CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification:

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

EC Number: **219-470-5**

CAS Number: **2440-22-4**

Index Number: **-**

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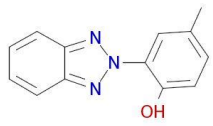
CONTENTS

1 IDENTITY OF THE SUBSTANCE

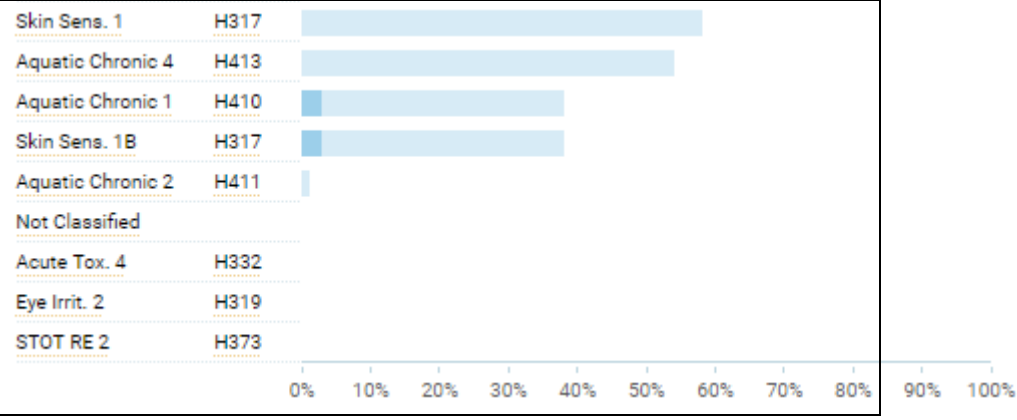
1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	2-(2H-1,2,3-benzotriazol-2-yl)-4-methylphenol
Other names (usual name, trade name, abbreviation)	2-(2*H*-benzotriazol-2-yl)-*p*-cresol 2-(2-Hydroxy-5-methylphenyl) benzotriazole ADK Stab LA 32 Arelite BT10 Benazol II Benazol P Cyasorb UV5365 Drometrizole Eversorb 71 Lowilite 55 Mark LA 32 Seikalizer AZ Sumisorb 200 Tinuvin P UV-P Uvasorb SV Uvinul 3033P Viosorb 520
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	219-470-5
EC name (if available and appropriate)	2-(2*H*-benzotriazol-2-yl)-*p*-cresol
CAS number (if available)	2440-22-4
Other identity code (if available)	-
Molecular formula	$C_{13}H_{11}N_3O$
Structural formula	
SMILES notation (if available)	CC1=CC(=C(C=C1)O)N2N=C3C=CC=CC3=N2
Molecular weight or molecular weight range	225.246 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable
Description of the manufacturing process and identity of the source (for UVCB substances only)	Not an UVCB
Degree of purity (%) (if relevant for the entry in Annex VI)	≤ 100

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self- classification and labelling (CLP)
2-(2*H*-benzotriazol-2-yl)-*p*-cresol (CAS No.: 2440-22-4; EC No.: 219-470-5)	< 100	-	

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 3: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current entry	no entry										
Dossier submitters proposal	tbd	2-(2*H*-benzotriazol-2-yl)-*p*-cresol	219-470-5	2440-22-4	Skin Sens.1 Aquatic Chronic 1	H317 H410	GHS07 GHS09 Warning	H317 H410		M = 10	
Resulting Annex VI entry if agreed by RAC and COM											

Table 4: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)		
Oxidising gases		
Gases under pressure		
Flammable liquids		
Flammable solids		
Self-reactive substances		
Pyrophoric liquids		
Pyrophoric solids		
Self-heating substances		
Substances which in contact with water emit flammable gases		
Oxidising liquids		
Oxidising solids		
Organic peroxides		
Corrosive to metals		
Acute toxicity via oral route	hazard class not assessed in this dossier	No
Acute toxicity via dermal route		
Acute toxicity via inhalation route		
Skin corrosion/irritation		
Serious eye damage/eye irritation		
Respiratory sensitisation		
Skin sensitisation	**harmonised classification proposed**	**Yes**
Germ cell mutagenicity	hazard class not assessed in this dossier	No
Carcinogenicity		
Reproductive toxicity		
Specific target organ toxicity-single exposure		
Specific target organ toxicity-repeated exposure		
Aspiration hazard		
Hazardous to the aquatic environment	**harmonised classification proposed**	**Yes**
Hazardous to the ozone layer	hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

There is no harmonised classification for this substance.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Concerning classification for hazardous to the aquatic environment

Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

Differences in self-classification. Disagreement with some notifiers and/or registrants, who did not classify the substance 2-(2*H*-benzotriazol-2-yl)-*p*-cresol for chronic aquatic toxicity or skin sensitisation.

Current self-classifications for chronic aquatic toxicity (as of June 2023):

- Aquatic Chronic 1: 371 of 924 (285 of 371 M(chronic) =1))
- Aquatic Chronic 2: 14 of 924
- Aquatic Chronic 4: 491 of 924
- No classification for aquatic environment: 48 of 924

Current self-classification for skin sensitisation (as of August 2023):

- Skin Sens. 1: 528 of 897
- Skin Sens. 1B: 339 of 897
- No classification for skin sensitisation: 30 of 897

Harmonised classification as Skin Sens. 1 would ensure adequate perception of the skin sensitisation hazard associated with the substance 2-(2*H*-benzotriazol-2-yl)-*p*-cresol , *inter alia* by setting the concentration limit for the classification of mixtures containing the substance to 1 %.

5 IDENTIFIED USES

2-(2*H*-benzotriazol-2-yl)-*p*-cresol is an ultraviolet light absorber and is used for UV protection in polymers, plastics, elastomers, adhesives, polycarbonates, polyurethanes and some cellulose esters and epoxy resins (ECHA, 2017).

6 DATA SOURCES

The primary source of data used in this report is the available information on the website of ECHA and in the registration dossiers.

Furthermore, to investigate the skin sensitising properties of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol, a literature screening in bibliographic databases was performed, including Web of Science, PubMed, Embase, Wiley Online Library, Scopus, CAS Sci Finder, and Science Direct. As search strings, the CAS and EC numbers and other names were used (including the usual name, trade name, and abbreviations, according to Table 1).

7 PHYSICOCHEMICAL PROPERTIES

Table 5: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20 °C and 101.3 kPa	Solid; Slightly yellow powder	REACH registration data	Visual observation
Melting/freezing point	130 °C	REACH registration data	Measured
Boiling point	Not applicable; Decomposes before boiling	REACH registration data	Measured
Relative density	1385 kg/m³ (at 20 °C)	REACH registration data	Measured
Vapour pressure	0 Pa (at 20 °C)	REACH registration data	Measured, calculated
Surface tension	The study does not need to be conducted because based on structure, surface activity is not expected or cannot be predicted	-	-
Water solubility	0.173 mg/L (at 20 °C; pH 6.5)	REACH registration data	Measured, calculated
Partition coefficient n-octanol/water	log Pow = 4.2 (at 25 °C, pH 6.3)	REACH registration data	Measured
Granulometry	MMD = 499 µm D10 = 151 µm D90 = 1303 µm < 4 µm = 0 % < 10 µm = 0 % < 100 µm = 5.7 %	REACH registration data	Measured
Stability in organic solvents and identity of relevant degradation products	The study does not need to be conducted because the stability of the substance is not considered to be critical.	-	-
Dissociation constant	In consequence of the very low water solubility the dissociation constant test could not be performed. Since the test compound has one dissociable functional group (-OH), in addition the dissociation constant has been calculated using ACD/Labs as recommended in the Guideline yielding a value of 8.15 at 25 °C (most acidic).	REACH registration data	Calculated
Viscosity	Not applicable. The substance is a solid.	-	-

The information in this table marked with „REACH registration data“ is based on the REACH registration dossier and ECHA’s public registration information as accessed on 2023-05-12.

8 EVALUATION OF PHYSICAL HAZARDS

Not addressed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Table 6: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Equivalent or similar to OECD TG 417; oral (gavage) Objective of the study: Distribution, excretion Pre-GLP Rats (Tif:RAIF (SPF)), 4 males Remarks: Radiolabelled substance was diluted with non-radiolabelled test substance Only 1 dose level tested (10 mg/kg bw/d) Metabolites not measured	Within 48 h after administration: ~ 91 % of test substance eliminated from the body. Between 6 and 24 h: peak of elimination with 56 % of the applied dose occurred in the urine. Between 0 and 6 h: only 9 % of the dose was found in the urine. After 168 h: 94 % of the dose was recovered, 69 % in the urine and 25 % in the faeces; residual radioactivity measured in most organs and tissues were below 0.02 µg/g. Levels significant above this value were detected only in kidney, aorta, and liver (0.10 - 0.22 µg/g).	The results indicate that the substance is well absorbed from the gastro-intestinal tract and eliminated via faeces and urine. Low bioaccumulation potential based on study results	(CIBA, 2009)

There is one study available investigating toxicokinetics of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol. The study was performed similar to OECD TG 417, using one dose of 10 mg/kg bw/d applied to four male rats by gavage. The main focus in this study was on distribution and excretion of the test substance. The results indicate that the substance is absorbed well from the gastro-intestinal tract and eliminated via faeces and urine. Metabolites of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol were not investigated.

Another study was provided on the dissemination site, performed according to OECD TG 417. However, 2-(2*H*-benzotriazol-2-yl)-*p*-cresol was used as a tracer only. The main object of investigation in this study was another test substance. Therefore, this study was not further assessed.

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

In a study performed similarly to OECD TG 417, with a main focus on distribution and excretion, 10 mg/kg bw/d of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol were absorbed well from the gastro-intestinal tract and eliminated via faeces and urine. Metabolites of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol were not investigated.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity

10.1.1 Acute toxicity - oral route

Not assessed in this dossier

10.1.2 Acute toxicity - dermal route

Not assessed in this dossier

10.1.3 Acute toxicity - inhalation route

Not assessed in this dossier

10.2 Skin corrosion/irritation

Not assessed in this dossier

10.3 Serious eye damage/eye irritation

Not assessed in this dossier

10.4 Respiratory sensitisation

Not assessed in this dossier

10.5 Skin sensitisation

Skin sensitisation is an immunological process consisting of two phases. During the first phase a low-molecular-weight chemical forms a hapten-protein-complex in the skin of naive individuals. A sequential set of events follows, leading to the production of allergen-specific memory T-cells, describing the induction of skin sensitisation. In the second phase (elicitation), exposure of the sensitised individual to the allergen leads to proliferation and activation of these T-cells, secretion of cytokines and mobilisation of other inflammatory cells resulting in the clinical outcome of allergic contact dermatitis (ECHA, 2017).

10.5.1 Animal data on skin sensitisation

Table 7: Summary table of animal studies on skin sensitisation

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure**	**Results**	**Reference**
According to OECD TG 406 GPMT GLP-compliant Reliability: 2, reliable with restriction Positive reactions in negative controls A (negative) control group of 10 animals (5 m/5 f) was treated with adjuvant and the vehicle during the induction period. Study report not available	Guinea pig, Pirbright White (Tif: DHP) Males/ females Test group: N = 10/sex Control group: N = 5/sex	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in study report: Tinuvin P EC no. 219-470-5 Analytical purity: > 98.1 %	Intradermal induction: 5 % of test substance in arachis oil; Freund's complete adjuvant (FCA)/saline mixture 1:1; test substance in FCA saline mixture Epicutaneous induction: 30 % in vaseline Epicutaneous challenge: 20 % in vaseline Positive control: 0.1 % of 1-chloro-2,4-dinitrobenzol	Positive Test item: 24 h-reading: 16/20 (80 %) 48 h-reading: 18/20 (90 %) Negative control: 24 h-reading: 1/10 (10 %) 48 h-reading: 2/10 (20 %) Positive control: 24 h-reading: 10/10 (100 %) 48 h-reading: 10/10 (100 %)	(CIBA-GEIGY, 1992)
LLNA, similar to OECD TG 429 According to (Kimber, 1989) GLP no information Reliability: 2, reliable with restriction Publication Deviations: Only 1 day following final application of the test substance, draining auricular lymph nodes (LN) were isolated, spontaneous proliferation of single LN cell suspensions was measured 24 h after incubation with 3HTdR in cell culture.	Mouse, Balb/c Female N = 3	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in publication: 2-(2-Hydroxy-5-methylphenyl) benzotriazole; Tinuvin P Purity: No information	0.25, 0.5, 1, and 2 % Vehicle: acetone: olive oil (AOO) (4:1)	Negative Exp. 1: C (%) / SI: 0 / -; 0.25 / 1.02; 0.5 / 1.42; 1 / 1.01; 2 / 1.22 Exp. 2: C (%) / SI: 0 / -; 0.25 / n. d.; 0.5 / 0.78; 1 / 1.46; 2 / 1.44 CLP criteria not applicable	(Ikarashi et al., 1994a)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
LLNA, similar to OECD TG 429 GLP no information Reliability: 2, reliable with restriction Publication Deviations: Group 1: Injection of mice with DMSO Group 2: 2 x intradermal injections of test substance in FCA emulsion Both groups: After 5 d, mice received test substance in AOO or AOO alone on each ear, for 3 consecutive days; next day, single cell suspension was prepared and cultured in presence of 3HTdR; 3HTdR incorporation measured after 24 h. Mice induced as above were challenged after 7 d for ear thickness measurements Only one concentration (1 %) tested	Mouse, Balb/c N = 3	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in publication: 2-(2-Hydroxy-5-methylphenyl) benzotriazole; Tinuvin P Purity: No information Vehicle for topical induction: acetone: olive oil (AOO)	Intradermal induction: Group 1: DMSO in FCA emulsion Group 2: 0.2 % of test substance in FCA, two injections (in total 50 µL) Both groups: 3 x topical induction, 1 % test of substance (25 µL) 1x Topical challenge, 1 % of test substance	Group 1 - Negative Intradermal injection DMSO, followed by topical exposure (1 %) on 3 consecutive days: Increase in ear thickness of 1.4 %, compared to controls SI < 3 Group 2 - Positive 2 x Induction by i.p. injection (0.2 % in FCA) followed by topical exposure (1 %) on 3 consecutive days: Increase in ear thickness of 20.5 %, compared to controls SI = 6.3	(Ikarashi et al., 1994b)
GPMT, modified GLP no information Reliability: 4, not assignable Publication in Japanese	Guinea pig No further information	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in publication: 2-(2-Hydroxy-5-methylphenyl) benzotriazole; Tinuvin P Purity: No information	<u>Induction:</u> ≥ 0.05 % <u>Challenge:</u> ≥ 0.025 %	Positive indication of skin sensitisation	(Yamano et al., 1993)

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure**	**Results**	**Reference**
Two separate GPMT GLP no information Reliability: 4, not assignable Secondary reports cited in (Lee et al., 2019) and (Burnett, 2008) Dose range-finding phase conducted to determine slightly irritating and sub-irritating concentrations for use in the booster (topical induction) and challenge phases, respectively. Occlusive patches with 5, 10, and 100 % test substance (in pet.), N = 10 Main study: 3 x 0.005 mL intradermal injections into the shaved upper back of each guinea pig; after one week, topical induction (0.1 g of the test substance) for 48 h; after further 2 weeks, challenge (0.1 g of the test substance) for 24 h	Guinea pig N = 10 (test item; control) No further information	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in publication: Drometrizole; 2-(2-Hydroxy-5-methylphenyl) benzotriazole Purity: No information	Intradermal induction: (1) 5 % test substance (corn oil); (2) 50 % aqueous Freund's complete adjuvant (FCA); (3) 5 % test substance in 50 % FCA Control: (1) 50 % FCA; (2) corn oil; (3) corn oil and 50 % FCA (1:1) Topical induction: 100 % (first test) or 10 % (second test; pre-treatment with 10 % sodium lauryl sulphate) of test substance in pet. Control: Only pet. Challenge: 10 % (first test) or 5 % (second test) of test substance in pet.	The following results were cited from secondary literature: *"No reactions were observed in the first control group, and one guinea pig in the first experimental group had a score of 1 (max. = 4) at 24 h and + at 48 h. In the second test, the control group had five and two ± reactions at 24 and 48 h, respectively. The experimental group had five and three ± reactions at 24 and 48 h, respectively, as well as a score of 1 at 24 h."* According to the investigators, in both studies no discernible potential for allergic skin sensitisation was observed.	(CTFA, 1978a; CTFA, 1978b)

There were several animal studies available investigating the skin sensitising potential of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol (Table 7). In general, the local lymph node assay (LLNA) investigates the induction of skin sensitisation, and guinea pig tests (guinea pig maximisation test (GPMT) and Buehler test) examine animals after the elicitation of skin sensitisation.

In a GPMT, according to OECD TG 406, ten animals per sex were intradermally injected with 5 % of the test substance 2-(2*H*-benzotriazol-2-yl)-*p*-cresol (purity: > 98.1 %) in arachis oil, followed by an epicutaneous induction using 30 % of the test substance in vaseline (CIBA-GEIGY, 1992). The concentration for intradermal induction was based on the solubility of the test substance in the vehicle and its local and systemic tolerability. The concentration for epicutaneous induction is based on a pre-test to determine the maximum sub-irritant concentration using 1, 5, 10, and 30 % of the test substance in vaseline. For epicutaneous challenge, a concentration of 20 % of the test substance was used, and it was cited that this concentration corresponds to the highest non-irritant concentration. Detailed study results of the pre-study, including readings of animals were not available to the DS. In the main study, 80 % (16/20) and 90 % (18/20) of the test substance-treated animals showed positive skin reactions 24 and 48 hours after challenge, respectively. However, negative control animals (induced with the adjuvant and the vehicle, challenged with the test substance at 20 %) showed positive reactions as well, resulting in 10 % (1/10) and 20 % (2/10) animals with skin reactions, 24 and 48 hours after challenge, respectively. Results from other control groups (induced with vehicle and challenged with vehicle) were reported as well, showing no positive reactions in 10 or 20 animals at readings after 24 or 48 hours after challenge. Positive control animals showed 100 % positive skin reactions. Altogether, 2-(2*H*-benzotriazol-2-yl)-*p*-cresol elicited skin sensitisation in guinea pigs. However, the number of positive reactions may be considered somewhat uncertain, because some positive skin reactions were observed in negative control animals as well, even though the number of positive animals in negative controls was much lower compared to animals induced with the test substance.

In an LLNA performed according to (Kimber, 1989), three female mice were treated with 2-(2*H*-benzotriazol-2-yl)-*p*-cresol at concentrations of 0.25, 0.5, 1, and 2 % in the vehicle acetone/olive oil (Ikarashi et al., 1994a). There is no information on the purity of the test substance available. At these low concentrations tested, there were no positive skin reactions detected. However, the study showed deviations from OECD TG 429 regarding the experimental schedule and preparation of local lymph node cells. Only one day after the final application of the test substance, draining auricular lymph nodes were isolated. Single cell suspensions were prepared and cells were cultured in the presence of 3H-methylthymidine (3HTdR). After 24 hours of cell culture, spontaneous proliferation of single local lymph node cells was measured by determination of 3HTdR incorporation. According to the experimental schedule of OECD TG 429, three days after the final application of the test substance, 3HTdR was injected into the mice and after further five hours local lymph node cells were prepared for determination of cell proliferation.

In another LLNA, with deviations from the OECD TG 429 (Ikarashi et al., 1994b), three mice were injected with DMSO. After five days, mice were treated on each ear with 1 % of the test substance 2-(2*H*-benzotriazol-2-yl)-*p*-cresol (no information on purity) in the vehicle AOO or the vehicle alone, for three consecutive days. The next day following final application, auricular lymph nodes were excised. A single cell suspension was prepared and cultured in the presence of 3HTdR, and 3HTdR incorporation was determined after 24 hours. Furthermore, challenge-induced ear swelling responses were measured. For this, mice were exposed as described above. After seven days, ear thickness was measured using an engineer's micrometre, followed by a challenge of mice with 1 % of the test substance. Ear thickness was measured again after 24 hours. According to the authors, a response was considered “positive” if ear thickness following challenge was at least 20 % increased, compared to the ear thickness before challenge. Following this protocol, mice treated with 1 % of the test substance did not show an increase in 3HTdR incorporation or in ear thickness (increase of 1.4 %) compared to controls (challenged with 1 % of the test substance for ear thickness measurements). However, in this study just one comparatively low concentration was tested. Furthermore, this study showed deviations from OECD TG 429 regarding the experimental schedule and preparation of local lymph node cells to determine cell proliferation as described for the study above (Ikarashi et al., 1994a).

For the sake of completeness, it is pointed out that during this study three mice received two intradermal injections using 0.2 % of the test substance in FCA emulsion instead of treatment with DMSO, followed by the protocol as described above. Mice receiving induction injections showed an increase in 3HTdR

incorporation compared to controls (SI = 6.3) and an increase in ear thickness after challenge of 20.5 %, compared to control animals.

Two further publications on GPMTs conducted with 2-(2*H*-benzotriazol-2-yl)-*p*-cresol were cited in the registration dossier. In a modified GPMT, concentrations > 0.05 % of the test substance used for induction and > 0.0025 % of the test substance used during challenge resulted in a *"positive indication of skin sensitisation"* (Yamano et al., 1993). However, detailed study information was not available to the DS. In the second publication, it was concluded that *"drometrizole was negative for sensitisation in two GPMTs", using 5 % of the test substance for intradermal induction, 100 % (first test) or 10 % (second test) for topical induction and 10 % (first test) or 5 % (second test) of the test substance for challenge*" (CTFA, 1978a; CTFA, 1978b). Original publications were not available to the DS. Therefore, both publications were not considered for further assessment.

10.5.2 Human data on skin sensitisation

Table 8: Summary table of human data on skin sensitisation – Clinical case reports

Test substance, Reference	**Relevant information about the study (as applicable)**	**Observations**
2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in report: Drometrizole; Tinuvin P CAS no. 2440-22-4 1 % in pet. (Kullberg and Hylwa, 2020)	A 55-year-old woman, with a 3- to 4-month history of diffuse pruritic papulovesicular genital dermatitis from proximal leg and mons throughout outer labia onto the buttocks (vaginal mucosa or anorectal tissue not involved); history of stress urinary incontinence, managed with daily sanitary pads (exclusively Poise daily liners) used over past 1 to 2 years. Patch testing: 2019 - 2020 North American Contact Dermatitis Group Screening series; several supplemental series including preservatives, emulsifiers, fragrances, personal care products, adhesive acrylates, antifungals, and select home products including her pads.	**Positive** Strong (++) reactions to Drometrizole 1 % pet., and adhesive portion of the Poise daily pad; Manufacturer indicated, “Drometrizole may be present in their liners”; none of the other patient`s allergens were present in this product. Patient´s dermatitis resolved with specific pad avoidance. Also strong reaction to bacitracin 20 % pet.; weak positive (+) reactions to beta hydroxy acid 2 % in pet. and the skin-side/fabric-side of the Poise daily pad.
2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in report: Drometrizole; 2-(2-Hydroxy-5-methylphenyl) benzotriazole CAS no. 2440-22-4 (Hald et al., 2018)	A 27-year-old woman, with a history of eczema at 3 different occasions: (1) eczema where the nose pads of a pair of sunglasses were in contact with the skin, (2) eczema on tops of her feet after using a pair of flip-flops with rubber straps, (3) eczema on her left wrist after using a Misfit watch with a wristwatch rubber strap. Patch testing: European baseline series (including departmental extensions), more specialised series with fragrances and rubber chemicals and plastics/glues, and test material from patient’s own nose support pads, wristwatch strap, and sandal rubber straps; application on the back under occlusion for 48 h (Finn Chambers). Patch test readings on day (D) 2, D 4, and D 8, according to ESCD guidelines. Chromatographic analyses performed with a high-performance liquid chromatography (HPLC) method suitable for identifying allergens in rubber items.	**Positive** Positive patch test reactions to Drometrizole (?+ on D 2; + on D 4; ?+ on D8); sandal rubber straps (+ on D 4; ?+ on D 8), and a doubtful reaction to the Misfit wristwatch strap on D4. The patient had no reaction to the sunglasses. Drometrizole could be identified in sunglasses (1.8 mg/g), in the wristwatch strap (0.7 mg/g), and in the strap from the rubber sandal (1.1 mg/g) after chromatographic analyses. Other rubber allergens not detected. After the patient ceased using the respective items, the eczema totally disappeared.

<table>
<tr><th>Test substance, Reference</th><th>Relevant information about the study (as applicable)</th><th>Observations</th></tr>
<tr><td>2-(2H-benzotriazol-2-yl)-p-cresol

Name of test substance as cited in report: Tinuvin P; 2-(2-Hydroxy-5-methylphenyl) benzotriazole

(Crépy et al., 2006)</td><td>A 35-year-old worker developed a facial rash after change of his protective glasses. The lesions were located where the edges of the glasses came into contact with the skin, with a clear boundary. They developed a few months after a change of brand of glasses and were caused by within 24 h of use. Since the patient stopped wearing them, he no longer has any rashes.

Path testing: Standard European battery, Chemotechnique plastic-glue battery, and an open test with the product scraped from the edge of the protective eyewear.</td><td>Positive

Clearly positive patch test reactions (+++) to 2-(2-Hydroxy-5-methylphenyl) benzotriazole (Tinuvin P) and the product scraped from the eyewear;

Manufacturer confirmed presence of 2-(2-Hydroxy-5-methylphenyl)-benzotriazole (Tinuvin P) used as an UV absorber in the blue PVC rim of the protective glasses.</td></tr>
<tr><td>2-(2H-benzotriazol-2-yl)-p-cresol

Name of test substance as cited in report: Tinuvin P; 2-(2-Hydroxy-5-methylphenyl) benzotriazole

5.0, 1.0, 0.1, and 0.01 % in pet.

(Arisu et al., 1992)</td><td>A 54-year-old female with a history of cosmetic contact dermatitis developed itchy erythema on shoulders, chest, and upper back after wearing underwear for one night. She bought the underwear and washed it several times before wearing. She put on the underwear for the first time and slept the night in it. The next morning, she noticed itchy erythema on her shoulders, chest and upper back. The outline of the eruption follows that of the underwear.

Two-day closed patch testing performed on her upper back, 3 x with Finn Chambers and Scanpore tape, including Tinuvin P (5.0 to 0.01 % in pet.). Readings were made 1 and 24 h after removal of the patch, according to ICDRG recommendations.

Tinuvin P was suspected as causative agent. HPLC analysis was performed to isolate substance from the spandex tape.</td><td>Positive

Positive patch test reactions to Tinuvin P:

<table><tr><td>C of Tinuvin P</td><td>2 d</td><td>3 d</td></tr><tr><td>5 % in pet.</td><td>++</td><td>++</td></tr><tr><td>1 % in pet.</td><td>++</td><td>++</td></tr><tr><td>0.1 % in pet.</td><td>+</td><td>+</td></tr><tr><td>0.01 % in pet.</td><td>+</td><td>+</td></tr></table>
Patch tests to Tinuvin P 5.0 % in pet. in 30 healthy adult volunteers did not show positive reactions.

Tinuvin P detected in extract from spandex tape (HPLC).

No cross-reaction to other benzotriazoles detected for the patient.</td></tr>
<tr><td>2-(2H-benzotriazol-2-yl)-p-cresol

Name of test substance as cited in report: Tinuvin P; 2-(2-Hydroxy-5-methylphenyl) benzotriazole

0.01, 0.1, and 1 % in pet.

(Kaniwa et al., 1991)</td><td>A patient reacted to the polyurethane elastomer (PUE) tape, used in a T-shirt. An analytical procedure was evaluated to investigate Tinuvin P in the PUE tape using GC-MS and HPLC.</td><td>Positive

Positive patch test reactions:

PUE tape after 48 h (+++) and 96 h (+++)

Extract of PUE tape, 1 % in pet, after 48 h (++) and 96 h (++)

<table><tr><td>C of Tinuvin P</td><td>48 h</td><td>96 h</td></tr><tr><td>1 % in pet.</td><td>+++</td><td>+++</td></tr><tr><td>0.1 % in pet.</td><td>++</td><td>++</td></tr></table></td></tr>
</table>

Test substance, Reference	Relevant information about the study (as applicable)	Observations
Publication in Japanese		0.01 % in pet. ++ ++ Tinuvin P detected in causative PUE tape.
2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in report: Tinuvin P; 2-(2-Hydroxy-5-methylphenyl) benzotriazole Purity > 99 % 1 % in pet. (Nikilasson and Björkner, 1989)	A 47-year-old male working as a bartender in a nightclub for 5 years, opening bottles and cans during the night. He often cut himself on bottle caps and cans. In 1984, he developed a tylotic eczema on the palms and volar aspects of the fingers, which got worse during working and cleared during longer periods of absence from work. Skin biopsy could not distinguish between psoriasis and tylotic eczema. For 1 year, he had also noticed eczema on his wrists right under a plastic watch strap. Patch testing: Swedish standard series, piece of patient's watch, and special plastics & glues series using the Finn Chamber technique for 48 h. Tinuvin P was suspected as causative agent. HPLC analysis was performed to detect Tinuvin P in watch strap.	**Positive** Strong positive patch test reaction to Tinuvin P 1 % in pet. (plastics & glues series); Tinuvin P 1 % in pet. was tested in 20 controls with negative results. Strong positive test reaction to plastic watch strap. Tinuvin P detected in watch strap (HPLC, maximum level estimated at 0.02 % (w/v)). The patient was patch test-negative to standard series or other benzotriazole compounds.
2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in report: Tinuvin P; 2-(2-Hydroxy-5-methylphenyl) benzotriazole (van Hecke and Vossaert, 1988)	A 57-year-old man developed a dermatitis after wearing a colostomy device (Squibb System 2), around the ostomy on the right abdominal skin down to the right thigh, exactly where the skin was covered by the appliance. Patch testing: Parts of the device and the European standard series and a plastic & glue series (Chemotechnique). The producer provided a non-Tinuvin-P-containing ostomy bag.	**Positive** Redness and oedema after 48 h to pieces of the plastic bag of the device Positive patch test reaction to 2-(2-Hydroxy-5-methylphenyl) benzo-triazole (Tinuvin P) The producer informed that Tinuvin P is used at concentrations of less than 0.5 % in the device. The patient did not develop dermatitis after contact with non-Tinuvin-P-containing ostomy bag.
2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in report:	A 37-year-old female medical secretary presented with swelling of eyelids and itching eruption on her face, starting one week before visiting the department of dermatology. She strongly suspected allergy to one of her facial cosmetic products. Immediately following the onset of eruption, she had stopped using these cosmetics, but had continued to use her nail	**Positive** Positive reactions to colour ingredients Synthetic Pearl I and II (containing bismuth oxychloride).

<table>
<tr><th>Test substance, Reference</th><th>Relevant information about the study (as applicable)</th><th>Observations</th></tr>
<tr>
<td>Tinuvin P; Drometrizole; 2-(2-Hydroxy-5-methyl-phenyl) benzotriazole

1 and 5 % in pet.

(De Groot and Liem, 1983)</td>
<td>varnish. On examination, her right upper eyelid was oedematous, and showed slight erythema and scaling; on the cheeks, a mild papular eruption was noted.

After eruption had subsided, patch tests were performed to standard series (ICDRG), pure nail varnish, and other cosmetics (N = 21).

After 48 h, all tests were negative, but after a further 2 days, positive reaction (+) to one of the nail varnishes was observed. Ingredients of the nail varnishes were tested separately (Food Inspection Service, Enschede).</td>
<td>
<table>
<tr><td></td><td>48 h</td><td>96 h</td></tr>
<tr><td></td><td colspan="2">Synthetic pearl I</td></tr>
<tr><td>10 % MEK</td><td>?+</td><td>+</td></tr>
<tr><td>pure</td><td>?+</td><td>++</td></tr>
<tr><td></td><td colspan="2">Synthetic pearl II</td></tr>
<tr><td>10 % MEK</td><td>?+</td><td>++</td></tr>
<tr><td>pure</td><td>?+</td><td>++</td></tr>
</table>
Patch test negative for all other ingredients

Patch-testing to constituents of Synthetic Pearl yielded positive reaction to Tinuvin P:
<table>
<tr><td>C of Tinuvin P</td><td>48 h</td><td>96 h</td></tr>
<tr><td>5 % in pet.</td><td>+</td><td>++</td></tr>
<tr><td>1 % in pet.</td><td>?+</td><td>?+</td></tr>
</table>
Patch testing to Tinuvin P 5 % in pet. was negative in 8 controls.
</td>
</tr>
<tr>
<td>2-(2H-benzotriazol-2-yl)-p-cresol

Name of test substance as cited in report: Tinuvin P; 2-(2-Hydroxy-5-methyl-phenyl)-benzotriazole

1 % in pet.

(Björkner and Niklasson, 1997)</td>
<td>A 69-year-old woman was retired since 1986 from work as librarian. For 25 years, she had dental gold and for many years, also acrylic composite restorative materials. In the last 8 years, she showed gingivitis (red, elevated, ulcerated, and bleeding) in her frontal upper jaw, more pronounced close to two teeth, one restored with gold and the other one with a certain composite filling (also lichenoid reactions in frontal upper gingiva detected).

Patch testing: extensive dental screening series from Chemotechnique Diagnostics using Finn Chambers according to ICDRG for 4 h. Readings after 72 h and one week.

Chemical analysis was performed to detect Tinuvin P in dental material (brand known from patient’s dentist) using HPLC analysis.</td>
<td>Positive

Positive patch test reaction to Tinuvin P, 1 % in pet. and gold sodium thiosulfate (5 % in pet.) from the dental screening series

Both substances previously tested negative in more than 20 controls

Tinuvin P present in the dental restorative material, detected by HPLC (maximum level estimated to be 0.09 %)</td>
</tr>
</table>

Test substance, Reference	Relevant information about the study (as applicable)	Observations
2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in report: Tinuvin P; 2-(2-Hydroxy-5-methyl-phenyl)-benzotriazole 1 % in pet. (Cronin, 1980) Cited in (Lee et al., 2019)	During 1974 – 1976, 4 women with contact dermatitis after using a facial cream containing Tinuvin P are reported. All women exhibited eczema on their face. One woman had eczema only on her eyelids. Two of the women who used the cream on other areas developed eczema on these areas. Patch testing was performed to Tinuvin P, 1 % in pet. and face cream.	**Positive** All 4 women showed positive patch test reaction to Tinuvin P, 1 % in pet. 2 of 3 women reacted positive to their face cream. 3 of the patients used one particular brand of cosmetics and the manufacturers have since withdrawn Tinuvin P from their products.

A literature search revealed ten publications on case reports, summarising the medical history of patients sensitised to 2-(2*H*-benzotriazol-2-yl)-*p*-cresol (Table 8). All patients showed positive patch test reactions to 2-(2*H*-benzotriazol-2-yl)-*p*-cresol. Furthermore, 2-(2*H*-benzotriazol-2-yl)-*p*-cresol as the causative agent was found in sanitary pads, protective glasses, the strap of a wristwatch, and the spandex tape of underwear, the polyurethane elastomer (PUE) tape of a T-shirt, nail varnish, a dental restorative material, and face cream.

Table 9: Summary table of human data on skin sensitisation - Diagnostic patch test studies

Type of data/report, reference	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**
Diagnostic patch test study Selected dermatitis patients (Peng et al., 2018)	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in study: Drometrizole 1 % in pet. CAS no. 2440-22-4	2015 – 2016: Retrospective review of medical records from female patients (in total 443) with facial dermatitis (FD) in Peking University People's Hospital Dermatology Clinics; patch testing with Chinese Baseline Series and Cosmetic Series and IQ chamber (Chemotechnique Diagnostics, Malmo, Sweden). FD divided into facial cosmetic dermatitis (FCD), in which lesions relate to the use of cosmetics, and non-FCD, in which dermatitis irrelevant to cosmetics. In the FCD group, 88 patients highly suspected of facial cosmetic allergic contact dermatitis were tested to the Cosmetic Series including 58 allergens. In the non-FCD group, the other 355 patients were tested to Chinese Baseline Series (60 allergens). The patch test was applied on the upper back for 48 hours; results were recorded on D 2 and 3 according to International Contact Dermatitis Research Group (ICDRG).	Positive 7/88 (7.9 %) Prevalence: 9 High frequency Low number of patients tested
Diagnostic patch test study Selected dermatitis patients (Tomar et al., 2005)	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in study: 2-(2-Hydroxy-5-methyl-phenyl) benzotriazole 1 % in pet.	50 patients (mean age 27.5 years, 35 females and 15 males) with clinically suspected cosmetic dermatitis were subjected to patch testing with a cosmetic and fragrance series, approved by the Contact and Occupational Dermatosis Forum of India (CODFI), and with selected allergens from the Indian Standard Series (ISS). Scoring ICDRG grading on D 2 and 4. Only reactions still positive on D 4 were considered positive. In total, 33 subjects were patch tested to 2-(2-Hydroxy-5-methylphenyl) benzotriazole.	Positive 1/33 (3 %) High frequency Low number of patients tested
Diagnostic patch test study Selected dermatitis patients (Tarvainen, 1995)	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in study: 2-(2-Hydroxy-5-methyl-phenyl) benzotriazole 1 % in pet.	1985 - 1992, 10 280 patients visiting the University Dermatology Clinic in Helsinki were patch tested with the standard series recommended by the Finnish Contact Dermatitis Group. In total, 839 (7 %) patients were tested with a plastics & glues series (based on anamnestic data) using the Finn Chamber method.	Negative 0/343

Human diagnostic patch test studies cover the elicitation phase and indicate previous sensitisation to a test substance in humans. There are few human patch test studies available from the literature, including selected dermatitis patients tested to 2-(2*H*-benzotriazol-2-yl)-*p*-cresol (Table 9).

Diagnostic patch test studies conducted with selected dermatitis patients show frequencies of occurrence of skin sensitisation of 7.9 % (Peng et al., 2018) and 3 % (Tomar et al., 2005), however, a low number of

patients was tested in these studies. In another patch test study on selected dermatitis patients no skin sensitisation to the test substance was observed (Tarvainen, 1995).

Table 10: Summary table of human data on skin sensitisation - Human predictive patch test studies

Type of data/report, reference	**Test substance**	**Relevant information about the study (as applicable)**	**Observations**
Human repeated insult patch test (HRIPT) Reliability: 2, reliable with restriction (suggested by registrant) (Hill Top, 1960)	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in study: Tinuvin P Purity: No information	59 subjects (9 men and 35 women, age of 20 to 50 years, and 3 men and 12 women over 50 years) received 24-hour patch exposures to 0.2 % of the test substance Tinuvin P in 0.5 % dimethyl phthalate, three times weekly - for three weeks, followed by a similar challenge exposure in the sixth week. Based on the information available (patch area of 3/4 x 7/8-inch, 0.5 mL of the test substance Tinuvin P at a concentration of 0.2 %), the dose per skin area was calculated by the DS to be ca. 230 µg/cm^2 (Strickland et al., 2023).	Negative 0/59
Clinical studies (incl. HRIPT and controlled use study) Not assignable Secondary reports on several sensitisation studies cited from (Cosmetic Ingredient Review, 1986)	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in study: Drometrizole 0.03 % and 1.0 %	*"Cosmetic products containing 0.03% to 1.0% Drometrizole produced no irritation, sensitization, photosensitization, or phototoxicity in a total of 436 subjects."* *"In a 3-year clinical therapeutic trial conducted to evaluate the effectiveness of two UV-absorbing preparations containing up to 5% Drometrizole, two hypersensitivity reactions were observed during 445 applications. A total of 145 patients were used, some of whom suffered from light dermatoses and light sensitivity."*	Negative 0/436
HRIPT Not assignable (CTFA, 1984) Cited in (Lee et al., 2019)	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in study: Drometrizole 0.5 %	Nail polish containing 0.5 % drometrizole was applied to upper back of 148 subjects by topical occlusive patches, every Monday, Wednesday, and Friday for 3 consecutive weeks. Scores were measured before new patches were attached. After a two-week break following last exposure, new patches were applied to untreated sites for 48 h. Reaction scores were determined at 48 and 96 h.	Negative 0/148
Human maximisation test (HMT) According to ECHA dissemination site: Documentation insufficient for assessment. (Kligman, 1964)	2-(2*H*-benzotriazol-2-yl)-*p*-cresol Name of test substance as cited in study: Tinuvin P 25 %	25 healthy young adults received 5 applications for 48 h, respectively, with 1-d interval between exposures (24-h pre-treatment with 6 % sodium lauryl sulphate to cause slight irritation; because test substance is non-irritating); concentration of 25 % of Tinuvin P in vaseline used for induction; 2 weeks after last exposure, challenge reaction by application of a patch with 10 % of the substance in pet. for 48 h (patch consisted of a 1.5 square-inch non-woven cloth onto which about 750 mg of the substance were applied). Readings were made after 48, 72, and 96 h.	Negative 0/25

Human predictive patch tests (HPPTs) were conducted as induction studies and included the human maximisation test (HMT) and human repeated insult patch test (HRIPT). The HPPTs followed non-guideline protocols and mostly, original reports were not available. According to the CLP Regulation (EC) No. 1272/2008, data from HPPT may be used in a weight of evidence approach for sub-categorisation by taking into account the dose per skin area (DSA) that induced skin sensitisation in humans (ECHA, 2017).

HPPT performed with 2-(2*H*-benzotriazol-2-yl)-*p*-cresol are available from the dissemination site and literature search and are summarised in Table 10. In a reliable HRIPT, a concentration of 0.2 % of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol did not induce skin sensitisation (Hill Top, 1960). The DSA was calculated by the DS (Strickland et al., 2023), revealing approx. 230 µg/cm^2. In other HRIPT and HMT, 2-(2*H*-benzotriazol-2-yl)-*p*-cresol did not induce skin sensitisation using concentrations from 0.03 % to 25 % (Cosmetic Ingredient Review, 1986; CTFA, 1984; Kligman, 1964). However, these HPPTs were not considered for further assessment because of their insufficient documentation.

10.5.3 Other studies relevant for skin sensitisation

Table 11: Summary table of other studies relevant for skin sensitisation - *in silico* data

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
Q(SAR) model, with limited documentation /justification Reliability 4: not assignable	2-(2*H*-benzotriazol-2-yl)-*p*-cresol EC no. 219-470-5	Identification of structural alerts for skin sensitisation by (QSAR), knowledge base version: Lhasa Ltd\LPS 11\DfW11.mdb	Identification of structural alert for protein binding	(CIBA, 2009)

The registrant submitted information on a Q(SAR) model identifying an alert for skin sensitisation, namely a structural alert for protein binding. However, the model is of limited documentation/justification and relevant information was not available for the DS.

The DS used the OECD QSAR toolbox to identify alerts for skin sensitisation for 2-(2*H*-benzotriazol-2-yl)-*p*-cresol.

- OECD QSAR Toolbox v. 4.6 (https://qsartoolbox.org)

Sensitisation: Protein binding potency Lys (DPRA 13 %), protein binding by OECD, protein binding by OASIS, protein binding potency Cys (DPRA 13 %), protein binding potency GSH, protein binding potency h-CLAT, protein binding alerts for skin sensitisation according to GHS, protein binding alerts for skin sensitisation by OASIS, Keratinocyte gene expression

Using the OECD QSAR Toolbox, no alerts for skin sensitisation were predicted for 2-(2*H*-benzotriazol-2-yl)-*p*-cresol.

It is important to note that the profiler used does not represent fully valid (Q)SAR predictions. It should be seen as an indicator of similar hazardous potential within a group/category, which later requires verification *in vitro* or *in vivo*.

10.5.4 Short summary and overall relevance of the provided information on skin sensitisation

In a GPMT performed according to OECD TG 406, animals were intradermally injected with 5 % of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol, followed by an epicutaneous induction using a concentration of 30 %, and animals were challenged with 20 % of the test substance (CIBA-GEIGY, 1992). In total, 80 % (16/20) and

90 % (18/20) of the animals showed positive skin reactions 24 and 48 hours after challenge, respectively. However, 10 % (1/10) and 20 % (2/10) of negative control animals showed positive skin reactions 24 and 48 hours after challenge with 20 % of the test substance, respectively. Nevertheless, the number of positive reactions in test animals was much higher, compared to negative controls and taking the unequivocal results of the positive controls into account, the data are considered valid to conclude that 2-(2*H*-benzotriazol-2-yl)-*p*-cresol acts as a skin sensitiser. However, data should be taken with care concerning sub-categorisation.

Two LLNA performed similar to OECD TG 429, investigated relatively low concentrations of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol. Concentrations of 0.25, 0.5, 1, and 2 % of the test substance did not result in a SI-value > 3 (Ikarashi et al., 1994a). In the other LLNA, only one concentration of 1 % of the test substance was investigated and did not increase local lymph node cell proliferation compared to controls (Ikarashi et al., 1994b). Both studies show deviations from OECD TG 429, regarding the experimental schedule and preparation of local lymph node cells. Draining auricular lymph nodes were isolated only one day following the final application of the test substance. Single cell suspensions were prepared and cells were cultured in the presence of 3H-methyl thymidine (3HTdR) for 24 hours, following determination of spontaneous proliferation of single local lymph node cells. Altogether, the substance EC no. 219-470 did not induce skin sensitisation at concentrations ≤ 2 % tested under the conditions of these studies. Nevertheless, a skin sensitising potential of the substance cannot be excluded.

There is evidence from human data that 2-(2*H*-benzotriazol-2-yl)-*p*-cresol acts as a skin sensitiser. Case reports from ten publications show patients with positive patch test reactions to the substance 2-(2*H*-benzotriazol-2-yl)-*p*-cresol. Furthermore, 2-(2*H*-benzotriazol-2-yl)-*p*-cresol was identified as the causative agent in several products used by the patients.

Diagnostic patch test studies conducted with selected dermatitis patients show relatively high frequencies of occurrence of skin sensitisation (7.9 % and 3 %, however a low number of patients were tested). Another patch test study does not show skin sensitisation to the test substance.

In a reliable HRIPT, 2-(2*H*-benzotriazol-2-yl)-*p*-cresol did not induce skin sensitisation using a concentration of 0.2 %. The DSA was calculated by the DS based on provided information and corresponds to approximately 230 µg/cm^2. Even though the HRIPT data are negative, a skin sensitisation potential of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol, when tested at DSA > 230 µg/cm^2, cannot be excluded.

10.5.5 Comparison with the CLP criteria

Reliable (at least reliability 2) and relevant experiments for animal and human data are compared with the CLP criteria, as laid down in the Guidance on the Application of the CLP criteria (Table 12).

Table 12: Comparison of human and animal data for skin sensitisation with CLP criteria

Reference(s)	**Criteria acc. to CLP regulation, as laid out in (ECHA, 2017)**	**Results**	**Resulting Classification**
Animal data			
GPMT (OECD TG 429) (CIBA-GEIGY, 1992)	<u>Skin Sens. 1A - Extreme potency:</u> ≥ 60 % sensitised guinea pigs at ≤ 0.1 % intradermal induction <u>Skin Sens. 1A - Strong potency:</u> ≥ 30 - < 60 % guinea pigs sensitised at ≤ 0.1 % intradermal induction or ≥ 60 % guinea pigs sensitised at > 0.1 - ≤ 1.0 % intradermal induction <u>Skin Sens. 1B - Moderate potency:</u> ≥ 30 - < 60 % guinea pigs sensitised at > 0.1 - ≤ 1.0 % intradermal induction or ≥ 30 % guinea pigs sensitised at > 1.0 % intradermal induction	Positive ≥ 30 % guinea pigs sensitised at > 1.0 % intradermal induction (80 % and 90 % (24 h and 48 h) positive at 5 % intradermal induction, however, positive reactions in negative controls (10 % (24 h) and 20 % (48 h))	**Skin Sens. 1** (not suitable for sub-categorisation)

LLNA (Similar to OECD TG 429) (Ikarashi et al., 1994a)	Skin Sens. 1A: 0.2 % < EC3 ≤ 2 %, Strong sensitiser EC3 ≤ 0.2 %, Extreme sensitiser Skin Sens. 1B: EC3 > 2 %, Moderate sensitiser	Negative Concentration ≤ 2 % tested Application of CLP criteria questionable	**No classification** **Skin Sens. 1 cannot be excluded**
Human data			
Human diagnostic patch test study Selected dermatitis patients (Peng et al., 2018; Tarvainen, 1995; Tomar et al., 2005)	Skin Sens. 1 Relatively low/moderate frequency (< 2.0 %) and relatively low exposure or relatively high frequency (≥ 2.0 %) and relatively high exposure Skin Sens. 1A Relatively high frequency (≥ 2.0 %) and relatively low exposure Skin Sens. 1B Relatively low/moderate frequency (< 2.0 %) and relatively high exposure	Frequency of occurrence of skin sensitisation either negative or "relatively high" Exposure unclear	**Skin Sens. 1** (not suitable for sub-categorisation)
Number of published cases (Arisu et al., 1992; Björkner and Niklasson, 1997; Crépy et al., 2006; Cronin, 1980; De Groot and Liem, 1983; Hald et al., 2018; Kaniwa et al., 1991; Kullberg and Hylwa, 2020; Nikilasson and Björkner, 1989; van Hecke and Vossaert, 1988)	Skin Sens. 1 Relatively low/moderate frequency (< 100 cases) and relatively low exposure or relatively high frequency (≥ 100 cases) and relatively high exposure Skin Sens. 1A Relatively high frequency (≥ 100 cases) and relatively low exposure Skin Sens. 1B Relatively low/moderate frequency (< 100 cases) and relatively high exposure	< 100 cases published "Relatively low/moderate" frequency of occurrence of skin sensitisation Exposure unclear	**Skin Sens. 1** (not suitable for sub-categorisation)
HPPT			
HRIPT (Hill Top, 1960)	Skin Sens. 1 Induction threshold from HRIPT or HMT ≤ 500 or > 500 µg/cm^2 Skin Sens. 1A Induction threshold ≤ 500 µg/cm^2 Skin Sens. 1B Induction threshold < 500 µg/cm^2	Negative at approx. 230 µg/cm^2	**No classification** **Skin Sens. 1 cannot be excluded**

In a GPMT performed according to OECD TG 406, an induction concentration of 5 % of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol, followed by an epicutaneous induction using a concentration of 30 %, and challenged with 20 % of the test substance, resulted in 80 % (16/20) and 90 % (18/20) of the animals with positive skin reactions, 24 and 48 hours after challenge, respectively (CIBA-GEIGY, 1992). However, negative control animals showed 10 % (1/10) and 20 % (2/10) positive skin reactions 24 and 48 hours after the challenge, respectively. Therefore, the absolute numbers of test animals with positive reactions may show some uncertainties. Nevertheless, the total number of positive reactions in induced animals is much higher compared to negative controls and the overall data (including the clearly positive control) support that 2-(2*H*-

benzotriazol-2-yl)-*p*-cresol acts as a skin sensitiser. Because of the occurrence of some positive reactions in the negative controls, the DS acknowledges some putative uncertainties on the true numbers of animals with positive skin reactions (albeit their high percentages, reaching 90 % at 48 h) at 5.0 % intradermal induction. Thus, the study results were not used for sub-categorisation. Moreover, induction concentrations below 5 % were not tested (to exclude Cat 1A).

In two LLNAs performed similarly to OECD TG 429, 2-(2*H*-benzotriazol-2-yl)-*p*-cresol did not induce skin sensitisation using concentrations ≤ 2 %. Higher concentrations were not tested and it cannot be excluded based on this result that the substance acts as a skin sensitiser. Deviations from the OECD TG 429 concerning the experimental schedule and determination of cell proliferation makes it questionable if the CLP criteria can be applied (concentration of 2 % tested as threshold to distinguish between a skin sensitiser with a strong or moderate potency; (ECHA, 2017)).

There is evidence from human data that 2-(2*H*-benzotriazol-2-yl)-*p*-cresol acts as a skin sensitiser. However, contact allergy to the substance appears to be rare based on the available data. Two human diagnostic patch test studies on selected dermatitis patients reveal a "relatively high" frequency of occurrence of skin sensitisation (≥ 2.0 %, relatively high frequency (ECHA, 2017)) in one human diagnostic patch test study no sensitisation to 2-(2*H*-benzotriazol-2-yl)-*p*-cresol was detected. The number of published case reports (< 100 cases) support a "relatively low/moderate" frequency of occurrence of skin sensitisation to 2-(2*H*-benzotriazol-2-yl)-*p*-cresol. Human data do not give information on the exposure of the test substance and are not suitable for sub-categorisation.

In a reliable HRIPT, approx. 230 µg/cm^2 of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol did not induce skin sensitisation, however induction of skin sensitisation at higher DSA cannot be excluded.

In the view of the DS, the positive GPMT and human clinical data have higher weight than the negative LLNA or HRIPT, which were obtained using comparatively low test concentrations (≥ 2 % or 230 µg/cm^2, respectively).

Altogether, 2-(2*H*-benzotriazol-2-yl)-*p*-cresol acts as a skin sensitiser as shown by human data. There are no OECD TG-conform and reliable animal data available to conclude on the potency of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol and therefore, available data do not allow for sub-categorisation.

10.5.6 Conclusion on classification and labelling for skin sensitisation

In conclusion, the DS proposes to classify 2-(2*H*-benzotriazol-2-yl)-*p*-cresol as skin sensitiser without sub-categorisation as **Skin Sens. 1 (H317 - May cause an allergic skin reaction)** and a GCL of 1 % (w/v).

10.6 Germ cell mutagenicity

Not assessed in this dossier

10.7 Carcinogenicity

Not assessed in this dossier

10.8 Reproductive toxicity

Not assessed in this dossier

10.9 Specific target organ toxicity-single exposure

Not assessed in this dossier

10.10 Specific target organ toxicity-repeated exposure

Not assessed in this dossier

10.11 Aspiration hazard

Not assessed in this dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Table 13: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
OECD Guideline 301 B	0 - 2 % CO_2 evolution after 28 days	Reliability 2 (Registrant: Reliability 1) Test concentration above water solubility limit. Derivations: The volume of the test solution was reduced from 3.0 L to 1.5 L. The CO_2 formed by biodegradation was absorbed with NaOH and determined on a carbon analyser.	Registration dossier (CIBA-GEIGY Ltd., 1989)
OECD Guideline 301 C	1% degradation after 4 weeks (based on BOD) 2% degradation after 4 weeks (based on HPLC)	Reliability 2	(NITE, 2023)
BIOWIN (v4.11)	Overall, not readily biodegradable BIOWIN 1: biodegrades fast (0.8108); BIOWIN 2: biodegrades fast (0.7851); BIOWIN 3: weeks-months (2.6829); BIOWIN 4: days-weeks (3.4939); BIOWIN 5: not readily degradable (0.2481); BIOWIN 6: not readily degradable (0.1597)	Reliability 2 2-(2*H*-benzotriazol-2-yl)-*p*-cresol is in the molecular weight range of the model's training sets. The molecular fragments used for calculation do not exceed the maximum number of such fragments per molecule observed in the training set. The training set for BIOWIN 1 and 2 does not contain benzotriazoles. BIOWIN 3 and 4 were trained on structurally related substance (2-(2H-enzotriazol-2-yl)-phenol). The validation set of BIOWIN 5 and 6 contained the structurally related 1H-Benzotriazole.	(BIOWIN v4.11)
Dissipation in biosolid-amended soils (biosolid application rate 60 t/ha; single and repeated application)	Dissipation in the field: DT_{50} = 113 days (single application) DT_{50} = 75 days (repeated application)	Reliability 2 No ultimate degradation, only dissipation	(Lai et al., 2014b)
Dissipation in biosolid-amended soils (biosolid application rates 5, 10, 20 and 40 t/ha; single and repeated application)	Dissipation in the field: DT_{50} = 99 – 149 days (single application) DT_{50} = 85 – 157 days (repeated application)	Reliability 2 No ultimate degradation, only dissipation	(Lai et al., 2014a)

11.1.1 Ready biodegradability

The ready biodegradability of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol was evaluated in a CO_2 Evolution Test according to OECD Guideline 301 B. The initial concentrations of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol used in this study were 11 mg/L and 20.1 mg/L. Activated sludge from a wastewater treatment plant was used as inoculum (concentration and adaptation not specified). Nonylphenol 10EO5PO solution (0.5 mL) was added to the test substance system, reference substance system and blank system. After 28 days, 0 % biodegradation at the lower concentration and 2 % biodegradation at the higher concentration were determined. The registrant noted that the results may not reflect the real degree of biodegradability as no method was available to maintain the substance in suspension. The reference compound aniline reached the pass level for ready biodegradability within 10 days.

Very similar results were obtained in a test according to OECD Guideline 301 C from the Japanese J-CHECK database. 100 mg/L test substance and 30 mg/L activated sludge was used. The degree of degradation after 4 weeks was determined by BOD measurement and HPLC, yielding 1 % and 2 %, respectively.

A prediction of the ready biodegradability of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol supports the result of the experimental study. Based on BIOWIN (see Table 13) the substance is predicted to be not readily biodegradable.

11.1.2 BOD_5/COD

No relevant data available

11.1.3 Hydrolysis

No relevant data available. Hydrolysis is not expected due to the absence of functional groups susceptible to hydrolysis.

11.1.4 Other convincing scientific evidence

No relevant data available

11.1.4.1 Field investigations and monitoring data (if relevant for C&L

2-(2*H*-benzotriazol-2-yl)-*p*-cresol and further phenolic benzotriazoles have been detected in sediment sections that date back years or even decades, both in samples downstream a former point source and in samples from urban estuaries (Cantwell et al., 2015; Lopez-Avila and Hites, 1980; Peng et al., 2017; Reddy et al., 2000; White et al., 2008). Detection of a substance in sediment layers dating back decades ago can be considered indicative of high persistence. Nevertheless, as monitoring data are very difficult to use for classification purpose the data will not be further considered for classification.

11.1.4.2 Inherent and enhanced ready biodegradability tests

No relevant data available

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

Lai et al. investigated the dissipation behaviour of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol and further phenolic benzotriazoles in the soil environment associated with biosolid applications (Lai et al., 2014b). Dewatered sludge from a WWTP in Beijing was applied onto agricultural land in Shandong, China. In the first experiment only one application was carried out for treatment (Treatment T1, biosolid application 60 t/ha, May 2007), while in the second experiment application was repeated every year (Treatment T2, biosolid application 60 t/h, October 2007-2010). In addition, there was a control site where no treatments were

conducted. In order to incorporate the sludge, the trial fields were ploughed to a depth of 20 cm. On the fields wheat and maize were cultivated.

Soil samples were taken monthly in a depth between 0 and 20 cm from October 2010 until October 2011 (except January and February 2011). Each sampling of the four replicates consisted of five subsamples that were mixed. The soil samples were extracted with methanol/dichloromethane (50:50, v/v) at 120 °C for 5 minutes in two cycles. Concentrations of the benzotriazoles were detected via GC-MS. For 2-(2*H*-benzotriazol-2-yl)-*p*-cresol the limit of detection was 0.47 ng/g (limit of quantification = 1.57 ng/g) for soil samples and 3.49 ng/g (limit of quantification = 11.6 ng/g) for biosolid sampled.

No 2-(2*H*-benzotriazol-2-yl)-*p*-cresol was detected in the soil samples from the control plots. Due to considerable variability of the concentration at the beginning of the measurements (increasing concentration; possible reasons: difficulties in obtaining a homogeneous sample during frost period and degradation of samples during storage until extraction), the authors performed the dynamic curve-fitting only between March 2011 and October 2011. For 2-(2*H*-benzotriazol-2-yl)-*p*-cresol dissipation half-lives of 113 days and 75 days were detected for T1 and T2, respectively. Transformation products were not determined.

A similar study from the same authors on the same type of test soil at the same location is available (Lai et al., 2014a). This study includes treatment groups with repeated biosolid applications every year within five years (repeated application at rates of 5, 10, 20 and 40 t/ha, October 2006 - 2010), groups with only one biosolid application (application at rates of 10, 20 and 40 t/ha, October 2010) and control sites. Soil samples were taken monthly in a depth between 0 and 20 cm from October 2010 until October 2011 (except January and February 2011). 2-(2*H*-benzotriazol-2-yl)-*p*-cresol was detected in all samples from sites with biosolid application, but not in the control groups. Concentrations of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol increased from October 2010 to March 2011 – an effect observed in the above study as well. Hence, in analogy to the approach from the related study, the authors performed dynamic curve fitting for the period of March 2011 to October 2011. The dissipation half-lives for 2-(2*H*-benzotriazol-2-yl)-*p*-cresol in the field trials were 85 – 157 days for repeated application and 99 – 149 days for single application.

Both studies consider only dissipation. However, for classification purpose ultimate degradation has to be demonstrated. Nevertheless, the results indicate that 2-(2*H*-benzotriazol-2-yl)-*p*-cresol is not rapidly degradable.

11.1.4.4 Photochemical degradation

No relevant data available

11.2 Environmental fate and other relevant information

No experimental data available

11.3 Bioaccumulation

Table 14: Summary of relevant information on bioaccumulation

Method	Results	Remarks	Reference
OECD Guideline 107 (shake flask method)	Log Kow = 4.2 (25 °C, pH = 6.3)	Reliability 2, no GLP	Registration dossier (CIBA-GEIGY Ltd., 1988a)
OECD Guideline 305	BCF_{Kgl} > 500 (lipid normalised, growth corrected)	Reliability 2 (Registrant Reliability 1) GLP	Registration dossier (BASF SE, 2020)
OECD Guideline 305 C	BCF = 180 – 410 L/kg (lipid normalised, test conc. 0.1 mg/L) BCF = 61 – 306 L/kg (lipid normalised, test conc. 0.01 mg/L)	Reliability 3 (Registrant Reliability 2) GLP	Registration dossier (NITE, 1998)

11.3.1 Estimated bioaccumulation

Not relevant for this dossier, as experimental data are available.

11.3.2 Measured partition coefficient and bioaccumulation test data

The registrant performed a study according to OECD 117 (shake flask method) to determine the log K_{OW}. The log K_{OW} is determined to be 4.2 at 25 °C.

Two BCF studies according to OECD 305 are provided.

The first study from 2020 assessed the bioconcentration potential of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol in juvenile rainbow trout (*Oncorhynchus mykiss*) according to the guideline OECD 305-I (aqueous exposure). The fish were exposed to the test substance at 0.5 µg/L in a flow-through-system for an uptake period of 35 days followed by a depuration period in clean water of 14 days. Over the entire test all water quality parameters were maintained within acceptable limits. All validity criteria were fulfilled, and thus this study is considered being valid. During the uptake phase concentration in test solution and fish was measured on 10 occasions. During the depuration phase the concentration in test solution was measured on four occasions and in fish on five occasions. Test substance concentrations in fish were determined by measuring the total radioactivity separately in edible (e.g. fillet) and non-edible (e.g. remaining carcass) portions and the whole fish value was calculated from the weight normalised sum of the individually measured portions.

Fish growth rate constant (kg) of 0.018 day^{-1} for test group was calculated and used for "growth-corrected" calculations. The overall mean lipid content of 3.2 % was used for lipid correction. The lipid normalised steady state bioconcentration factor (BCF_{ss}) of 1623 L/kg was similar to the lipid normalised and growth corrected kinetic (BCF_{Kgl}) of 1456 L/kg indicating that steady state might have been reached. According to the OECD 305 guidance a steady-state is reached in the plot of test substance concentration in fish (C_f) against time when the curve becomes parallel to the time axis and three successive analyses of C_f made on samples taken at intervals of at least two days are within ± 20 % of each other, and there is no significant increase of C_f in time between the first and last successive analysis. According to this, it needs to be concluded that steady state was not reach in the current study. The C_f curve did not become parallel to the time axe but fluctuated during the uptake phase. Steady state was not reached at the end of the uptake period as (1) there was an extreme intermediate drop in C_f between day 21 and day 35, (2) the three last C_f values of the uptake phase (day 28, 31, 35) are not within ± 20 % of each other. The derived steady state value is considered as not reliable by the DS.

The kinetic derived growth and lipid corrected BCF_{kgL} given in the study report is 1456 L/kg. The corresponding experimentally derived uptake rate constant k_1 of 1166 L/kg/day is in the range of model expectation but due to fluctuation and the subsequent large confidence interval the fitted k_1 is questionable. The experimentally derived k_2 value might be considered as reliable and used for BCF estimation together with estimated uptake rate k_1 (Goss et al., 2018) using the OECD BCF Estimation Tool. However, due to questionable increase in average C_f within only a few hours at the starting day of the depuration phase (day 35: 383 µg/g, day 35.125: 532) the growth corrected k_2 value of 1.24 d^{-1} was refitted by the DS based on the raw data. A k_2 value of 0.39 d^{-1} (one compartment, log normal transformation, $\lambda = 0.43$) was estimated. The OECD BCF Estimation Tool (Version 2) was used to calculate BCF values. The majority of these BCF values (11 out of 14) was >> 500.

The second study from 1998 assessed the bioconcentration potential of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol in carp (*Cyprinus carpio*) according to the old guideline OECD 305-C. Therefore, not all requirements of the current OECD 305 guideline are fulfilled. The fish were exposed to the test substance at 1, 0.1, and 0.01 mg/L in a flow-through-system for an uptake period of 8 weeks followed by no depuration phase. The first test concentration of 1 mg/L exceeded the water solubility of 0.173 mg/L and was therefore not reliable and disregarded. For the remaining two test concentrations it is unclear if the water quality were maintained within acceptable limits over the entire test as details not given in the summary report. Using a single sample for one analysis, the test water samples from the 2nd and 3rd concentration range were analysed twice a week,

respectively, during the exposure period, totalling 16 analyses per conc. range. In addition, two test fish samples from each test concentration were analysed 2, 4, 6, and 8 weeks after the initiation of exposure, totalling four analyses per conc. range. The test fish from the control conc. range was analysed before initiation and after completion of exposure, using two fish per analysis.

The lipid content (3.6 %) is only given for the start of the exposure period. Therefore, it is unclear if the lipid content changed during the test period. BCF values (not lipid normalised) range from 130 – 295 L/kg and 44-220 L/kg for the test concentration 0.1 and 0.01 mg/L. Using the available lipid content, the lipid normalised BCF values ranged from 180 – 410 and 61 – 306 L/kg. No information on fish growth is available and growth correction of the BCF values was not performed. Due to the limited information on lipid content, missing growth correction, and the fact that the study is performed according to the old OECD 305 guidance the BCF values have medium to high uncertainty.

In summary, both studies have shortcomings. The study from 2020 and the respective BCF values are considered to be more certain than the study from 1998. As the study from 2020 was performed according to the current OECD 305 guideline including all adaptions to state of science. The BCF is therefore concluded to be > 500 L/kg.

11.4 Acute aquatic hazard

Table 15: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Results[1]	Remarks	Reference
OECD TG 203 (deviations: length 38 to 54 mm instead of 40 to 60 mm)	*Oncorhynchus mykiss* (previous name: *Salmo gairdneri*)	CAS 2440-22-4 Vehicle used (DMF)	96 h-LC_{50} > 0.17 mg/L (n)	Reliability 1	(Springborn Smithers Laboratories, 2004)
OECD TG 203 (deviation: vehicle concentration exceeds 100 mg/L)	*Danio rerio* (previous name: *Brachydanio rerio*)	CAS 2440-22-4 Vehicle used (1-methyl-2-pyrrolidon and alkylphenol-polyglykol-ether)	96 h-LC_{50} > 100 mg/L (n)	Reliability 2 Slight deposit observed in highest test concentration observed + no analytical verification of test concentrations	(CIBA-GEIGY Ltd., 1988b)
OECD TG 202 (deviation: test duration only 24 h as it is an old study)	*Daphnia magna*	CAS 2440-22-4 Vehicle used (Alkylphenol-polyglykol-ether)	24 h-EC_{50} > 1000 mg/L (n)	Reliability 2 Slight deposit in test concentrations + no analytical verification of test concentrations	(CIBA-GEIGY Ltd., 1988c)
OECD TG 201	*Raphidocelis subcatpitata* (previous names: *Pseudokirchneriella subcapitata*, *Selenastrum capricornutum*)	CAS 2440-22-4	72 h-E_rC_{50} > 0.0822 mg/L (m)	Reliability 1	(Noack Laboratorien GmbH, 2018)

[1] results based on the measured (m) or on the nominal (n) concentration

11.4.1 Acute (short-term) toxicity to fish

Two acute toxicity studies to fish are available from the registration dossier.

In the key study (Springborn Smithers Laboratories, 2004) *Oncorhynchus mykiss* was exposed for 96 h to the test substance under semi-static conditions. The test was conducted according to OECD TG 203. The concentrations tested were: 0.022, 0.037, 0.061, 0.10 and 0.17 mg/L (nominal). The geometric mean measured concentrations were: 0.009, 0.017, 0.026, 0.052, and 0.075 mg/L. As vehicle DMF (CAS 68-12-2) was used. Ten fish per treatment level and controls were exposed. No effects (on mortality) were observed.

A supporting study conducted according to OECD TG 203 in 1988 with *Danio rerio* under static conditions also did not show effects on mortality or behaviour up to the highest concentration tested (CIBA-GEIGY Ltd., 1988b). Here, the vehicle concentration exceeded the maximum recommended in the OECD test guideline.

Another supporting study mentioned in the registration dossier was conducted as part of a fish BCF study in accordance with OECD TG 305. As the test duration of this study was only 48 hours, it is not described here.

11.4.2 Acute (short-term) toxicity to aquatic invertebrates

The key study and only available short-term toxicity study to aquatic invertebrates (CIBA-GEIGY Ltd., 1988c) is a study conducted according to an old test guideline which follows mainly the OECD TG 202 but has only a test duration of 24 instead of 48 hours. *Daphnia magna* was exposed under static test conditions to nominal concentrations of 58, 100, 180, 320, 580 and 1000 mg/L. A vehicle was used with a concentration of 4 mg/L. A slight deposit was observed in all test concentrations. No effects were observed in the test.

11.4.3 Acute (short-term) toxicity to algae or other aquatic plants

The study (Noack Laboratorien GmbH, 2018) was conducted according to OECD TG 201 used *Raphidocelis subcatpitata* (previous names: *Pseudokirchneriella subcapitata*, *Selenastrum capricornutum*) as test organism under static test conditions without vehicle. The test concentrations were verified using an LC-MS/MS method. The geometric mean measured test concentrations were: 0.167, 0.660, 1.57, 6.48, 17.5 and 82.2 µg/L. All validity criteria were fulfilled as the increase of the cell growth in the control cultures was 401-fold, the mean coefficients of variation of section-by-section specific growth rates in the control cultures was 14.1 % and the coefficient of variation of average specific growth rates during the whole test period in replicate control cultures was 0.99 %. The temperature range during the test period was 22.0 to 23.0 °C and the increase of pH value after 72 hours was 0.86 units. The 72 h-E_rC_{50} was higher than the maximum tested concentration of 0.0822 mg/L (m).

11.4.4 Acute (short-term) toxicity to other aquatic organisms

No data available

11.5 Long-term aquatic hazard

Table 16: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results[1]	Remarks	Reference
OECD TG 211	*Daphnia magna*	CAS 2440-22-4 Vehicle used (DMF, 0.1 mL/L)	21-d NOEC = 0.013 mg/L (n) **21-d NOEC = 0.0083 mg/L (m)**	Reliability 1	(BASF SE, 2011)
OECD TG 201	*Raphidocelis subcapitata* (previous names: *Pseudokirchneriella subcapitata, Selenastrum capricornutum*)	CAS 2440-22-4	72-h E_rC_{10} of 0.0588 mg/L (m)	Reliability 1	(Noack Laboratorien GmbH, 2018)

[1] Results based on the measured (m) or on the nominal (n) concentration; results in bold = relevant for classification and labelling

11.5.1 Chronic toxicity to fish

No data available

11.5.2 Chronic toxicity to aquatic invertebrates

A test according to OECD TG 211 is reported in the registration dossier conducted with *Daphnia magna* under semi-static test conditions using a vehicle as well as analytical verification of the test concentrations (BASF SE, 2011). All test solutions were visibly colourless and clear throughout each renewal period. The nominal test concentrations were: 0.0013, 0.0041, 0.013, 0.041 and 0.130 mg/L, and the mean measured concentrations were: 0.0007, 0.0025, 0.0083, 0.0216 and 0.120 mg/L. A significant effect on parent mortality after 21 days was observed in the two highest test groups. The NOEC for reproduction as well as adult mortality is 0.0083 mg/L (based on time weighted mean measured concentrations).

11.5.3 Chronic toxicity to algae or other aquatic plants

The chronic result of the study (Noack Laboratorien GmbH, 2018) conducted according to OECD TG 201 using *Raphidocelis subcapitata* (previous names: *Pseudokirchneriella subcapitata, Selenastrum capricornutum*) was an 72-h E_rC_{10} of 0.0588 mg/L (geometric mean measured). (For the test description see section 11.4.3, please.)

11.5.4 Chronic toxicity to other aquatic organisms

No data available

11.6 Comparison with the CLP criteria

11.6.1 Acute aquatic hazard

Table 17: Comparison with criteria for acute aquatic hazards

	Criteria for acute environmental hazards	**2-(2*H*-benzotriazol-2-yl)-*p*-cresol**	**Conclusion**
Acute Aquatic Toxicity	Cat. 1: $LC_{50}/EC_{50}/ErC_{50} \leq 1$ mg/L	Fish: 96-h $LC_{50} > 0.17$ mg/L (n) Daphnia: 24-h $EC_{50} > 1000$ mg/L (n) Algae: 72-h $E_rC_{50} > 0.0822$ mg/L (m)	**Not acute toxic for aquatic organisms**

11.6.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

Table 18: Comparison with criteria for long-term aquatic hazards

	Criteria for environmental hazards	**2-(2*H*-benzotriazol-2-yl)-*p*-cresol**	**Conclusion**
Rapid Degradation	Half-life hydrolysis < 16 days Readily biodegradable in a 28-day test for ready biodegradability (> 70 % DOC removal or > 60 % theoretical oxygen demand, theoretical carbon dioxide)	No data available 0 - 2 % biodegradation after 28 days → not readily biodegradable	**Not rapidly degradable**

	Criteria for environmental hazards	2-(2*H*-benzotriazol-2-yl)-*p*-cresol	Conclusion
Bioaccumulation	Log Kow ≥ 4 BCF ≥ 500	Log Kow = 4.2 BCF > 500	**High potential for bioaccumulation**
Aquatic Toxicity	Non-rapidly degradable substances: Cat. 1: NOEC ≤ 0.1 mg/L Cat. 2: NOEC ≤ 1 mg/L (based on Table 4.1.0 (b) (i) of the CLP Regulation) Surrogate approach in absence of appropriate chronic toxicity reference data (based on Table 4.1.0 (b) (iii) of the CLP Regulation): Not rapidly degradable substances and/or bioaccumulative substances: Cat. 1: E/LC_{50} ≤ 1 mg/L Cat. 2: E/LC_{50} > 1 to ≤ 10 mg/L Cat. 3: E/LC_{50} > 10 to ≤ 100 mg/L	Fish: not available. Daphnia: 2-d NOEC = 0.0083 mg/L (m) Algae: 72-h E_rC_{10} of 0.0588 mg/L (m) Fish: 96-h LC_{50} > 0.17 mg/L (n)	**Aquatic Chronic 1, M= 10** Based on *Daphnia magna*

11.7 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Acute aquatic hazard:

All valid E/LC_{50} values from the short-term toxicity tests on fish, aquatic invertebrates or algae are above the maximum achievable water solubility or 1 mg/L.

Therefore, no acute aquatic classification is necessary based on the criteria given in Table 4.1.0 (a) and Table 4.1.3 of the CLP Regulation.

Chronic aquatic hazard:

2-(2*H*-benzotriazol-2-yl)-*p*-cresol is not rapidly degradable and has a high potential for bioaccumulation in the aquatic environment, as the BCF is higher than 500.

Chronic toxicity data are available for aquatic invertebrates and algae but not for fish. The most sensitive valid long-term toxicity value is the 21-d NOEC of 0.0083 mg/L (m) for *Daphnia magna*. This results in a classification of 2-(2*H*-benzotriazol-2-yl)-*p*-cresol as Aquatic Chronic 1 (M= 10) based on the criteria given in Table 4.1.0 (b) (i) and Table 4.1.3 of the CLP Regulation.

For fish the Surrogate approach based on Table 4.1.0 (b) (iii) of the CLP Regulation has to be used. As no effects occurred up to the maximum achievable water solubility, no classification based on these results is justified.

12 EVALUATION OF ADDITIONAL HAZARDS

Not assessed in this report

13 ADDITIONAL LABELLING

Not relevant

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