Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Phenolic benzotriazoles

Evaluation statement

1 October 2024

Draft

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AICIS evaluation statement

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Phenolic benzotriazoles

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Reason for the evaluation

Evaluation Selection Analysis indicated a potential human health risk.

Parameters of evaluation

Chemicals in this group are structurally related phenolic benzotriazoles that are listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation statement is a human health risk assessment for all identified industrial uses of the chemicals in this group.

These chemicals have been assessed as a group as they are structurally similar and have similar use patterns.

In this evaluation the chemicals will be referred to as:

- drometrizole (CAS No. 2440-22-4)
- bumetrizole (CAS No. 3896-11-5)
- octrizole (CAS No. 3147-75-9)
- UV-234 (CAS No. 70321-86-7)
- UV-571 (CAS No. 23328-53-2).

They may also be referred to by their CAS name or number.

Summary of evaluation

Summary of introduction, use and end u`se

The phenolic benzotriazoles are used internationally as UV absorbers or light stabilisers in a variety of consumer and commercial products. Based on Australian and international use data, drometrizole, octrizole and bumetrizole have some, but not extensive, use in personal care products (cosmetics). Typical use concentrations are <1% although bumetrizole has reported use, up to 10% in nail products. The three chemicals and UV-234 also have reported use in domestic products including adhesives and sealants, paints and coatings and scented candles.

The chemicals have a range of commercial uses and site-limited uses such as in the manufacture of rubber and plastic products including food packaging materials.

Human health

Summary of health hazards

Identified health hazards are based on available data for chemicals in this evaluation. For sensitisation and repeated dose toxicity, these chemicals have been sub-grouped for the purposes of read-across based on the substitution pattern on the phenol ring.

Based on the available data, most of the chemicals are expected:

- to have low acute oral and dermal toxicity
- to be not irritating to the skin and eyes
- not to have genotoxic potential.

Although limited data are available for carcinogenicity, reproductive and developmental toxicity, there was no evidence of effects in the available studies.

Chemicals with a methyl group substituent in the para position (drometrizole, bumetrizole, UV-571 and CAS No.101697-89-6) have structural alerts for protein binding via Michael addition when either autoxidation or skin metabolism is simulated.

Based on available data, drometrizole is a skin sensitiser. Drometrizole shows positive response rates of ≥30% following intradermal induction at >1% in a guideline guinea pig maximisation test (GPMT). Negative results were reported in 2 LLNA when tested to 2%. There is evidence from human data that the chemical acts as a skin sensitiser. However, contact allergy to the substance appears to be rare.

Available data for bumetrizole do not show evidence of sensitisation and drometrizole is expected to be more dermally available than the other chemicals. Therefore, read-across from drometrizole to other chemicals with a methyl group substituent in the para position is not considered appropriate. However, effects following autoxidation cannot be ruled out. The available data indicate that chemicals with a branched alkyl substituent in the para position are not skin sensitisers.

The available data indicate a difference in the systemic toxicities between chemicals in the group. The liver is the target organ for toxicity for phenolic benzotriazoles. However, the toxicity level and mode of action varies depending on the type and degree of substitution.

Based on the available data, these chemicals are not expected to cause effects at doses warranting classification (100 mg/kg bw/day). Kidney toxicity is observed with some chemicals but typically at higher doses than when liver toxicity is observed.

Limited inhalation data are available. Based on the available data, the chemical drometrizole may have moderate acute inhalation toxicity. However, data are not sufficient to warrant classification.

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

Hazard classifications relevant for worker health and safety

The chemical drometrizole (CAS No. 2440-22-4) satisfies the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for worker health and safety as follows.

Health hazards	Hazard category	Hazard statement
Skin sensitisation	Skin sens. 1B	H317: May cause an allergic skin reaction

All other chemicals do not satisfy the criteria for classification according to the GHS. This evaluation does not consider classification of physical hazards and environmental hazards.

Summary of health risk

Public

Based on the available use information, the public may be exposed to these chemicals, particularly drometrizole and bumetrizole:

- in personal care products (cosmetics)
- from incidental skin and eye contact if used in domestic products.

Typical use concentrations are <0.1%, although higher concentrations have been identified.

These chemicals have potential to cause potential systemic long term effects (effects on the liver). Using a worst case scenario model, the margin of exposure (MOE) for use in cosmetics was >100, indicating that these chemicals are unlikely to pose a risk of adverse systemic effects. As exposures to the public from other sources (use of domestic products or potential migration from articles) is expected be lower to that estimated from cosmetics, it is unlikely that there is a risk to the public relating to systemic effects.

Although drometrizole is a skin sensitiser, contact allergy to the substance appears to be rare based on the available data. Given data indicating drometrizole is not extensively used, the low concentrations typically used in personal care and domestic products, and toxicology data showing limited sensitisation potential at these concentrations, 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 chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the sensitisation effects (drometrizole), potential systemic effects at higher doses and uncertainty of inhalation effects, 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 risk** section).

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) updates the Hazardous Chemical Information System (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.

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

- using local exhaust ventilation to prevent the 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 chemicals.

For drometrizole these control measures should be supplemented with:

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

Measures required to eliminate or manage risk arising from storing, handling and using these hazardous chemicals depend on the physical form and the manner in which the chemicals are used.

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 SWA 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 proposes to be satisfied that the identified risks to human health from the introduction and use of these 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

Phenolic benzotriazoles are a class of UV light absorbers. For the purpose of this evaluation, these chemicals have been assessed as a group based on their structural similarity (see **Chemical identity**) and their similar uses.

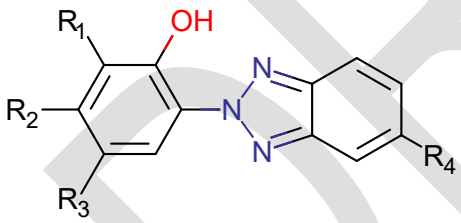
The chemicals have been sub-grouped for the purposes of read across based on the substitution pattern on the phenol ring (see **Chemical identity**).

Some phenolic benzotriazoles listed on the Inventory have previously been assessed under the former National Industrial Chemicals Notification and Assessment Scheme (NICNAS). These chemicals are not being reevaluated but information on some of these chemicals is included in the evaluation for read across purposes.

Chemical identity

The phenolic benzotriazoles in this group contain a substituted phenol attached to a benzotriazole structure at the 2-position (see **Table 1**). These chemicals contain mono- and di-substituted phenols that have alkyl or aryl substituents at *ortho*, *meta* and/or *para* positions. Most of the disubstituted chemicals have various substituents at both the *ortho* and *para* positions of the phenolic ring, except for CAS No. 101697-89-6 which has a substituent in the *meta* position instead of the *ortho* position. Two of the disubstituted chemicals have a chlorine substituent at the 5 position of the benzotriazole ring.

Table 1 – Summary of substituents on the phenolic benzotriazoles in this evaluation



CAS number	Phenol substitution	*ortho* (R_1)	*meta* (R_2)	*para* (R_3)	R_4
2440-22-4	mono	H	H	methyl	H
3147-75-9	mono	H	H	1,1,3,3-tetramethylbutyl	H
3147-76-0	mono	H	H	*tert*-butyl	H
3864-99-1	di	*tert*-butyl	H	*tert*-butyl	Cl
3896-11-5	di	*tert*-butyl	H	methyl	Cl
23328-53-2	di	dodecyl	H	methyl	H
70321-86-7	di	1-methyl-1-phenylethyl	H	1-methyl-1-phenylethyl	H

CAS number	Phenol substitution	*ortho* (R_1)	*meta* (R_2)	*para* (R_3)	R_4
101697-89-6	di	H	*tert*-butyl	methyl	H

CAS number 2440-22-4

CAS name Phenol, 2-(2*H*-benzotriazol-2-yl)-4-methyl-

Molecular formula $C_{13}H_{11}N_3O$

Associated names Drometrizole

2-(2*H*-Benzotriazol-2-yl)-*p*-cresol

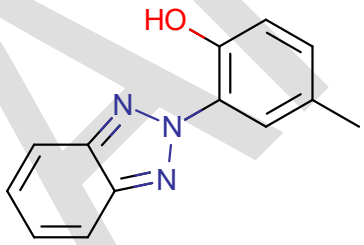
2-(2*H*-Benzotriazol-2-yl)-4-methylphenol

2-(2'-Hydroxy-5'-methylphenyl)benzotriazole

Molecular weight (g/mol) 225.25

SMILES (canonical) OC1=CC=C(C=C1N2N=C3C=CC=CC3=N2)C

Structural formula



CAS number 3147-75-9

CAS name Phenol, 2-(2*H*-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)-

Molecular formula $C_{20}H_{25}N_3O$

Associated names Octrizole

UV 329

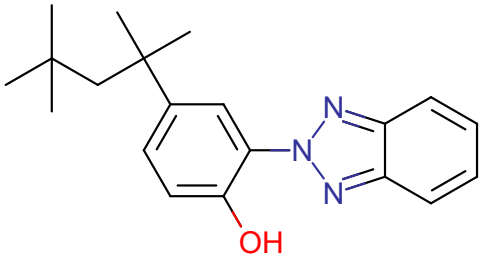
2-(2*H*-Benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol

2-(2-Hydroxy-5-*tert*-octylphenyl)benzotriazole

Molecular weight (g/mol) 323.43

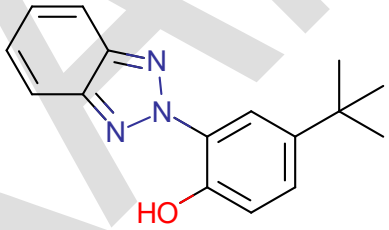
SMILES (canonical) OC1=CC=C(C=C1N2N=C3C=CC=CC3=N2)C(C)(C)CC(C)(C)C

Structural formula

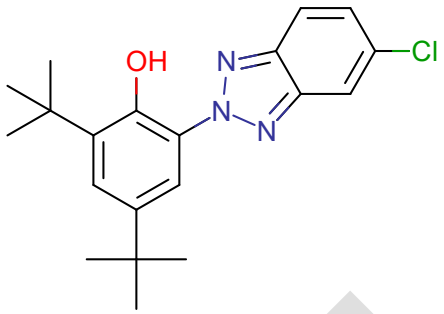


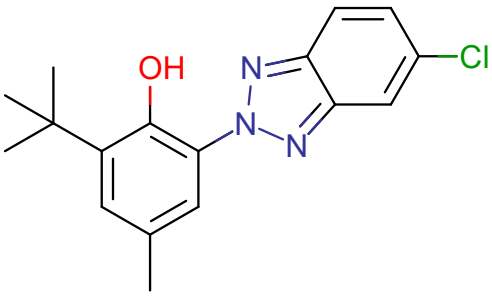
CAS number	3147-76-0
CAS name	Phenol, 2-(2*H*-benzotriazol-2-yl)-4-(1,1-dimethylethyl)-
Molecular formula	$C_{16}H_{17}N_3O$
Associated names	2-(2*H*-Benzotriazol-2-yl)-4-*tert*-butylphenol 2-(2-Hydroxy-5-*tert*-butylphenyl)benzotriazole
Molecular weight (g/mol)	267.33
SMILES (canonical)	OC1=CC=C(C=C1N2N=C3C=CC=CC3=N2)C(C)(C)C

Structural formula



CAS number	3864-99-1
CAS name	Phenol, 2-(5-chloro-2*H*-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)-
Molecular formula	$C_{20}H_{24}ClN_3O$
Associated names	UV 327 2,4-Di-*tert*-butyl-6-(5-chlorobenzotriazol-2-yl)phenol 2-(2'-Hydroxy-3',5'-di-*tert*-butylphenyl)-5-chlorobenzotriazole
Molecular weight (g/mol)	357.88

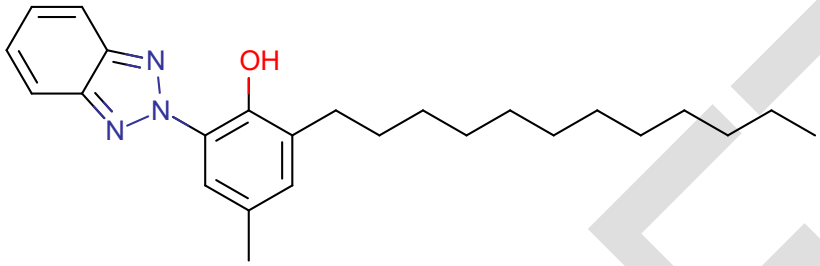
SMILES (canonical)	ClC=1C=CC2=NN(N=C2C1)C3=CC(=CC(=C3O)C(C)(C)C)C(C)(C)C
Structural formula	

CAS number	3896-11-5
CAS name	Phenol, 2-(5-chloro-2*H*-benzotriazol-2-yl)-6-(1,1-dimethylethyl)-4-methyl-
Molecular formula	$C_{17}H_{18}ClN_3O$
Associated names	Bumetrizole UV 326 2-(2'-Hydroxy-3'-*tert*-butyl-5'-methylphenyl)-5-chlorobenzotriazole
Molecular weight (g/mol)	315.80
SMILES (canonical)	ClC=1C=CC2=NN(N=C2C1)C3=CC(=CC(=C3O)C(C)(C)C)C
Structural formula	

CAS number	23328-53-2
CAS name	Phenol, 2-(2*H*-benzotriazol-2-yl)-6-dodecyl-4-methyl-
Molecular formula	$C_{25}H_{35}N_3O$

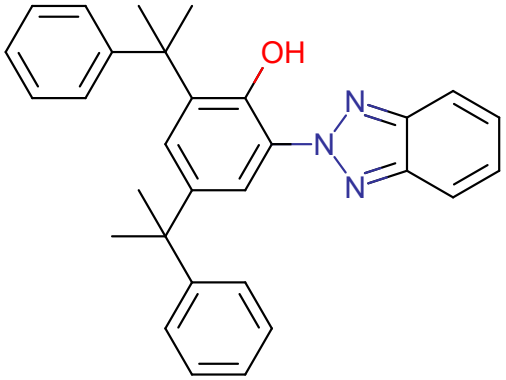
Associated names	UV 571 *p*-Cresol, 2-(2*H*-benzotriazol-2-yl)-6-dodecyl- 2-(2-Hydroxy-3-dodecyl-5-methylphenyl)benzotriazole
Molecular weight (g/mol)	393.57
SMILES (canonical)	OC=1C(=CC(=CC1CCCCCCCCCCCC)C)N2N=C3C=CC=CC3=N2

Structural formula



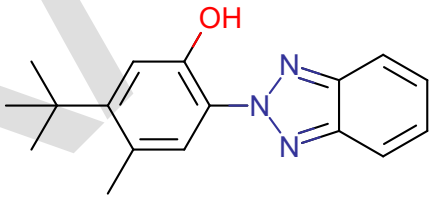
CAS number	70321-86-7
CAS name	Phenol, 2-(2*H*-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)-
Molecular formula	$C_{30}H_{29}N_3O$
Associated names	UV 234 2-(2*H*-Benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol 2-[2'-Hydroxy-3',5'-bis(α,α-dimethylbenzyl)phenyl]benzotriazole
Molecular weight (g/mol)	447.57
SMILES (canonical)	OC=1C(=CC(=CC1C(C=2C=CC=CC2)(C)C)C(C=3C=CC=CC3)(C)C)N4N=C5C=CC=CC5=N4

Structural formula



CAS number	101697-89-6
CAS name	Phenol, 2-(2*H*-benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-methyl-
Molecular formula	$C_{17}H_{19}N_3O$
Associated names	2-(2*H*-Benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-methylphenol
Molecular weight (g/mol)	281.35
SMILES (canonical)	OC=1C=C(C(=CC1N2N=C3C=CC=CC3=N2)C)C(C)(C)C

Structural formula



Relevant physical and chemical properties

Available data indicates that chemicals in this group are powders. The melting points for most of the chemicals are similar, ranging from 92.6 to 148.8°C with reported vapour pressures <0.0001 Pa. Drometrizole has the highest reported water solubility (0.173mg/L) and lowest reported octanol-water coefficient (4.2). Although data are not available for all chemicals in this group the water solubility for the other chemicals were <0.005 mg/L at 20°C and the log K_{OW} were >6 at 20–25°C. The pKa range from 8.07 to 9.64 (Government of Canda 2021; REACH n.d.-a–e; CAS n.d.).

Introduction and use

Australia

Limited Australian specific information is available about the introduction, industrial use and end use of the chemicals.

Based on Australian commercial website information drometrizole (CAS No. 2440-22-4) and bumetrizole (CAS No. 3896-11-5) are ingredients in personal care products (cosmetics) including nail polish, lip gloss and hair products. Octrizole (CAS No. 3147-75-9) is an ingredient in scented candles as reported in publicly available information.

Drometrizole also has a reported non-industrial use including in sunscreen (TGA n.d.).

International

The following international uses have been identified through:

- Registration, Evaluation, Authorisation and Restriction of Chemicals dossiers (REACH n.d.-a–e)
- the Organisation for Economic Cooperation and Development SIDS Initial Assessment Report (OECD 2017)
- Government of Canada Assessment (Government of Canada 2021)
- Galleria Chemica (Chemwatch n.d.)
- Substances and Preparations in the Nordic countries (SPIN n.d.)
- the European Commission Cosmetic Ingredients and Substances (CosIng) database (EC n.d.)
- IFRA Transparency List (IFRA n.d.)
- United States Environmental Protection Agency (US EPA) Chemical Data Reporting 2012, 2016 and 2020
- Consumer Products Information Database (DeLima Associates n.d.)
- US Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary (Personal Care Products Council n.d.)
- Cosmetic Ingredient Review for drometrizole (CIR 2008).

Three chemicals (drometrizole; octrizole; bumetrizole) are included in the list of fragrance ingredients used in consumer goods published by the IFRA (IFRA n.d.).

The chemicals also have reported cosmetic uses and function as light stabilisers. Drometrizole has previous reported use in a range of products categories including bath, fragrances, colouring and non-colouring hair care, manicuring, shaving, skin care, and suntan preparations. The majority of uses were in nail products followed by hair shampoos. Typically reported concentrations were <0.1% with a maximum concentration of 1%. Reported use frequency in the United States of America (USA) has significantly declined over time. Octrizole has identified use in soaps at a concentration of 0.1%. Bumetrizole has reported use in make-up such as blushers and lip make-up at a concentration of 0.1% and nail care products such as nail polish and nail glue at a concentration of 10%.

The chemicals have reported commercial uses in:

- adhesives and sealants

- binding agents in paints, lacquers and varnishes
- cleaning and washing agents
- lubricants and additives
- flame retardants and extinguishing agents
- corrosion inhibitors
- construction materials
- sealing and caulking materials
- surface treatment
- metal treatment and coating
- printing and publishing recorded media
- automotive fuel.

Some commercial uses may also be used in domestic applications. Drometrizole has been identified in adhesive/sealants at a concentration of 1%. Octrizole has reported use in scented candles and UV 234 (CAS No. 70321-86-7) has reported use in paints at 0.1%.

These chemicals have reported site limited uses including in the manufacture of:

- rubber and plastic products including food packaging materials
- transport equipment and vehicles
- paper products
- chemicals and chemical products
- fabricated metal products and basic metals.

Drometrizole has reported non-industrial uses in agricultural products, insecticides, pest control and dental adhesives.

Existing Australian regulatory controls

AICIS

No specific controls are currently applicable to these chemicals.

Public

No specific controls are currently applicable to most chemicals in this group.

Workers

These chemicals are not listed as hazardous on the Safe Work Australia (SWA n.d.) Hazardous Chemicals Information System (HCIS). No exposure standards are available for these chemicals in Australia (SWA).

International regulatory status

Exposure standards

No specific exposure standards were identified for these chemicals

Canada

A draft screening assessment of a group of benzotriazoles including the chemicals (CAS Nos. 3147-75-9; 3896-11-5; 70321-86-7) concluded that this group of benzotriazoles do not meet the criteria under paragraphs 64(a) or (b) of the Canadian Environmental Protection Act, 1999 (CEPA) as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends. These chemicals also do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health (Government of Canada 2021).

Europe

European Union (EU) food contact materials (FCM) and articles regulation has listed the chemicals (CAS No. 2440-22-4; 3864-99-1; 3896-11-5) with the total specific migration limit (SML(T)) of 30 mg/kg as the sum of substances in group, and the chemical (CAS No. 70321-86-7) with a SML of 1.5 mg/kg (see Annex 1 – Authorised substances; ECHA 2024a).

Switzerland's Ordinance of the Federal Department of Home Affairs (FDHA) on materials and articles intended to come into contact with foodstuffs has listed the chemicals (CAS No. 2440-22-4; 3864-99-1; 3896-11-5) with the SML(T) of 12 mg/kg, and the chemical (CAS No. 70321-86-7) with a SML of 1.5 mg/kg, and unspecified SML for other 2 chemicals (CAS No. 3147-75-9; 3147-76-0) (see Annex 10 – List of permitted substances for the production of packaging inks, and related requirements; Switzerland FDHA 2024).

United States of America

Code of Federal Regulations Title 21 has listed the following chemicals with concentration limits for use in polymers or resins in contact with certain types of food under some identified conditions of use (see Section 178.2010 – Antioxidants and/or stabilizers for polymers; US FDA 2024):

- Drometrizole at levels not to exceed 0.25%–0.50% by weight
- UV-234 (CAS No. 70321-86-7) at levels not to exceed 0.5%–3.0% by weight
- Octrizole at levels not to exceed 0.5% by weight.

The Cosmetic Ingredient Review (CIR) Expert Panel determined that given its low dermal penetration (insoluble in water) the use of drometrizole at concentrations of ≤1% in cosmetics is considered safe (CIR 2008).

Human exposure

Public

There will be exposure of the public to certain members of the group, particularly drometrizole and bumetrizole, through the use of personal care products (cosmetics) and domestic products. The main route of exposure is expected to be dermal. These chemicals are not expected to be volatile due to their low vapour pressures.

Data on typical use patterns of product categories containing the chemicals were derived from published sources (SCCS 2023) and are shown in Table 2. For the purposes of public exposure assessment, Australian use patterns for the various product categories are assumed to be similar to those in Europe. In calculating exposure estimates the following assumptions were applied:

- absorption (A) rate (oral and dermal) of 100% (worst-case scenario)
- a lifetime average body weight (BW) of 60 kg
- a retention factor of 1 is used if the product not removed or washed off immediately
- products were chosen based on highest frequency of use, reported personal care products in Australia and highest product amount for reported international uses (moisturiser)
- concentration based on the maximum reported concentrations reported in certain products for drometizole and bumetrizole (CIR 2008; Government of Canada 2021)
- The skin around the nails has a surface area of about 4 cm^2, corresponding to about 9% of the total area of nails and skin and; thereby, contributing to the systemic dose. A typical application of liquid nail polish contains 2000 mg of product. Therefore, it is estimated that the amount (A) of nail polish in direct contact with skin is 9% × 2000 mg/day = 180 mg/day (Danish EPA 2008).

Table 2. Daily systemic exposure to cosmetic and personal care products for drometrizole

Type of exposure	Product	Amount (mg/day)	C (%)	RF (unitless)	A (%)	Daily systemic exposure (mg/kg bw/day)
Hair care	Shampoo	10460	0.1	0.01	100	0.0017
Skin care	Moisturiser	7820	0.1	1	100	0.1303
Make up	Lipstick/lip salve	57	0.1	1	100	0.0009
Nail care	Nail polishes	180*	10	1	100	0.3000
Total						0.433

Daily systemic exposure = (A × C × RF × A)/BW
(A = amount applied; RF = retention factor; A = absorption; BW = body weight, C = chemical concentration)
*Danish EPA 2008

The above calculation estimates a worst case scenario daily exposure value for the chemicals.

Health hazard information

Toxicokinetics

Based on the available physicochemical, toxicological and toxicokinetic data for these chemicals (drometrizole and the structurally related chemical UV-320), these chemicals in this group are expected to be absorbed after oral exposure. Dermal absorption data for any of these chemicals are not available. Drometrizole has the lowest molecular weight and log K_{ow} and therefore is expected to have the highest dermal bioavailability.

The chemical bond between the benzotriazole group and the aromatic ring is likely to be very strong and able to resist hydrolysis. The aliphatic group side chains of the phenol ring are also able to resist hydrolysis (ECHA 2014). Therefore, these chemicals are unlikely to be metabolised. This is supported by data on the structurally related chemical UV-320.

Drometrizole (CAS No. 2440-22-4)

In a toxicokinetic study (similar to OECD TG 417), radiolabelled drometrizole was rapidly absorbed and eliminated within 48 hours (91%) following gavage administration of 10 mg/kg bw in 4 Tif:RAIf (SPF) male rats. About 9% of the dose was found in the urine between 0–6 hours and peaked at 56% between 6–24 hours. After 7 days, elimination was almost complete with 69–73% in the urine and 25–27% in the faeces. Distribution to the kidney, aorta, and liver was minimal (0.10–0.22 µg/g) (CIR 2008; REACH n.d.-a).

In another toxicokinetic study (OECD TG 417), radiolabelled drometrizole was administered by gavage to Sprague Dawley (SD) rats (4/sex/dose) as traces of another substance at near 0 and 0.05 mg/kg bw. Distribution after 6 hours was 64–66% (low dose) and 65–69% (high dose) in the gastrointestinal tract (GIT), 2–3% in the kidney and liver, and negligible in whole blood, plasma, and all other tissues. There were no differences between sexes (REACH n.d.-a).

In humans, drometrizole was also quickly absorbed, conjugated, and excreted in the urine within 6 hours (79%) after a single oral dose of 0.3 mg/kg bw in 3 volunteers (2 males and 1 female). Elimination half-lives in blood and urine were 1.3 hours and 0.7 hours in acute phase, and 7.7 hours and 6.6 hours afterwards, respectively (REACH n.d.-a).

UV-320 (CAS No. 3846-71-7)

The structurally related chemical UV-320 (CAS No. 3846-71-7) was shown to be well absorbed but not metabolised in a gavage toxicokinetic study (OECD 2017).

Acute toxicity

Oral

Based on the available data, chemicals in this group are expected to have low acute oral toxicity.

Drometrizole (CAS No. 2440-22-4)

The median lethal dose (LD50): >5000 mg/kg bw in rats and mice in 6 studies (CIR 2008; REACH n.d.-a)

- In an acute oral toxicity study (similar to OECD TG 423 Acute Toxic Class Method), mortalities in rats were (5/10) at 10000 mg/kg bw between 48 hours and 14 days. Surviving animals showed sedation, dyspnoea, curved position and ruffled fur within 2 hours after treatment at ≥4640 mg/kg bw and recovered within 8–10 days.
- In an acute oral toxicity study (similar to OECD TG 420 Fixed Dose Procedure), mice showed ventral position and increased respiration at 5000 mg/kg bw, and 1/5 each died at 2500 and 5000 mg/kg bw.

Bumetrizole (CAS No. 3896-11-5)

In a GLP compliant acute oral toxicity study (OECD TG 423), Crj:CD(SD) female rats (n=6) were treated a single dose (2000 mg/kg bw) of bumetrizole. The reported LD50 was >2000 mg/kg bw (REACH n.d.-b).

A number of other LD50 values for the chemical (CAS No. 3896-11-5) have been reported (REACH n.d.-b):

- >7750 mg/kg bw in rats
- >5000 mg/kg bw in mice
- >5000 mg/kg bw in rats
- >5000 mg/kg bw in Wistar rats.

LD50 values reported for the other group members (REACH n.d.-c–e) were:

- >10,000 mg/kg bw in male rats (CAS No. 3147-75-9)
- >2000 mg/kg bw in female Wistar rats (CAS No. 3147-76-0)
- >7750 mg/kg bw in rats (CAS No. 70321-86-7).

Dermal

Based on the available data, chemicals in this group are expected to have low acute dermal toxicity.

The following LD50s were reported for (REACH n.d.-a–e):

- Drometrizole (CAS No. 2440-22-4): >2000 mg/kg bw in rats and rabbits, and >3000 mg/kg bw in guinea pigs
- >5000 mg/kg bw in male rabbits (CAS No. 3147-75-9)
- >2000 mg/kg bw in rats (CAS No. 3896-11-5)
- >2000 mg/kg bw in rats (CAS No. 70321-86-7).

Inhalation

Limited data are available. Based on the available data, the chemical drometrizole may have moderate acute inhalation toxicity but data are not sufficient to warrant classification.

Drometrizole (CAS No. 2440-22-4)

Three studies available that are reported to be similar to OECD TG 403 (REACH n.d.-a):

- median lethal concentration (LC50) >0.59 mg/L/4 hours (aerosol) (82% particles <7 µm). Mortalities in rats (M 2/9 and F 2/9) within 24 hours. Surviving animals showed tachypnoea, asynchronous extremities, lateral or ventral position and apathy after exposure, and recovered within 48 hours.
- LC50 >1.42 mg/L/4 hours and >48.9 mg/L/4 hours (dust) (time extrapolated from >163 mg/L/1.2 hours). No effects or mortalities were reported in these 2 studies.

Corrosion/Irritation

Skin irritation

Based on the available data, chemicals in this group are not considered to be skin irritants.

Drometrizole (CAS No. 2440-22-4)

In a skin irritation study, CFE rats (5/sex) were treated with 50% drometrizole in 0.5% carboxymethylcellulose for 24 hours under occlusive conditions and observed for 8 days. The following mean scores were reported for the animals: 0 for erythema and 0 for oedema. The chemical was not considered to be a skin irritant (REACH n.d.-a).

Octrizole (CAS No. 3147-75-9)

In a skin irritation study, 6 rabbits were treated with 0.5 g of the chemical (CAS No. 3147-75-9) for 24 hours under occlusive conditions. The following mean scores were reported for 6 animals: 0 for erythema and 0 for oedema. The chemical was not considered to be a skin irritant (REACH n.d.-c).

2-(2H-Benzotriazol-2-yl)-4-(1,1-dimethylethyl)phenol (CAS No. 3147-76-0)

In a GLP compliant in vitro skin corrosion assay conducted according to OECD TG 431, 25 mg in 50 µL distilled water the chemical (CAS No. 3147-76-0) was applied to reconstructed human epidermis EpiDerm™ for 3 and 60 minutes. The mean tissue viability was 98.4% and 104.3% after 3 and 60 minutes, respectively. Substances that reduce viability to less than 50% after 3 minutes are classified as corrosive. Therefore, the chemical is considered unlikely to have potential to cause corrosion in vivo following application (REACH n.d.-d).

Bumetrizole (CAS No. 3896-11-5)

In a skin irritation study, New Zealand White (NZW) rabbits (3/sex) were treated with the chemical (CAS No. 3896-11-5, 50% w/w) for 24 hours under occlusive conditions. Observations were recorded at 24, 48 and 72 hours and 7 days after patch removal. The following mean scores were reported for individual animals: 0.33 (for animals 1–5) and 1.33 (for animal 6) for erythema, and 0 (for animals 1–5) and 0.33 (for animal 6) for oedema. The reactions were fully reversible within 48 hours. The chemical was not considered to be a skin irritant (REACH n.d.-b).

In a skin irritation study, NZW rabbits (3/sex) were treated with the chemical (CAS No. 3896-11-5) (0.5 g) as a paste in polypropylene glycol/saline to intact and abraded skin under occlusive conditions for 24 hours. After the exposure period, the sites were washed and reactions were observed for 7 days. Some slight irritation was observed and was fully reversible in 72 hours. The chemical was not considered to be a skin irritant (OECD 2009).

Eye irritation

Based on the available data, chemicals in this group are not considered at most to cause slight eye irritation.

Drometrizole (CAS No. 2440-22-4)

In a non-guideline eye irritation study, drometrizole (100 mg) was instilled into the eyes of 6 rabbits (strain unspecified). The overall irritation scores reported at 1, 2, 3, 4 and 7 days respectively were: 2/110, 1/110, <1/110, <1/110 and 0/110. The mean scores reported were: conjunctival redness 1/20, corneal opacity 0/80 and iritis 0/10. The observed effects were fully reversible in 7 days. The chemical was not considered to be irritating to the eyes (REACH n.d.-a).

Drometrizole at 1% concentration in a nail polish was minimally to moderately irritating to rabbit eyes, if followed by rinsing, but mildly to severely irritating in unrinsed eyes (CIR 2008). The eye irritation potential of other ingredients in the formulation are unknown.

Octrizole (CAS No. 3147-75-9)

In a non-GLP compliant eye irritation study conducted similarly to OECD TG 405, 0.1 g of the chemical (CAS No. 3147-75-9) was instilled into 1 eye each of 6 rabbits (strain unspecified). The eyes were observed 24, 48 and 72 hours after treatment. The following mean scores were reported at 24, 48 and 72 hours: corneal opacity 0/4, iritis 0/2 and conjunctival redness 0/3. Chemosis score was not performed. The chemical was not considered to be irritating to the eyes (REACH n.d.-c).

2-(2H-Benzotriazol-2-yl)-4-tert-butylphenol (CAS No. 3147-76-0)

In a GLP compliant ex vivo eye corrosivity/irritation study conducted according to OECD TG 437, 0.75 mL of 20% w/v solution in sodium chloride 0.9% w/v of the chemical (CAS No. 3147-76-0) was applied to 3 bovine corneae per experiment. The mean in vitro irritancy score (IVIS) was 1.1 (IVIS >55 is regarded as serious eye damage and IVIS ≤3 is UN GHS No Category). Based on the criteria of the assay, the chemical did not meet the GHS criteria for classification (REACH n.d.-d).

Bumetrizole (CAS No. 3896-11-5)

In a non-GLP compliant eye irritation study conducted similarly to OECD TG 405, the chemical (CAS No. 3896-11-5) (40 mg) was instilled into one eye each of 6 albino rabbits. Reactions were observed for 72 hours. The following mean scores were reported at 24, 48 and 72 hours: corneal opacity 0/4, iritis 0/2 and conjunctival redness 0/3 (for animals 1-5) and 0.67/3 (for animal 6). Chemosis score was not reported. Mild conjunctivitis was observed in one animal and was fully reversible in 72 hours. The chemical was not considered to be an eye irritant (OECD 2009; REACH n.d.-b).

In a non-GLP compliant eye irritation study conducted similarly to OECD TG 405, the chemical (CAS No. 3896-11-5) was instilled into one eye each of 6 NZW rabbits. Reactions were observed for 72 hours. The following mean scores were reported at 24, 48 and 72 hours: corneal opacity 0/4 and iritis 0/2. Mean scores for animals 1, 2, 3, 4, 5 and 6 respectively were: conjunctival redness (out of 3) 0.33, 1, 0.33, 0.33, 0.67 and 0, chemosis (out of 4) 0.33, 0.67, 0, 0, 0.33 and 0. The observed effects were fully reversible in 72 hours. The chemical was not considered to be irritating to the eyes (REACH n.d.-b).

UV 234 (CAS No. 70321-86-7)

In a non-GLP compliant eye irritation study conducted similarly to OECD TG 405, 0.1 g of the chemical (CAS No. 70321-86-7) was instilled into 1 eye each of 6 Himalayan rabbits. The eyes were observed 1, 2, 3, 4, and 7 days after treatment. The eyes were washed in animals 1-3 but not in animals 4-6. Mean scores for animal 1 were: corneal opacity 0.66/4, conjunctival redness 0/3, and chemosis 0/4. Mean scores for animal 2 were: corneal opacity

0/4, conjunctival redness 0/3 and chemosis 0/4. Mean score for animal 3 was: corneal opacity 1.33/4. Mean scores for animals 4, 5 and 6 were: corneal opacity 0/4, conjunctival redness 0/3 and chemosis 0/4. The mean iritis score reported at 24, 48 and 72 hours for all animals was 0/2. The observed effects were fully reversible in 7 days. The chemical was not considered to be irritating to the eyes (REACH n.d.-e).

Observation in humans

Daily topical application of drometrizole at 1% for 8 weeks did not cause irritation or eczematous reactions in 300 patients (with or without dermatosis) (CIR 2008).

In a modified Draize-Shelanski-Jordan repeat-insult patch test to evaluate irritation and sensitisation, nail polish containing 0.5% drometrizole was applied topically to the upper back of 148 subjects, 3 days/week for 3 consecutive weeks. After a 2 week rest period, each subject received 2 consecutive challenge patches and each were applied for 48 hours on a previously untreated site. No irritation or sensitisation reactions were observed (CIR 2008).

Drometrizole at 1% in peach kernel oil applied to the back of 100 female subjects for 48 hours did not cause primary skin irritation (CIR 2008).

Two nail products containing 0.30% and 0.03% drometrizole were not irritating in 53 and 48 subjects, respectively (CIR 2008).

Nail polish containing 1% drometrizole was applied to a site on the arm of 20 subjects for 24 or 48 hours. Only one subject had a reaction (±score, maximum =4) from the nail polish (CIR 2008).

Sensitisation

Skin sensitisation

Chemicals with a methyl group substituent in the para position (drometrizole, bumetrizole, UV-571 and CAS No.101697-89-6) have structural alerts for protein binding via Michael addition when either autoxidation or skin metabolism is simulated.

Based on available data, drometrizole is a skin sensitiser. Drometrizole shows positive response rates of ≥30% following intradermal induction at >1% in a GPMT. Negative results were reported in 2 LLNA. Although the chemical was only tested to 2% this indicates that the EC3 would be >2%. The weight of evidence from the animal data supports sub-categorisation. There is evidence from human data that the chemical acts as a skin sensitiser. However, contact allergy to the substance appears to be rare based on the available data.

Data available for bumetrizole do not show evidence of sensitisation and drometrizole is expected to be more dermally available than the other chemicals. Therefore read across from drometrizole to other chemicals with a methyl group substituent in the para position is not considered appropriate. However effects following autoxidation cannot be ruled out. The available data indicate that chemicals with a branched alkyl substituent in the para position are not skin sensitisers.

Chemicals with a methyl group substituent in the para position

Drometrizole (CAS No. 2440-22-4)

In a GPMT conducted according to OECD TG 406, intradermal induction was performed on 10 male and 10 female Pirbright White guinea pigs using 5% drometrizole (purity >98.1%) in peanut oil and topical induction with 30% of the drometrizole in Vaseline. The animals challenged with 20% of drometrizole in Vaseline. After challenge, reactions were reported in 80% (16/20) and 90% (18/20 animals) at 24 and 48 hour readings, respectively. Negative controls had skin reactions in 20% (2/10) animals at the 48 hour reading (ECHA 2024b; REACH n.d.-a).

In a non-guideline GPMT, intradermal induction was performed on 10–17 female Hartley guinea pigs using 0.005–5% drometrizole in olive oil and topical induction with 25% drometrizole in petrolatum. The animals challenged with drometrizole (up to 5%) in acetone. The number of reactions after challenge were not reported. However, at least 1 animal per group showed a reaction after induction with 0.05% or more (REACH n.d.-a; Yamano et al. 2001).

In 2 non-guideline GPMTs, intradermal induction was performed on 10 guinea pigs (strain not reported) using 5% drometrizole in corn oil and topical induction with 100% (1st study) or 10% (2nd study) in petrolatum. The animals challenged with 10% (1st study) or 5% (2nd study) drometrizole in petrolatum. The purity of drometrizole was not reported. After challenge with 10% drometrizole 1/10 animals had a positive reaction (score of 1, maximum of 4 (24 hours; and score of + (48 hours)). After challenge with 5%, the test group had some reactions described as ±. However, a similar number of reactions were observed in the control group (CIR 2008; ECHA 2024b; REACH n.d.-a).

In 2 non-guideline local lymph node assays (LLNA) in mice, the reported stimulation indices (SI) were below 3 (0.78–1.44) after treatment with concentrations of 0.25–2% of drometrizole in acetone:olive oil (4:1). The estimated concentration to produce a three fold increase in lymphocyte proliferation (EC3) was not calculated in the study because no SI value was >3 (ECHA 2024b; REACH n.d.-a).

Bumetrizole (CAS No. 3896-11-5)

In a GPMT conducted according to OECD TG 406, intradermal induction was performed on Pirbright white guinea pigs (10/sex) using 5% of the chemical in peanut oil and topical induction with 30% of the chemical in petrolatum. The animals challenged with 20% of the chemical in petrolatum. After challenge, reactions were reported in 5% (1/20) and 0% (0/20) of the animals at 24h and 48h readings, respectively (OECD 2009; REACH n.d.-b).

In an acute dermal photoirritation dose response test, topical induction was performed on 20 male Hartley guinea pigs using 5% of the chemical in petrolatum. The animals were challenged with 20, 50 or 100% of the chemical in petrolatum. Irradiation with UV-A and UV-B was performed after topical application at a dose of 2 minimal erythemal dosage of UV-B and 10 J/cm^2 of UV-A. After challenge with 20% of the chemical, irradiation was performed at a dose of 10 J/cm^2 of UV-A. After challenge, positive reactions were reported in 20% (4/20) and 35% (7/20) animals at 24h and 48h readings, respectively (REACH n.d.-b).

In a mouse ear swelling test, female Balb/c mice challenged with 2% of the chemical. No positive reactions were reported (REACH n.d.-b).

In a non-guideline GPMT, intradermal induction was performed on guinea pigs (n=11) using 5% of the chemical in olive oil and topical induction with 25% of the chemical in petrolatum. The animals challenged with 0.025, 0.25 and 25% of the chemical (vehicle unspecified). After challenge with 0.025, 0.25 and 25% of the chemical, reactions were reported in 0% (0/11) of the animals at 48h and 72h readings (REACH n.d.-b).

Chemicals with a branched alkyl group substituent in the para position

Octrizole (CAS No. 3147-75-9)

In a GPMT conducted according to OECD TG 406, intradermal induction was performed on 10 male and 10 female Pirbright White guinea pigs using 5% octrizole in peanut oil and topical induction with 30% octrizole in Vaseline. The animals were challenged with 10% drometrizole in Vaseline. No skin reactions were observed after the challenge (REACH n.d.-c).

UV 234 (CAS No. 70321-86-7)

In a GPMT conducted according to OECD TG 406, intradermal induction was performed on Pirbright Hartley guinea pigs (10/sex) using 1% of the chemical in sesame oil and topical induction with 30% of the chemical in petrolatum. The animals challenged with 30% of the chemical in petrolatum. After challenge, reactions were reported as 0% (0/20 animals) for the animals (REACH n.d.-e).

2-(2H-Benzotriazol-2-yl)-4-(1,1-dimethylethyl)phenol (CAS No. 3147-76-0)

In an in vitro skin sensitisation study performed conducted according to OECD TG 442C (direct peptide reactivity assay (DPRA)), the chemical (CAS No. 3147-76-0) was dissolved in acetonitrile and mixed with 0.5 mM cysteine- and lysine-containing peptides. The final concentration of the chemical was 5 mM and 25 mM for cysteine and lysine, respectively. After 22 hours, there was no change in peptide depletion, indicating that the chemical is not likely to form allergy inducing haptens by binding to cysteine or lysine residues in proteins. Therefore, the chemical was considered negative in the assay (REACH n.d.-d).

In silico data (all chemicals)

The chemicals with a chlorine substituent at the 5 position of the benzotriazole ring, CAS Nos. 3864-99-1 and bumetrizole (CAS No. 3896-11-5), have a structural alert for protein binding based on the endpoint-specific profiling functionality of the Organisation for Economic Co-operation and Development (OECD) QSAR Application Toolbox (OECD QSAR Toolbox version 4.5) (OECD 2022). These chemicals have an alert (monohaloarenes) for the third key event (dendritic cell activation) of the skin sensitisation AOP in the in vitro h-CLAT assay. The other chemicals in the group had no structural alerts for skin sensitisation (without metabolic simulation).

Chemicals with a methyl group substituent in the para position (drometrizole (CAS No. 2440-22-4), bumetrizole (CAS No. 3896-11-5), UV-571 (CAS No. 23328-53-2) and CAS No. 101697-89-6) have structural alerts for protein binding via Michael addition when either autoxidation or skin metabolism is simulated.

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 was utilised to estimate the skin sensitisation potential of the chemicals in this evaluation. These chemicals did not fire any alerts for skin sensitisation (Lhasa Limited 2018).

Observation in humans

Drometrizole (2440-22-4)

There are 10 clinical case reports summarising the medical history of patients sensitised to drometrizole. The patients had been exposed to drometrizole in sanitary pads, protective glasses, watch strap, underwear spandex tape, elastomer of a t-shirt, nail varnish, dental material and face cream. Diagnostic patch-tests in selected dermatitis patients indicated low to relatively high frequency of sensitisation. Human repeated insult patch tests (HRIPT) were mainly negative (see Table 3. In a reliable HRIPT the highest concentration that did not induce sensitisation in HRIPT was 0.2% (equivalent to approximately 230 µg/cm^2). Although higher concentrations did not elicit sensitisation in other HRIPT these were not considered to have sufficient documentation to establish the dose per skin area (ECHA 2024b). No skin reactions were reported in a human maximisation test using 25% drometrizole (CIR 1986; ECHA 2024b; Stoeva et al. 2023).

Table 3 – Summary of human patch testing with drometrizole

Number of subjects	Type of study	Subject details	Concentration and vehicle	Positive reactions (%) (no. cases)
88	Diagnostic patch test	Selected dermatitis patients	concentration unknown	7.9 (7)
33	Diagnostic patch test	Selected dermatitis patients	1% in pet.	3 (1)
343	Diagnostic patch test	Selected dermatitis patients	1% in pet.	0 (0)
329	Diagnostic patch test	Selected dermatitis patients (dental personnel)	1% in pet.	0 (0)
59	HRIPT	Unselected subjects	0.2% in dimethyl phthalate	0 (0)
145	Clinical trial	Patients some with dermatoses and light sensitivity	up to 5%	1.4 (2)
148	HRIPT	Not available	0.5% (nail polish)	0 (0)
48	HRIPT	Not available	0.3% + UV	2.1 (1)
25	Maximisation test	Unselected subjects	25% (induction) 10% (challenge)	0 (0)

Bumetrizole (CAS No. 3896-11-5)

In a human patch test, bumetrizole (CAS No. 3896-11-5) (0.3% in dimethyl phthalate) was applied under occlusive conditions to the skin of 59 volunteers on alternate days 3 times/week for 5 weeks. Challenge was applied to the original contact site after 14 days of no contact with the chemical and challenge was terminated after 24 hours. One person was observed to have slight erythema after the third application during induction; however, this was not observed after subsequent applications. No reactions were observed during challenge. The chemical was not considered to be a skin sensitiser in humans (OECD 2009).

Repeat dose toxicity

Oral

The available data indicate a difference in the systemic toxicities between the chemicals of the group. The liver is the target organ for toxicity for phenolic benzotriazoles. However the toxicity level and mode of action varies depending on the type and degree of substitution. Kidney toxicity is observed with some chemicals but typically at higher doses than liver toxicity.

Based on available data, the chemicals have been sub-grouped as:

- disubstituted phenolic benzotriazoles
- monosubstituted phenolic benzotriazoles.

Structurally related hindered phenolic benzotriazoles (which contained branched alkyl substituents at both the *ortho* and *para* positions) caused liver effects at low doses warranting classification (NICNAS 2019). Two chemicals in this group have similar bulky substituents at both the *ortho* and *para* positions (CAS No. 3864-99-1 and CAS No. 70321-86-7). The available data indicate that CAS No. 3864-99-1 may have the same mode of action as the structurally related chemicals, but effects only occur at much higher doses. The available data indicate that CAS No. 70321-86-7 has a different mode of action and causes effects at much higher doses. Limited data are available for the other chemicals with alkyl substituents at both the *ortho* and *para* positions (bumetrizole, UV-571 and CAS No. 101697-89-6). Based on data for bumetrizole, these chemicals are not expected to cause effects at doses warranting classification. No data are available for CAS No.101697-89-6 which has a substituent in the *meta* position instead of the *ortho* position.

Based on the available data, the mono-substituted phenolic benzotriazoles (drometrizole, octrizole and CAS No. 3147-76-0) are not expected to cause effects at doses warranting classification.

Monosubstituted phenolic benzotriazoles

Drometrizole (CAS No. 2440-22-4)

In a 90 day repeated dose toxicity study in rodents (similar to OECD TG 408), Wistar rats (10/sex/dose) were treated with the chemical in feed at 0, 0.2, 1 or 5% (approximately 0, 100, 500, 2500 mg/kg bw/day). Not all effects were assessed and reported, including individual animal data and absolute organ weights. Numbers of erythrocytes were decreased, and leucocytes were increased with a trend in male rats at high dose. Changes in relative organ weights were dose dependent, including increased liver weight (males M 19–29%, females F 13–24%), increased spleen weight (M 5–12%, F 12–14%), reduced testicle weight (7–10%), and increased adrenal weight (F 12–16%) at mid and high doses, respectively. Increased relative kidney weights (M 9–14%, F 4–9%) were statistically significant at high dose. Histopathological findings included a distinct nephropathy in males from mid dose, such as nephrosis with hyperplastic tubules in severe cases, compared with findings of a single nephrotic tubule in 3/40 female rats. In the liver, slight centrilobular hypertrophy of hepatocytes was observed (M 2/10 7/10 5/10, F 0/10 1/10 5/10 animals), with noticeable pathological changes in 2 male rats at high dose. The spleen, pancreas and heart muscle also showed histopathological changes. The no observed adverse effect level (NOAEL) was 0.2% or 100 mg/kg bw/day in rats, based on organ weight and correlated

histopathological changes in the liver and kidney at higher doses (Feron et al. 1992; REACH n.d.-a).

In a 90 day repeated dose toxicity study in non-rodents (similar to OECD TG 409), Beagle dogs (6/sex/dose) were treated with drometrizole in feed at 0, 1000, 3000 or 10000 ppm. High dose animals had decreased food consumption and body weight gain, as well as increased serum gamma glutamyl transpeptidase (GGT) activity. Increased alanine aminotransferase (ALT) and increased relative liver weight by 21–28% (dose dependent) were seen at ≥3000 ppm. The no observed effect level (NOEL) was 1000 ppm (approximately 31.75–34.60 mg/kg bw/day in male and female dogs, respectively) (CIR 2008; REACH n.d.-a).

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), Crl:CD(SD) rats (12/sex/dose including 5 males for recovery and 5 non-pregnant females for satellite group) were administered drometrizole by gavage at 0, 30, 100 or 300 mg/kg bw/day for 42 days (males) or 42–53 days (females until lactation day 4). In male rats, relative and absolute weights of liver were increased at ≥30 and 300 mg/kg bw/day, respectively. In female rats, relative and absolute weights of liver were increased at ≥100 mg/kg bw/day, and of kidney at 300 mg/kg bw/day. The organ weight effects were reversible at the end of the 14 day recovery period. Hypertrophy of the centrilobular hepatocytes was observed in males at 300 mg/kg bw/day and in females at ≥100 mg/kg bw/day. Kidney lesions characterised by increased incidences of eosinophilic body in the proximal tubules of males at 300 mg/kg bw/day (irreversible), and by hydropic degeneration and regeneration in the proximal tubules of females at ≥100 mg/kg bw/day (reversible). The NOAEL was 30 mg/kg bw/day, based on reversible increases in relative liver weight without histopathological correlation in male rats at ≥30 mg/kg bw/day, and adverse liver and kidney effects in female rats at ≥100 mg/kg bw/day (REACH n.d.-a).

In a 2 year toxicity study (similar to OECD TG 452), CFY rats (50/sex/dose) were treated with drometrizole in feed at 0, 100, 300, 1000 or 3000 ppm. Male body weight gain and female food intake showed slight decreases at 3000 ppm. The NOEL was 1000 ppm (approximately 47–58 mg/kg bw/day) (CIR 2008; REACH n.d.-a).

The chemical was tested for transcriptome responses in mouse liver at 2, 4, 8, and 24 hrs after single oral administration at 100, 300, or 1000 mg/kg bw. The chemical weakly induced transcription of genes encoding Nrf2-dependent phase II enzymes. Chemical activation of Nrf2 in mice resulted in induction of genes encoding UDP-glucuronosyltransferases in the liver (OECD 2017). In a short term toxicity study the significantly increased activities of aminopyrine N-demethylase UDP glucuronosyltransferase activity were observed (CIR 2008).

Octrizole (CAS No. 3147-75-9)

In a 30 day repeated dose toxicity study (conducted prior to the availability of OECD TGs), Wistar rats (5/sex/dose) were treated with the chemical in feed at 0, 1.25, 2.5 or 5% (approximately 0, 1286, 2594, 5658 mg/kg bw/day). No indices of toxicity were found by macroscopic and microscopic examinations up to the highest dose. The NOAEL was 5658 mg/kg bw/day in this study (REACH n.d.-c).

The chemical was tested for transcriptome responses in mouse liver at 2, 4, 8, and 24 hrs after single oral administration at 100, 300, or 1000 mg/kg bw. The chemical enhanced transcription of phase I Cyp2 genes but induction levels were low (OECD 2017).

Disubstituted phenolic benzotriazoles

Bumetrizole (CAS No. 3896-11-5)

In a 90 day repeated dose toxicity study in rodents (similar to OECD TG 408), Wistar rats (10/sex/dose) were treated with the chemical in feed at 0, 400, 1000, 2500 or 10000 ppm (equivalent to 0, 25.0–28.9, 62.0–70.6, 153.9–176.0, 637.4–740.1 mg/kg bw/day (M–F)). Alkaline phosphatase (ALP) activity slightly decreased in females at 10000 ppm, and glucose-6-phosphatase activity increased in both sexes at ≥2500 ppm. In high dose females, relative weights of the liver and kidney were increased by 10.7% and 6%, respectively. Histopathological changes in the kidneys, thyroid and lungs were frequently observed in the treatment groups. However, these effects were not considered adverse by the study author given their incidences were low in the control group, and the severity was not dose dependent. The NOAELs were 637–740 mg/kg bw/day in male and female rats, respectively (REACH n.d.-b).

In a 90 day repeated dose toxicity study in non-rodents (similar to OECD TG 409), Beagle dogs (4/sex/dose, including 1/sex for recovery) were treated with the chemical in feed at 0, 200, 1000 or 5000 ppm (equivalent to 0, 6.2–6.5, 29.6–32.2, 168–153 mg/kg bw/day M–F). One mid dose female was sacrificed showing a pain reaction on palpitation of the abdomen, possibly due to a myocardial lesion. Body weight loss (7% in females only) and reductions of packed cell volume, red blood cell, and haemoglobin values were seen in both sexes at high dose. Increases in relative organ weights were dose dependent, reaching statistical significance at high dose in males (liver 48%) and at all doses in females (liver 14%, 24%, 43%; heart 11%, 16%, 20%). Given that although no correlated histopathological changes were observed, the liver weight increases were notable, particularly at the high dose, the NOAELs were considered to be 29.6–32.2 mg/kg bw/day (REACH n.d.-b).

In a 28 day repeated dose toxicity study (similar to OECD TG 407), Wistar rats (5/sex/dose) were treated with the chemical in feed at 0, 400, 1000, 2500 or 10000 ppm. Slight increases in relative liver weight were observed in female rats (6%, 11%, 14% at ≥1000 ppm) with no associated histopathology. The NOAEL was 10000 ppm or 1005 mg/kg bw/day in rats (REACH n.d.-b).

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), Crj:CD(SD) rats (12/sex/dose including 6/sex for recovery) were administered the chemical by gavage at 0, 62.5, 250 or 1000 mg/kg bw/day for 42 days (males) or 44–56 days (females until lactation day 6). No toxicologically significant effects were reported. The NOAEL was 1000 mg/kg bw/day in rats (REACH n.d.-b).

In a combined chronic toxicity and carcinogenicity study (similar to OECD TG 453), SD rats (50/sex/dose) were treated with the chemical in feed at 0, 1000, 3000 or 10000 ppm (equivalent to 0, 37.7–50.4, 113.2–147.7, 382.6–501.9 mg/kg bw/day M–F) for 104 weeks. Red cell parameters were reduced in all animals at 10000 ppm during the first 52 weeks, with marked reductions in males at week 77 and in females at 3000 ppm at week 25. Clinical chemistry changes at 10000 ppm (including increased alkaline phosphatase (ALP), increased glucose, and decreased albumin levels) were temporary and hence not considered of toxicological significance. Relative liver weight was increased in males at 1000 or 10000 ppm, and in females at 3000 ppm without a dose relationship or associated histopathological changes. The reported NOEL was 3000 ppm (113.2–147.7 mg/kg bw/day) in rats, based on overall effects at the high dose on body and organ weights, clinical chemistry and haematology (REACH n.d.-b).

In a 2 year carcinogenicity study (similar to OECD TG 451), Tif:MAGf (SPF) mice (50/sex/dose) were treated with the chemical in feed at doses of approximately 0, 0.7, 6 or

60 mg/kg bw/day. The NOAEL was 60 mg/kg bw/day, the highest dose tested in mice (REACH n.d.-b).

UV 234 (CAS No. 70321-86-7)

In a 90 day repeated dose toxicity study (OECD TG 408), RAlf (SPF) rats (10/sex/dose; 10/sex for recovery) were treated with the chemical in feed at 0, 50, 300, 2000 or 10000 ppm (equivalent to 0, 3.7, 22.1–22.5, 152.7–155.1, 779.5–802.2 mg/kg bw/day M–F). Mean absolute and relative liver to body and liver to brain weights significantly increased in males at ≥2000 ppm (ranging 15.4–32%) and in females at ≥300 ppm (ranging 15.4–34%). The organ weight effects were not reversible following recovery in both sexes at ≥2000 ppm, and associated with histological changes, such as slight to moderate hypertrophy and/or cytoplasmic vacuolisation of hepatocytes (M 6/10 10/10, F 5/10 9/10 9/10 animals at respective doses at the end of treatment, and M 6/10 10/10, F 1/10 2/10 7/10 animals at the end of 4 week recovery period). The reported NOAEL was 22.3 mg/kg bw/day in rats, based on irreversible liver weight increases and irreversible microscopic changes at ≥153.9 mg/kg bw/day (REACH n.d.-e).

In a 28 day repeated dose toxicity study (OECD TG 407), Tif: RAlf (SPF) rats (10/sex/dose) were treated with the chemical in feed at 0, 300, 2000 or 10000 ppm (equivalent to 26.0–25.9, 170.9–177.2, 922.8–944.7 mg/kg bw/day M–F). Mean absolute and relative liver to body and liver to brain weights significantly increased in females only at ≥300 ppm (ranging 26–43.4%). In male rats, absolute and relative weights of kidney increased at 10000ppm (ranging 8–9%), and those of adrenal increased at ≥2000 ppm (ranging 17–21.9%). All treated females showed correlated liver vacuolisation, and 1/10 high dose male had focal liver necrosis. There were no changes to liver enzyme activities, biochemistry or haematology parameters. The reported NOAEL was 933.8 mg/kg bw/day in rats, the highest dose tested in this study (REACH n.d.-e)

The chemical was tested for transcriptome responses in mouse liver at 2, 4, 8, and 24 h after single oral administration at 100, 300, or 1000 mg/kg bw. The chemical increased transcription of genes encoding phase II enzymes but with low induction levels (OECD 2017).

2,4-di-tert-butyl-6-(5-chloro-2H-benzotriazol-2-yl)phenol (CAS No. 3864-99-1)

In combined repeated dose and reproductive/screening toxicity study, rats (10 rats/sex/dose) were given the substance by gavage at 0, 2.5, 25, or 250 mg/kg bw/day. Males were dosed for a total of 56–57 days and females for a total of 55–69 days, including mating, pregnancy, and up to day 3 of lactation.

Significant increases in serum albumin and albumin/globulin ratio at 25 mg/kg bw/day and higher and ALP levels at 250 mg/kg bw/day were noted in males. The absolute and relative weights of the liver were significantly increased in males at 25 mg/kg bw/day and higher. These weights did not fully reverse in the high dose males after recovery. No changes in these parameters were observed in females of any dose group. As the changes observed in this study were not accompanied by significant histopathological anomalies the NOAEL and NOEL of this study were determined as 250 mg/kg bw/day in both sexes and 2.5 mg/kg bw/day in male, respectively (OECD 2017).

In a 90 day feeding study, rats (strain and number not specified) were fed a diet containing the substance at 0, 5, 15, or 45 ppm for 90 days. Increased weight of the liver was found in high dose males only. Histopathology revealed slightly enlarged hepatocytes containing homogeneous cytoplasm in males fed 15 ppm or higher. Serum aspartate aminotransferase

(AST), alanine aminotransferase (ALT), and ALP levels were unaltered. Glucose 6-phosphatase activity in liver of male rats was increased at 15 ppm or higher. It was concluded that rats fed up to 45 ppm did not show obvious hepatotoxicity or any other organ toxicity (OECD 2017).

In a 90 day feeding study in dogs, Beagle dogs (3/sex/dose) were treated with the chemical for 90 days in the diet at 15, 30, 60, 120, or 240 mg/kg bw/day. Increased liver weights and increased activity of serum ALP was seen in several Beagle dogs at 60 mg/kg bw/day . No distinct dose related histopathological changes in the liver were observed. Dose related changes in kidney consisted of adhesions and homogeneous inclusions in the glomeruli were observed at 60 mg/kg bw/day or higher. NOAEL in this study was determined as 30 mg/kg bw/day (OECD 2017).

The chemical was tested for transcriptome responses in mouse liver at 2, 4, 8, and 24 hrs after single oral administration at 100, 300, or 1000 mg/kg bw. The chemical induced transcription of CAR- and PXR-dependent CYP genes, Nrf2-dependent Phase II enzymes, and Keap1/Nrf2-dependent phase II enzymes. The transcriptional profile of was similar to the structurally related chemical UV-320 although the induction levels were lower (except for PPAR-mediated Cyp4) (OECD 2017).

Genotoxicity

Based on the available data, the chemicals in this group are not considered to have genotoxic potential. Although in silico data indicates potential genotoxic activity the available in vitro and in vivo data was negative.

In vitro

Negative results were reported for the following in vitro assays:

Drometrizole (CAS No. 2440-22-4)

- A bacterial reverse mutation assay (**OECD TG 471**) in *Salmonella typhimurium* TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation at concentrations up to 810 µg/mL (REACH n.d.-a).
- A mammalian gene mutation assay (**OECD TG 476**) in the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations up to 25 µg/mL (REACH n.d.-a).
- Non-guideline bacterial reverse mutation assays in *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 1538 with and without metabolic activation at concentrations up to 100 µg/plate (REACH n.d.-a).

Octrizole (CAS No. 3147-75-9)

- A bacterial reverse mutation assay (**OECD TG 471**) in *S. typhimurium* TA 98, TA 100, TA 1535 and TA 1537 and *Escherichia coli* WP2 *uvrA* with and without metabolic activation at concentrations up to 5000 µg/plate (REACH n.d.-c).
- A mammalian gene mutation assay (**OECD TG 476**) in the HPRT locus in CHO cells with and without metabolic activation at concentrations up to 200 µg/mL (REACH n.d.-c).
- A mammalian chromosome aberration assay (**OECD TG 473**) in Chinese hamster lung fibroblasts (V79) with and without metabolic activation at concentrations up to 50 µg/mL (REACH n.d.-c).

2-(2H-Benzotriazol-2-yl)-4-(1,1-dimethylethyl)phenol (CAS No. 3147-76-0)

- A bacterial reverse mutation assay (**OECD TG 471**) in *S. typhimurium* TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* WP2 *uvrA* with and without metabolic activation at concentrations up to 5000 µg/plate (REACH n.d.-d).

Bumetrizole (CAS No. 3896-11-5) (REACH n.d.-b)

- A bacterial reverse mutation assay (**OECD TG 471**) in *S. typhimurium* TA 98, TA 100, TA 1535 and TA 1537 and *E. coli* WP2 *uvrA* with and without metabolic activation at concentrations up to 1250 µg/plate.
- A mammalian chromosome aberration assay (**OECD TG 473**) in Chinese hamster lung with and without metabolic activation at concentrations up to 2400 µg/mL for the short treatment method and 1200 µg/mL for the continuous treatment method.
- A non-guideline bacterial reverse mutation assay in *S. typhimurium* TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation at concentrations up to 162 µg/plate.

UV 234 (CAS No. 70321-86-7) (REACH n.d.-e)

- A non-guideline bacterial reverse mutation assay in *S. typhimurium* TA 98, TA 100, TA 1535 and TA 1537 with and without metabolic activation at concentrations up to 2025 µg/plate.
- A non-guideline unscheduled DNA Synthesis (UDS) assay in rat hepatocytes with and without metabolic activation at concentrations up to 50 µg/mL.

Structurally related chemicals

The structurally related chemicals UV-320 (CAS No. 3846-71-7) and UV-328 (CAS No. 25973-55-1) were negative in in vitro assays including bacterial reverse mutation assays, gene mutation assays and chromosome aberration tests (NICNAS 2019).

In vivo

Negative results were reported for the following in vivo tests:

Drometrizole (CAS 2440-22-4) (REACH n.d.-a)

- a mammalian erythrocyte micronucleus test (OECD TG 474), Chinese hamsters (n=3/sex/dose) were treated with drometrizole by gavage at doses of 0, 500, 1000 or 2000 mg/kg bw/day mg/kg bw/day. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity.
- a mammalian bone marrow chromosomal aberration test (OECD TG 475), Chinese hamsters (n=6 females, 4 males/dose) were administered drometrizole by gavage at doses of 0, 500, 1000 or 2000 mg/kg bw/day. The incidence of chromosome aberrations in bone marrow did not increase in any of the treated groups, indicating a lack of clastogenicity.
- a non-guideline mammalian bone marrow chromosome aberration test with limited study details, mice (6/sex/dose) were treated with drometrizole at doses of 630, 1250 or 2500 mg/kg bw. The incidence of chromosome aberrations in bone marrow did not increase in any of the treated groups, indicating a lack of clastogenicity.

- a dominant lethal assay (OECD TG 478), NMRI mice (20 males/dose) were administered drometrizole by gavage at doses of 0, 1000 or 3000 mg/kg bw/day. Dominant lethal mutations were not observed.

Bumetrizole (CAS No. 3896-11-5) (REACH n.d.-b)

- a non-guideline dominant lethal assay, NMRI mice (20 males, 40 females/dose) were administered bumetrizole by gavage at doses of 0, 1000 or 3000 mg/kg bw/day. Dominant lethal mutations were not observed.
- a non-guideline mammalian erythrocyte micronucleus test, Chinese hamsters (6/sex/dose) were treated with bumetrizole by gavage at doses of 0, 500, 1000, or 2000 mg/kg bw/day. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity.
- a non-guideline mammalian bone marrow chromosome aberration test, Chinese hamsters (4/sex/dose) were treated with bumetrizole by gavage at doses of 0, 500, 1000 or 2000 mg/kg bw/day. The incidence of chromosome aberrations in bone marrow did not increase in any of the treated groups, indicating a lack of clastogenicity.

UV 234 (CAS No. 70321-86-7) (REACH n.d.-e)

- a non-guideline mammalian erythrocyte micronucleus test, Chinese hamsters (3/sex/dose) were treated with the chemical by gavage at doses of 0, 1250, 2500 or 5000 mg/kg bw. The incidence of micronuclei in bone marrow polychromatic erythrocytes did not increase in any of the treated groups, indicating a lack of clastogenicity.
- a sister chromatid exchange assay, Chinese hamsters were treated with the chemical by gavage at doses of 0, 1250, 2500 or 5000 mg/kg bw. Sister chromatid exchange did not increase in any of the treated groups.

In silico

The chemicals (drometrizole, bumetrizole, CAS Nos. 23328-53-2, 70321-86-7 and 101697-89-6) have structural alerts for DNA binding via Michael addition based on the mechanistic profiling functionality of the OECD QSAR Application Toolbox (OECD 2022). The chemicals in this group have end-point specific structural alerts for in vivo mutagenicity via H-acceptor-path3-H-acceptor (potential interaction with DNA and/or proteins via non-covalent binding, such as DNA intercalation or groove-binding). There were also alerts for mutagenicity and chromosome aberration for several metabolites (S9) of the chemicals in this evaluation (except for CAS No. 70321-86-7).

The knowledge based expert system Deductive Estimation of Risk from Existing Knowledge (DEREK) Nexus version 6.0.1 (Lhasa Limited 2018) was utilised to estimate the genotoxic potential of the chemical. The chemical is predicted positive with an alert for chromosome damage in vitro based on data for benzotriazoles and indoles. The chemicals did not match any structural alerts or examples for (bacterial in vitro) mutagenicity.

The QSAR modelling using OASIS-TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator) version 2.31.2 predicted that the chemical induce chromosomal aberrations in vitro (OASIS LMC n.d.). The predictions were >80% in domain of the genotoxicity model and based on alerts for Michael-type addition to quinoid structures. The chemicals were predicted negative for Ames mutagenicity.

Carcinogenicity

Based on the available data, the chemicals in this group are not expected to be carcinogenic following oral exposure.

Drometrizole (CAS No. 2440-22-4)

In a 2 year study (OECD TG 452), CFY rats were treated with drometrizole in feed at concentrations of 0, 100, 300, 1000 or 3000 ppm (see **Repeat dose toxicity** – **oral** section). No carcinogenic potential was observed. The NOAEL was 3000 ppm which corresponds to 142 and 169 mg/kg bw/day for males and females respectively (CIR 2008; REACH n.d.-a).

In a 2 year study, Tif:MAGf (SPF) mice (50/sex/dose) were treated with drometrizole in feed at concentrations of 0, 5, 50, or 500 ppm (see **Repeat dose toxicity – oral** section). No carcinogenic potential was observed. The NOAEL was 500 ppm which corresponds to 62–64 mg/kg bw/day (REACH n.d.-a).

In a non-guideline study with limited study details, R3 female mice (n=50) were injected subcutaneously once with drometrizole at a dose of 5 mg and also given in feed continuously until the end of their lifetime at a concentration of 0.5 mg. No increase in tumour incidence was reported (REACH n.d.-a).

Bumetrizole CAS No. 3896-11-5

In a 2 year study, Tif MAGF (SPF) mice (50/sex/dose) were treated with bumetrizole in feed at concentrations of 0, 5, 50, or 500 ppm (approximately 0, 0.66, 6.33, or 61.72 mg/kg bw/day (males); 0, 0.65, 5.95 or 58.94 mg/kg bw/day (females)). No carcinogenic potential was observed. The NOAEL was 500 ppm which corresponds to 58.94–61.72 mg/kg bw/day (REACH n.d.-b).

In a combined chronic toxicity and carcinogenicity study, SD rats (50/sex/dose) were treated with bumetrizole in feed at concentrations of 0, 1000, 3000 or 10,000 ppm (equivalent to 0, 37.7, 113.2 or 382.6 mg/kg bw/day (males); 0, 50.4, 147.7, or 501.9 mg/kg bw/day (females)) for 104 weeks. No carcinogenic potential was observed. The NOAEL was 10,000 ppm which corresponds to 382.6–501.9 mg/kg bw/day (REACH n.d.-b).

Reproductive and development toxicity

Limited information on reproductive and developmental toxicity. There was no evidence of effects in the available studies.

Drometrizole (CAS No. 2440-22-4)

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), Crl:CD(SD) rats (12/sex/dose, 5 for recovery/satellite groups) were administered drometrizole by gavage at doses of 0, 30, 100, or 300 mg/kg bw/day for 42 days (males) or 42–53 days (females) (see **Repeat dose toxicity – oral** section). Reproductive performance parameters were not adversely affected including oestrous cycle, copulation, fertility, delivery and lactation. The number of pups, implantation, sex ratio of pups, pup viability during 4 days of lactation and pup weight were not adversely affected. No external abnormalities or macroscopic findings were observed in any pup. The NOAEL was 300 mg/kg bw/day for the reproductive and developmental effects (REACH n.d.-a).

In a prenatal developmental toxicity study, pregnant SD rats (25/dose) were treated with drometrizole by gavage at doses of 0, 150, 500 or 1000 mg/kg bw/day from gestation day (GD) 6–15. No maternal toxic effects were observed except for a slight increase in feed consumption towards the end of treatment. No adverse effects on embryonic or foetal development were observed except for a slight increase in the incidence of anasarca (slight oedema-like changes of the siabcutis) at the highest dose. There was a slight decrease in the number of incompletely and unossified phalangeal nuclei of the hind-limb at the mid dose only which was not considered to be treatment-related. The NOAEL was 1000 mg/kg bw/day for maternal toxicity and developmental effects (REACH n.d.-a).

In a prenatal developmental toxicity study, pregnant NMRI mice (30/dose in the treatment group; 60 in control group) were treated with drometrizole by gavage at doses of 0, 150, 500 or 1000 mg/kg bw/day from GD 6–15. No maternal toxic effects were observed except for a markedly increased feed intake at the highest dose level, and slightly decreased feed intake at the mid-dose level. At the low dose level, increased incidence of phalangeal nuclei of the forelimb and the sternebrae showed incomplete ossification, which was not considered to be treatment related. The NOAEL was 1000 mg/kg bw/day for maternal toxicity and developmental effects (REACH n.d.-a).

Bumetrizole (CAS No. 3896-11-5)

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422), Crj:CD(SD) rats (12/sex/dose; 6 in recovery group) were treated with bumetrizole by gavage at doses of 0, 62.5, 250 or 1000 mg/kg bw/day for 42 days (males) or 44–56 days (females). No adverse effects on the parental reproduction and development of the offspring were observed. The NOAEL was 1000 mg/kg bw/day for reproductive and developmental effects (REACH n.d.-b).

In a rodent dominant lethal test, male NMRI mice (20 males/dose, 40 females/dose) were treated by gavage single doses of 0, 1000 or 3000 mg/kg bw. No significant differences in the mating ratio, number of implantation or embryonic deaths between the treatment groups. The NOAEL was 3000 mg/kg bw (REACH n.d.-b).

UV 234 (CAS No. 70321-86-7)

In a prenatal developmental toxicity study (OECD TG 414), pregnant RAIf (SPF) rats (24/dose) were treated by gavage at doses of 0, 300, 1000 or 3000 mg/kg bw/day from GD 6–15. Partial abortion was observed in one dam in the 1000 and 3000 mg/kg bw/day groups. Haemorrhagic changes of the uterine epithelium were observed in one female and no left uterine horn in another female in the high dose group (3000 mg/kg bw/day). The mean number of corpora lutea and mean number of implantation sites were slightly decreased which were not statistically significant in the high dose group. The average female body weight of the foetus in the 300 mg/kg bw/day group, and the average male and female and overall average weight of the foetus in the 1000 mg/kg bw/day group were significantly decreased. However, all these observations were not dose related, and thus not considered to be treatment related. The NOAEL for maternal and developmental toxicity was 3000 mg/kg bw/day (REACH n.d.-e).

Human health risk characterisation

Critical health effects

Based on available data the public will most likely be exposed to drometrizole and bumetrizole. The critical health effects for risk characterisation for chemicals are systemic effects (organ weight changes and histopathological changes) following repeated oral exposure. Drometrizole may also cause sensitisation.

The NOAEL for drometrizole (100 mg/kg bw/day) derived from a non-guideline (similar to OECD TG 408) 90 day repeated oral toxicity (see **Repeat dose toxicity**) was chosen as the point of departure for risk characterisation.

Public risk

Systemic exposure risk

An MOE methodology was used to characterise the risk to human health associated with systemic exposure to the chemical. The MOE methodology is commonly used to characterise risks to human health associated with exposure to chemicals (ECB 2003).

The MOE risk estimate provides a measure of the likelihood that a particular adverse health effect will occur under the conditions of exposure. As the MOE increases, the risk of potential adverse effects decreases. To decide whether the MOE is of sufficient magnitude, expert judgment is required. Such judgments are usually made on a case-by-case basis and should consider uncertainties arising in the risk assessment process such as the completeness and quality of available data, the nature and severity of effect(s) and intra/inter species variability. In general, a MoE value ≥100 is considered acceptable to account for intra- and inter-species differences.

The MOE methodology was used to characterise the public health risks from exposure through simultaneous use of all categories of cosmetic and personal care products.

The combined, worst-case scenario internal dose from the chemical via dermal exposure was determined to be 0.433 mg/kg bw/day (see **Human exposure** section; Table 2). Based on this value the calculated MOE was 231.

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