kg bw/day in males and 59,115, 287, 606,1242 mg/kg bw/day in females) for 28 days. Decreases in mean body weights were observed for all treated animals. The average food consumption was slightly reduced in males at the two highest doses. No mortality or treatment related gross lesions were observed at necropsy. The NOAEL was reported to be > 1113 mg/kg bw/day (males) and > 1242 mg/kg bw/day (females) (ECHA 2022; REACH n.d.).

Dermal

No data are available for chlorendic acid. Based on the available data for chlorendic anhydride these chemicals are not expected to cause severe systemic health effects following repeated dermal exposure. The observed effects of chlorendic anhydride were limited to local effects (skin irritation) or occurred at high doses only (stomach mucosal erosions and ulcerations).

In a non-GLP compliant, 3-week dermal study in NZW rabbits (n=4/sex/group), chlorendic anhydride powder moistened with saline was applied to clipped or abraded backs of rabbits at 0, 100, 500 or 2,500 mg/kg bw/day. No mortality was observed in any of the treated groups. Weight loss was observed in all animals in high dose groups. No treatment related changes were seen in urinalysis and haematological and biochemical investigations. Dermal irritation was observed at all doses. Based on microscopic examination, the skin response was characterised as 'mild'. Stomach mucosal erosions and ulcerations were found at necropsy in the two highest dose groups (IPCS 1996).

Inhalation

Based on the available data, these chemicals are not expected to cause serious systemic health effects following repeated inhalation exposure. The observed effects of chlorendic anhydride were limited to local effects including reversible ocular and nasal irritation and inflammation in the respiratory organs in rats treated with chlorendic anhydride.

In a non GLP compliant, 28-day inhalation study, similar to OECD 412, albino rats (n=5/sex/dose) were exposed to concentrations of 0, 0.134 and 0.273 mg/L chlorendic acid dust for 6 hours per day, 5 days/week. No mortality was observed during the study. Hepatocytomegaly of centrilobular hepatocytes was observed in male and female rats exposed to 0.134 and 0.273 mg/L of the chemical. Liver and brain weight was increased in both sexes exposed to 0.273 mg/L of the chemical (ECHA 2022).

In a 28 day inhalation study, Charles River CD rats (n=10/sex/dose) were exposed to 0, 0.11, 0.99 or 9.97 mg/L (nominal concentrations) of chlorendic anhydride dust for 6 hours per day, 5 days/week. All animals survived the study. Weight gain was observed in male rats exposed to 9.97 mg/L chlorendic anhydride. Relative liver weights of males were decreased in all treated groups. The absolute and relative weight of the thyroid glands were decreased in females of the two highest dose groups. All animals exhibited treatment related ocular and nasal irritation, salivation and alopecia following the daily exposures. Statistically significant differences in haematocrit and erythrocyte values (males and females), haemoglobin (males), leukocytes (females), alkaline phosphatase levels (males and females) and glucose and serum glutamic pyruvic transaminase levels (males) were observed. Dark red foci and dark red discolouration in the lungs and dark red or brown foci in the glandular part of the stomach were observed at necropsy in all treated groups. Treatment related microscopic changes of a haemorrhagic inflammatory nature in the lungs and of an inflammatory nature in the trachea, nasal turbinates and stomach mucosa were observed in all treated rats (ECHA 2022; IPCS 1996).

Genotoxicity

Based on the weight of evidence of the available data, chemicals in this group are not expected to be genotoxic. Although some positive results were observed in in vitro studies, in vivo studies were all negative.

In vitro

Chlorendic acid

Negative results were reported for the chemical in bacterial reverse mutation assays conducted in accordance with NTP test guidelines (similar to OECD TG 471) in *Salmonella typhimurium* strains:

- TA98, TA100, TA1535 and TA1537 with and without metabolic activation at concentrations up to 7690 µg/plate (IPCS 1996)
- TA98, TA100, TA1535 and TA1537 and TA 1538 with and without metabolic activation at concentrations up to 7500 µg/plate (IPCS 1996).

Mainly negative results were reported following in a microscreen prophage-induction assay with *Escherichia coli* at seven dose levels ranging from 0.4 to 25.7 mM, with and without metabolic activation. A single positive reaction was reported at the highest dose level with metabolic activation (IPCS 1996).

Positive results were reported for the chemical in:

- a L5178Y/TK+/- mouse lymphoma assay in the absence of S9 activation at concentrations 1300-1700 µg/mL. The highest (cytotoxic) dose showed a positive effect; an increase of total mutant clones, relative total growth depression and increase in mutation frequency (IPCS 1996; NTP 1987). The chemical was not tested in presence of S9. Similar findings were reported in another study (IPCS 1996)
- a standard transformation assay using BALB/c-3T3 cells without exogenous activation at concentrations of 2–4 mM (IPCS 1996)
- an in vitro micronucleus test (OECD TG 487) in human lymphocytes with and without metabolic activation at concentrations 0–2000 µg/mL (ECHA 2022).

Chlorendic anhydride

Negative results were reported for the chemical in:

- a bacterial reverse mutation assay conducted in accordance with NTP test guidelines (similar to OECD TG 471) in *S. typhimurium* TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation at concentrations up to 500 µg/plate (IPCS 1996)
- a chromosome recombination assay (OECD TG 481) in *Saccharomyces cerevisiae* (yeast) tester strain *D4*, exposed to the chemical at doses up to 500 µg/plate *with and without* metabolic activation (IPCS 1996)
- L5178Y/TK+/- mouse lymphoma assay at concentrations up to 0.24 mg/ml without, and up to 0.32 mg/ml with, an S9 activation system (IPCS 1996)
- a standard transformation assay using BALB/c-3T3 cells without exogenous activation at concentrations of 0.005-0.078 mg/ml. Significant increase in transformation frequency was observed at 0.01 mg/ml, however, it was regarded as non-treatment related (IPCS 1996).

Positive results were reported in unscheduled DNA synthesis assay in human WI-38 cells at dose levels up to 0.5 mg/ml (IPCS 1996).

In vivo

Chlorendic acid

Negative results were reported for the chemical in:

- a DNA damage study in SD rats administered two doses of the chemical at 159 mg/kg bw by gavage (IPCS 1996)
- a sex-linked recessive lethal (SLRL) test in *Drosophila melanogaster* similar to OECD TG 477 at doses of 2000 and 15,000 mg/kg bw. (IPCS 1996)
- a non-guideline, non-GLP compliant replicative DNA synthesis assay in (male rats), at doses of 450 or 900 mg/kg bw by oral application or subcutaneous injection (IPCS 1996)
- a GLP compliant, combined mammalian erythrocyte micronucleus test (OECD TG 474) and in vivo mammalian alkaline comet assay (OECD TG 489) SD (CrI:CD(SD)/rats) (n=6 male/dose) at doses of 175, 350 and 700 mg/kg bw (ECHA 2022).

Chlorendic anhydride

Negative results were observed in a non-GLP compliant dominant lethal assay similar to OECD TG 478, CD-1 mice (n=20/male/dose) at doses of 0, 22, 74 or 223 mg/kg (IPCS 1996).

In silico

No alerts were identified for both chemicals in vitro mutagenicity in bacteria (Ames) in the knowledge based expert system, DEREK Nexus, version 6.0.1 (Lhasa Limited). There were negative predictions for in vitro mutagenicity for both chemicals in SARAH Nexus, version 3.0.0 (Lhasa Limited) and OASIS-TIMES.

Carcinogenicity

Based on the available data, chemicals in this group are considered to be carcinogenic following oral exposure. Chlorendic acid exposure (via diet) resulted in benign and malignant tumours in multiple organs and in both sexes of rats and in male mice. In rats, neoplastic lesions were found in the liver of both sexes and in lungs and pancreas of males. Neoplastic lesions of the liver and lungs were found in male mice which metastasised to the lung. Given the structural similarity and the ability of chlorendic anhydride to hydrolyse to chlorendic acid both of these chemicals are considered to have carcinogenic potential for humans, warranting hazard classification as Cat. 1B carcinogen.

In a GLP compliant, 2 year carcinogenicity study conducted according to National Toxicology Program (NTP) test guidelines, F344/N rats (n=50/sex/dose) were fed a diet containing 0, 620 or 1250 ppm chlorendic acid (equivalent to approximately 27 and 56 mg/kg bw for males, and 39 and 66 mg/kg bw for females).

Survival and food consumption of treated rats were similar to those of the controls. Mean body weight of treated high dose males and females were decreased. There was no evidence of the chemical effect on physical appearance or behaviour (NTP 1987).

Observations of neoplastic lesions included statistically significant increased incidences in:

- liver neoplastic nodules in both sexes (males at 620 and 1250 ppm, females at 1250 ppm)
- hepatocellular carcinoma in females at 1250 ppm
- acinar cell adenoma of the pancreas in males at 1250 ppm
- alveolar or bronchiolar adenoma in males at 1250 ppm).

In a GLP compliant, 2 year carcinogenicity study conducted according to National Toxicology Program (NTP) test guidelines, B6C3F1/N mice (n=50/sex/dose) were fed a diet containing 0, 620 or 1250 ppm chlorendic acid (equivalent to approximately 89 and 185 mg/kg bw/day for males and 100 and 207 for females mg/kg bw per day) for 103 weeks. Survival and food consumption of treated mice were similar to those of the controls. Mean body weight of treated high dose males and females were decreased. No clinical signs of toxicity were observed in treated mice (NTP 1987).

Hepatocellular adenomas, hepatocellular carcinomas, and hepatocellular adenomas or carcinomas (combined) in male mice occurred with significant positive trends. The increased incidences of hepatocellular adenomas in high dose males and of hepatocellular carcinomas and hepatocellular carcinomas or adenomas (combined) in dosed males were statistically significant. Hepatocellular carcinomas metastasised to the lung in a dose dependent manner. Alveolar/bronchiolar adenomas and alveolar/bronchiolar adenomas or carcinomas

(combined) in female mice occurred with significant positive trends, although statistical significant increases were not noted.

In an initiation promotion assay in rat liver, groups of male and female F344 rats were given a single oral dose of 10 mg/kg bw of diethylnitrosamine followed by a 70% partial hepatectomy 24 hours later. After a 2 week recovery period, animals were fed a diet containing 0, 620 or 1250 mg/kg diet (equivalent to 0, 31 and 62.5 mg/kg bw/day) chlorendic acid for 6 months. The number of altered hepatic foci were significantly increased at both dose levels, indicating that the chemical may be able to promote tumorigenesis. Tumour promoting activity of chlorendic acid was supported by another short term study in neonatal rats (IPCS 1996).

The IARC concluded that chlorendic acid is possibly carcinogenic to humans (Group 2B) based on sufficient evidence of cancer in experimental animals (IARC 1990).

The USA Department of Health and Human Services concluded that chlorendic acid is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals (NTP 2021).

Reproductive and developmental toxicity

There is insufficient data to determine whether chemicals in this group affect fertility. Repeat dose toxicity studies indicate that these chemicals do not cause damage to reproductive organs. There was no evidence of tissue alterations in the testes and ovaries in the highest dose groups in either mice (2000 mg/kg bw/day) or rats (500 mg/kg bw/day) in 13 week oral repeated dose toxicity studies (see **Repeated dose toxicity: oral**).

There is uncertainty regarding the potential of chlorendic anhydride to cause developmental toxicity. Only one study is available. While increased post implantation losses were reported in the two highest dose groups, the magnitude of these increases in individual animals were not reported. In the substance evaluation conclusion document for chlorendic anhydride (ECHA 2022) it was also pointed out that this study may not have been conducted to the limit dose, which could prevent the differentiation of effects between the dams and the offspring

In a non-GLP compliant, prenatal developmental toxicity study similar to OECD TG 414, pregnant Charles River CD rats (25/dose) were administered chlorendic anhydride by gavage once daily at 0, 25, 100 or 400 mg/kg bw/day on gestational days (GD) 6–15. Dams were sacrificed on GD 20 and the fetuses examined.

There was a slight increase in matted fur red nasal discharge and anogenital staining in dams at 400 mg/kg bw/day. Dam bodyweights were decreased during first three treatment days but overall, there was an increase in body weight. Changes in foetal sex ratio was observed at 25 mg/kg bw/day. However, this was not considered treatment related. An increased mean number of post-implantation losses at 100 or 400 mg/kg bw/day was observed. However, the significant increase in the mean number of post implantation losses in the 100 and 400 mg/kg bw/day dose groups was only slightly higher than the historical control mean, and magnitudes for individual animals were not reported. No significant differences were observed between treated and control animals in the following: mean number of corpora lutea, viable or non-viable fetuses, mean foetal body weights and foetal malformations (IPCS 1996). The maternal no observed adverse effect level (NOAEL) was 100 mg/kg bw/day based on the significant decreased maternal body weight and weight gain at 400 mg/kg/day. The reported NOAEL for foetal effects (increased number of post-implantation loss at 400 and 100 mg/kg-bw/day) was 25 mg/kg bw/day (ECHA 2022).

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