CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

Captan (ISO) 1,2,3,6-tetrahydro-*N*-(trichloromethylthio)phthalimide

EC Number: **205-087-0**

CAS Number: **133-06-2**

Index Number: **613-044-00-6**

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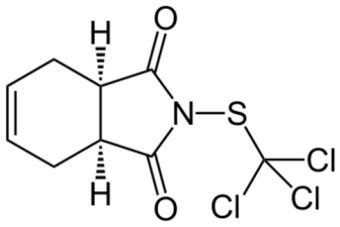
CONTENTS

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)	(3aR,7aS)-2-[(trichloromethyl)sulfanyl]-3a,4,7,7a-tetrahydro-1H-isoindole-1,3(2H)-dione 1,2,3,6-tetrahydro-N-(trichloromethylthio)phthalimide
Other names (usual name, trade name, abbreviation)	Captan
ISO common name (if available and appropriate)	Captan
EC number (if available and appropriate)	205-087-0
EC name (if available and appropriate)	
CAS number (if available)	133-06-2
Other identity code (if available)	CIPAC: 40
Molecular formula	C9H8Cl3NO2S
Structural formula	
SMILES notation (if available)	-
Molecular weight or molecular weight range	300.6 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	-
Description of the manufacturing process and identity of the source (for UVCB substances only)	-
Degree of purity (%) (if relevant for the entry in Annex VI)	Min 910 g/kg

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)**
none			

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
PCMM 594-42-3	Max 5 g/kg	-	H301, H311, H314, H330,	No
Folpet 133-07-3	Max 10 g/kg	H317, H319, H332, H351, H400	-	No
CCl4 56-23-5	Max 0.1 g/kg	H301, H311, H331, H351, H372, H412, H420	-	No

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
none					

Table 5: Test substances (non-confidential information) (this table is optional)

Identification of test substance	Purity	Impurities and additives (identity, %, classification if available)	Other information	The study(ies) in which the test substance is used

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 6:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	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 Annex VI entry	613-044-00-6	Captan (ISO) 1,2,3,6-tetrahydro-N-(trichloromethylthio)phthalimide	205-087-0	133-06-2	Carc. 2 Acute Tox. 3 Eye Dam. 1 Skin Sens. 1 Aquatic Acute 1	H351 H331 H318 H317 H400	GHS09 GHS08 GHS05 GHS06 Dgr	H351 H331 H318 H317 H400		M=10	
Dossier submitters proposal	613-044-00-6	Captan (ISO) 1,2,3,6-tetrahydro-N-(trichloromethylthio)phthalimide	205-087-0	133-06-2	**Retain** Carc. 2 Eye Dam. 1 Aquatic Acute 1 **Add** STOT RE 1 Aquatic Chronic 1 **Modify** Acute Tox 2 Skin Sens. 1A	**Retain** H351 H318 H317 H400 **Add** H372 H410 **Modify** H330	**Retain** GHS05 GHS06 GHS08 GHS09 Dgr	**Retain** H351 H318 H317 **Add** H372 **Modify** H330 H410		**Retain** M=10 **Add** inhalation: ATE = 0.22 mg/L (dusts and mists) Skin Sens.: SCL ≥ 0.001% M=10 M=1	
Resulting Annex VI entry if agreed by RAC and COM	613-044-00-6	Captan (ISO) 1,2,3,6-tetrahydro-N-(trichloromethylthio)phthalimide	205-087-0	133-06-2	Carc. 2 Acute Tox. 2 STOT RE 1 Eye Dam. 1 Skin Sens. 1A Aquatic Acute 1 Aquatic Chronic 1	H351 H330 H372 H318 H317 H400 H410	GHS05 GHS06 GHS08 GHS09 Dgr	H351 H330 H372 H318 H317 H410		inhalation: ATE = 0.22 mg/L (dusts and mists) Skin Sens.: SCL ≥ 0.001% M=10 M=1	

Table 7: Reason for not proposing harmonised classification and status under public consultation

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

Captan was originally included in Annex I of the EU Council Directive 91/414/EEC with Commission Directive 2007/5/EC (entry into force on 1 October 2007). The active substance was deemed to be approved under Regulation (EC) 1107/2009 via Implementing Regulation (EU) 540/2011 with an entry in Annex Part A of said regulation. With Commission Implementing Regulation (EU) No 2021/745, a new expiry date of the approval of Ccaptan was set to 31st July 2022.

In accordance with Commission Regulation (EU) 844/2012 of 18 September 2012, the ADAMA Agriculture BV and Arysta LifeScience S.A.S. submitted a joint dossier through consultant GAB Consulting GmbH to support the renewal of the approval of Ccaptan. Austria acting as the Rapporteur Member State (RMS) evaluated all aspects of the renewal dossiers via a Draft Renewal Assessment Report (DRAR). The DRAR was the subject of a peer review by the Co-RMS Italy.

The RMS also paid attention to new criteria for classification and labelling according to Regulation (EC) 1272/2008. Regarding human health, the following harmonised classification is available (Table 3.1 of Annex VI of Regulation (EC) No 1272/2008 as amended): Acute Tox. 3 – H331, Eye Dam. 1 – H318, Skin Sens. 1 – H317, and Carc. 2 – H351. The RMS proposes to add classification for chronic toxicity (STOT RE 1 – H372) and to update classification for skin sensitisation (Skin Sens. 1A – H317). Furthermore, new acute inhalation toxicity studies, not yet available in the EFSA peer review process, were submitted for this CLH dossier. In the light of these new studies the RMS proposes to modify Acute Tox from Category 3 to Acute Tox 2 (inhalation). Regarding ecotoxicity, a new proposal for classification and labelling has been established (H400 and H412 instead of current H400), based on the new studies with adverse endpoints included in the supplementary dossier for the renewal.

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[B.] Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

no justification is needed (PPP active substance)

5 IDENTIFIED USES

Captan belongs to the class of phthalimide family.

Captan is fungitoxic in action preventing disease infection and establishment. Captan inhibits mycelial growth from germinating spores, but has no curative effect on already established infections.

Captan is an active ingredient which works by contact and has a multi-site activity. Applied preventatively, it is highly effective against many fungal diseases. Captan has a broad action spectrum and can be used on many crops.

At the cellular level, captan would act at the same time on several processes like cellular respiration, cell walls synthesis (or membrane permeability) and microtubules involved in cell division and cell structure. All these activities induce inhibition of spore germination and mycelium development. Target sites of captan are numerous and not completely identified. The effect on cell respiration inhibition would result in blockage or delay in chemical reactions caused by an interaction between captan and many chemical groups.

Two examples can be cited:

- The oxidation of certain molecules such as glucose and acetate usually metabolized by spores. Captan inactivates the enzymes of glycolysis Krebs cycle and respiratory chain.

- The delay of certain metabolic reactions due to the binding of captan or its metabolites to thiol groups. These interactions result in production of a non- toxic amide and thiophosgen which is very reactive with thiol groups.

These reactions would involve co-enzymes and enzymes usually involved in catalysing reactions of cellular metabolism. Then, the cellular activity would be slowed down until the captan concentration is sufficient for its binding to thiol groups.

At the membrane level, captan would notably act on the synthesis of lipid and protein molecules. Inhibition of spore germination by captan would be caused by blockage of various substance use like keto acid, oxygen and molecules issue from catabolism (carbohydrates and lipids).

Field of use envisaged:

Agriculture: Horticulture (vegetable and fruit production)

The uses as declared in the REACH submission are as follows:

Formulation or re-packing:

Formulation of preparations for rubber production (Use descriptors: ERC3; PROC 1 / PROC 2 / PROC 3 / PROC 4 / PROC 5 / PROC 8a / PROC 9 / PROC 14)

Formulation into mixture (Use descriptors: ERC3; PROC 1 / PROC 2 / PROC 3 / PROC 4 / PROC 5 / PROC 8b / PROC 9 / PROC 14; PC 32)

Uses at industrial sites:

Production of tyres and rubber goods, industrial (Use descriptors: ERC6d; PROC 1 / PROC 2 / PROC 3 / PROC 4 / PROC 5 / PROC 8a / PROC 9 / PROC 10 / PROC 14 / PROC 21; SU 11)

Manufacture of rubber products (Use descriptors: ERC6d; PROC 1 / PROC 2 / PROC 3 / PROC 4 / PROC 5 / PROC 8b / PROC 9 / PROC 10 / PROC 14 / PROC 21; SU 11; PC 32)

Widespread uses by professional workers:

Production of rubber goods, professional (Use descriptors: ERC8c / ERC8f; PROC 5 / PROC 8a / PROC 10 / PROC 13 / PROC 14 / PROC 19 / PROC 21; SU 11)

Manufacture of rubber products (Use descriptors: ERC8f; PROC 5 / PROC 8a / PROC 10 / PROC 13 / PROC 14 / PROC 19 / PROC 21; SU 11; PC 32)

Service life:

Outdoor manipulation of rubber products, professional (Use descriptors: ERC10a / ERC11a; PROC 21; AC 1; AC 2; AC 10)

Rubber articles (Use descriptors: ERC10a / ERC11a; PROC 21; AC 1; AC 2; AC 10)

6 DATA SOURCES

DRAR – Draft renewal assessment report for captan

7 PHYSICOCHEMICAL PROPERTIES

Table 8: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Solid	EFSA (2020)	observed
Melting/freezing point	Melting point: 172°C	EFSA (2020)	EC A.1
Boiling point	Decomposition on melting starting at 173 °C	EFSA (2020)	EC A.2
Relative density	Not determined	-	-
Vapour pressure	4.2 x 10^{-6} Pa (20 °C)	EFSA (2020)	EC A.4
Surface tension	63 mN/m at 20 °C	EFSA (2020)	EC A.5
Water solubility	4.9 mg/L in purified water (20 °C) 4.8 mg/L at pH 5 (20 °C) 5.2 mg/L at pH 7 (20 °C) No value at pH 9 due to rapid hydrolysis of captan	EFSA (2020)	EC A.6
Partition coefficient n-octanol/water	log P_{OW} = 2.5 at 20 °C	EFSA (2020)	EC A.8
Flash point	Not applicable	-	Melting point above 40°C
Flammability	Not classified as flammable	EFSA (2020)	EC A.10
Explosive properties	Not explosive	EFSA (2020)	EC A.14
Self-ignition temperature	Not self-igniting	EFSA (2020)	EC A.16
Oxidising properties	Not oxidising	EFSA (2020)	EC A.17
Granulometry	Not determined	-	-
Stability in organic solvents and identity of relevant degradation products	Not determined	-	-
Dissociation constant	Captan does not dissociate at the pH ranges encountered in aqueous solution	EFSA (2020)	Theoretical assessment based on structure
Viscosity	Not applicable	-	-

8 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 9: Summary table of toxicokinetic studies

Method	Results	Remarks	Reference
Absorption, distribution, metabolism and excretion by oral route			
USEPA 85-1 Excretion and tissue retention of a single oral dose (10 mg/kg) in the rat.	Rapidly excreted after single oral administration of 10 mg/kg bw [^{14}C]-cyclohexene ring-labelled captan. Urine = 82% and faeces = 9% of total radioactivity, 48-h post-dose. Tissue residues negligible, highest concn in kidneys <0.01% administered radioactivity. Excretion profiles similar for both sexes.		R-5829 Study 1 (1990)
USEPA 85-1 Excretion and tissue retention of a single oral dose (500 mg/kg) in the rat.	Principal elimination in urine from single oral dose of [^{14}C]-cyclohexene ring-labelled-captan (500 mg/kg bw), virtually no retention in tissues or metabolism to exhaled carbon dioxide. No sex differences in rate or route of elimination, which was complete by 96 hours. Elimination slightly prolonged compared to single oral dose of 10 mg/kg captan.		R-5830 Study 2 (1990)
Meets essential criteria of USEPA 85-1 Repeat oral administration of unlabelled captan (10 mg/kg bw) over a 14 day period followed by a single oral dose of [^{14}C]-ring-labelled-captan (10 mg/kg bw).	Similar results to those obtained without pre-administration of unlabelled captan (Study 1, 1990). Radioactivity principally eliminated via urine with virtually no retention in the tissues. No sex differences in rate or route of elimination, which was essentially complete within 48 hours after dosing. Therefore, pre-dosing of rats no effect on the route or rate of elimination of a single oral dose of [^{14}C]-ring-labelled-captan.		R-5832 Study 3 (1990)
USEPA 85-1 Biotransformation study in the rat.	Main metabolites identified in the urine are: 4,5-cyclohexene-1,2-dicarboximide (THPI, 11%); 3-hydroxy-4,5-cyclohexene-1,2-dicarboximide (3OH-THPI, 42%); 5-hydroxy-4,5-cyclohexene-1,2-dicarboximide (5OH-THPI, 6%); 4,5-epoxy-1,2-dicarboximide (THPI-epoxide, 5%); 4,5-dihydroxy-1,2 dicarboximide (4,5-diOH THPI, 6%); 1-amido-2-carboxy-4,5-cyclohexene (THPAM, 7%) and	No significant differences in the quantities of most of the urinary metabolites were noted between both sexes or dosing regimes. Significant differences in the quantities of certain metabolites in the faecal extracts between the dosing regimes and sexes.	R-5831 Study 4 (1990)

Method	Results	Remarks	Reference
	6-hydroxy-1-amido-2-carboxy-4,5-cyclohexene (3-OH THP-amic acid, 13%). Two further unidentified metabolites were present and accounted for 4% and 2% of the urinary radioactivity. Faecal extracts from rats administered low and high doses contained 7% and 43%, respectively of a metabolite tentatively identified as captan. Consistent with saturation of absorption at higher dose level. Many metabolites detected in urine were also found in the faecal extracts, indicating excretion via bile occurs. THPI, 35% faecal metabolites, 3 OH-THPI and 5 OH-THPI were major urine metabolites. Amount of metabolites in faeces dependant on sex and dosing regime and ranged from 11% to 27% at high and low dose, respectively. 4.5-diOH THPI (3.9%), THPAM (5.2%) and polar metabolites only present in small amounts.		
USEPA 85-1 Evaluation of the in vivo metabolism of captan in rats.	Single oral 10 mg/kg bw: major route of excretion–urine, 45-50% ; faeces, 15%, over 96 hours. ~23% eliminated as CO_2. Rapidly excreted in males and female rats with about 80% within 24 h. Tissue residues <2%. Repeated oral 10 mg captan/kg bw for 14 days prior to the administration of 10 mg/kg bw [^{14}C]-trichloromethyl labelled captan had negligible effect on the routes and rates of elimination. Single oral administration of 500 mg/kg bw [^{14}C]-trichloromethyl labelled captan: slower excretion, ~24% in 24 hours. Faeces was major route of excretion ~40%; urine = 25%, expired CO_2 = 15%; volatile organics, 4-7%. Distribution in tissues similar to low dose. Thiazolidine-2-thione-4-carboxylic acid (TTC) and dithio-bis-methanesulfonic acid and disulfide monoxide derivative (DMS and DMS-O) identified in urine, accounting	[^{14}C]-trichloromethyl labelled captan	R-4988 Study 5 (1988)

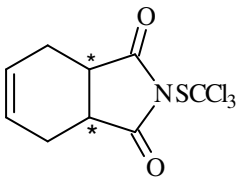
Method	Results	Remarks	Reference
	for 22.7% and 65% (combined DMS and DMS-O) of the urinary radioactivity, respectively. TTC in faeces of high dose group. % absorption reduced at high doses, unmetabolised captan detected in faecal extracts from 500 mg/kg bw animals. Characterisation of volatile radioactivity were inconclusive.		
Not guideline study Comparative metabolism of captan in the rat and mouse.	Biotransformation and excretion was similar in rats and mice. However, absorption and elimination rate in mouse was faster than in rat. Gastric retention longer and the gastric mucosal pH was lower in the rat than in the mouse. In high dose, higher duodenal levels of captan in mouse compared to rat. Duodenal pH in male mice preconditioned with 500 or 5000 ppm dietary captan, much lower than pH in control mice. Suggests absorption of captan in rats is dose dependent. Biotransformation of captan occurs in the gastrointestinal tract. Low doses, high proportion is extensively metabolised prior to absorption; higher doses, incompletely metabolised and a proportion is excreted unchanged. Captan not detected in tissues, only in faeces. Metabolic cleavage of nitrogen-sulphur bond.	Gastrointestinal fate of captan in rats and mice compared for single oral doses of 5 or 250 mg/kg bw of [^{14}C]-trichloromethyl-labelled captan following pre-treatment with dietary exposures to 5000 ppm of captan during 90 or 148 days.	TMN-0383 Study 6 (1985)
Toxicokinetics of captan and folpet biomarkers in orally exposed volunteers – Not guideline. Published. Reliable with restrictions	The study supports the *in vitro* data that the major pathways of metabolism are similar in experimental animals and in humans. Also toxicokinetics appear to be comparable between species. THPI is considered to be a biomarker for captan in conjunction with a clearly defined exposure to captan.	The results of this toxicokinetic study with human volunteers following oral administration may be regarded as supplemental data despite the fact that, for ethical reasons, toxicological studies carried out on humans are not accepted according to the preamble (13) of Regulation (EC) 1107/2009.	Berthet (2012b) R-31005
Absorption, distribution, metabolism and excretion by other routes			
The Stability of Captan and Folpet in Whole Blood. No guideline.	Captan degrades rapidly in whole human blood at 37°C to THPI; half-life = 0.97 seconds. No other short term degradates		R-11143 Study 8 (1999)

Method	Results	Remarks	Reference
	or intermediates present. Captan absorbed dermally will degrade rapidly in blood, hence effective exposure of other organs or tissues to the molecule is zero.		
Measurement of the half-life of thiophosgene in human blood – no guideline.	Thiophosgene disappears rapidly when added in excess to human whole blood *in vitro*. Half-life = 0.6 s. Neither captan (nor thiophosgene are likely to reach sensitive target organs distant to the mucosal surface of the gastrointestinal tract. Further supports the captan mode of action.		R-17121 Study 9 (2004)
Comparative *in vitro* metabolism of [^{14}C]-Captan using rat and human liver microsomes. No guideline.	Observed transformations of [^{14}C]-captan dominated by N-S cleavage and protein reactivity. Biological metabolism (THPI hydroxylation) less significant (≤ 25%). Reactions in rat and human liver microsomes similar and no unique human metabolite was observed.		R-34966 Study 10 (2015)
Captan - Waiver for an intravenous study on oral bioavailability.	Not applicable.	Consideration of the excretion data from other studies enabled the bioavailability to be estimated (>85%). A separate oral bioavailability study was not, therefore, necessary.	Report No. 961562-CA-050101-1 Study 7 (2014)
A detailed urinary excretion time course study of captan and folpet biomarkers in workers for the estimation of dose, main route-of-entry and most appropriate sampling and analysis strategies. No guideline. Publication. Reliable with restrictions	Only two individuals exposed as operators. Exposure to captan more important during spraying period than harvest activities. Modelling simulation indicated dermal exposure is main route for both operators and re-entry workers.	Supplementary information only	Berthet (2012a) R-31005
Toxicokinetics of captan and folpet biomarkers in dermally exposed volunteers. No guideline. Reliable with restrictions	Toxicokinetic parameters (T_{max}, $T_{1/2}$, V_d) in humans for THPI were different upon oral and dermal application. Supports *in vitro* data that the major pathways of metabolism are similar in experimental animals and in humans. Toxicokinetics appear to be comparable between species. Dermal absorption was low despite the fact that captan was dissolved in acetone and applied on a rather large skin surface area.	The results of this toxicokinetic study with human volunteers following dermal administration may be regarded as supplemental data despite the fact that, for ethical reasons, toxicological studies carried out on humans are not accepted according to the preamble (13) of Regulation (EC)	Berthet (2011) R-29191

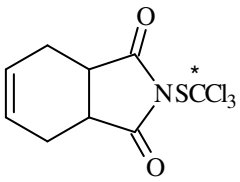
Method	Results	Remarks	Reference
		1107/2009.	
Toxicokinetic modelling of captan fungicide and its tetrahydrophthalimide biomarker of exposure in humans. No guideline. Published.	Metabolism and toxicokinetics of captan are conserved and similar for experimental animals and humans.		Heredia-Ortiz (2012)

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

Captan has been extensively studied in a series of guideline and non-guideline investigations. Radiolabels have been incorporated in the cyclohexene ring, and the trichloromethylthio side-chain. The cyclohexene ring was shown to be the most stable, and the trichloromethylthio side-chain the least stable parts of the molecule. Terminal half-life of the parent material in human blood at 37°C was 0.97 seconds.



[^{14}C]-cyclohexene ring-labelled captan



[^{14}C]-trichloromethyl-labelled captan

Figure 1: Different labelling positions in the captan molecule

Following oral administration of radiolabelled captan to male and female rats, the radiolabelled moieties are absorbed well. Following a single oral administration of 10 mg/kg bw [^{14}C]-cyclohexene ring-labelled captan to rats, urinary and faecal excretion was monitored over a period of seven days. The excretion profiles of male and female rats were very similar. Urinary excretion predominated with 81% and 8–9% of the administered radioactivity excreted in the urine and faeces, respectively, over a period of 48 hours post-dosing. Tissue residues were negligible with the highest concentration being present in the kidneys at <0.01% of the administered radioactivity. Excretion was also monitored over seven days following the single oral administration of 500 mg/kg bw [^{14}C]-cyclohexene ring-labelled captan to rats. Again, there was little difference in the excretion profiles between males and females; the urinary route of metabolism predominated. Over a period of 96-hours, 69–73% and 23–25% of the radioactivity was excreted in the urine and faeces, respectively. Tissue residues were negligible in males and females, with the highest radioactivity proportion present in the blood (2 µg captan equivalents/g). Repeat oral administration of 10 mg/kg bw captan for 14 days prior to the administration of 10 mg/kg bw [^{14}C]-cyclohexene ring-labelled captan had a negligible effect on the routes and rates of elimination of a single oral dose of the radiolabelled substance.

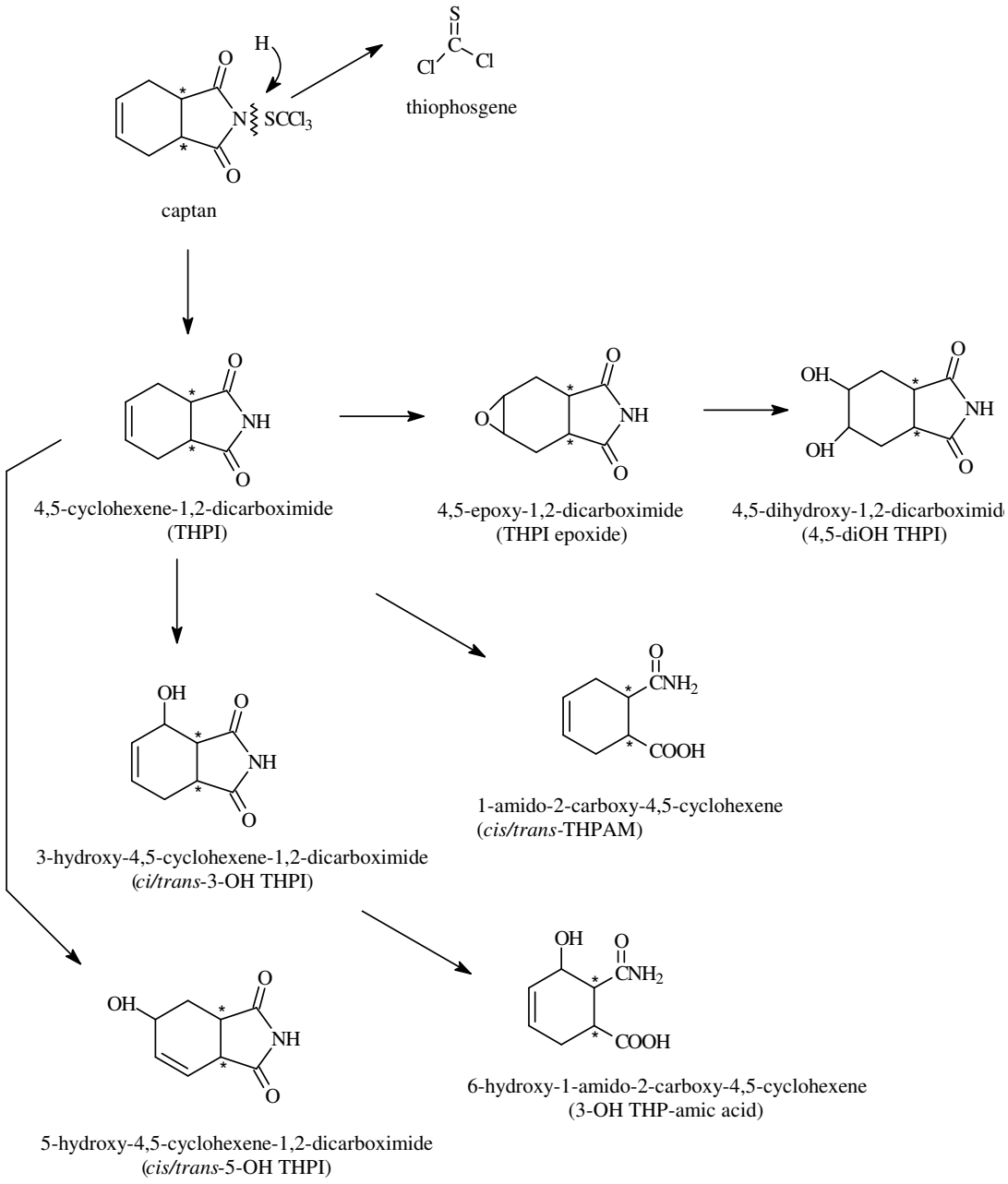


Figure 2: Proposed metabolic pathway of [^{14}C]-cyclohexene ring-labelled captan in the rat

The quantitation and identification of a total of seven urinary metabolites were assessed from these studies: 3OH-THPI (42%), 5OH-THPI (6%), 3-OH THP-amic acid (13%), THPI (11%), THPAM (7%), 4,5-diOH THPI (6%) and THPI-epoxide (5%). Two further unidentified metabolites were present and accounted for 4% and 2% of the urinary radioactivity. Radioactivity which could not be matched to identified metabolites accounted for 7% of the urinary radioactivity. No significant differences in the quantities of urinary metabolites were noted between the sexes or dosing regimes. Faecal extracts from rats administered the low and high doses of captan, contained 7% and 43% of an unidentified metabolite (according to the study report this metabolite is possibly captan, no analytical method for captan is described in this report). THPI accounted for 35% of faecal metabolites. 3OH-THPI and 5OH-THPI were major faecal metabolites. The amounts of these metabolite in faeces were dependent on sex and dosing regime. 4,5-diOH THPI, THPAM and polar metabolites were only present in small amounts.

The metabolism of captan was studied using the [^{14}C]trichloromethyl-labelled form, using the same regime followed for the studies carried out with [^{14}C]-cyclohexene ring-labelled captan. Following a single oral

administration of 10 mg/kg bw [^{14}C]-captan, the major route of excretion was via the urine with 45–50% and 14–22% excreted in the urine and faeces over 96 hours. A further 22–23% of radioactivity was eliminated as $^{14}CO_2$. Radioactivity was rapidly excreted in males and females with the majority (77–82%) excreted within 24 hours. At sacrifice less than 2% of the administered radioactivity was present in the tissues. Repeat oral administration of 10 mg/kg bw captan for 14 days prior to the administration of 10 mg/kg bw [^{14}C]-trichloromethyl-labelled captan had a negligible effect on the routes and rates of elimination of a single oral dose of the radiolabelled substance. Excretion of radioactivity following a single oral administration of 500 mg/kg bw [^{14}C]-trichloromethyl-labelled captan was slower with only 21–24% excreted in 24 hours. In contrast with the low dose, faeces was the major route of excretion, accounting for 33–40% of the administered dose, compared to and 23–27% via the urine and 15% in expired $^{14}CO_2$. Exhaled volatiles accounted for 4–7% of the administered radioactivity. The distribution in the tissues was similar to that following administration of 10 mg/kg bw. Three major metabolites were present in the urine; thiazolidine-2-thione-4-carboxylic acid (22.7% urinary radioactivity), dithio(bis methane sulphonic acid) and its S-oxide (together accounting for 65% of the urinary radioactivity). Very little radioactivity could be recovered from the faeces, but the urinary metabolites described and captan were present.

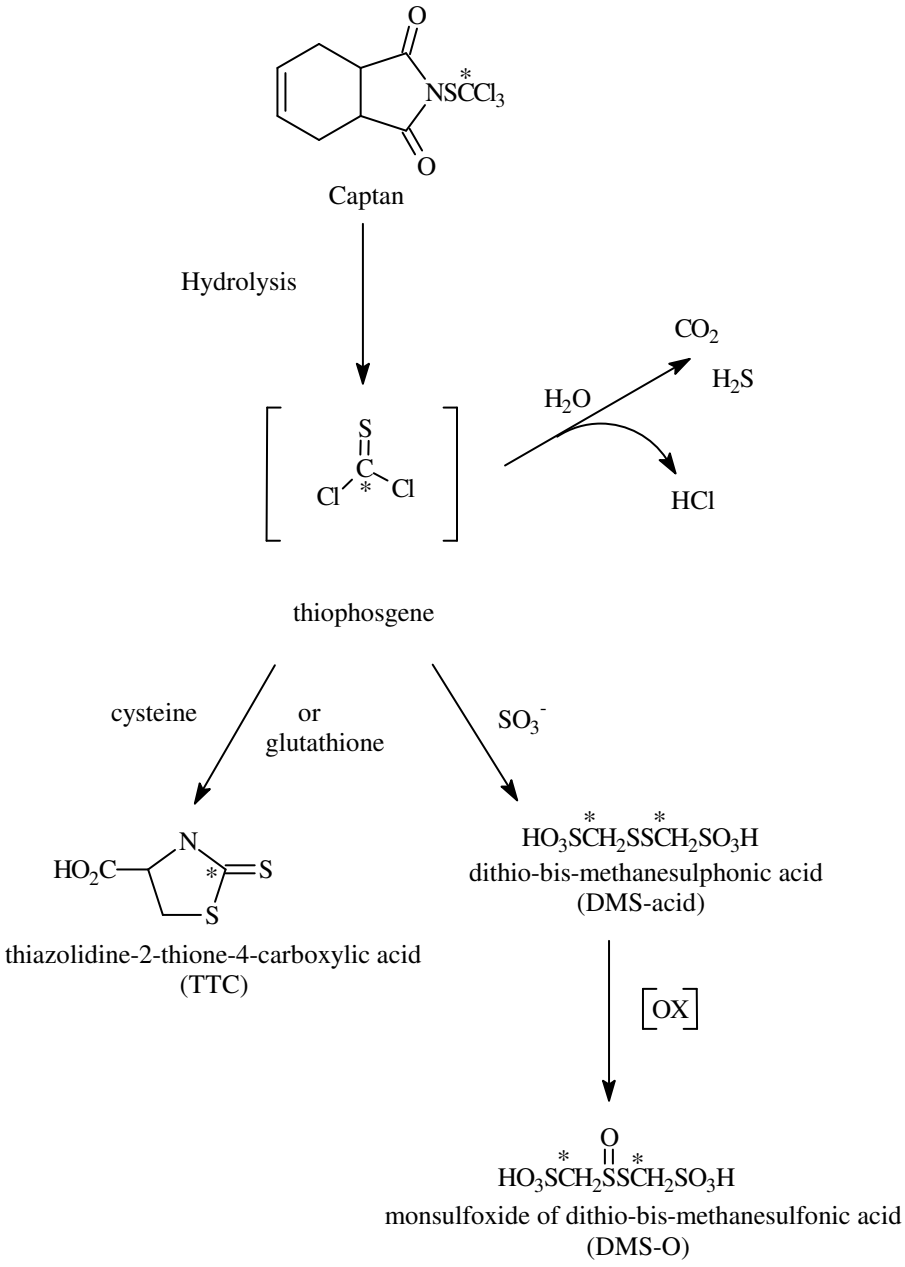


Figure 3: Proposed metabolic pathway of [^{14}C] trichloromethyl labelled captan in rats

The gastrointestinal fate of captan in rat and mouse was compared involving administration of single oral doses of 5 or 250 mg/kg bw [^{14}C]-trichloromethylthio labelled captan to animals, pre-treated by dietary exposure to 5000 ppm captan for 90 or 148 days. Elimination of [^{14}C]-trichloromethylthio labelled captan following oral gavage was greater in the mouse compared to the rat. Gastric retention of captan was longer and the gastric mucosal pH lower in the rat compared to the mouse. Levels of duodenal captan and metabolites were proportionately higher in the mouse at high doses compared to low doses. In the rat the proportions were similar at both doses and similar to those in the low dose mouse. In the high dose group, markedly higher duodenal levels of captan were found in the mouse compared to the rat. The duodenal pH of the male mice preconditioned with 500 or 5000 ppm dietary captan, was significantly lower than the pH in control mice. It is suggested that these findings may be important in explaining the observed species differences for duodenal carcinogenicity in the mouse and rat.

The results of the studies described above indicate that the absorption of captan in rats is dose dependent. Biotransformation of captan occurs in the gastrointestinal tract. At low doses a high proportion or all of the administered captan is metabolised prior to absorption, whilst at higher doses captan is incompletely metabolised and a proportion is excreted unchanged. Captan undergoes metabolic cleavage of the nitrogen-sulphur bond, which probably occurs rapidly since no metabolites with an intact nitrogen-sulphur bond have been detected in the excreta, although elimination of both radiolabelled forms was rapid. There was no evidence for dose-related changes in the relative proportions of metabolites formed from either the tetrahydrophthalimide or trichloromethyl moieties. Although biotransformation and excretion were similar in the rat and mouse, captan was absorbed more rapidly in mice at higher doses and higher concentrations of captan and/or its metabolites were retained in the mouse duodenum. There is no evidence for accumulation of radiolabel with time.

The proportion of absorbed dose after administering radioactive captan exceeded 85%. Using this data to estimate bioavailability, and in accordance with current guidance, the external dose and systemic dose can be considered as equal. Thus, it was not necessary to investigate the oral bioavailability further.

The major pathways of metabolism have been shown to be similar in experimental animals and in humans. Also toxicokinetics appear to be comparable between species. THPI is considered to be a biomarker for captan in conjunction with a clearly defined exposure to captan.

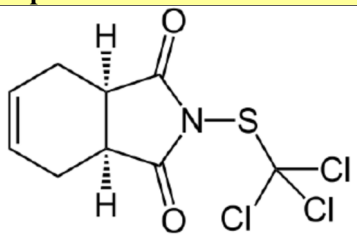
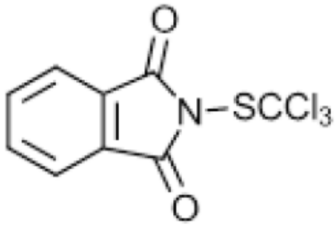
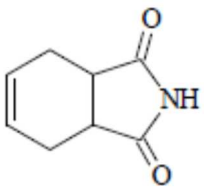
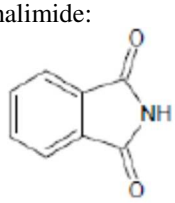
Thiophosgene disappears rapidly when added in excess (100 µg/mL) to human whole blood *in vitro*. The half-life was calculated to be 0.6 seconds. This demonstrates why neither captan (with the DT_{50} of 0.97 seconds in human blood) nor thiophosgene are likely to reach sensitive targets distant to the mucosal surface of the gastrointestinal tract and as part of the mechanism data it further supports the captan mode of action.

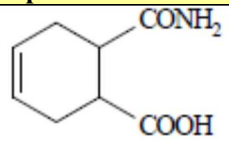
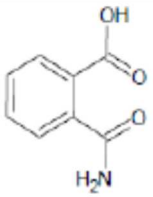
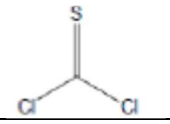
Dermal absorption was observed to be low in a toxicokinetic study with human volunteers following dermal administration. Furthermore, systemic exposure to captan is unlikely as the data demonstrates that degradation of the parent compound is rapid in blood, leading to the conclusion that radioactivity recovered from the systemic circulation is composed of metabolites of captan.

8.2 Comparison captan and folpet

Captan and folpet belong to the group of phthalimide fungicides. They both share the same toxicophore (i.e. trichloromethylthio-side chain), which is responsible for the irritating properties. These irritating properties are claimed to be responsible for several hazard classes (i.e. acute Tox, Skin and Eye Irrit., Carc and STOT-RE). In the table below similarities are listed that support a read-across between these substances.

Table 10: Comparison folpet and captan and folpet

	Captan	**Folpet**
Chemical structure		
Proposed classification	Carc. 2 Acute Tox. 2 (inhalation) STOT RE 1 Eye Dam. 1 Skin Sens. 1A Aquatic Acute 1 Aquatic Chronic 1	Carc. 2 Acute Tox 2 (inhalation) STOT RE 1 Skin Irrit. 2 Eye Dam. 1 Skin Sens. 1A Aquatic Acute 1 Aquatic chronic 1
Absorption	> 80% (based on urinary excretion within 48 h)	> 80% (based on urinary excretion within 48 h)
Distribution	Widely distributed following initial absorption, but tissue residues negligible because of rapid excretion	Widely distributed following initial absorption, but tissue residues negligible because of rapid excretion
Metabolism	Metabolic cleavage of nitrogen-sulphur bond resulting in thiophosgene and THPI (1,2,3,6-tetrahydrophthalimide; 11% in urine) occurs in GI tract prior absorption. Thiophosgene is conjugated with glutathione (GSH) and excreted as thiazolidine and mineralised to CO_2, HCl and H_2S. Hydroxylation of THPI resulting in 3-OH-THPI (42% in urine) or 5-OH-THPI (6% in urine), or metabolism of THPI to THPI-epoxide (5% in urine) (and further to the diol- 6% in urine) or THPAM (*cis/trans*-6-carbamoyl-3-cyclohexene-1 carboxylic acid) (7% in urine) (through opening of cyclohexene ring).	The trichloromethylthio (TCM) side chain generates thiophosgene via hydrolysis and its rapid reaction with thiols. Thiophosgene is conjugated with glutathione (GSH) and excreted as thiazolidine and mineralised to CO_2, HCl and H_2S. Removal of the side-chain by hydrolysis or by detoxification mechanisms yields phthalimide (10% in urine), which is further metabolised to phthalamic acid (80% in urine), which may be converted to phthalic acid.
Excretion	Rapid and extensive (app. 95 % within 48 h); ring-labelled captan is excreted mainly via urine (75% within 24 h, 5% via faeces), trichloromethyl-labelled captan is also excreted via the pulmonary route as CO_2 (up to 25%; 40-50% via urine, up to 20% via faeces)	Rapid and extensive (> 95 % within 48 h), mainly via urine (90 % within 24 h, 5 % via faeces within 48 h). No study measuring CO_2 traps is available with folpet.
Similar metabolites	THPI:  THPAM:	Phthalimide:  Phthalamic acid:

	Captan	Folpet
		
Toxicophore	The trichloromethylthio (TCM) side chain which generates thiophosgene: 	

9 EVALUATION OF HEALTH HAZARDS

Acute toxicity

9.1 Acute toxicity – oral route

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 11: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels, duration of exposure**	**Value LD_{50}**	**Reference**
Acute oral (gavage) Guideline: OECD 401 (1987) GLP: Yes	Rat (Sprague-Dawley) 5/sex/group	Captan technical (Batch: 4102; Purity: not reported) Vehicle: Distilled water	2000 mg/kg bw Single oral dose followed by 14 days observation	**Both sexes:** >2000 mg/kg bw	R-6290 Study 1 (1991)
Acute oral (gavage) Guideline: ≅ OECD 401 (1981) GLP: No	Rat (Sprague-Dawley) 10/sex/group	Captan technical (Batch: WRC 4921-26-12; Purity: not reported) Vehicle: Corn oil	5000 mg/kg bw Single oral dose followed by 14 days observation	**Both sexes:** >5000 mg/kg bw	R-4367 Study 2 (1984)
Acute oral (gavage) Guideline: 40 CFR 163.80-3 ≅ OECD 401 Not GLP	Rat (Sprague-Dawley) 5/sex/group Test 1 10/sex/group Test 2	Captan technical (Batch: SX-1345 Purity: not reported) Vehicle: 0.7% carboxymethylcellulose and 1.0% Tween 80 in distilled water	Test 1: 0, 5000, 6500, 8300, 10800 or 14000 mg/kg Test 2M: 0, 7800 mg/kg Test 2F: 0, 7200 mg/kg Single oral dose followed by 14 days observation	**Males:** 7000 (5100 – 9600) mg/kg bw **Females:** 6170 (3800 – 10010) mg/kg bw	TMN-0705 Study 3 (1982)
Acute oral	Mouse	Captan	1500, 1890,	**Both sexes:**	R-3585

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
(gavage) Guideline: ≅ OECD 401 (1981) GLP: No	(CFI) 5/sex /group	Batch: (not specified Purity: 92.7%) Vehicle: 1% methylcellulose	2380 or 3000 mg/kg Single oral dose followed by 14 days observation	2110 (1901 – 2342) mg/kg bw	Study 4 (1983)

Table 12: Summary table of human data on acute oral toxicity

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 13: Summary table of other studies relevant for acute oral toxicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

9.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

The acute toxicity of captan was assessed in mouse (1 study) and rat (3 studies) following overnight fast and administration by oral gavage. The studies were conducted between 1982 and 1991 and aligned with the test guideline OECD 401 (acute oral toxicity) versions 1981 and 1987. Current OECD guidelines on acute oral toxicity (OECD 420 (2001), OECD 423 (2001) and OECD 425 (2008)) use a tiered dosing approach, use fewer animals and include animal welfare improvements. However, current guideline study data would not be considered more accurate. There were no deviations from the OECD 401 protocol, therefore the current data is considered scientifically valid to derive an acute oral LD_{50} for captan in rodents.

In an acute oral toxicity study (Study 1, 1991), a group of 5 male and 5 female rats was given a single oral dose of captan technical as a suspension in distilled water at a dose level of 2000 mg/kg bw and observed for 14 days. No mortalities and no signs of systemic toxicity were recorded during the study. All animals showed expected body weight gain during the study and there were no abnormalities detected at necropsy. The acute oral median lethal dose was > 2000 mg/kg bw.

In a second acute oral toxicity study (Study 2, 1984), groups of 10 rats/sex were given a single oral dose of captan technical at 0 (corn oil vehicle) or 5000 mg/kg bw and observed for 14 days. Gross pathological examinations were performed on all animals (except for those cannibalised).

Following a dose of 5000 mg/kg bw, 2 males died on days 1 and 12 and one female died on day 4. Clinical signs observed in the majority of treated animals were mild to moderate depression, ptosis, diarrhoea, salivation, lacrimation, stained fur, red stained muzzles, anogenital stains, piloerection and easy agitation. Other signs observed were alopecia, bloated appearance, thin appearance, ataxia, dyspnea and chromodacryorrhea. Males and females that survived appeared normal by days 4 and 6, respectively, except for alopecia in 3 males and 3 females which persisted throughout the observation period. Control animals appeared normal throughout the study.

At *post mortem* examination, observations in the male rats that died during the test were salivation, bloated appearance, reddened lungs, dark edged and/or dark liver, bloated gastrointestinal tract, test material-like fluid in the stomach and small darkened kidneys. The female that died was cannibalised and necropsy was not possible. The acute oral LD_{50} was > 5000 mg/kg bw to male and female rats.

A third acute oral toxicology study (Study 3, 1982) in rats examined captan technical at (test 1) 0, 5000, 6500, 8300, 10800 and 14000 mg/kg bw in groups of 5 male and 5 female rats or (test 2) 0, 7800 mg/kg bw in groups of 10 males and 0, 7200 mg/kg bw 10 females. Captan technical was delivered to fasted rats by oral gavage in 0.7% carboxymethyl cellulose/1.0% Tween 80 and animals observed for 14 days. In test 1 and 2, clinical signs of toxicity included diarrhoea, reduced food consumption, decreased motor activity, ocular and nasal discharge, weakness, ataxia, tremors, bloody urine and collapse. In test 1, 14000 mg/kg bw, 5/5 males and females died between 3.5 hour and 4 days post exposure. In the 10800 mg/kg bw group 4/5 males and females died between days 3 and 7 with the remaining animals recovering by day 13. In animals exposed to 8300 mg/kg bw, 4/5 males and 5/5 females died with the remaining animal recovering by day 6. At 6500 mg/kg bw 1/5 males and 2/5 females died (day 5) with remaining males recovering between days 2-5 and females recovering in 4-5 days. No mortality occurred the 5000 mg/kg bw dose groups of either sex. In test 2, 10/10 females died between 1 and 11 days, and 8/10 males died between 1-7 days. The surviving animals recovered between 4 and 6 days.

Post mortem examination revealed stomach lesions, red lungs and kidneys, mottled livers. Histological examination revealed multifocal acute gastric mucosal necrosis and multifocal acute ulcerative gastritis. The acute oral LD_{50} was 7.0 (CI: 5100 – 9600) mg/kg bw (male rats) and 6170 (CI: 3800 – 10010) mg/kg bw (females rats).

A fourth acute oral toxicity study was conducted in the mouse. (Study 4, 1983) Groups of 5/sex/dose were given a single oral dose at 1500, 1890, 2380 or 3000 mg/kg bw and observed for 14 days.

Following a dose of 1500 mg/kg bw there were no mortalities and clinical signs included reduced activity, reduced reflexes, tremor and abdominal ache. At 1890 mg/kg bw, one male died on day 1 and one female died on day 2. At this dose level, clinical signs included reduced activity, reduced frequency of respiration, staggering, tremor and abdominal ache. At 2380 mg/kg bw, 3 males and 1 female died on day 1, 1 female died on day 2 and 1 male and 1 female died on day 7. Clinical signs at this dose level included reduced activity, reduced frequency of respiration, staggering, tremor, ataxia, apathy, convulsions and abdominal ache. At 3000 mg/kg bw, all animals died on day 1 and clinical signs included reduced activity, reduced frequency of respiration, staggering, tremor, convulsions, abdominal ache, exophthalmus, apathy, ataxia, sedation and coma. Surviving animals exhibited signs of sedation and reduced reflexes. There was a dose dependant reduction in body weight gain.

Macroscopic examination of the abdominal cavity revealed hyperaemia of the gastrointestinal tract. The kidneys of some animals were lighter in colour and the livers of some animals were swollen. The acute oral LD_{50} of captan in mice, calculated for males and females combined, was 2110 mg/kg bw (confidence intervals 1901 – 2342 mg/kg bw).

In conclusion, the main findings following acute oral exposure to captan were consistent with gastrointestinal irritation in the high dose groups.

9.1.2 Comparison with the CLP criteria

Three studies in rats and one in the mouse have demonstrated that captan technical is of low acute oral toxicity. As the acute oral median lethal dose is greater than the upper criterion of 2000 mg/kg bw, the data do not meet the criteria for classification and labelling.

9.1.3 Conclusion on classification and labelling for acute oral toxicity

No classification required.

9.2 Acute toxicity - dermal route

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 14: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Value LD_{50}	Reference
Acute dermal Guideline: ≅ OECD 402 (1981) GLP: No	Rabbit (Stauffland albino) 5/sex/group	Captan technical (Batch: WRC 4921-26-12; Purity: not reported) Vehicle: none	2000 mg/kg bw Single 24 hour exposure to clipped normal and abbraided skin followed by 14 days observation	**Both sexes:** > 2000 mg/kg bw	R-4378 Study 1 (1984)
Acute dermal Guideline: OECD 402 (1981) GLP: Yes	Rat (Crl:CD(SD) BR Vaf plus) 5/sex/group	Captan technical (Batch: 231408 Purity: not reported) Vehicle: distilled water	2000 mg/kg bw Single 24 hour exposure to clipped skin followed by 14 days observation	**Both sexes:** > 2000 mg/kg bw	R-5464 Study 2 (1989)
Acute dermal Guideline: OECD 402 (1981) GLP: yes	Rat (Sprague-Dawley) 5/sex/group	Captan technical (Batch: 4102 Purity: not reported) Vehicle: None.	2000 mg/kg bw Single 24 hour exposure followed by 14 days observation	**Both sexes:** > 2000 mg/kg bw	R-6291 Study 3 (1991)

Table 15: Summary table of human data on acute dermal toxicity

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 16: Summary table of other studies relevant for acute dermal toxicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

9.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

In an acute dermal toxicity study (Study 1, 1984) a group of rabbits (5/sex) was given a single dermal application for 24 hours at a dose of 2000 mg/kg bw. The skin was abraded on half of the animals and left intact on the others. A concurrent control (2/sex) was sham treated. All animals were observed for clinical signs for at least 14 days after treatment and were necropsied at the end of the observation period. There were no mortalities. All animals appeared normal throughout the observation period, except two rabbits which had wet areas around the eyes on days 4 and 5. There were no signs of dermal irritation. No abnormalities were observed at necropsy. The control animals appeared normal throughout the study. The acute dermal LD_{50} was > 2000 mg/kg bw in male and female rabbits.

In a second acute dermal toxicity study (Study 2, 1989), a group of 5 male and 5 female rats were given a single 24-hour dermal application at a dose of 2000 mg/kg bw. The test substance was applied at a

concentration of 72.7% w/v in distilled water to the intact, clipped lumbar skin. Animals were observed for 14 days for clinical signs. Body weights were recorded on days 1, 8 and 15. On day 15, animals were killed and subjected to macroscopic *post mortem* examination. There were no mortalities and no signs of systemic toxicity or dermal irritation. All animals showed the expected gain in body weight during the study. No abnormalities were observed at necropsy. The acute dermal LD_{50} was > 2000 mg/kg bw in male and female rats.

A third acute dermal toxicity study was conducted in a group of 5 male and 5 female rats at a dose of 2000 mg/kg bw (Study 3, 1991). The test substance was uniformly applied to an area of shorn skin which had previously been moistened with distilled water. Animals were observed for mortality and clinical signs for 14 days after treatment. Body weights were recorded at weekly intervals. At the end of the study, animals were killed and subjected to gross pathological examination. There were no mortalities and no signs of systemic toxicity or dermal irritation. All animals showed the expected gain in body weight during the study. No abnormalities were observed at necropsy. The acute dermal LD_{50} was > 2000 mg/kg bw.

9.2.2 Comparison with the CLP criteria

Two studies in rats and one in the rabbit have demonstrated that captan technical is of low acute dermal toxicity. As the acute dermal median lethal dose is greater than the upper criterion of 2000 mg/kg bw, the data do not meet the criteria for classification and labelling.

9.2.3 Conclusion on classification and labelling for acute dermal toxicity

No classification required.

9.3 Acute toxicity - inhalation route

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 17: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, , form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** **LC_{50}**	**Reference**
Acute inhalation Guideline: OECD 403 (1981) GLP: Yes MMAD of 4.95 - 6.51 µm (recommended: 1-4 µm); the respirable fraction (< 4 µm) is therefore to low and consequently the acute inhalation toxicity is underestimated. Reliable with restrictions	Rat (CD (Sprague-Dawley)) 5/sex/group	Captan technical (Batch: 630077 Purity 98.1%) Aerosol: MMAD 4.95 – 6.51 µm	0.43, 0.82, 1.36 mg/L Single 4 hour (nose-only) exposure followed by 14 days observation	**Both sexes:** 1.16 (0.65 – 1.66) mg/L **Males:** 1.21 (0.75 – 1.66) mg/L **Females:** 1.05 (0.21 – 1.89) mg/L	R-8072 Study 1 (1995)
Acute inhalation Guideline: OECD 403 (1981)	Rat (Sprague-Dawley)	Captan technical (Batch: 4102 Purity: not	0.23, 0.94, 4.81 mg/L Single 4 hour	**Both sexes:** 0.78 (0.49 – 1.23) mg/L	R-6292 Study 2 (1991)

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, , form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** **LC_{50}**	**Reference**
GLP: Yes	5/sex/group	reported) Aerosol: MMAD 1.6 – 1.8 µm	(nose-only) exposure followed by 14 days observation	**Males:** 0.90 (0.43 – 1.9) mg/L **Females:** 0.67 (0.36 – 1.22) mg/L	
Acute inhalation Guideline: US EPA (1982) GLP: No Deviations from OECD 403 (2009): - 10 animals per sex and concentration were tested instead of 5 - Particle size of low and high concentration was measured once instead of twice during exposure - MMAD > 4 µm for mid and high concentration - geometric standard deviation > 3 for mid concentration	Rat (Sprague-Dawley) 10/sex/group	Captan technical (Batch: # DCC-0303, Purity: not reported) Aerosol: MMAD 2.95-5.8 µm	0, 0.56, 0.71 and 1.39 mg/L Single 4 hour (whole-body) exposure followed by 14 days observation	**Males:** 0.72 (0.54 – 0.95) mg/L **Females:** 0.87 (0.67 – 1.13) mg/L	T-11933 Study 3 (1985)
Acute inhalation US EPA OPPTS 870.1300 (1998) GLP: Yes Deviations from OECD 403 (2009): - Housing temperature was outside the desired range (16-27°C) - Housing relative humidity was outside the desired range (up	Rat (Sprague-Dawley) 5/sex/group	Captan technical (Batch: PJE0805LS Purity: 91.66%) Aerosol: MMAD 2.545-2.979 µm (milled test substance) 7.399 µm (non-milled test substance)	0.072, 0.648 and 2.28 mg/L (milled test substance) 0.668 mg/L (non-milled test substance) Single 4 hour (nose-only) exposure followed by 14 days observation	**milled test substance** **Both sexes:** 0.272 (0.159-0.466) mg/L **Males:** 0.22 (0.084 – 0.579) mg/L **Females:** 0.322 (0.156 – 0.664) mg/L **non-milled test substance** **Both sexes:** >	00-5439 Study 4 (2000)

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, , form and particle size (MMAD)	Dose levels, duration of exposure	Value LC_{50}	Reference
to 87%) - MMAD of 7.399 for non-milled test substance Reliable for the milled test substance Reliable with restrictions for the non-milled test substance due to the limited amount of respirable fraction				0.668 mg/L **Males:** > 0.668 mg/L **Females:** > 0.668 mg/L	

Table 18: Summary table of human data on acute inhalation toxicity

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 19: Summary table of other studies relevant for acute inhalation toxicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

9.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

In an acute inhalation toxicity study (Study 1, 1995), groups of young adult rats (5/sex) were exposed by inhalation to captan technical as a single four-hour exposure (nose only) at nominal concentrations of 2.3, 4.45 and 6.23 mg/L captan (achieved concentrations 0.43, 0.82 and 1.36 mg/L captan). A control group was exposed to compressed air only. All animals were observed for 14 days after exposure and body weights were recorded daily. At the end of the observation period all animals were killed and subjected to a gross examination *post mortem* and selected organs were weighed.

At a concentration of 1.36 mg/L, 1 female died during the first 30 minutes of exposure and a further 3 males and 2 females were found dead the following morning. One male and 2 females died overnight following exposure at 0.82 mg/L. One female was found dead on the morning after exposure at 0.43 mg/L.

Clinical signs were evident in all groups during the first 2 hours of exposure and generally persisted for up to day 6. Clinical signs included wet fur, hypothermia, pigmented staining of the snout, piloerection, underactivity, hunched posture, reduced respiratory rate, exaggerated respiratory movements, gasping, rales, ungroomed appearance, pigmented orbital secretion, thin appearance, closed eyes and pallor of the skin. The signs were similar at all concentrations but were more persistent at the highest concentration (1.36 mg/L).

Animals that died overnight exhibited weight loss prior to death. On days 1-3 body weights were generally lower than pre-study values for animals exposed to captan. Thereafter, body weight gain for surviving animals was generally similar to the controls.

Necropsy findings in animals that died were confined to the respiratory system and included hepatisation of the lungs, incomplete lung collapse when the trachea was cut, pale or clear aerated fluid in the trachea, pale brown material or fluid in the nasal cavity, soft pale amorphous material in the larynx and clear fluid in the thoracic cavity. There were no treatment-related changes in animals that survived to scheduled termination. The acute (4-hour) inhalation median lethal concentration (LC_{50}) was 1.21 mg/L and 1.05 mg/L in males and females, respectively. The combined sex median lethal concentration (LC_{50}) was 1.16 mg/L (95% confidence limits 0.65 - 1.66 mg/L).

In a second acute inhalation toxicity study (Study 2, 1991), groups of young adult Sprague-Dawley strain rats (5/sex) were exposed by inhalation to captan technical as a single four-hour exposure (nose only) at nominal concentrations of 0.4, 1.8 and 12.6 mg/L captan (achieved concentrations 0.23, 0.94 and 4.81 mg/L captan). All animals exposed to 4.81 mg/L died or were killed *in extremis* during exposure. At 0.94 mg/L, 1 male died during exposure, 2 males and 2 females died or were killed *in extremis* after completion of exposure and another 2 females died on the day following exposure. There were no deaths of animals exposed at 0.23 mg/L. Clinical signs included hunched posture, lethargy, piloerection, ataxia, ptosis, gasping, laboured and noisy respiration and red/brown stains around the snout. Isolated incidents of pallor of the extremities, dehydration and frequent sneezing were noted. Surviving animals at 0.94 mg/L appeared normal on day 7 and animals at 0.23 mg/L appeared normal by day 5 following exposure.

During the first week after exposure, 1 male and 1 female from the 0.94 mg/L group showed very slight body weight loss. Body weight gain was normal in surviving animals during the second week.

Animals that died or were killed *in extremis* showed similar abnormalities at necropsy including lungs that appeared haemorrhagic, swollen and fluid filled. In addition, pale lungs, patchy pallor of the liver and reddening or congestion of the small intestine was noted in animals exposed to 4.81 mg/L. Additional observations in two animals that died in the 0.94 mg/L group included signs of fluid in the nasal and/or oral tract, fluid in the lung cavity, dark liver and haemorrhage, reddening or congestion of the small intestine.

The acute inhalation median lethal concentration (LC_{50}) was 0.90 mg/L and 0.67 mg/L in males and females, respectively. The combined sex LC_{50} was 0.78 mg/L (95% confidence limits 0.49 - 1.23).

In a third acute inhalation toxicity study (Study 3, 1985), groups of young adult Sprague-Dawley strain rats (10/sex) were exposed by inhalation to captan technical as a single four-hour exposure (whole body) at nominal concentrations of 0, 2.69, 3.92 and 6.81 mg/L captan (achieved concentrations 0, 0.56, 0.71 and 1.39 mg/L captan). All males and 8/10 females exposed to 6.81 mg/L died. At 0.71 mg/L, 5/10 males and 5/10 females died within 3 days. One female died on Day 1 and 3/10 males died within 2 days at 0.56 mg/L. No mortalities were observed in the control group. Clinical signs during exposure included, lethargy, salivation and breathing difficulties. After the exposures, nearly all rats exposed to captan technical exhibited stains about the face and many showed laboured breathing for varying lengths of time. Among surviving rats most of the clinical signs were temporary. Additional clinical signs included reduced activity, chromodacryorrhea, chromorhinorrhea and stains about the facial area.

The males at 0.56 and 0.71 mg/l showed significant body weight depression on Days 2, 7 and 13. The female rats showed significant depression only on study Day 2 at all three exposure levels. The female rats at 0.56 and 0.71 mg/l dose levels had recovered to control level by study Day 7. The body weights for male rats, although still significantly depressed, exhibited partial recovery by study Day 7. Animals that died showed common abnormalities including lungs that appeared reddened, mottled, failed to collapse properly. These observations appeared dose-related. The eyes were cloudy-white in several of the rats that died at the 0.71 and 1.39 mg/l exposure levels during observation period. Few males and females rats, surviving to the end of the study hat abnormal findings, which were considered incidental by the study author.

The acute (4-hour) inhalation LC50 for rats exposed to captan was 0.72 mg/L (95th confidence interval : 0.54-0.95) and 0.87 mg/L (95th confidence interval : 0.67-1.13) in males and females, respectively.

The forth acute inhalation toxicity study (Study 4, 2000) was designed to include a comparison of testing the milled test substance (three exposure levels), with smaller particle size and the non-milled (typical

manufactured product) test substance (one exposure level) with larger particles. In this study, groups of young adult Sprague-Dawley strain rats (5/sex) were exposed by inhalation to captan technical as a single four-hour exposure (nose-only) at nominal concentrations of 0.21, 1.4 and 4.5mg/L milled captan (achieved concentrations 0.072, 0.648 and 2.28 mg/L captan) and 5.1 mg/L non-milled captan (achieved concentrations 0.668 mg/L captan). The 2.28, 0.648 and 0.072 mg/L exposures to the milled substance resulted in respective mortalities of 100, 80 and 10% within 3 days after exposure. No mortality occurred in the group exposed to the non-milled test substance. The only sign of toxicity during the exposure period to the milled test substance was laboured breathing (0.648 and 2.28 mg/L) and poor condition (2.28 mg/L). There were no signs of toxicity noted during the 0.0720 mg/L exposure to the milled test substance. The only sign of toxicity during the exposure period to the non-milled test substance was laboured breathing. Among surviving animals from all exposure groups signs of toxicity noted immediately following the exposure included clear or red nasal discharge, chromodacryorrhea, excessive salivation, laboured breathing and moist rales. Among surviving animals from all exposure groups, responses similar to those seen immediately after the exposure were seen during the first week after exposure with recovery, in general, during the second week after exposure.

Most surviving animals exposed to the milled substance lost weight during the first week after exposure. However, all these animals gained weight during the second week after exposure. All animals exposed to the non-milled substance gained weight during both weeks after exposure. Macroscopic test substance-related findings were red mucinous material in the nasal cavity and fluid in the trachea and lung. Animals found dead had red lungs. The relationship, if any, of this finding to the test substance is not clear according to the study author because red lungs are a common finding in animals which are not exsanguinated prior to post-mortem examination. Scattered red foci in the lungs of rats terminally sacrificed are usually due to agonal haemorrhages.

The acute (4-hour) inhalation LC50 for rats exposed to milled captan was 0.22 mg/L (95th confidence interval: 0.084-0.579) and 0.322 mg/L (95th confidence interval : 0.156-0.664) in males and females, respectively. The combined sex LC50 for milled captan was 0.272 mg/L (95% confident limits 0.159-0.466 mg/L). LC50 of non-milled captan was greater than 0.668 mg/L for both sexes combined.

9.3.2 Comparison with the CLP criteria

All reliable acute inhalation toxicity studies show LC50 values which are below the upper cut-off value for a dust/mist of 5 mg/L and consequently captan meets the criteria for classification Three acute inhalation toxicity studies show similar effects and indicate that captan is moderately toxic via the inhalation route, which would confirm current classification. In these studies the median lethal dose is in the range 0.72 – 1.16 mg/L. However, LC50 in Study 4 is 0.22 mg/L in males and 0.322 mg/L in females (combined 0.272 mg/L) for milled captan, which is below the ATE for category 2.

An ATE of 0.22 mg/L is proposed based on the lowest LC50 in females from a fully reliable study (i.e. Study 4, milled captan).

9.3.3 Conclusion on classification and labelling for acute inhalation toxicity

As the lowest acute toxicity estimate (ATE) for captan is in the range $0.05 < \text{ATE} \leq 0.5$ mg/L the appropriate classification is Acute toxicity Cat 2 H330: Fatal if inhaled. An ATE of 0.22 mg/L is proposed.

9.4 Skin corrosion/irritation

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 20: Summary table of animal studies on skin corrosion/irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
Acute dermal	Rabbit (New	Captan technical	Single 4 hour application of	Mild irritant	R-6293

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results -Observations and time point of onset -Mean scores/animal -Reversibility	Reference
irritation Guideline: OECD 404 (1981) GLP: Yes	Zealand White) 3 males	(Batch: 4102 L/7 Purity: not reported) Vehicle: distilled water	0.5g (moistened) followed by observation at 1, 24, 48 and 72 hours after exposure.	Slight erythema in all animals at 1 and 24 hours after removal of the dressing, slight erythema in 1 animal at 48 hours Mean scores: Erythema: 0.33, 0.67, 0.33 Oedema: 0, 0, 0 Fully reversible by 72 hours	Study 1 (1991)

Table 21: Summary table of human data on skin corrosion/irritation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 22: Summary table of other studies relevant for skin corrosion/irritation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

9.4.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

In a primary dermal irritation study (Study 1, 1991), a group of young adult New Zealand White rabbits were given a single 4-hour application of 0.5 g of captan technical (moistened with distilled water) to clipped skin of the flank under a semi-occlusive dressing. The skin reactions were evaluated 1, 24, 48 and 72 hours after removing the dressings according to the Draize scale. Very slight erythema was noted at all treated skin sites one and 24 hours after patch removal and at one treated skin site at the 48-hour observation. All treated skin sites appeared normal 72 hours after treatment.

No skin irritating effects were observed in acute dermal toxicity studies (see section 8.2). Furthermore, in contrast to folpet (the sibling of captan), only slight effects were observed in a repeated dose dermal toxicity study (see section 8.12), wherby the vehicle in the folpet study was mineral oil while captan was applied in water. Folpet and captan belong to the group of phthalimide fungicides. There is no evidence for systemic exposure towards the intact parent molecules, which both incorporate the reactive toxicophore, i.e. the trichloromethylthio side-chain. This side chain generates the volatile thiophosgene both via hydrolysis and its rapid reaction with thiols. Accordingly, irritative effects are observed before entering the systemic compartment at the site of first exposure (e.g. GI-tract).

9.4.2 Comparison with the CLP criteria

The basis for a positive response with regard to skin irritation is the individual rabbit value averaged over days 1, 2, and 3. The mean score for each individual animal is used as a criterion for classification. Skin irritant Category 2 is used if:

a) In a study with 3 rabbits at least 2 animals show a mean score of 2.3 or above.

b) In case of 6 rabbits if at least 4 out of 6 rabbits show a mean score per animal of ≥ 2.3 ≤ 4.0 for erythema/eschar or for oedema.

As none of the animals showed a mean score of ≥ 2.3 for erythema or oedema, the data do not meet the criteria for classification and captan technical is considered to be non-irritant to the skin.

9.4.3 Conclusion on classification and labelling for skin corrosion/irritation

No classification required.

9.5 Serious eye damage/eye irritation

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 23: Summary table of animal studies on serious eye damage/eye irritation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results - Observations and time point of onset - Mean scores/animal - Reversibility	Reference
Acute eye irritation Guideline: OECD 405 (1987) GLP: Yes	Rabbit (New Zealand White) 1 female	Captan technical (Batch: 4102 Purity: not reported) Vehicle: none	82 mg (equivalent to 0.1 mL) Single application into conjunctival sac of one eye	Irritating There was a dulling of the normal lustre of the corneal surface and iridial inflammation at 1 hour after treatment. Diffuse corneal opacity, iridial inflammation, severe conjunctival irritation and haemorrhage of the nictitating and conjunctival membranes at the 5 hour observation. The animal was killed for humane reasons after the 5 hour observation.	R-6294 Study 1 (1991)
Acute eye irritation Guideline: ≅ OECD 405 (1981) GLP: No	Rabbit (New Zealand White) 9 female	Captan technical (Batch: SX-1367 Purity: not reported)	100 mg Single application into conjunctival sac of one eye 6 animals – eyes unflushed 3 animals – eyes flushed for 1 minute 30 seconds after treatment	Unrinsed eyes: Irritating Slight to complete corneal opacity and severe conjunctival irritation were observed in most rabbits by 24 hours after treatment and persisted throughout the day-21 observation period. Iritis and pannus were also observed during the study. Mean scores/animal (24, 48 and 72 hours): Cornea: 2.3, 2.3, 0.3, 2.3, 0.7, 2.7 Iris: 1, 1, 1, 1, 0.3, 1 Conjunctiva (redness): 3, 3, 3, 3, 3, 3 Conjunctiva (chemosis): 2.7, 3.3, 2.3, 2.3, 2, 3 Reversibility: not fully reversible after 21 days. Rinsed eyes: no corneal opacity was observed during the 21-day observation period. Iritis was observed at 24 hours in one animal. Slight to severe conjunctival irritation was observed through to 96 hours. Mean scores/animal (24, 48 and 72 hours): Cornea: 0, 0, 0 Iris: 0, 0, 0.3 Conjunctiva (redness): 0.3, 0.3, 2.7 Conjunctiva (chemosis): 0, 0, 1	R-6334 Study 2 (1982)

				Reversibility: fully reversible in 7 days	

Table 24: Summary table of human data on serious eye damage/eye irritation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 25: Summary table of other studies relevant for serious eye damage/eye irritation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

9.5.1 Short summary and overall relevance of the provided information on serious eye damage/eye irritation

In a primary eye irritation study (Study 1, 1991), 82 mg (equivalent to 0.1 mL) of undiluted captan technical was administered into the conjunctival sac of one rabbit. Ocular damage/irritation was evaluated approximately 1 and 5 hours following administration according to the Draize scale. Administration of captan technical to the rabbit eye resulted in areas of diffuse corneal opacity, iridial inflammation and severe conjunctival irritation. Other adverse ocular reactions noted were a dulling of the normal lustre of the corneal surface and haemorrhage of the nictitating and conjunctival membranes. The animal was killed for humane reasons immediately after the five hour observation.

In a second primary eye irritation study (Study 2, 1982), 100 mg of undiluted captan technical was administered into the conjunctival sac of one eye of each of nine rabbits. The other eye served as the control. Thirty seconds after treatment, eyes of three of the rabbits were rinsed with 250 mL distilled water over a period of one minute. All eyes were assessed for ocular reactions at 1 hour and 1, 2, 3, 4, 7, 10, 14, 17 and 21 days after administration.

In unrinsed eyes, slight to complete corneal opacity and severe conjunctival irritation were observed in most rabbits by 24 hours after treatment and persisted throughout the day-21 observation period. Iritis and pannus were also observed during the study.

In rinsed eyes, no corneal opacity was observed during the 21-day observation period. Iritis was observed at 24 hours in one animal. Slight to severe conjunctival irritation was observed through to 96 hours. All eyes appeared normal by day 7.

9.5.2 Comparison with the CLP criteria

Substances are classified as having irreversible effects on the eye (eye damage/eye irritation Category 1) if, when applied to the eye of an animal, a substance produces:

at least in one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within an observation period of normally 21 days

and/or

at least in 2 of 3 tested animals, a positive response of:
corneal opacity ≥ 3 and/or
iritis > 1.5

calculated as the mean scores following grading at 24, 48 and 72 hours after installation of the test material.

In two primary eye irritation studies (Dreher, 1991d; Bullock, 1982b) severe ocular irritation was observed which in one study had not fully recovered after 21 days. Consequently, captan technical warrants classification for eye damage.

9.5.3 Conclusion on classification and labelling for serious eye damage/eye irritation

The appropriate classification for captan technical is Eye Damage Cat 1, H318: Causes serious eye damage.

9.6 Respiratory sensitisation

No specific studies are available in the data set to address respiratory sensitisation.

9.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

No formally recognised and validated animal tests currently exist for respiratory sensitisation. There is evidence of respiratory irritation in repeated dose inhalation studies in rats and captan is a skin sensitiser. However, in humans, medical surveillance data on manufacturing plant personnel and monitoring studies have been conducted for over 40 years and no evidence of respiratory sensitisation has been reported.

9.6.2 Comparison with the CLP criteria

As there are no specific animal data and no evidence in humans that captan exposure can lead to specific respiratory hypersensitivity classification is not possible.

9.6.3 Conclusion on classification and labelling for respiratory sensitisation

No classification.

9.7 Skin sensitisation

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 26: Summary table of animal studies on skin sensitisation

<table>
<tr><th>Method, guideline, deviations if any</th><th>Species, strain, sex, no/group</th><th>Test substance,</th><th>Dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr>
<td>Maximisation test
Guideline: OECD 406 (1981)
GLP: Yes</td>
<td>Guinea pig (Dunkin-Hartley), females
Sighting study: 4 females for selection of concentration for intradermal injection (0.1, 0.4, 1 and 5%), 2 females for selection of concentration for topical</td>
<td>Captan technical (Batch: 4102 Purity not reported)
Vehicle: arachis oil
Positive control: 2,4-dinitrochlorobenzene</td>
<td><u>Intradermal Induction D0</u>: 0.1% w/v for intradermal injections.
<u>Topical induction D7:</u> 50% w/v for 48 hours 7 days after intradermal induction.
<u>Challenge</u> D 21: 10% w/v topically for 24 hours 2 weeks after topical</td>
<td>Sensitising
No. animals with positive signs of skin reactions:
<table>
<tr><th></th><th>24 hours</th><th>48 hours</th></tr>
<tr><td>Test Group</td><td>16/20*</td><td>14/20*</td></tr>
<tr><td>Control Group</td><td>0/10</td><td>0/10</td></tr>
</table>
* adverse reactions prevented assessment of test animals
Sensitisation rate: 100%</td>
<td>R-6295
Study 1 (1991)</td>
</tr>
</table>

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
	induction (5, 10, 25 and 50%) Main study: 30 Females: (20 test and 10 control)		induction. Challenge sites were scored 24 and 48 hours after removal of the dressing.		

Table 27: Summary table of human data on skin sensitisation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 28: Summary table of other studies relevant for skin sensitisation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

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

In a dermal sensitisation study with captan technical (Study 1, 1991), young adult Dunkin-Hartley guinea pigs (20 test and 10 controls) were evaluated by means of the Magnusson and Kligman maximisation test. Two main procedures were involved in the study; (a) the potential induction of an immune response; (b) a challenge of that response.

In the main study, a 0.1% w/v concentration of test substance in arachis oil was used for the intradermal induction injections and a 50% w/w concentration of the test substance in arachis oil was used for the topical induction applications. Control animals were treated in a similar way but with vehicle alone. For the 24 hour challenge exposure, all test and control animals were given a topical application of a 10% w/w concentration of the test substance in arachis oil on one flank and vehicle alone on the other flank. Skin reactions were evaluated approximately 24 and 48 hours later.

Following challenge with the test material, positive skin responses were noted in 16 and 14 animals after 24 and 48 hours, respectively. Adverse reactions prevented the accurate evaluation of erythema at test material sites in 4 of the 20 animals at 24 hours. At 48 hours, these reactions persisted in 1 animal and developed in a further 3 animals. At no time were adverse reactions noted at the vehicle control sites in test animals or at any sites of control animals. The overall sensitisation rate was 100%.

In separate positive control study, 2,4-dinitrochlorobenzene (DNCB), produced a satisfactory response under the conditions of the test.

9.7.2 Comparison with the CLP criteria

Materials are classified as a skin sensitiser in sub-category 1A if, in a guinea pig maximisation test:

≥ 30 % responding at ≤ 0.1 % intradermal induction dose
Or
≥ 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose

In the study by Dreher (1991e) 100% of animals responded positively at an intradermal induction dose of 0.1%. Thereby skin reactions were considered as sensitisation rate of 100%. This corresponds to the potency of an extreme skin sensitiser. Therefore, an SCL of 0.001% should be set. Consequently, captan meets the criteria for classification.

9.7.3 Conclusion on classification and labelling for skin sensitisation

The appropriate classification for captan is Skin sensitisation Cat 1A H317: May cause an allergic skin reaction with a SCL of 0.001%.

9.8 Germ cell mutagenicity

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 29: Summary table of mutagenicity/genotoxicity tests in vitro

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
Reverse mutation in bacteria OECD 471 GLP	Captan technical (batch: 941381319; purity 96.5%) Solvent: DMSO	*Salmonella typhimurium* strains TA98. TA100, TA1535, TA1537 and *Escherichia coli* strain WP2 uvrA	Pre-experiment with and without metabolic activation: 3.16. 10, 31.6, 100, 316, 1000, 2500, 5000 µg/plate Experiment 1 with and without metabolic activation: 0.050, 0.158, 0.500, 1.58, 0.500, 1.58, 50, 158 and 500 µg/plate	Positive in all strains, plate incorporation without and with metabolic activation. Toxicity without metabolic activation ≥158 µg/plate strain TA98, ≥50 µg/plate remaining strains Toxicity with metabolic activation ≥50 µg/plate strain TA1537, ≥158 µg/plate remaining strains	R-38477 Study 8 (2017)

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
Reverse mutation in bacteria No guideline quoted Not GLP Deviations from OECD 471 (1997): Numerous deviations, e.g.: only one strain (TA100) tested instead of the recommended four *S. typhimurium* strains and one *E. coli* strain; not tested in presence of an appropriate metabolic activation system (S9); only two instead of at least five different analysable concentrations tested. Limited acceptability	Captan (batch: SX-1086; purity not reported) Solvent: DMSO	*Salmonella typhimurium* strain TA100	10 and 25 µg/mL (with and without 7.5 and 10 µg/mL glutathione or cysteine)	Positive without glutathione or cysteine Glutathione and cysteine inhibited the *in vitro* mutagenic potential of captan in a dose-dependent manner No inhibitory effect of non-thiol amino acids	R-9246 Study 9 (1985)
Reverse mutation in bacteria Publication, no guideline quoted, Not GLP Deviations from OECD 471 (1997):Numerous deviations, e.g.: testing in the *S. typhimurium* strains TA1536 and TA1538 is not recommended anymore; the test substance was not tested in the recommended *S. typhimurium* strains TA98 and TA100 and in one *E. coli* strain; only one instead of at least five different analysable concentrations was tested. Limited acceptability	Captan (batch: not reported; purity: 93%) Solvent: DMSO	*Salmonella typhimurium* TA1535, TA1536, TA1537 and TA1538	0, 20 µg/plate (with and without S-9)	Positive in TA1535 with and without metabolic activation	Carere *et al*. (1978) R-2615

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
In vitro chromosome aberration test in human lymphocytes. OECD 473 GLP	Captan technical (batch: 941381319; purity 96.4%- Please note that this purity does agree with report although the same batch is 96.5% in the other two studies with same batch) Solvent: DMSO	Human lymphocytes	Without metabolic activation 0.02, 0.04, 0.05, 0.06 mM With metabolic activation 0.01, 0.02, 0.04 and 0.06 mM	Positive chromosome aberration **without** metabolic activation. No biologically relevant increase **with** metabolic activation. No precipitation. Toxicity 0.04 mM without metabolic activation, 0.02 mM with metabolic activation	R-38479 Study 10 (2018)
Mammalian cytogenicity (sister chromatid exchange and chromosomal aberrations) Publication, no guideline quoted, Not GLP Deviations from OECD 473 (2014): Numerous deviations, e.g.: no testing in presence of metabolic activation; cell proliferation was apparently measured by BrdU incorporation; only exposure to captan for 26.5 hours was tested; only cells with chromosomal aberrations excluding gaps were scored; at least 300 metaphases should be scored per concentration and exposure time Limited acceptability	Captan (batch: not reported; purity: 99.9%) Solvent: DMSO	Chinese hamster cell V79 cell line	0, 0.6, 1.5, 3, 4.5 and 6 x 10^{-5}M	Positive	Tezuka *et al.* (1980) R-2715

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
Cytogenicity (chromosomal aberrations) Publication, no guideline quoted, Not GLP Deviations from OECD 473 (2014): Numerous deviations, e.g.: no demonstration of exponential cell growth/no stimulation of cell division; no testing in presence of metabolic activation; only cells with chromosomal aberrations excluding gaps were scored; at least 300 metaphases should be scored per concentration and exposure time Not acceptable	Captan (batch: not reported; purity: > 98%) Solvent: DMSO	Human diploid fibroblasts	0, 0.5, 1.5, 3.0 and 4.0 µg/mL	Negative for mutagenicity. No chromosome aberrations. Mitotic inhibition at all tested concentrations	Tezuka *et al.* (1978) R-1666
In vitro mammalian cell gene mutation (HPRT locus) OECD 476 GLP	Captan technical (batch: 941381319; purity 96.5%) Solvent: DMSO	Chinese hamster V79 cells	Without metabolic activation: 0.0002, 0.0005, 0.0007, 0.001, 0.002, 0.004 mM With metabolic activation: 0.002, 0.005, 0.01, 0.02, 0.03, 0.04 mM	Positive gene mutation **without** metabolic activation. No biologically relevant increase **with** metabolic activation.	R-38478 Study 11 (2017)
Mammalian cell gene mutation (Mouse lymphoma assay) No guideline quoted GLP Deviations from OECD 476 (2015): The current OECD testing guideline 476 does not support the measurement of mutation at the thymidine kinase (TK) locus anymore, only at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) and at the xanthine-guanine phosphoribosyl transferase (XPRT) locus.	Captan (Merpan technical; batch: 610541; purity: 92% by HPLC) Solvent: DMSO	Mouse lymphoma L5178Y cells	Experiments 1 and 2 without S9: 0, 0.025, 0.05, 0.1, 0.2, 0.3 and 0.4 Experiment 1 with S9: 0, 3.125, 6.25, 12.5, 25, 50 and 100 µg/mL (without S-9) Experiment 2 with S9: 0, 6.25, 12.5, 20, 25, 37.5 and 50 µg/mL Experiment 3 with S9: 0, 20, 25, 30, 35, 40 and 45 µg/mL	Positive (without S-9) Negative (with S-9)	R-4319 Study 12 (1986)

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
Mammalian cell gene mutation Publication, no guideline quoted Not GLP Deviations from OECD 476 (2015): No testing in presence of metabolic activation; no historical control data is available	Captan (batch: not reported; purity: not reported) Solvent: DMSO	Chinese hamster ovary cells CHO-K1BH4	0, 0.1, 0.25, 0.5, 1.0, 2.0, and 4.0 µg/mL (without activation) Three experiments	Positive	O'Neill *et al.* (1981) R-3487

Table 30: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells in vivo

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
Bone marrow micronucleus test OECD 474. Deviations: None GLP	Merpan (captan; batch: 610541; purity: 94%) Solvent: 0.5% CMC and 0.5% acetic acid	Mouse: CD1 15 sex/group high dose and control 5 mice/sex/group low and mid dose Mice were killed after 24 hours (all groups), 48 and 72 hours (control and high dose group)	Single oral gavage dose. 0, 40, 200 and 1000 mg/kg bw Incidence of micronucleated cells per 1000 polychromatic cells scored for each animal	Negative Highest dose: MTD as determined in a preliminary toxicity study Positive control group included	R-3666 Study 1 (1985)
Mouse spot test No guideline quoted, equivalent to but pre-dating 87/302/EEC Not GLP	Captan (batch: not reported; purity: 92.2%) Solvent: diet	Pregnant C57B1/6J mice (mated with T-strain males) Offspring scored for spots on day 12 and at the time of weaning	Diet 0, 100, 1000 and 5000 ppm from day 8 through to day 12 of pregnancy	Negative Positive control group included.	TMN-0834 Study 2 (1981)
Mammalian bone marrow cytogenicity study No guideline quoted Not GLP Deviations from OECD 475 (2014): Cytotoxicity (mitotix	Captan (batch: 702/38; purity: not reported) Solvent: 0.5% gum tragacanth	Rat: CD 6 males/dose	Five 0, 200, 400 and 800 mg/kg bw/day by oral gavage on 5 consecutive days. Bone marrow slides prepared and 100 plates examined "blind" to treatment	Negative. Positive control group included.	R-1735 Study 3 (1979)

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
index) was not determined; only 100 metaphases per animal instead of 200 were examined; no historical control data is available					
Mammalian bone marrow cytogenicity study Publication, no guideline quoted Not GLP Deviations from OECD 475 (2014): Cytotoxicity was not determined; very poor reporting of methods and results Limited acceptability	Captan (batch: not reported; purity: 96.5%) Solvent: Tween 40	Mouse: strain not reported 5-7 mice/group	Five consecutive daily doses of 0, 100, 400, 800 and 1000 mg/kg bw/day Mice killed 6 hours after last dose. 1000 cells per animal scored for chromosome aberrations	Positive Positive control group included.	Feng and Lin (1987) TMN-0826
Mammalian bone marrow cytogenicity study Publication, no guideline quoted Not GLP Deviations from OECD 475 (2014): Numerous deviations, e.g.: Maximum tolerated dose was exceeded; only one dose level was tested; irrelevant route of exposure (intraperitoneally); at least 200 metaphases per animal should be analysed; a product (Captan 50 WP) containing 50% technical captan was tested instead of the technical active substance, therefore this study can be used as additional information only. Not reliable/ acceptable	Captan 50 WP (batch number 01007-10; purity: 50%) Solvent: 0.9% saline	Mouse strain: Upjohn Swiss albino 3 - 6 males/group	Single intraperitoneal (i.p.) administration, 250 mg/kg bw/day Sacrificed at 6, 12, 30 and 54 hours after treatment. Bone marrow cells extracted, slides prepared and 100 metaphases per animal, examined	Negative [Results of the study suggest that captan does not result in chromosomal damage *in vivo*. However, it cannot be stated with certainty that captan does not result in chromosomal breakage due to the presence of metacenteric chromosomes in some animals treated i.p.] Mortalities in treated animals scheduled for sacrifice at 6, 12, 30 and 54 hours 0, 25, 20 and 68% greater than control. Positive control group included.	Fry and Ficsor (1978) R-2576

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
In vivo investigation of gene mutation in transgenic mouse liver and duodenum. OECD 488 GLP	Captan (batch number 94138718; purity: 94.96% %) Vehicle mouse diet	Transgenic Mice Strain CD2-LacZ80/HazfBR (Muta™Mouse) [SPF] 0, 600, 2000, and 6000 ppm captan in diet (equivalent to mean test substance intakes of 0, 85.3, 273, and 776 mg/kg bw/day, respectively 6/group – 5/group evaluated	Administered for 28 consecutive days, and then after an additional 3 days for mutant manifestation following the last administration, the liver and duodenum were removed and mutant frequencies were determined.	Did not induce gene mutations in the liver or duodenum of transgenic mice (was negative) under the conditions in this study. Positive control group included	Report No. G514 (564-030) Study 4 (2016)
Duodenal cytogenicity studies. Publication, no guideline quoted, Not GLP Limited acceptability	Captan (batches: not reported; purity: 94% for experiments 1, 2 and 5; 99, 92.4 and 50% for experiments 3 and 4) Solvent: 1% gum tragacanth and 0.05% Tween 40; diet experiment 1 only	Mouse strains: C57 Bl/6J for experiment 1, CD1 for remaining experiments	1) Fed 0, 8000 and 16000 ppm in diet for seven days, sacrificed day 8 2) Oral gavage 5 consecutive days 0, 200 or 2000 sacrificed 4 hours after the final dose. 3) Oral gavage 5 consecutive days of 3 different purities of captan (99%, 92.4%, 50%) at 0, 200 and 2000 mg/kg bw, sacrificed 24 hours after treatment. 4) As experiment 3 followed immediately by the intraperitoneal administration of 1,2-dimethyl-hydrazine (DMH) 5) 1300 mg/kg bw L-butathione-S,R-sulphoximine (BSO) or vehicle; after 4 hours oral dose of 0, 50, 100, 200, 400, 2000 or 4000 captan. Duodenal glutathione concentration determined at time of captan administration	Negative Captan did not give increase in nuclear aberrations per crypt cell in any experiment. Glutathione levels in the duodenal epithelium, 4 hours after BSO administration ↓ 55 ± 11% ($p < 0.01$) but no differences in the incidence of nuclear aberrations between animals pre-treated with BSO and control at any dose level of captan	Chidiac and Goldberg (1986) R-6346

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
			and after 24 hours. 4-6 mice per group. All experiments: Ten crypts scored per duodenal section, starting as near as possible to the pylorus and moving distally.		
Unscheduled DNA synthesis Consistent with OECD Guideline 486 GLP	Captan (batch: WRC 11240-37-1; purity: 91.2%) Solvent: corn oil	Rat: Alpk:APfSD (Wistar-derived) 5 males/dose/time point, two independent experiments	Oral gavage 0, 500, 1000, 2000 mg/kg bw Sacrificed 4 and 12 hours after treatment Hepatocytes incubated with [^{3}H]-thymidine for 4 hours, two highest concentrations selected for assessment of unscheduled DNA synthesis (UDS).	Negative Tested up to limit dose in the absence of toxicity i.e. 2000 mg/kg bw	TMN-0835 Study 5 (1990)
Dominant lethal assay No guideline quoted, Not GLP Deviations from OECD 478 (2016): Unclear whether the negative control and the positive control would meet the current acceptability criteria; according to OECD 478, the Dominant Lethal factor is estimated as: (post-implantation deaths/total implantations per female) x 100; in contrast, only early resorptions were considered for mutagenicity in this study, whereas the frequency of late deaths was considered "non-genetic" by the study author; unclear whether statistical significance was analysed for mutagenicity data in this study	Captan (batch: not reported; purity: 89%) Solvent: diet	Rat: Charles River strain albino mice 15 males/group, untreated virgin females	In diet for 8 weeks 0, 500, 3000 and 7000 ppm After 8 weeks treatment, each male was housed with three untreated virgin females for one week, females were removed and replaced by three new virgin females. Repeated for total of eight weeks. Females killed 14 days after start of mating period and uterine contents assessed.	Negative Positive control included	TMN-0850 Study 6 (1977)

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
Not reliable/ acceptable					
Dominant lethal assay Publication, no guideline quoted Not GLP Deviations from OECD 478 (2016): Poor reporting, information missing (e.g. whether administration via gavage or feed, body weights, food consumption and clinical sings not measured or not reported, no rationale for selected doses, etc.); at least three treated dose groups should be analysed (instead of two) in order to provide sufficient data for dose response analysis; insufficient number of pregnant females (should provide at least 400 implants); for a single treatment up to five daily doses, the mating period should be 8 weeks for mice (instead of 6 weeks); females should remain with the males for at least the duration of one oestrus cycle/1 week (instead of 2-4 days); statistical method not stated Limited acceptability	Captan (batch: not reported; purity: > 98%) Solvent: 5% gum arabic	Mouse C3H, 15 males/group, 10 weeks of age. Mated with untreated virgin SLC-ICR females	Oral gavage treated for 5 consecutive days with 0, 200 or 600 mg/kg bw/day	Negative Positive control EMS included.	Tezuka *et al*. (1978) R-1666
Dominant lethal assay. Not GLP, Publication Deviations from OECD 478 (2016): Poor reporting, information missing (e.g. body weights, food consumption and clinical sings, no rationale for selected	Captan (batch and purity not stated) Vehicle: carboxymethyl-cellulose (CMC)	Rats and mice 15 male rats and 15 male mice mated to untreated virgin females for 10 and 12 weeks Treated male rats were mated with one female per week, mice	Five days either i.p (2.5, 5 and 10 mg/kg bw/day) or oral intubations (50, 100, and 200 mg/kg bw/day)	Increase in mean early deaths observed after administration of captan to rats and mice suggests that captan may exhibit mutagenic properties when orally administered in repeated doses	Collins (1972)

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
doses, etc.); only early foetal deaths were reported instead of complete post-implantation deaths (early + late) Limited acceptability		with two females per week		for five days. Positive control Triethylene-melamine	
Modified dominant lethal test. One of 174 test agents tested for mutagenicity in mice Publication, pre-dates test guideline Not GLP Deviations from OECD 478 (2016): No result data was reported for captan except the mortality data for the tested males; at least three treated dose groups should be analysed in order to provide sufficient data for dose response analysis; vehicle not clearly stated; low number and relatively high mortality of tested males; for two out of three i.p. studies, the mating period was only 3 weeks instead of 8; only early foetal deaths were considered instead of complete post-implantation deaths (early + late) Not acceptable	Captan (batch and purity not stated) Vehicle: either	ICR/Ha Swiss mice. 5 to 11 males /group.	Single i.p. injection at 9, 12, 15 and 30 mg/kg bw or by a single oral intubation at 500 and 800 mg/kg bw or by oral intubation for five consecutive days at 25 and 50 mg/kg bw/day	Negative	Epstein *et al.* (1972)
Chromosomal aberrations mouse spermatogonia and spermatocytes Publication, pre-dates test guideline Not GLP Deviations to OECD 483 (2016): Poor reporting; no	Captan (batch: not reported; purity: 96.5%) Solvent: Tween 40:	Mouse: strain not reported	Five consecutive daily doses of 0, 100, 400, 800 or 1000 mg/kg bw/day Mice killed 6 hours after last dose. 5-7 animals per group, 100 cells per animal scored for chromosome aberrations	Positive	Feng and Lin (1987) TMN-0826

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
positive control tested (only in the assay of sperm morphology); the interval between colchicine injection and sacrifice was 2 hours instead of 3-5 hours; the ratio of spermatogonial mitosis to first and second meiotic metaphases was not reported; statistical method not stated Limited acceptability					
Review of *in vivo* genotoxicity. Review article, no guideline quoted Not GLP Reliability assessment was not considered applicable, as this statement of the applicant summarised and critically evaluated studies on germ cell genotoxicity, both published and unpublished. When accepted, these argumentations have been included under the respective studies.	Captan	n/a	n/a	In summary, there is overwhelming evidence that the genotoxic potential of captan is not expressed *in vivo*: It is concluded that captan does not present a risk of genotoxicity in humans, neither in somatic cells nor in germ cells	Report No. 562961-CA-050403-1 Study 7 (2017)
Supporting study					
Stability in whole human blood No OECD TG available.	[U-phenyl -^{14}C] folpet stability in whole human blood, no OECD TG available.	Heparinised whole blood from one healthy human	Incubated *in vitro* at 37°C for time intervals ranging from zero to ca. 31 seconds. Fractions assayed by scintillation to quantify captan, and degradate 1,2,3,6-tetrahydrophthalimide (THPI)	Degradation of captan in human blood was time-dependent and exceptionally rapid, with a calculated half-life of 0.97 seconds, Loss of captan was accompanied by a time-dependent appearance of THPI. All captan was converted to THPI by the end of the 31 second	R-11143 Study 13 (1999)

Method	Test substance	Organisms/ strain	Concentrations tested	Result	Reference
				incubation period. Incubation of radiolabelled captan in normal saline for 60.4 seconds at 37°C was quantitatively recovered as parent material, demonstrating that whole blood was required for conversion.	
Tetrahydrophthalimide (THPI)) studies- THPI is the main metabolite of captan which is systemically available (please refer to section 7.1)					
Reverse mutation in bacteria OECD 471 GLP Deviations to OECD 471 (1997): No historical control data provided.	THPI (batch: 279-071-01; purity 98.9%) Solvent: DMSO	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535 and TA 1537	First experiment was carried out as a plate incorporation test and the second as a preincubation test. Five concentrations ranging from 100 to 5000 µg/plate Metabolic activation included	Negative in all strains. No signs of cytotoxicity were noted up to the top concentration of 5000 µg/plate in the plate.	R-24810 Study 14 (2009a)
In vitro chromosome aberration test in CHO cells. OECD 473 GLP Deviations to OECD 473 (2016): Number of examined metaphases was lower than recommended in the guideline (200 instead of 300), but in line with the (old) guideline from 1997. However, as the responses were clear, this is considered a minor deviation.	THPI (batch: 279-071-01; purity 98.9%) Solvent: DMSO	Chinese hamster ovary (CHO-K1) cells	2 exposure times without S9 mix: 4 and 20 hours, and 1 exposure time with S9 mix: 4 hours Max. 2500 µg THPI/mL in the experiments without and with metabolic activation (4-h exposure) and 625 µg/mL (in the second experiment without metabolic activation (20-h exposure).	No indications of mutagenic properties with respect to chromosomal or chromatid damage Precipitation was noted at the top concentration of 2500 µg/mL	R-24809 Study 15 (2009b)
TK (Thymidine Kinase) locus in L5178Y TK+/- cells OECD 476 GLP	Cis-1,2,3,6-Tetrahydro-phthalimide (batch 919100; purity 99%)	TK (Thymidine Kinase) locus in L5178Y TK+/- mouse lymphoma cells	2 independent experiments, with and without a metabolic activation system (S9 mix)	No mutagenic activity in the mouse lymphoma assay, in the presence or in the absence of S9 No toxicity was induced at any of the dose-levels	R-34855 Study 16 (2014)

Table 31: Summary table of human data relevant for germ cell mutagenicity

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

9.8.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

A number of genotoxicity studies have been carried out with captan, both *in vitro* and *in vivo*. There are three recent *in vitro* studies conducted to GLP and current OECD guidelines. Older *in vitro* studies were not conducted to GLP but are included for completeness.

Captan was mutagenic with and without metabolic activation in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2 uvrA (Study 8, 2017). Captan was also found to be mutagenic in bacterial cell systems without metabolic activation, in reverse mutation studies in bacteria with *Salmonella typhimurium* strains TA100 (Study 9, 1985) and TA1535 (Carere *et al*., 1978). Carere reports positive results for strain TA1535 with metabolic activation. However Carver found that the presence of glutathione or cysteine diminished or even abolished the mutagenicity of captan *in vitro*. There was no similar inhibitory effect of non-thiol amino acids.

In a study in Chinese hamster V79 cells (Study 11, 2017) captan caused gene mutation **without** metabolic activation (S9). No biologically relevant increase in chromosome aberration was observed **with** metabolic activation. The presence of S9 has also been shown to affect gene mutation in mammalian mouse lymphoma L5178Y cells (Study 12, 1986) where the assay was also positive without S9 but negative with S9.

Captan has been shown to induce gene mutations and chromosomal damage *in vitro* in studies in mammalian cells i.e. Chinese hamster ovary cells (Tezuka *et al*., 1980 and O'Neill *et al*., 1981). However, Tezuka *et al*. (1978) report no chromosome aberrations or cytogenicity in human diploid fibroblasts. Captan was clastogenic in human lymphocytes in the absence of metabolic activation but there was no increase in chromosome aberrations with metabolic activation (Study 10, 2018).

Generally negative results have been reported from *in vivo* assays on somatic cells when captan is administered by gavage or in diet. There are two existing *in vivo* studies with captan using validated testing methods i.e. studies conducted to GLP and consistent with modern guidelines. These are both negative and are a mouse bone marrow micronucleus assay (Study 1, 1985) and an unscheduled DNA synthesis assay in rat hepatocytes (Study 5, 1990). In both studies the highest dose was a limit dose as recommended in the relevant OECD guideline or an MTD as determined in a preliminary toxicity study.

There is one publication reporting a relatively recent *in vivo* study (Study 4, 2016) where captan was administered in diet to groups of transgenic mice to investigate gene mutation in the liver and duodenum. There was no evidence of gene mutation in either tissue. The majority of the other *in vivo* studies in somatic cells also gave negative results. These included cytogenetic assays in rat bone marrow oral gavage (Study 3, 1979); i.p (Fry and Ficsor, 1978), and mouse spot tests (Study 2, 1981). The most relevant results to the effects seen in rodent carcinogenicity studies are from a series of nuclear aberration assays in mouse duodenum reported by Chidiac and Goldberg (1986). The potential target tissue was examined in an extensive series of chromosome aberration assays. In this case duodenum is the site of carcinogenic activity in the mouse and the negative genotoxicity results together with the *in vivo* investigative studies performed (section 8.9) are considered to demonstrate that effects seen in carcinogenicity studies are due to a non-genotoxic mechanism.

It is noted that positive results in cytogenetic assays in mouse bone marrow (both micronuclei and chromosomal aberrations) have been reported in a single paper where technical captan from the Danyan Chemical plant in China was administered by gavage (Feng and Lin, 1987). There are also reports of positive effects in germ cells (chromosomal aberrations mouse spermatogonia and spermatocytes) in the same paper. These findings are inconsistent with other *in vivo* data generated for captan but as this was a published paper lacking in experimental details, the reason for the positive results cannot be determined.

In vivo studies with germ cells include 2 key dominant lethal studies and 2 further supporting studies. Three of these gave negative results in mice via the diet (Study 6, 1977), via oral gavage (Tezuka *et al.,* 1978) and via oral gavage and i.p administration (Epstein *et al*., 1972) with a fourth giving negative results in rats and mice via the i.p. route (Collins, 1972). Equivocal results were obtained by Collins in both rats and mice following oral administration. When findings were expressed as decreased total implants per pregnant female, no mutagenic effect was observed but an increase in the mean number of early deaths was observed at the highest dose at week 1, and with the two highest doses at week 2 there were reductions in the total number of implants per pregnancy. This result is considered equivocal as genetically damaged zygotes mainly result in pre-implantation losses, with consequent reduction of the total number of implants per pregnancy but there was no reduction in the mean number of implants after captan treatment.

Further investigative work (summarised in section 8.9) looked at a possible direct interaction of captan and DNA. Purification of liver, jejunum and duodenum samples from captan-treated mice using caesium chloride fractionation, failed to show that radioactivity was actually bound to DNA (section 8.9, Table 32, Study 5, 1991 and Annex Human Health Study 3.9.4.1). This was confirmed in further *in vitro* and *in vivo* investigations (section 8.9, Table 32, Study 6, 1993 and Annex Human Health Study 3.9.4.2) which did not demonstrate any clear evidence for a reaction of captan or its breakdown products with DNA.

The potential genotoxicity of captan has been reviewed by a team of experts (Arce *et al*., 2010). Their review of the collective data for captan and the similar substance, folpet, shows that the compounds have *in vitro* mutagenic activity but are not genotoxic *in vivo*. "This dichotomy is primarily due to the rapid degradation of folpet and captan in the presence of thiol-rich matrices typically found *in vivo*. Genotoxicity has not been found in the duodenum, the mouse tumour target tissue." The authors conclude that captan presents an unlikely risk of genotoxic effects in humans.

Degradation of captan in human blood (Study 13, 1999) was time-dependent and exceptionally rapid, with a calculated half-life of 0.97 seconds, modelled by a first-order equation (given as µg captan = 0.643 (e-0.718t)). Loss of captan was accompanied by a time-dependent appearance of THPI. All captan was converted to THPI by the end of the 31 second incubation period. Incubation of radiolabelled captan in normal saline for 60.4 seconds at 37°C was quantitatively recovered as parent material, demonstrating that whole blood was required for conversion. This study demonstrated that any systemically available captan will degrade rapidly in whole human blood, to degradates also seen in rat studies. Furthermore, the metabolite, THPI has been investigated (Study 14 and 15, 2009 a and b and Study 16, 2014) and found not to be mutagenic in bacterial or mammalian cells or to cause chromosome aberrations or cytogenicity in Chinese hamster ovary cells. THPI did not result in an increase in the incidence of nuclear aberrations in duodenal crypts (Chidiac and Goldberg, 1986).

9.8.2 Comparison with the CLP criteria

Captan is metabolised very rapidly by whole human blood to THPI, a metabolite which is not genotoxic. Therefore captan will not reach germ cells *in vivo*. On the basis of the available evidence it is considered that captan will not induce heritable mutations in the germ cells of humans.

Mainly negative results have been reported from *in vivo* assays on somatic cells. Positive results have been reported from a single study with limited reliablilty due to very poor reporting of methods and results (e.g. cytotoxicity was not determinded), where technical captan was administered by gavage in cytogenetic assays in mouse bone marrow (both micronuclei and chromosomal aberrations). Given by gavage or with diet, captan was tested with negative results in cytogenetic assays in rat bone marrow, in the mouse micronucleus and mouse spot tests, as well as in a nuclear aberration assay in mouse duodenum (the site of oncogenic activity in the mouse). Captan also produced negative results in an unscheduled DNA synthesis assay in rat hepatocytes. Negative results have also been obtained in a mouse bone marrow cytogenetic study after i.p. administration of captan. Finally, a fully reliable *in vivo* transgenic mouse study supports non-genotoxicity *in vivo* with more recent data.

Although captan is genotoxic *in vitro* in simple cellular systems, a series of *in vivo* and *in vitro* studies indicate that thiol groups in metabolically competent cells can effectively detoxify the captan. The negative results with captan in numerous *in vivo* genotoxicity assays can be explained by this effective detoxification of captan.

The only target organ for tumour identified in rodent carcinogenicity studies is the duodenum in mice. A series of non-guideline *in vivo* chromosome aberration assays tests to determine the genotoxicity of captan in duodenal crypt cells (Chidiac and Goldberg, 1986) as well as a negative transgenic rodent assay in duodenum (study 4) are considered to support other evidence for a non-genotoxic mechanism for increased tumours which are seen only in the mouse duodenum.

9.8.3 Conclusion on classification and labelling for germ cell mutagenicity

No classification.

9.9 Carcinogenicity

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 32: Summary table of animal studies on carcinogenicity

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Combined Chronic Toxicity/ Carcinogenicity Study Guideline not reported but consistent with OECD 453 (1981). No major deviations. GLP Rat: Charles River CD 50/sex/group for carcinogenicity 10/sex/group interim kill after 12 months 10/sex/group interim kill after 18 months	Captan technical, (batch: SX944; purity: 89%) 0, 25, 100 and 250 mg/kg bw/day in diet For up to 2 years	**Non-neoplastic findings** **<u>250 mg/kg bw/day</u>** ↓ Body weight: mean 20.1% males, 19.4% females week 104 ↑ Liver weight: 36% males; kidney weight 28% 18 months ↑ Hepatocellular hypertrophy: 10/10 males, 8/10 females 18 months (0/10 controls) **<u>100 mg/kg bw/day</u>** ↓ Body weight: mean 11.9% males, 18.9% females week 104 **<u>25 mg/kg bw/day</u>** No treatment-related findings **Neoplastic findings** No treatment related increases in tumour incidence.	R-9282 Study 1 (1982)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Carcinogenicity study Guideline not reported but consistent with OECD 451 (1981). No major deviations. GLP Rat: Cpb:WU Wistar random. 50/sex/group	Merpan technical, (batch and purity not reported). 0, 125, 500 and 2000 ppm in diet (eq. to 0, 5, 24 and 98 mg/kg bw/day). For 130 weeks	**Non-neoplastic findings** **2000 ppm (98 mg/kg bw/day)** ↓ Body weight: 7.8 and 8.8% males after 364 and 728 days respectively, 10.0 and 10.2% females after 364 and 728 days respectively ↓ Food consumption: 11.9% males, 10.0% females overall mean to day 252 ↓ Food utilisation efficiency: 0.293 g growth/g food/week males week 1 (control 0.416); 0.286 females week 1 (control 0.371) ↑ Liver weight: 15% relative to body weight males **500 ppm (24 mg/kg bw/day)** No treatment-related findings **125 ppm (5 mg/kg bw/day)** No treatment-related findings **Neoplastic findings** No treatment related increases in tumour incidence.	R-3608 Study 2 (1983)

<table>
<tr><th>Method, guideline, deviations if any, species, strain, sex, no/group</th><th>Test substance, dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td>Carcinogenicity study

Guideline not reported but consistent with OECD 451 (1981). No major deviations but increased number of animals per group.

GLP

Mouse: CD-1 (ICR derived).

80/sex/group</td><td>Captan technical, (batch: SX-944; purity: 90.7%)
0, 2000, 6000, and 10000 ppm in diet weeks 1-4.

0, 6000, 10000 and 16000 ppm in diet weeks 5-113</td><td>Non-neoplastic findings

<u>16000 ppm (1890/1880 mg/kg bw/day in males/females)</u>

↓ Survival: males 68% week 75 [control 83%]

↓ Body weight: 21.9% males, 20.3% females week 52

↓ Food consumption: 17.6% males;16.5% females week 52

↑ Duodenum mucosal hyperplasia: 24/75 males and 34/76 females [control 3/74 and 6/72]

<u>10000 ppm (1030/1080 mg/kg bw/day in males/females)</u>

↓ Body weight: 9.0% males, 12.2% females week 52

↓ Food consumption: 10.3% males; 6.1% females week 52

↑ Duodenum mucosal hyperplasia: 36/72 males and 37/76 females [control 3/74 and 6/72]

<u>6000 ppm (599/634 mg/kg bw/day in males/females)</u>

↓ Body weight: 2.9% males, 8.7% females week 52

↓ Food consumption: 7.5% males; 6.6% females week 52

↑ Duodenum mucosal hyperplasia: 39/73 males and 33/78 females [control 3/74 and 6/72]

Neoplastic findings

Increase in duodenal adenomas and adenocarcinomas in all groups, both sexes. Decrease in liver tumours in males receiving 16000 ppm and in lung tumours in males receiving 10000 and 16000 ppm. The number of thymic lymphosarcomas was slightly increased ($p < 0.09$) in high-dose females (4/26) compared to the control (0/30).

<table>
<tr><td>MALES</td><td></td><td colspan="4">Dose level (ppm)</td></tr>
<tr><td></td><td></td><td>0</td><td>6000</td><td>10000</td><td>16000</td></tr>
<tr><td>Duodenum</td><td>No. examined</td><td>74</td><td>73</td><td>72</td><td>75</td></tr>
<tr><td></td><td>Adenocarcinoma</td><td>1</td><td>10</td><td>14</td><td>30</td></tr>
<tr><td></td><td>Adenoma</td><td>1</td><td>11</td><td>7</td><td>11</td></tr>
<tr><td>Liver</td><td>No examined</td><td>80</td><td>80</td><td>78</td><td>80</td></tr>
<tr><td></td><td>Hepatocellular adenoma</td><td>17</td><td>12</td><td>12</td><td>3</td></tr>
<tr><td>Lung</td><td>No. examined</td><td>80</td><td>80</td><td>77</td><td>78</td></tr>
<tr><td></td><td>Adenocarcinoma</td><td>15</td><td>15</td><td>7</td><td>1</td></tr>
<tr><td></td><td>Papillary adenoma</td><td>15</td><td>20</td><td>4</td><td>10</td></tr>
<tr><td>FEMALES</td><td></td><td colspan="4">Dose level (ppm)</td></tr>
<tr><td></td><td></td><td>0</td><td>6000</td><td>10000</td><td>16000</td></tr>
<tr><td>Duodenum</td><td>No. examined</td><td>72</td><td>78</td><td>76</td><td>76</td></tr>
<tr><td></td><td>Adenocarcinoma</td><td>0</td><td>17</td><td>14</td><td>20</td></tr>
</table>
</td><td>R-8292
Study 3 (1981)</td></tr>
</table>

<table>
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<tr><td></td><td></td><td>
<table>
<tr><td></td><td>Adenoma</td><td>2</td><td>10</td><td>8</td><td>12</td></tr>
<tr><td>Thymus</td><td>No. examined</td><td>30</td><td>57</td><td>54</td><td>26</td></tr>
<tr><td></td><td>Lymphosarcoma</td><td>0</td><td>3</td><td>2</td><td>4</td></tr>
</table>
</td><td></td></tr>
<tr><td>Carcinogenicity study

Guideline not reported but design based on OECD 451 (1981). Deviations: tissues examined limited to GI tract, lungs and grossly abnormal tissues, increased number of animals per group.

Duodenal sections re-evaluated in 1994.

GLP

Mouse: CD-1 (ICR derived).

100/sex/group</td><td>Captan technical, (batch: SX-1086; purity: 89%)

0, 100, 400, 800 and 6000 ppm in diet.

For 94 weeks (22 months)</td><td>
Non-neoplastic findings

<u>6000 ppm (924.8/1042.7 mg/kg bw/day in males/females)</u>

↑ Mortality: males 35% 14 months [control 15%]

↓ Body weight: approx. 5% males in first year; approx. 7% females weeks 1-94

↑* Duodenum focal mucosal hyperplasia: 12/84 males and 20/91 females [control 4/91 and 11/85]

↑* Duodenum lymphoid proliferation: 23/84 males and 18/91 females [control 9/91 and 10/85]

<u>800 ppm (122.8/141.9 mg/kg bw/day in males/females)</u>

↓ Body weight: 6.9% males week 1 only

↑* Duodenum lymphoid proliferation: 18/81 females [control 10/85]

<u>400 ppm (60.9/70.4 mg/kg bw/day in males/females)</u>

No significant treatment-related findings

<u>100 ppm (15.1/17.7 mg/kg bw/day in males/females)</u>

No significant treatment-related findings

* All microscopic incidences of findings in the duodenum from Anonymous (1994)

<u>Neoplastic findings</u>

Increase in benign duodenal neoplasia in females at 6000 and 800 ppm and possibly in males at 6000 ppm. Increase in duodenal adenocarcinoma in both sexes at 6000 ppm.
<table>
<tr><td>MALES</td><td colspan="5">Dose level (ppm)</td></tr>
<tr><td>Duodenum</td><td>0</td><td>100</td><td>400</td><td>800</td><td>6000</td></tr>
<tr><td>No. examined</td><td>91</td><td>83</td><td>93</td><td>87</td><td>84</td></tr>
<tr><td>Adenocarcinoma</td><td>0</td><td>0</td><td>0</td><td>0</td><td>2</td></tr>
<tr><td>Adenoma</td><td>2</td><td>3</td><td>0</td><td>1</td><td>4</td></tr>
<tr><td>FEMALES</td><td colspan="5">Dose level (ppm)</td></tr>
<tr><td>No. examined</td><td>85</td><td>82</td><td>83</td><td>81</td><td>91</td></tr>
<tr><td>Adenocarcinoma</td><td>0</td><td>0</td><td>0</td><td>0</td><td>1</td></tr>
<tr><td>Adenoma</td><td>3</td><td>1</td><td>1</td><td>7</td><td>3</td></tr>
<tr><td>Adenoma with atypia</td><td>0</td><td>0</td><td>0</td><td>0</td><td>3</td></tr>
</table>
All incidences from Anonymous (1994)
</td><td>R-7995/
R-9775a

Study 4
(1983/1982/1994)</td></tr>
</table>

Table 33: Summary table of human data on carcinogenicity

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Epidemiology retrospective cohort mortality study 134 employees from the Calhio Chemical Company plant in Perry, Ohio, USA potentially exposed	Captan technical grade and its analogue, folpet. During the follow up period, representative full shift total dust samples showed the time weighted average mean exposure to captan of 1.00 mg/m^3 (packer warehousemen), 1.50 mg/m^3 (maintenance mechanics), 1.54 mg/m^3 (captan operators) and 0.83 mg/m^3 (THPI operator). Mean captan exposure levels for packer warehousemen and captan operators were 0.64 and 0.21 mg/m^3, respectively.	An epidemiologic study of mortality within a cohort of captan workers: male employees (including terminated, retired or deceased employees) who had worked in production or maintenance for a minimum 3 months during the period from 1 January 1954 through to 31 December 1976. The second report describes the deaths among the original cohort which occurred during an extended follow up period from 1 January 1977 through to 31 December 1983. Confounders were not described in the report, except for the two individuals, who died of cancer.	No excess deaths in persons starting work before the age of 35 or among persons who died since 1975. No evidence that persons who worked for longer periods of time had excess mortality in comparison to those who worked for fewer than five years. Workers categorised as having moderate exposure had a greater excess of deaths from 'all deaths' and from cancer than workers who were categorised as having high exposure. Two individuals had cancer (case 2: Adenocarcinoma in the head of the pancreas case 11: malignant lymphoma). Case 2 was an employee who worked only three and one-half months as a packer/ laborer. He died six years later at the age of 53. He had previously been employed at a bakery and was working a bakery salesman at the time of his death. No medical information was available after his termination from the pant. Case 11 was a 59 year old employee who worked in maintance for 21 years. He smoked 1.5 packs of cigarettes daily. There was no evidence to suggest that captan, or its analogue folpet, was carcinogenic to humans at the levels of exposure experienced by the workers. **Conclusion**: No duodenal cancers were observed. These data, while limited, support the conclusion that captan is not a human carcinogen.	Wagner Palshaw (1980 and 1987) R-4641

Table 34: Summary table of other studies relevant for carcinogenicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
DNA binding study in the mouse Investigative study, no applicable guidelines. Not GLP	1) [^{35}S]-captan (radiochemical purity:> 98%, specific activity 888 MBq/mM) single dose oral gavage 900 mg/kg bw,	Six hours post-dose, animals were sacrificed, stomach, duodenum, liver and bone marrow were sampled and DNA extracted and purified. Radioactivity associated with DNA extracts was measured by liquid	Results indicated that captan was associated with the DNA fraction from all tissues examined. **Conclusion**: results from the caesium chloride fractionation, failed to confirm that radioactivity was actually covalently bound to DNA.	R-5548 Study 5 (1991)

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Mouse: CD-1 100/males /group	2) [^{14}C]-1-methyl-1-nitrosourea (positive control) single dose oral gavage 80 mg/kg bw 3) vehicle control	scintillation counting (LSC). Further purification of liver, jejunum and duodenum were carried out using caesium chloride gradient ultracentrifugation and analysed for radioactivity by LSC and UV spectrophotometry.		
In vitro and *in vivo* studies to assess the chemical degradation and potential to react with DNA Investigative study, no applicable guidelines. GLP *In vitro* calf thymus *In vivo* Mouse: CD-1; 6-12 males/group	*In vitro* [^{14}C]-trichloromethyl captan (chemical purity:99.9%, radiochemical purity:95%; specific activity 52.5 - 59.2 KBq/µmol), final concentration 0.1 to 0.2% v/v *In vivo* [^{35}S]-N-acetyl cysteine, 2-oxo-[35S]-thiazolidine-4-carboxylate or 2-thioxo-[35S]-thiazolidine-4-carboxylate single dose by oral gavage	*In vitro* [^{14}C]-captan was incubated with calf thymus DNA, chemical degradation of captan and the potential of captan (to react with DNA *In vivo* mice were administered a single dose, livers removed and the DNA isolated. DNA samples fractionated using a caesium gradient	*In vitro* approximately 0.3% of the radioactivity was associated with the DNA. The study failed to demonstrate any clear evidence for a reaction of captan or its breakdown products with DNA *In vivo* high covalent binding indices found for captan can be attributed to sulphur exchange and incorporation into trace amounts of contaminating protein always present in DNA samples. Radioactivity was separated from the main DNA peak using caesium gradient. **Conclusion:** covalent binding indices of such binding are questionable in the context of significant *in vivo* genotoxicity. Consequently, the duodenal tumours seen in mice may arise from a mechanism other than one involving a direct interaction of captan and DNA	R-7106 Study 6 (1993)
Time course study of changes in the small intestine and stomach Investigative study, no applicable guidelines. GLP Mouse: CD-1 25 males per group, 5 per time point	Captan (batch: WRC14264-13-1; purity: 89.4%) 3000 ppm in diet *Ad libitum* fed and pair fed control groups	5 mice per group sacrificed after 1, 3, 7, 14 or 28 days. Animals examined during in life phase, gross pathology and microscopic examination of duodenum, ileum, jejunum and stomach	**3000 ppm** Day 1 No treatment related findings Day 3: ↓ Body weight 14.7%; ↑ Duodenal findings: 4/5 crypt cell hyperplasia; 3/5 shortening of villi; 2/5 general disorganisation of villus enterocytes. Days 7, 14 and 28 ↓ Body weight approx. 11%; ↑ Duodenal findings; all animals crypt cell hyperplasia + shortening of villi + general disorganisation of villus enterocytes + immature cells at villus	R-8923 Study 7 (1996)

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			tips The incidence of treatment-related findings in other gastrointestinal tissues was lower than in the duodenum. **Conclusion:** the results are consistent with an irritant mode of action on the duodenal villus epithelium, resulting in an increased loss of villus cells and concomitant chronic hyperplasia of the crypt epithelium	
Investigation of duodenal hyperplasia Investigative study, no applicable guidelines. GLP Mouse: CD-1 5 males and 5 females per group	Captan (batch: WRC14264-13-1; purity: 89.4%) 0, 400, 800, 3000 or 6000 ppm in diet 56 days	Animals examined during in life phase, given single intraperitoneal injection of bromodeoxyuridine (BRDU) approximately one hour prior to sacrifice. At termination duodenal hyperplasia was evaluated by microscopic examination, assessment of the mean number of cells in the crypt cell population, measurement of BRDU labelling index and measurement of villus height to crypt height. The stomach, jejunum and ileum were evaluated for histopathological changes.	**6000 ppm** ↑ duodenal findings both sexes (diffuse hyperplasia of crypt cells both sexes, [localised to the first 7 cm of the duodenum after the pylorus of the stomach]; crypt cell mitoses; villus shortening) ↑ crypt cell population 86.7% males, 87.1% females ↑ labelling index 45.0% males 54.2% females; ↓ villus to crypt height ratio 64.8% males 76.3% females **3000 ppm** ↑ duodenal findings both sexes (diffuse hyperplasia of crypt cells, crypt cell mitoses; villus shortening) ↑ crypt cell population 157.7 % males 50% females ↑ labelling index 45.0% males 56.8% females; ↓ villus to crypt height ratio 74.1% males and 55.9% females **800 ppm** ↑ duodenal findings females only (hyperplasia of crypt cells; villus shortening) ↑ crypt cell population 20.1% males, 16.1% females **Conclusion**: Quantitative changes reflecting the duodenal hyperplasia were seen at doses of 800 ppm and above. The NOEL for pathological change, including duodenal inflammation and hyperplasia was 400 ppm in males and females	R-8193 Study 8 (1995)
Identification of preneoplastic alteration Investigative study, no applicable guidelines. GLP	Captan (batch: EHC 0355-27 [WRC-4912-26-12]; purity: 89.1%) 0 or 6000 ppm 3, 6, 9, 12 or 18 months	Pathological changes in the stomach and small intestines were determined: haematoxylin and eosin (H & E) morphology; mucins morphology; iron accumulation, morphology; radioautography, morphology; histochemical	**Conclusion**: Lifetime exposure to captan resulted in dilatation of the proximal small intestine, diffuse hyperplasia of columnar epithelium of the proximal small intestine, an increased incidence of focal hyperplasia of columnar epithelium of the small intestine. Part-time exposure of mice to captan	R-8271 Study 9 (1985)

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Mouse: CD-1 35/sex/group Reliable with restrictions	treatment continuously in diet. Partial exposure groups had 6 or 12 months of treatment followed by periods without treatment: 6/6, 6/12, 12/6, 12/8.	(AP; G6PDH; GGT) and non-protein bound reduced sulphydryls	did not produce an increase in the incidence of focal hyperplasia of columnar epithelium of the small intestine. Increased incidence of neoplasia was observed in mice exposed for 6 months with 6 months recovery and in mice exposed for 12 months with 6 - 8 months recovery. However, there was not an increased incidence of neoplasia in mice exposed for 6 months and allowed to recover for 12 months.	
Investigation of duodenal sulfhydryl levels Investigative study, no applicable guidelines. Not GLP Rat: Sprague-Dawley CD rats 35/sex/group (5/sex/time point)	Captan (batch: EHC 0065-46; purity not reported) 0, 20, 200 or 2000 mg/kg bw in corn oil Single oral dose	Duodenal sulphydryl levels determined after 2, 4, 24, 48, 72, 120 and 240 hours	**2000 mg/kg bw** ↑ duodenal sulphydryl levels from 4 h peak at 72 h 61.8% males, 75.8% females **200 mg/kg bw** ↑ duodenal sulphydryl levels from 2 h peak at 48 h 61.2% males, 24 h 49.0% females **20 mg/kg bw** ↑ duodenal sulphydryl levels from 4 h peak at 24 h 47.4% males, 24.0% females All values similar to control after 240 hours. **Conclusion**: The onset, magnitude and duration of the effect were similar to that recorded in a separate study in mice. Increased duodenal sulphydryl levels do not provide additional information to explain the oncogenicity recorded in mice but not rats.	R-4685 Study 10 (1982)
Effect of dietary captan on soluble thiol content of liver and duodenal tissues. Investigative study, no applicable guidelines. Not GLP Mouse: Female Swiss Webster	Captan (batch: 60106 Lot 4; purity not reported) Administered in diet at 0, 4000, 8000 or 16000 ppm for 35 days (Group 1) or 0, 500, 1000, 2000, 4000, 8000 or 16000 ppm for up to 213 days (Group 2).	Two mice were sacrificed and the left hepatic lobe and the duodenum from the pyloric sphincter to the crossover of the colon were removed concentration of soluble thiols was measured by absorbance	**16000 ppm** ↑ Mean soluble thiol in duodenum 219% **8000 ppm** ↑ Mean soluble thiol in duodenum 199% **4000 ppm** ↑ Mean soluble thiol in duodenum 180% **2000 ppm** ↑ Mean soluble thiol in duodenum 175% **1000 ppm** ↑ Mean soluble thiol in duodenum 159% **500 ppm**	TMN-0771 Study 11 (1980)

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			↑ Mean soluble thiol in duodenum 140% **Conclusion:** The administration of captan in the diet at 500 - 16000 ppm led to increased levels of soluble thiols in the duodenum, but not liver, of mice. This may reflect an adaptive response to exposure to compounds requiring glutathione for detoxification	
Bioavailability of captan to the duodenum Investigative study, no applicable guidelines. GLP Mouse: CD-1 6 animals/ untreated; 35 animals/treated groups.	Captan (batch: 14264-13-1; purity: 89.4%) [1,2 14C] cyclohexane captan (radiochemical purity: 99.1%; specific activities 46.1 and 6.4 MBq/mM) Dose levels: 0, 400 or 3000 ppm in diet for eight days. Diet then substituted by diets containing [1,2 14C] cyclohexane captan (400 and 3000 ppm groups)	First study: 6 animals killed 6, 12, 18, 24 and 30 hours after introduction of radiolabelled diet and gastrointestinal tract removed and blood and urine samples taken. Second study: 5 animals per group were sacrificed 12 and 24 hours after introduction of radiolabelled diet and blood, stomach, stomach contents, duodenal sections and duodenal section contents were processed Tissues were analysed for total radiolabel and captan/metabolite content by HPLC with UV and radiochemical detection	Radiolabel reached a low, and dose dependent, steady state level in the duodenum following dietary administration of captan. The radiolabel found was associated with the duodenal contents rather than the tissue. There was no accumulation of radiolabel in the gastrointestinal tract. Captan was detected in the stomach in a few animals. No parent captan was detected in the duodenum, blood and urine. Captan was degraded in the stomach before reaching the duodenum. However, the pH in the duodenum is higher than that in the stomach and captan is more stable under acidic conditions. Furthermore, some captan was found in the stomach whereas only metabolites were found in the duodenum. **Conclusion:** Although some slight degradation of captan may have occurred in the stomach, the major degradation site is considered to be in the duodenum where degradation occurred very rapidly, prior to the first analysis six hours after administration of the last captan dose	R-8746 Study 12 (1996)
Autoradiography studies Investigative study, no applicable guidelines. GLP Mouse: Crl: CD (ICR)BR 6 males/ group	[^{35}S] captan (radiochemical purity:≥ 99%, specific activity 888 MBq/mM). Single oral dose 900 mg/kg bw	2 animals killed 6, 24 and 120 hours after dosing. One animal was used for whole body radiography; from the other, portions of stomach, duodenum and ileum were taken and bisected for microscopic autoradiography	**Conclusion:** Captan is largely excreted via the gastrointestinal and urinary tracts. The majority of radiolabel had been excreted after five days. There was no evidence of long-term retention of captan in the duodenum, demonstrating its rapid degradation.	R-7105 Study 13 (1992)
Application of Tailored Bradford-Hill Considerations for Evaluating Weight of	Chromium (VI)	Applicability of AOP and mode of action to captan	AOP for non-genotoxic induction of cytotoxicity and regenerative hyperplasia by a threshold mechanism promotes duodenal tumors in mice based on hexavalent chromium, which is stated to be similar to observations	Becker *et al*. (2015)

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Evidence to develop AOPs. Publication			for folpet and captan	
Oral exposure, 28 day feeding study Publication. No applicable guidelines GLP: In vivo phase only. Mice B6C3F1. 20 females/group (10 used for recovery) Data from Cr(VI) are not used in this evaluation	Captan (Batch: not reported Purity: 98.3%) 28 days administration, satellite animals allowed to recover for 28 days. Diet contained 6000 and 16000 ppm diet. 16000 ppm diet was reduced to 12000 ppm from day 10.	Study compared histopathological changes in the duodenum of female mice exposed to captan, folpet or Cr(VI). 3 pieces of duodenum sampled/animal and denoted as proximal (1 cm), middle (4 cm) and distal (7 cm) from the gastric pylorus Sections embedded in wax blocks for transverse sectioning. Stained with H&E and examined for villus histiocytic cellular infiltrates, villus atrophy/blunting, villous enterocyte vacuolation, and villus single cell necrosis Crypt epithelial hyperplasia examined by immunohistochemistry for Ki67 staining.	General observations: 2 animals (16000 ppm) died week 1, a third euthanised moribund. Dose decreased to 12000 ppm from day 10. No further clinical signs observed on 12000 ppm or 6000 ppm dose groups. Food consumption sporadically reduced in 12000 ppm group. Overall no difference between any group. 28-day exposure: Dose dependent observations predominantly in proximal duodenum. Crypt epithelial hyperplasia (Minimal to mild). Villous enterocyte hypertrophy (minimal to moderate). Increased mononuclear cell infiltrates in villi (minimal to mild) rarefaction of the lamina propria (minimal to mild) 28-day exposure followed by 28-day recovery. The prevalence and severity of all observations were diminished. **Conclusion:** Observations consistent with a mechanism of action of chronic mucosal toxicity followed by regenerative hyperplasia.	Thompson *et al.* (2017)
Gene expression analysis for oral exposure, feeding study (Thompson, 2017) Publication No applicable guidelines Gene expression not GLP: Mice B6C3F1. 20 females/ group (10 used for recovery) Data from Cr(VI) are not used in this evaluation	Captan (Batch: not reported Purity: 98.3%) 28-day feeding study with 28-day recovery group 28 days administration, satellite animals allowed to recover for 28 days Diet contained 6000 and 16000 ppm diet. 16000 ppm was reduced to 12000 ppm	Transcriptomic analysis of captan 16000 ppm diet reduced to 12000 ppm diet from study day 10 3 pieces of duodenum sampled/animal and denoted as proximal (1 cm), middle (4 cm) and distal (7 cm) from the gastric pylorus RNA was prepared from sectioned small intestine and subjected to whole genome transcriptomic analysis comparing captan, folpet and Cr(VI) exposed animals on randomly selected samples (n=7) from each dose group. Pathway analysis was performed, and the data phenotypically anchored to the observed histopathology reported	Transcriptomic pathway analysis revealed that the response in the duodenum is consistent with direct cellular and histopathological evidence for enterocyte cytotoxicity followed by regenerative hyperplasia. Pathways upregulated included cellular metabolism, stress, inflammation/immune response and cell proliferation, including upregulation in hypoxia inducible factor 1 (HIF-1) and activator protein 1 (AP1) signalling pathways. Genomic analysis consistent with the observed intestinal histopathology.	Chappell *et al.* (2019)

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
	from day 10.	from the same animals in Thompson *et al*. (2017).		
Review article discussing the weight of evidence (WOE), biological plausibility according to the WHO/ICPS human relevance framework for small intestinal (SI) tumours developing via a mechanism of action of SI enterocyte cytotoxicity followed by regenerative hyperplasia. Publication Data from Cr(VI) are not used in this evaluation	Captan, folpet and Cr(VI).	Data are evaluated according to the OECD 2018 guidance for developing an AOP and compared to the WHO/IPCS human relevance framework. Endpoints evaluated are: Temporality, Molecular initiating event (MIE), key events 1 and 2 (KE1 and KE2). Alternative MOA, and overall assessment of the AOP (biological domain of applicability, essentiality of the KE and KE relationships KER, and evidence assessment and quantitative considerations for KERs).	**AOP:** **(M)IE:** villous enterocyte toxicity **KE1:** Sustained crypt cell proliferation/hyperplasia **KE2:** mutation/transformation **Essentiality of key events:** (M)IE: STRONG evidence for villous enterocyte toxicity. KE1: STRONG evidence for sustained crypt cell proliferation/hyperplasia KE2: STRONG evidence for mutation/transformation **Biological plausibility:** (M)IE=>KE1: Strong evidence that villous enterocyte cytotoxicity leads to crypt cell proliferation/hyperplasia KE1=>KE2: STRONG evidence that sustained crypt cell proliferation/hyperplasia leads to mutation and transformation. KE2=>AO: STRONG evidence that transformation leads to intestinal tumours in mice. **Empirical support for KERs:** (M)IE=>KE1: Strong evidence that villous enterocyte cytotoxicity leads to crypt cell proliferation/hyperplasia KE1=>KE2: STRONG evidence that sustained crypt cell proliferation/hyperplasia leads to mutation and transformation. KE2=>AO: STRONG evidence that transformation leads to intestinal tumours in mice **Bradford Hill considerations:** Proposed AOP and KEs are highly supported by (95% confidence) the WOE. **Conclusion: Based on the overall WOE for this AOP and its associated KEs, it can be used for regulatory applications including hazard and risk assessment.**	Bhat *et al*. (2020)

9.9.1 Short summary and overall relevance of the provided information on carcinogenicity

The non-human data for captan comprises 4 rodent carcinogenicity studies conducted to GLP and similar to current OECD guidelines. In two studies in rats, animals were fed captan in the diet for up to 2 years (Study 1, 1982) or 130 weeks (Study 2, 1983). There were no treatment related increases in tumour incidence in either study. The no effect levels for carcinogenicity were 2000 ppm (98 mg/kg bw/day) and 250 mg/kg bw/day respectively, the highest doses investigated. These dose levels represented an MTD in both studies based on significantly reduced body weights in both sexes.

In a study carried out to investigate the potential carcinogenicity of captan in mice (Study 3, 1981) with doses of 0, 6000, 10000 and 16000 ppm in diet from weeks 5-113, a significantly higher incidence in mortality was observed in 16000 ppm males. There was an increased incidence of duodenal adenomas and adenocarcinomas in both males and females at all dose levels. Conversely there was a decrease in liver tumours in males receiving 16000 ppm and in lung tumours in males receiving 10000 and 16000 ppm. The number of thymic lymphosarcomas was slightly, but not clearly dose- related, increased ($p < 0.09$) in high-dose females (4/26) compared to the control (0/30).

In a further carcinogenicity study (Study 4, 1983), mice were fed 0, 100, 400, 800 or 6000 ppm captan in diet for 94 weeks (22 months). The study included 100 mice per sex per group (twice the guideline recommendation) and microscopic examination was confined to GI tract, lungs and grossly abnormal tissues. Mortality was increased in the 6000 ppm dose group males during the first 14-months of the study. Mortality in females was comparable to the controls. Duodenal sections were re-evaluated in 1994 (Study 4, 1994). It was concluded that there was an increase in benign duodenal neoplasia in females at 6000 and 800 ppm and possibly in males at 6000 ppm. There was an increase in duodenal adenocarcinoma in both sexes at 6000 ppm. Although adenoma was present in control males and females, there were no adenocarcinomas in the control mice. Focal mucosal hyperplasia was increased in 6000 ppm males and females. On the basis of an increased incidence of malignant and/or benign neoplasm of duodenal crypt cells in females at 800 ppm, and both sexes at 6000 ppm, the NOAEL for carcinogenicity in this study is 400 ppm (61 mg/kg bw/day).

There is some epidemiological data relating to humans exposed to captan (Wagner Palshaw, 1980 and 1987). No duodenal cancers were observed in the 134 workers included in the study. These data, while limited, are considered to support the conclusion that captan is not a human carcinogen.

It is concluded that captan is not an *in vivo* genotoxicant. Although captan induces gene mutation in microbial systems, the mutation frequency is greatly diminished or eliminated by the addition of thiol containing components. Some investigations have focused on the sulphur-containing substances in the duodenum. Study 10 (1982) found increased duodenal sulphydryl levels in both rats and mice treated with captan and it was concluded that the results did not provide additional information to explain the oncogenicity recorded in mice but not rats. In study 11 (1980) captan in the diet at 500 - 16000 ppm led to increased levels of soluble thiols in the duodenum, but not liver, of mice. It was concluded this may reflect an adaptive response to exposure to compounds requiring glutathione for detoxification.

Other experimental studies indicate that the duodenal tumours seen in mice arise from a mechanism other than one involving a direct interaction of captan and DNA. Purification of liver, jejunum and duodenum samples from treated mice using caesium chloride fractionation, failed to show that radioactivity was actually bound to DNA (Study 5, 1991). This was confirmed in further *in vitro* and *in vivo* investigations (Study 6, 1993) which did not demonstrate any clear evidence for a reaction of captan or its breakdown products with DNA. In Study 12 (1996) mice were fed diets containing captan then substituted diets containing [1,2 ^{14}C] cyclohexane captan. It was concluded that although some slight degradation of captan may have occurred in the stomach, the major degradation site was the duodenum where degradation occurred very rapidly, prior to the first analysis six hours after administration of the last captan dose.

Additional work concentrates on the findings in the duodenum following treatment of mice with captan. In Study 7 (1996) mice were fed 3000 ppm captan in diet and sacrificed after 1, 3, 7, 14 or 28 days. Effects were evident from day 3 which were consistent with an irritant mode of action on the duodenal villus epithelium, resulting in an increased loss of villus cells and concomitant chronic hyperplasia of the crypt epithelium. In a second study (Study 8, 1995) mice were fed 0, 400, 800, 3000 or 6000 ppm captan in diet for 56 days,

quantitative changes reflecting the duodenal hyperplasia were seen at doses of 800 ppm and above. The NOEL for pathological change, including duodenal inflammation and hyperplasia was 400 ppm in males and females.

Neoplasia in the duodenum and potential recovery after long term administration of captan was investigated in Study 9 (1985). An increased incidence of neoplasia was observed in mice exposed for 6 months with 6 months recovery and in mice exposed for 12 months with 6 - 8 months recovery. However, there was not an increased incidence of neoplasia in mice exposed for 6 months and allowed to recover for 12 months. This supports the conclusion that prolonged irritation of the duodenum is required to lead to a neoplastic response and suggests that recovery may be possible after a prolonged period.

Work carried out more recently (Thompson *et al*., 2017 and Chappell, *et al*., 2019) specifically to investigate the effect of captan (also hexavalent chromium and folpet), on mouse duodenal toxicity using histopathological evidence and phenotypically anchoring the observations to global gene and pathway analysis in the same tissue samples. It was concluded that the events that occurred in response to a 28-day dietary exposure to female mice to captan (6000 and 12000 ppm) were consistent with histopathological findings (minimal to mild/moderate crypt epithelial hyperplasia, villous enterocyte hypertrophy, increased mononuclear cell infiltrates in villi, rarefaction of the lamina propria) of chronic cytotoxicity in intestinal enterocytes. Duodenal crypts were unaffected by direct cytotoxicity. Global gene and pathway analysis confirmed these findings were plausible at the transcriptional levels and reported over representation of cellular metabolism, stress, inflammation/immune cell response, and cell proliferation pathways, including activation of hypoxia initiation factor 1 (HIF-1) and activator protein 1 (AP1) which have been shown to be related to intestinal injury and angiogenesis/carcinogenesis. These data are completely consistent with the proposed adverse outcome pathway (AOP) captan duodenal tumorigenesis in mice.

There is evidence supporting a non-genotoxic mechanism of carcinogenicity in the mouse, associated with the irritant nature of captan. Studies showed no evidence of covalent binding of captan with DNA and the lack of nuclear aberrations in duodenal crypt cells. This is supported by the fact that there is a threshold for duodenal tumours in mice: there is a clear NOAEL for tumours at 60.9 mg/kg bw/day for males.

The proposed mechanism for duodenal tumour induction in the mouse is that at high doses, captan degradation in the duodenum results in the formation of the irritant thiophosgene, leading to villus cell damage and irritation and as a result there is enhanced cell replication. This in turn leads to crypt cell hyperplasia, adenoma and ultimately carcinoma. In conclusion, there is a large body of evidence that the oncogenic effect manifested in the mouse duodenum results from a non-genotoxic mechanism for which a NOAEL has been established.

Recent data evaluating an AOP for mouse small intestinal tumours (Bhat *et al*., 2020) concluded that the AO (mouse small intestinal carcinogenesis) was mediated by an initiating event (sustained enterocyte cytotoxicity). Captan is stable in the stomach but readily breaks down to thiophosgene in the higher pH of the small intestine (SI). SI enterocytes rapidly slough of intestinal villi into the lumen of the SI. Enterocytes are terminally differentiated, and sustained damage dose not lead to an AO due to the short life span. However, cytotoxicity and cell death results in increased turnover of enterocytes (MIE), resulting in chronic sustained crypt cell proliferation/hyperplasia (KE1), providing increased opportunity for spontaneous mutations to develop (KE3). Intestinal histopathology and transcriptomic pathway analysis are completely consistent with the molecular initiating event being sustained enterocyte cytotoxicity. It is well understood that sustained hyperplasia can progress to adenoma and carcinoma if prolonged. Minimally 6-months exposure to carcinogenic doses of captan are required to drive intestinal tumours and the MIE and KE1 are reversible following prolonged cessation of exposure. As per the OECD guidance on development of an AOP, biological plausibility, essentiality and empirical support have been confirmed using modified Bradford Hill considerations (Becker *et al*., 2015). The WOE is also required to rule out other potential MOA, and no mutations have been observed in the mouse duodenum after 90-days exposure to captan. The extensive evidence for this AOP along with knowledge on human exposure to captan show that human exposures are orders of magnitude lower than those associated with the KEs in this AOP, supporting the use of this AOP in regulatory applications including hazard and risk assessment. Nevertheless, no differences in toxicokinetic behaviour of captan between mice and human are evident and from a qualitative perspective the proposed MoA can be also established in humans.

Table 35: Compilation of factors to be taken into consideration in the hazard assessment

Species and strain	Tumour type and background incidence	Multi-site responses	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Route of exposure	MoA and relevance to humans
Rat: Charles River CD	No increase in tumour incidence	n/a	n/a	n/a	n/a	n/a	Oral diet	n/a
Rat: Cpb:WU Wistar	No increase in tumour incidence	n/a	n/a	n/a	n/a	n/a	Oral diet	n/a
Mouse: CD-1	Duodenal adenoma and adeno-carcinoma. Rare < 1% in CD-1 mouse	No, reduced tumours in male lung and liver	Yes	Yes	Both	Pronounced effect on body weight all doses, high dose exceeds guideline maximum	Oral diet	Non genotoxic mechanism potentially relevant to humans
Mouse: CD-1	Duodenal adenoma and adeno-carcinoma	No, but examination confined to GI tract, lungs and abnormal tissues	Yes	n/a	Both	No	Oral diet	Non genotoxic mechanism quantitatively not relevant to humans

9.9.2 Comparison with the CLP criteria

Carcinogenicity attributable to oral administration of captan has been demonstrated in a single species (mouse) and in a single target tissue (duodenum) in two independent studies. There is no evidence of a similar finding in the rat. Investigative studies have shown that the duodenal effects are the result of long term administration resulting in localised irritation in the duodenum. This is a non-genotoxic mechanism due to a high dose direct effect of captan on the tissue and clear no effect levels have been established.

By default, carcinogenic effects in experimental animals are considered relevant to humans and are considered for classification as carcinogens. Only when there is sufficient evidence showing that a certain type of tumour is not relevant to humans should this tumour type be excluded for classification. The limited epidemiological data available showed no evidence of duodenal tumours in exposed workers.

In the context of the WHO/IPCS human relevance framework a MoA analysis was conducted by Bhat et al. 2020 concluding that, the KEs become quantitively implausible in humans after accounting for background levels of human exposure. Nevertheless, the authors also concluded that the KEs are qualitatively plausible in humans.

Therefore, classification of captan as Carc. 2, H351 should remain.

9.9.3 Conclusion on classification and labelling for carcinogenicity

No change in classification of captan is warranted. Captan is proposed to be classified for carcinogenicity, Cat. 2.

9.10 Reproductive toxicity

9.10.1 Adverse effects on sexual function and fertility

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 36: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Reproduction toxicity Three generation / 2 litters Non-guideline, non-standard design with significant deviations in design and reporting cf. current TG OECD 416 (2001) Deviations to OECD 416 (2001): No 1:1 mating, pairs without progeny were not evaluated to determine the cause of infertility, oestrus cycle and sperm parameters were not evaluated, data on sexual maturation were not evaluated, no organ weights were determined, no histopathology was performed.	Captan (technical batch number SX944, purity 89 %) 0, 25, 100, 250, 500 mg/kg bw/day continuously in diet	***Parental toxicity*** **<u>500 mg/kg bw/day</u>:** F0: ↓ body weight (males 17%, females 13% - week 14); ↓ average food consumption (males 19%, females 24%). F1: ↓ body weight (males 28%, females 24% - week 47); ↓ average food consumption (males 22%, females 20%. F2: ↓ body weight (males 21%, females 22 % - week 79); ↓ average food consumption (males 18%, females 19%). **<u>250 mg/kg bw/day:</u>** F0: ↓ body weight (males 19%, females 9% - week 14); ↓ average food consumption (males 15%, females 15%). F1: ↓ body weight (males 16%, females 14% - week 47); ↓ average food consumption (males 14%, females 12%). F2: ↓ body weight (males 17%, females 15 % - week 79); ↓ average food consumption (males 13%, females 4%). **<u>100 mg/kg bw/day:</u>** F0: ↓ body weight (males 8% (NS), females 6% - week 14); ↓ average food consumption (males 5%, females 6%). F1: ↓ body weight (males 7% (NS), females 8% - week 47); ↓ average food consumption (males 5%, females 2%). F2 ↓ body weight (males 7% (NS), females 6 % - week 79); ↓ average food consumption (males 4%). **<u>25 mg/kg bw/day:</u>** No effects. Parental NOAEL: ♂ 25 mg/kg bw/d; ♀: 100 mg/kg bw/d ***Reproduction toxicity*** **<u>500 mg/kg bw/day</u>:** No effects. NOAEL: 500 mg/kg bw/d ***Pup toxicity***	R-6340 Study 1 (1982)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Not GLP Rat, CR COBS®CD® 15 males and 30 females/ group		**500 mg/kg bw/day:** F1a: ↓ survival days 1-4 (93% cf. 99% control); ↓ litter size day 0, 16%; ↓ pup weight day 1, 18%, day 21 males 34%, females 35%. F1b: ↓ survival days 1-4 (93% cf. 99% control); ↓ litter size day 0, 26.5%; ↓ pup weight day 1, 17%, day 21 males 38%, females 40%. F2a: ↓ survival days 1-4 (85% cf. 99% control); ↓ litter size day 0, 12.5%; ↓ pup weight day 1, 17%, day 21 males 44%, females 40.5%. F2b: ↓ survival days 1-4 (96% cf. 99% control); ↓ litter size day 0, 15%; ↓ pup weight day 1, 10%, day 21 males 31%, females 32%. F3a: ↓ survival days 1-4 (89% cf. 98% control); ↓ litter size day 0, 3%; ↓ pup weight day 1, 14.5%, day 21 males 33%, females 32%. F3b: ↓ survival days 1-4 (93% cf. 99% control); ↓ litter size day 0, 3%; ↓ pup weight day 1, 13%, day 21 males 39.5%, females 39%. **250 mg/kg bw/day:** F1a: ↓ survival days 1-4 (92% cf. 99% control); ↓ litter size day 0, 11%; ↓ pup weight day 1, 12%, day 21 males 17%, females 18%. F1b: ↓ litter size day 0, 8%; ↓ pup weight day 1, 8%, day 21 males 21%, females 21%. F2a: ↓ survival days 1-4 (95% cf. 99% control); ↓ pup weight day 1, 13%, day 21 males 30%, females 28%. F2b: ↓ litter size day 0, 8%; ↓ pup weight day 1, 10%, day 21 males 25%, females 24%. F2c: ↓ foetal body weight gestation day 19 9.5%. F3a: ↓ pup weight; day 1 7%, day 21 males 17%, females 17%. F3b: ↓ pup weight; day 1 7%, day 21 males 20%, females 21%. **100 mg/kg bw/day:** F1a: ↓ pup weight: day 1 8%, day 21 males 9%, females 10%. F1b: ↓ pup weight: day 1 8%, day 21 males 7%, females 7%. F2a: ↓ pup weight; day 1 4%, day 21 males 13%, females 13%. F2b: ↓ pup weight; day 1 7%, day 21 males 13%, females 13%. F3a: ↓ pup weight; day 1 3%, day 21 males 8%, females 6%. F3b: ↓ pup weight; day 1 4%, day 21 males 8%, females 9%. **25 mg/kg bw/day:** F1a: ↓ pup weight; day 1 7%, day 21 males 2%, females 3%. F1b: ↓ pup weight; day 1 4%, day 21 males 1%, females 1%. F2a: ↓ pup weight; day 1 1%, day 21 males 6%, females 4%. F2b: ↓ pup weight; day 1 7%, day 21 males 4%, females 5%. F3a: ↓ pup weight; day 1 1%, day 21 males 2.5%, females 1%.	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		F3b: ↓ pup weight; day 1 1%, day 21 males 3%, females 5%. Offspring NOAEL: 25 mg/kg bw/d	
Reproduction toxicity One generation / one litter Non-guideline, supplementary to previous study Deviations to OECD 415 (1983): The study met the essential criteria of the test guideline. GLP Rat, CR COBS®CD® 15 males and 30 females/ group	Captan (technical batch number SX944, purity not reported) 0, 6, 12.5, 25 mg/kg bw/day continuously in diet	***Parental toxicity*** No effects at any dose level. Parental NOAEL: 25 mg/kg bw/d ***Reproduction toxicity*** No effects at any dose level. NOAEL: 25 mg/kg bw/d ***Pup toxicity*** **25 mg/kg/day:** ↓ mean pup weight (5.3% day 4, 6.4% day 7, 5.6% day 14 - NS). **12.5 mg/kg bw/day:** No effects. Offspring NOAEL: 25 mg/kg bw/d	R-6339 Study 2 (1982)

NS: not statistically significant

Table 37: Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No reported evidence of adverse health effects in humans				

Table 38: Summary table of other studies relevant for toxicity on sexual function and fertility

A number of endocrine assays have been conducted and are summarised in the following table.

Assay	Results
Study 14, 2012b: OPPTS 890.1150: Androgen Receptor Binding Assay (Rat Prostate)	Negative: Captan does not interact with the androgen receptor.

Assay	Results
Study 10, 2012a: OPPTS 890. 1400: Hershberger Assay Accepted with limitations, as only one dose group in each assay (agonist and antagonist) was examined for changes in androgen dependent tissues	Negative: Captan does not exhibit agonist or antagonist activity in castrated male rats.
Study 16, 2012: OPPTS 890. 1200: Human Recombinant Aromatase Assay	Equivocal: The mean aromatase activity was 60.3% of control at 10^{-5} M, compared to 0.74% for the positive control.
Study 13, 2012a: OPPTS 890. 1250: Estrogen Receptor Binding Assay	Negative: Captan does not interact with the rat estrogen receptor.
Study 15, 2012c: OPPTS 890. 1300: Estrogen Receptor Transcriptional Activation Assay	Negative: Captan is not an agonist to hERα in the HeLa-9003 model.
Study 17, 2012: OPPTS 890.1550: Steroidogenesis Assay Supplementary information (reliable with restrictions)	Captan effects were inconsistent across three runs. There was a decrease in estradiol in one run; a decrease in testosterone in another run and no effects in a third run (albeit at a high dose that was three orders of magnitude lower). A valid third confirmatory run is missing. Therefore, the experimental results are not interpretable.
Study 9, 2011: OPPTS 890.1600: Uterotrophic Assay	Negative: Captan did not affect uterine weight (i.e. show estrogen activity) in ovariectomized rats.
Study 11, 2012b: OPPTS 890.1450: Pubertal Assay in Male Rats	Androgen-dependent tissue weights (ventral prostate, LABC) and serum testosterone were significantly decreased at doses at or above MTD.
Study 12, 2012c: OPPTS 890.1500: Pubertal Assay in Female Rats	Delay in vaginal opening, day of first estrus, decreased number of corpora lutea, and decreased pituitary gland, ovarian, and uterine weights at MTD.

The results of the assays have been considered in a weight of evidence analysis according to the EFSA/ECHA Guidance for the identification of endocrine disruptors. It was concluded that captan does not meet the ED criteria for humans.

9.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

Captan has been evaluated for adverse effects on sexual function and fertility in one rat study three generation, 2 litters per generation, reproduction study (Study 1, 1982). Study 1 commenced in July 1978, prior to GLP and prior to EPA and OECD test guidelines. Although the study seems to have been conducted reasonably well, there are a number of deviations and omissions in the study design and reporting, from the current test guideline requirements, OECD 416, 2001. The most notable omissions include no evaluation of oestrus cyclicity, no evaluation of sperm, no calculation of pre-coital interval, no evaluation of pup physical development or sexual maturation, no parental or pup organ weights, parental or pup histopathology. Adverse effects on parental animals were observed at 250 and 500 mg/kg bw/day in the form of reduced body weight and food consumption. The parental NOAEL was concluded to be 100 mg/kg bw/day, based on differences from control body weights and food consumption of less than 10%.

There was no indication of an adverse effect of captan on reproduction, despite the lack of detail and clarity in the reporting

A one generation was study was subsequently conducted (Study 2, 1982), presumably to investigate the effects of captan at lower doses. This GLP study was non-guideline. The results were consistent with the three generation study in that the parental NOEL was 25 mg/kg bw/day, the reproductive NOEL was > 25 mg/kg bw/day and the NOAEL for pup effects was 25 mg/kg bw/day.

In summary, there are no adverse effects of captan on the sexual function and fertility of parental rats at dose levels that induce toxicity.

9.10.3 Comparison with the CLP criteria

Adverse effects on sexual function and fertility

Any effect of substances that has the potential to interfere with sexual function and fertility. This includes, but is not limited to, alterations to the female and male reproductive system, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behaviour, fertility, parturition, pregnancy outcomes, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems.

There were no adverse effects on sexual function and fertility in the rat to warrant classification of captan as a human reproductive toxicant.

9.10.4 Adverse effects on development

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 39: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Developmental toxicity US EPA 83-3 Deviations to OECD 414 (2001): The study met the essential criteria of the test guideline. Dosing occurred solely during the period of organogenesis. GLP Rat, CR CD Sprague-Dawley origin 22 mated females/group	Captan (batch BN 331552, purity 91%) 0, 18, 90, 450 mg/kg bw/day by oral gavage on gestation days 6-15 Vehicle 0.5% CMC + 0.05% acetic acid	***Maternal toxicity*** **450 mg/kg bw/day:** ↑Hair loss 6/22 cf. 1/21 controls; unclean/ungroomed 3/22 cf. 0/21 controls; ↓ food consumption (46.6% days 7-9); ↓ body weight: weight loss of 15.5 g cf. gain of 10.4 g controls, days 6-9; ↓ gain (9.5%, days 6-20). Corrected maternal bw (marginal decrease of 2%) **90 mg/kg bw/day:** ↓ food consumption (17.5% days 7-9), ↓ body weight gain (43.3%, days 6-9; 3.9%, days 6-20 – not significant)- not considered adverse, corrected maternal bw (marginal decrease of 2%) **18 mg/kg bw/day:** No effects. ***Developmental toxicity*** **450 mg/kg bw/day:** ↓ foetal body weight (6.3%); ↑ minor skeletal variations (foetal incidence of extra 14th rib (unilateral + bilateral 13/164 (7.9%) cf. 2/169 (1.2%) controls), (foetal incidence of reduced ossification of pubis 8/164 (4.9%) cf. 1/169 (0.6%) controls), (litter incidence of one or two thoracic vertebral hemicentra incompletely fused 16/22 (13.3%) cf. 8/22 (9.4%) controls not dose-related – incidence at 18 mg/kg/day 13/22 (15.7%). **90 mg/kg bw/day:** No effects.	R-4364 Study 3 (1987a)
Developmental toxicity US EPA 83-3 (OECD	Captan (batch	***Maternal toxicity*** **100 mg/kg bw/day:**	R-6148 Study 4

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
414, 1981); Deviations to OECD 414 (2001): The study met the essential criteria of the test guideline. However, overall the pregnancy rate was low (55-65%) in all dose groups including the control group. Dosing occurred solely during the period of organogenesis. Corrected body weight data were not presented in the study report. GLP Rabbit, New Zealand White 20 inseminated females/group	WRC 11240-37-1, purity 91.2%) 0, 10, 30, 100 mg/kg bw/day by oral gavage on gestation days 7-19 Vehicle corn oil	Few faeces in all rabbits cf. 7 controls; mucus in faeces in 2, 0 in controls, diarrhoea in 5, 0 in controls; ↓ food consumption (70.9% days 7-10; 65.3% days 7-19); ↓ body weight: weight loss of 142.5 g cf. gain of 15.6 g days 7-10; weight loss of 159.3 g cf. gain of 238.2 g controls, days 7-19). **30 mg/kg bw/day:** Few faeces in 14 rabbits cf. 7 controls; ↓ food consumption (30.7% days 7-10; 22.6% days 7-19), ↓ body weight: weight loss of 68 g cf. gain of 15.6 g controls, days 7-10; ↓ gain (76% days 7-19). **10 mg/kg bw/day:** No effects. ***Developmental toxicity*** **100 mg/kg bw/day:** ↓ foetal body weight (16.8%); ↑ post-implantation loss (22.6% cf. 6.6% controls), early deaths (10.7% cf. 3.1% controls), late deaths 11.9% cf. 3.5% controls); ↑ malformation (9.3% cf. 1% controls)- ↑ foetuses with major defects of the head- no consistent evidence of a treatment-relationship due to the diverse nature of the abnormalities (please refer to Table 3.10.1.5-5 in Annex Human Health for further details); ↑ minor external/visceral defects only (8.4% cf. 0.8% controls); ↓ skeletal ossification: odontoid partially ossified (41.2% cf. 26.5% controls); normal length extra 13th ribs (74.1% cf. 50.0% controls); 27 pre-sacral vertebrae (45.9% cf. 20.6% controls); asymmetric development of 1st sacral vertebrae (29.4% cf. 19.6% controls); asymmetric development of 2nd sacral vertebrae (23.5% cf. 14.7% controls); ↓ ossification of 2nd to 7th lumbar transverse processes. **30 mg/kg bw/day:** ↑ minor external/visceral defects only (7.0% cf. 0.8% controls), ↑ foetuses with major defects of the head- no consistent evidence of a treatment-relationship due to the diverse nature of the abnormalities (please refer to Table 3.10.1.5-5 in Annex Human Health for further details), ↓ skeletal ossification: odontoid partially ossified (40.0% cf. 26.5% controls); normal length extra 13th ribs (64.0% cf. 50.0% controls); 27 pre-sacral vertebrae (57.3% cf. 20.6% controls); asymmetric development of 1st sacral vertebrae (26.7% cf. 19.6% controls); asymmetric development of 2nd sacral vertebrae (18.7% cf. 14.7% controls); ↓ ossification of 2nd to 7th lumbar transverse processes. **10 mg/kg bw/day:** No effects	(1991)
Developmental toxicity US EPA 83-3 Deviations from study protocol and deviations from OECD 414 (2001): An incidence of mis-	Captan (batch BN 331552, purity 91%) 0, 10, 40, 160 mg/kg bw/day by	***Maternal toxicity*** **160 mg/kg bw/day:** Few/no faeces 12/16 rabbits cf. 0/16 controls; ↓ food consumption (83.3% days 8-10; 53.4% days 15-19); ↓ body weight: weight loss of 282 g cf. gain of 9 g controls days 7-10; weight loss of 124 g cf. gain of 144 g controls, days 7-19). Corrected maternal bw (↓ of 6%)	R-4429 Study 5 (1987)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
dosing occurred (9 animals - 1, 4 and 4 from low, intermediate and high dose group, respectively – received three times their nominal dose. The mis-dosed animals were removed from the study and replaced, and 4 additional control animals were added). At least 5 cases of mortality not related to treatment with captan occurred (including 2 cases of lung dosing and one pasteurella infection). Dosing occurred solely during the period of organogenesis. Low number of dams per dose group. GLP Rabbit, New Zealand White At least 14 mated females/ group Supplementary information (reliable with restrictions)	oral gavage on gestation days 7-19 Vehicle 0.5% CMC + 0.05% acetic acid	**40 mg/kg bw/day:** ↓ food consumption (6.7% days 8-10; 16.6% days 15-19). - not considered adverse. Corrected maternal bw (marginal ↓ of 2%) **10 mg/kg bw/day:** No effects. ***Developmental toxicity*** **160 mg/kg bw/day:** 2 abortions; 1 total resorption, ↑ post-implantation loss (13.2% cf. 5.8% controls, excluding total resorption); ↑ skeletal variations: 13th lumbar rib bilateral (79% foetuses cf. 57% controls); articulation of ilium with 1st or 1st & 2nd sacral vertebra (bilaterally 23% foetuses cf. 44% controls); reduced / incomplete ossification of hyoid (24% foetuses cf. 19% controls). **40 mg/kg bw/day:** No effects.	
Developmental toxicity Pre-guideline Animals were obtained from three different sources, Chesire Rabbit Farms (Cheshire), Ranch Rabbits (Sussex) and Buxted Rabbit Co. Ltd. (Sussex). Low number of dams per dose group. Large differences between initial group mean body weights among dose groups. Corrected body weight data were not presented in the study report.	Captan (batch SX-1086, purity 89%) 0, 6, 12, 25, 60 mg/kg bw/day by oral gavage on gestation days 6-28 Vehicle 0.5% CMC	***Maternal toxicity*** **60 mg/kg bw/day:** ↑ incidence of non-specific signs such as anorexia, reduced faecal output and water intake; weight loss days 6-10, ↓ body weight gain days 6-29. **25 mg/kg bw/day:** ↑ incidence of non-specific signs such as anorexia, reduced faecal output and water intake; ↓ body weight gain days 6-29. **12 mg/kg bw/day:** ↓ body weight gain days 18-29. **6 mg/kg bw/day:** No effects. ***Developmental toxicity*** **60 mg/kg bw/day:** Non-significant ↓ gravid uterine weight (13.5%); ↓ litter weight	TMN-0787 Study 6 (1981)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
GLP Rabbit, New Zealand White 15 mated females/ group Supplementary information (reliable with restrictions)		(7.7%); ↓ foetal weight (7.9%); ↓ crown rump length (3.6%). **25 mg/kg bw/day:** No effects.	
Developmental toxicity OECD Test guideline 414 (1981) Deviations: The weight of the gravid uterus was not recorded for females 35, 43, 57 and 61 due to an error. The vehicle was corrected to 0.5% w/v Tween 80 with 0.7% w/v carboxymethylcellulose. These deviations are considered not to affect the scientific validity of the study. GLP Rabbit, New Zealand White 25 mated females/group	Captan (batch BN 601 385 40, purity 95.1%) 0, 10, 20, 45 mg/kg bw/day by oral gavage on gestation days 6-28 Vehicle 0.5% Tween 80 + 0.7% CMC	***Maternal toxicity*** **45 mg/kg bw/day:** Thin build 14/25, little water drunk 20/25, few faeces 25/25; ↓ body weight: weight loss of 0.09 kg cf. no gain in controls days 6-8; weight gain of 0.06 kg cf. gain of 0.26 kg controls, days 6-29); ↓ food consumption days 6-21 (50.6% of controls day 6); ↑ eosinophils infiltration of duodenum 12/25 cf. 4/25 controls. No effect on corrected bw **20 mg/kg bw/day:** Thin build 5/25, little water drunk 14/25, few faeces 16/25; ↓ body weight: weight loss of 0.04 kg cf. no gain in controls days 6-8; weight gain of 0.13 kg cf. gain of 0.26 kg controls, days 6-29); ↓ food consumption days 6-20 (27.2% of controls day 6). No effect on corrected bw **10 mg/kg bw/day:** Thin build 5/25, little water drunk 10/25, few faeces 10/25; ↓ body weight: weight loss of 0.02 kg cf. no gain in controls days 6-8; weight gain of 0.15 kg cf. gain of 0.26 kg controls, days 6-29); ↓ food consumption days 13-20. No effect on corrected bw ***Developmental toxicity*** **45 mg/kg bw/day:** 1 total resorption; ↑ early resorptions (1.0 cf. 0.4 controls); ↑ post-implantation loss (15.3% cf. 4.9% controls); ↓ foetal weight (13.8%); ↑ incidence of 12/13 or 13/13 ribs (78% of foetuses cf. 52% controls); ↑ incidence of 20 thoracolumbar vertebrae (49% foetuses cf. 16% controls); ↑ off set alignment of pelvic girdle (4% cf. 2% controls); incompletely ossified/unossified epiphyses, astragalus, pubes and/or metacarpals/phalangestotal incidence 73, control 31; atelectatic lungs 11 (4 controls); absent ureter/kidney 4/180 (2.22% of foetuses cf. 0% controls) **20 mg/kg bw/day:** No effects.	R-18199 Study 7 (2006)

Table 40: Summary table of human data on adverse effects on development

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No reported evidence of adverse health effects in humans				

Table 41: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
A Review of the Potential to Induce Developmental Toxicity	Captan	To investigate the potential of captan to induce developmental effects in mammalian species with respect to potential classification	• The half-life of captan in human blood at 37°C is 0.97 seconds. This very short half-life indicates that in humans and mammalian prenatal developmental toxicity studies, the developing offspring *in utero* will not be exposed to captan. • The principal metabolite, tetrahydrophthalimide (THPI) may reach the developing offspring following maternal administration of captan. • A series of directly comparable rabbit developmental toxicity studies, conducted in 2005, provide clear evidence that neither captan and its metabolite THPI, nor the structurally related chemical folpet and its metabolite, phthalimide induce malformation in the rabbit. • Review of other rabbit developmental toxicity studies, including those in the published literature, confirm that neither captan nor THPI induce malformation in the rabbit. • Review of rat developmental and reproduction toxicity studies, including those in the published literature, confirm that neither captan nor THPI induce malformation in the rat. • Review of the data available in the published literature confirm that neither captan nor THPI induce malformation in the mouse or primate. • Review of developmental toxicity studies including those in the published literature confirm that the structurally similar chemical folpet, and its metabolite phthalimde, do not induce malformation in several species including the rat and rabbit.	Position paper (2018), Project No.000101576
THPI Developmental toxicity OECD 414 (2001)	THPI (batch S17363, purity 98.4%) 0, 5, 10 or 22.5 mg/kg	Study of Captan's primary metabolite. Dosed at 22.5 mg/kg bw/day, the molar equivalent of 45 mg Captan/kg bw/day, the	***Maternal toxicity*** **22.5 mg/kg bw/day:** No effects ***Developmental toxicity*** **22.5 mg/kg bw/day:**	R-18202 Study 8 (2006)

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
GLP Rabbit, New Zealand White 25 mated females/group	bw/day by oral gavage on gestation days 6-28 Vehicle: CMC + Tween 80	highest dose tested by Study 8 (2006).	No effects	

9.10.5 Short summary and overall relevance of the provided information on adverse effects on development

The developmental toxicity of captan (and its metabolite THPI, Study 9) was investigated in five prenatal developmental toxicity studies, one in rats (Study 3, 1987) and five in rabbits (Study 4, 1991; Study 5, 1987; Study 6, 1981; Study 7 and 8, 2006). Four studies predate the current OECD Test Guideline Number 414 (2001). Study 6 (1981) and Studies 7 and 8 (2006) include the recommended extended dosing period (i.e. from implantation to one day prior to the day of scheduled kill). All studies, except studies 5 and 6 which are only supplementary, are considered adequate and relevant for evaluation of the potential of captan to induce developmental effects. No evidence of teratogenicity was observed in either species, nor in the generational studies in rat.

Table 42: Summary results from developmental toxicity studies

Study	Species	Dose levels (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Effects
Study 1 (1982) (Generational study)	Rat	0, 25, 100, 250, 500	Maternal: 100 Offspring: 25	Maternal: ↓ body weight, ↓ food consumption Offspring: ↓ pup weight (more pronounced at higher doses) at 250 and 500 mg/kg bw/d: ↓ pup survival at lactation Day 4 at 250 mg/kg bw/day of the F1a, F2a and F3a litters, reaching statistical significance for the F2a and F3a litters. Consistent treatment-related reductions in pup survival were observed at lactation day 4 at 500 mg/kg bw/day in the litters of all three generations ↓ litter size was reduced in F1a and F1b litters in all treatment groups (reaching statistical significance for the F1b litter at 500 mg/kg bw/d) compared to the controls. In the F2a and F2b litters, the litter sizes were reduced at 250 and 500 mg/kg bw/day compared to the controls (significant only for the F1b litter at 500 mg/kg bw/day)
Study 2 (1982) (Generational study)	Rat	0, 6, 12.5, 25	Maternal: 25 Offspring: 25	Maternal: No effects Offspring: Pup weights at 25 mg/kg bw/day were marginally and not statistically significantly ↓ (not considered adverse)
Study 3 (1987)	Rat	0, 18, 90, 450	Maternal: 90 Developmental: 90	Maternal: ↓ body weight & food intake, clinical signs Developmental: ↓ foetal body weight; ↑ minor skeletal observations.
Study 4 (1991)	Rabbit	0, 10, 30, 100	Maternal: 10 Developmental: 10	Maternal: ↓ body weight & food intake (marked at 100 mg/kg/day), clinical signs Developmental: At 100 mg/kg bw/day, ↓ foetal body weight; ↑ post-implantation loss, ↑ malformations equivocal. At 30 & 100 mg/kg bw/day, ↑ minor skeletal

Study	Species	Dose levels (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Effects
				observations, ↑ foetuses with major defects of the head- no consistent evidence of a treatment-relationship due to the diverse nature of the abnormalities.
Study 5 (1987) Supplementary information	Rabbit	0, 10, 40, 160	Maternal: 40 Developmental: 40	Maternal: ↓ body weight & food intake (marked at 160 mg/kg bw/day), low incidence of abortion at 160 mg/kg bw/day, clinical signs Developmental: ↑ post-implantation loss; no malformation; ↑ minor skeletal observations.
Study 6 (1981) Supplementary information	Rabbit	0, 6, 12, 25, 60	Maternal: 6 Developmental: 25	Maternal: ↓ body weight, clinical signs Developmental: ↓ foetal body weight (not statistically significant), marginally ↓crown rump length.
Study 7 (2006)	Rabbit	0, 10, 20, 45	Maternal <10 Developmental 20	Maternal: ↓ body weight & food intake, clinical signs Developmental: ↓ foetal weight, ↑ post-implantation loss, ↑ minor skeletal observations.
Study 8 (2006) THPI	Rabbit	0, 5, 10, 22.5	Maternal: 22.5 Developmental: 22.5	Maternal: No effect Developmental: No effect

Reductions in litter size in the three generation study with captan (Study 1, 1982) were mostly marginal and not consistently obersered in the treated groups (please refer to table 3.10.1.1-6 in the Annex Human Health). Effects on pup survival were limited to highest dose group of 500 mg/kg bw/d (please refer to table 3.10.1.1-6 in the Annex Human Health). At this dose group body weight and food consumption was reduced around 20%. There is a clear effect of 100, 250 and 500 mg/kg bw/day on pup body weight at birth through to weaning but the numerical differences (mostly not statistically significant) at 25 mg/kg bw/day are judged not to represent an adverse effect of treatment. No other adverse effects of captan on the development of the offspring were observed in the generational studies.

In a prenatal developmental toxicity study, captan did not induce foetal malformation in the rat at the highest dose level administered, 450 mg/kg bw day. Advers effects in rat included reduced foetal body weight and an increase in a small number of skeletal variations in the presence of some maternal toxicity (Study 3, 1987a). The developmental NOAEL was equal than the maternal NOAEL.

Rabbit studies with captan and THPI

Four prenatal developmental toxicity studies with captan have been conducted in the rabbit. The developmental effects were generally similar across the studies. Foetal malformations were seen in all studies and were sometimes of highest incidence at the highest doses of captan tested. Thereby, no consistent evidence of a treatment-relationship could be observed due to the diverse nature of the abnormalities. The malformations were considered to be spontaneous in origin and part of the spectrum of change occurring in the NZW rabbit. One prenatal developmental toxicity study with THPI was conducted in the rabbit. THPI has a structure similar to thalidomide which is a known teratogenic substance in the rabbit. The dose rates used were precisely comparable with those of captan by Study 7 (2006). Single malformations were recorded at 5 and 10 mg/kg bw/day. These were considered to be spontaneous in origin and were not related to the administration of THPI.

In both species, captan induced effects on the foetus in the presence of maternal toxicity which was marked in the rabbit at ≥ 100 mg/kg bw/day. Effects above this dose level included reductions in food consumption > 65%, clinical signs and weight loss during pregnancy. At 100 and 160 mg/kg bw/day, resorption and possibly abortion are likely to be attributed to maternal toxicity. At lower dose levels, the effects on the foetus were confined to reduced body weight and an increase in minor skeletal observations, of a transient nature causing no permanent structural impairment. These effects might be secondary to the maternal toxicity (ie.e. clinical

signs and reductions in food consumption, also not so pronounced as at higher doses) and not a direct effect of captan on foetal development.

Captan is considered not to induce any effect which interferes with normal development of the conceptus.

A Review of the Potential of captan to Induce Developmental Toxicity (Position Paper, 2018) was undertaken reached the following cinclusions:

The half-life of captan in human blood at 37°C is 0.97 seconds. This very short half-life indicates that in humans and mammalian prenatal developmental toxicity studies, the developing offspring in utero will not be exposed to captan. The principal metabolite, tetrahydrophthalimide (THPI) may reach the developing offspring following maternal administration of captan.

• A series of directly comparable rabbit developmental toxicity studies, conducted in 2005, provide clear evidence that neither captan and its metabolite THPI, nor the structurally related chemical folpet and its metabolite, phthalimide induce malformation in the rabbit.

• Review of other rabbit developmental toxicity studies, including those in the published literature, confirm that neither captan nor THPI induce malformation in the rabbit.

• Review of rat developmental and reproduction toxicity studies, including those in the published literature, confirm that neither captan nor THPI induce malformation in the rat.

• Review of the data available in the published literature confirm that neither captan nor THPI induce malformation in the mouse or primate.

• Review of developmental toxicity studies including those in the published literature confirm that the structurally similar chemical folpet, and its metabolite phthalimde, do not induce malformation in several species including the rat and rabbit.

9.10.6 Comparison with the CLP criteria

In the classification system, adverse effects on development of the offspring include any effect which interferes with normal development of the conceptus, either before or after birth, and resulting from exposure of either parent prior to conception, or exposure of the developing offspring during prenatal development, or postnatally, to the time of sexual maturation.

The effects seen were considered to be a consequence of the maternal toxicity induced and of a transient nature. There were no effects to warrant classification of captan as a developmental toxicant.

9.10.7 Adverse effects on or via lactation

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 43: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Reproduction toxicity Three generation / 2 litters Non-guideline,	Captan (technical batch number SX944, purity 89 %) 0, 25, 100, 250, 500	***Parental toxicity*** **<u>500 mg/kg bw/day</u>:** F0: ↓ body weight (males 17%, females 13% - week 14); ↓ average food consumption (males 19%, females 24%). F1: ↓ body weight (males 28%, females 24% - week 47); ↓ average food consumption (males 22%, females 20%). F2: ↓ body weight (males 21%, females 22 % - week 79); ↓ average food	R-6340 Study 1 (1982)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
non-standard design with significant deviations in design and reporting cf. current TG OECD 416 (2001) Not GLP Rat, CR COBS®CD® 15 males and 30 females/ group	mg/kg bw/day continuously in diet	consumption (males 18%, females 19%). **250 mg/kg bw/day:** F0: ↓ body weight (males 19%, females 9% - week 14); ↓ average food consumption (males 15%, females 15%). F1: ↓ body weight (males 16%, females 14% - week 47); ↓ average food consumption (males 14%, females 12%). F2: ↓ body weight (males 17%, females 15 % - week 79); ↓ average food consumption (males 13%, females 4%). **100 mg/kg bw/day:** F0: ↓ body weight (males 8% (NS), females 6% - week 14); ↓ average food consumption (males 5%, females 6%). F1: ↓ body weight (males 7% (NS), females 8% - week 47); ↓ average food consumption (males 5%, females 2%). F2 ↓ body weight (males 7% (NS), females 6 % - week 79); ↓ average food consumption (males 4%). **25 mg/kg bw/day:** No effects. Parental NOAEL: ♂ 25 mg/kg bw/d; ♀: 100 mg/kg bw/d ***Reproduction toxicity*** **500 mg/kg bw/day:** No effects. NOAEL: 500 mg/kg bw/d ***Pup toxicity*** **500 mg/kg bw/day:** F1a: ↓ survival days 1-4 (93% cf. 99% control); ↓ litter size day 0, 16%; ↓ pup weight day 1, 18%, day 21 males 34%, females 35%. F1b: ↓ survival days 1-4 (93% cf. 99% control); ↓ litter size day 0, 26.5%; ↓ pup weight day 1, 17%, day 21 males 38%, females 40%. F2a: ↓ survival days 1-4 (85% cf. 99% control); ↓ litter size day 0, 12.5%; ↓ pup weight day 1, 17%, day 21 males 44%, females 40.5%. F2b: ↓ survival days 1-4 (96% cf. 99% control); ↓ litter size day 0, 15%; ↓ pup weight day 1, 10%, day 21 males 31%, females 32%. F3a: ↓ survival days 1-4 (89% cf. 98% control); ↓ litter size day 0, 3%; ↓ pup weight day 1, 14.5%, day 21 males 33%, females 32%. F3b: ↓ survival days 1-4 (93% cf. 99% control); ↓ litter size day 0, 3%; ↓ pup weight day 1, 13%, day 21 males 39.5%, females 39%. **250 mg/kg bw/day:** F1a: ↓ survival days 1-4 (92% cf. 99% control); ↓ litter size day 0, 11%; ↓ pup weight day 1, 12%, day 21 males 17%, females 18%. F1b: ↓ litter size day 0, 8%; ↓ pup weight day 1, 8%, day 21 males 21%, females 21%.	

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		F2a: ↓ survival days 1-4 (95% cf. 99% control); ↓ pup weight day 1, 13%, day 21 males 30%, females 28%. F2b: ↓ litter size day 0, 8%; ↓ pup weight day 1, 10%, day 21 males 25%, females 24%. F2c: ↓ foetal body weight gestation day 19 9.5%. F3a: ↓ pup weight; day 1 7%, day 21 males 17%, females 17%. F3b: ↓ pup weight; day 1 7%, day 21 males 20%, females 21%. **100 mg/kg bw/day:** F1a: ↓ pup weight: day 1 8%, day 21 males 9%, females 10%. F1b: ↓ pup weight: day 1 8%, day 21 males 7%, females 7%. F2a: ↓ pup weight; day 1 4%, day 21 males 13%, females 13%. F2b: ↓ pup weight; day 1 7%, day 21 males 13%, females 13%. F3a: ↓ pup weight; day 1 3%, day 21 males 8%, females 6%. F3b: ↓ pup weight; day 1 4%, day 21 males 8%, females 9%. **25 mg/kg bw/day:** F1a: ↓ pup weight; day 1 7%, day 21 males 2%, females 3%. F1b: ↓ pup weight; day 1 4%, day 21 males 1%, females 1%. F2a: ↓ pup weight; day 1 1%, day 21 males 6%, females 4%. F2b: ↓ pup weight; day 1 7%, day 21 males 4%, females 5%. F3a: ↓ pup weight; day 1 1%, day 21 males 2.5%, females 1%. F3b: ↓ pup weight; day 1 1%, day 21 males 3%, females 5%. Offspring NOAEL: 25 mg/kg bw/d	
Reproduction toxicity One generation / one litter Non-guideline, supplementary to previous study GLP Rat, CR COBS®CD® 15 males and 30 females/ group	Captan (technical batch number SX944, purity not reported) 0, 6, 12.5, 25 mg/kg bw/day continuously in diet	***Parental toxicity*** No effects at any dose level. Parental NOAEL: 25 mg/kg bw/d ***Reproduction toxicity*** No effects at any dose level. NOAEL: 25 mg/kg bw/d ***Pup toxicity*** **25 mg/kg/day:** ↓ mean pup weight (5.3% day 4, 6.4% day 7, 5.6% day 14 - NS). **12.5 mg/kg bw/day:** No effects. Offspring NOAEL: 25 mg/kg bw/d	R-6339 Study 2 (1982)

Table 44: Summary table of human data on effects on or via lactation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No reported evidence of adverse health effects in humans				

Table 45: Summary table of other studies relevant for effects on or via lactation

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

9.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

The reproduction studies of captan (Study 1 and 2, 1982) have been described previously in section 8.10.1 & 8.10.2. There was no indication of impaired nursing behaviour or decreased pup viability during lactation. The results of the study do not indicate any direct, adverse effect on the offspring due to transfer of the chemical via the milk or to the quality of the milk.

9.10.9 Comparison with the CLP criteria

The classification is intended to indicate when a substance may cause harm due to its effects on or via lactation and is independent of consideration of the reproductive or developmental toxicity of the substance. There were no effects to warrant classification of captan, for effects on or via lactation.

9.10.10 Conclusion on classification and labelling for reproductive toxicity

No classification.

9.11 Specific target organ toxicity-single exposure

Table 46: Summary table of animal studies on STOT SE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
Summarised in other sections			

Table 47: Summary table of human data on STOT SE

Type of data/report	Test substance	Route of exposure Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 48: Summary table of other studies relevant for STOT SE

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No relevant studies				

9.11.1 Short summary and overall relevance of the provided information on specific target organ toxicity – single exposure

In standard single dose oral, dermal and inhalation toxicity studies there was no evidence of specific target organ toxicity. Clinical signs at lethal dose levels in oral and inhalation studies (> 1000 mg/kg bw, > 0.072 mg/L) included: reduced activity, ataxia, convulsions, coma, sedation and reduced reflexes, as well as more general signs of toxicity. In all studies, except two (acute oral in mouse; Study 4, 1983 and acute inhalation in rat, Study 4, 2000), the symptoms were transient.

Following clinical signs were described in the acute oral Study 4 (1983)- in brackets animal number affected:

1500 mg/kg bw: Reduced activity (No. 1, 2, 3) and reflexes (No. 2), tremor (No. 2) and abdominal ache (No. 3)
1890 mg/kg bw: Reduced activity (No. 1, 2, 3), tremor (No. 3), abdominal ache (No. 3), reduced frequency of respiration (No. 2) and staggering (No. 2) (2 mortalities within 48 hours- one of them is animal No. 3)
2380 mg/kg bw: Reduced activity (No 1, 2, 3, 4), ataxia (No. 3), apathy (No. 3), abdominal ache (No. 4), reduced frequency of respiration (No. 2), staggering (No. 2) and convulsions (No.3) (5 animals died within 24 hours- one of them is animal No. 2, 2 late mortalities- one of them is animal No. 4)
3000 mg/kg bw: Reduced activity (No. 1, 2, 3, 4, 5), tremor (No. 3), abdominal ache (No. 3), reduced frequency of respiration (No. 2), ataxia (No. 4), apathy (No. 4), sedation (No. 4), coma (No. 5) and exophthalmos (No. 2) (all animals died within 24 hours)

All the affected animals were males, while the females did not exhibit clinical symptoms. It is not clear from the study report, which or if all these symptoms persisted during the study period.

The only test concentration without mortality in the acute inhalation studies was 0.23 mg/L. At this dose ataxia was seen immediately following exposure but by 1 hour after dosing only more general signs were present (hunched posture, lethargy, piloerection, decreased respiratory rate and ptosis) and all animals were fully recovered by day 5. No histopathological evaluation was performed in the acute inhalation toxicity studies.

Following persisting clinical signs were described in the acute inhalation Study 4 (2000)- in brackets animal number affected:

Milled captan:

0.072 mg/L: Snout alopecia (1/4 surviving males)

0.648 mg/L: Moist rales (1/1 surviving males), general alopecia (1/1 surviving females)

2.28 mg/L: no surviving animals beyond Day 1

Non-milled captan:

0.668 mg/L: Snout alopecia (1/5 surviving males, 1/5 surviving females)

There were no clinical signs of toxicity in the acute dermal studies at a dose level of 2000 mg/kg bw.

In repeated dose studies no target organ was identified and there were no effects occurring after single exposures that were considered as evidence of specific target organ toxicity.

9.11.2 Comparison with the CLP criteria

Specific target organ toxicity (single exposure) is defined as specific, non-lethal target organ toxicity arising from a single exposure to a substance. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed effects are considered.

There was no evidence from single or repeated dose studies of non-lethal target organ toxicity arising from a single exposure below the upper cut–off values (2000 mg/kg bw oral; 5 mg/L inhalation).

Furthermore, transient organ effects i.e. respiratory tract irritation or narcotic effects can lead to a STOT-SE classification.

All clinical effects are signs of general systemic toxicity and occurred in most studies at dose levels, where mortality was observed.

Furthermore, irritation effects in the respiratory tract are sufficiently characterized by the Acute inhalation toxicity category 3 classification proposal. While acute respiratory irritation is likely, based on the available data, which would potentially justify a STOT-SE Category 3 classification, the Acute inhalation toxicity category 3, is based on the same underlying irritation effect which results in oedema and subsequent mortality. The classification proposal of category 3 is more protective than a STOT-SE 3 classification and requires the application of personal protective equipment, which in practice protects against respiratory irritation. Further, the respiratory tract is no specific target organ.

9.11.3 Conclusion on classification and labelling for STOT SE

No classification.

9.12 Specific target organ toxicity-repeated exposure

If not stated otherwise in the summary tables, the studies are considered as fully reliable.

Table 49: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**	**Reference**
Preliminary oral toxicity No relevant guideline GLP Dog, Beagle 2/sex/group Supplementary information (reliable with restrictions due to low animal number, i.e. 2/group/sex)	Captan technical (Lot/batch: WRC 4921-16-15; purity: not reported) Oral (capsule) Dose: 0, 30, 100, 300, 600, 1000 mg/kg bw/day 28 days	**1000 mg/kg bw/day:** *Clinical signs:* increased incidence of emesis *Body weight*: loss of body weight males 27.4%, females 18.9% week 4 *Food consumption:* ↓ males 57.8%, females 45.9% *Micropathology*: 1 male fatty change in the liver and collecting tubes of the kidney. **600 mg/kg bw/day:** *Clinical signs:* increased incidence of emesis *Body weight*: loss of body weight males 16.0%, females 14.8% week 4 *Food consumption:* ↓ males 36.9%, females 50.2% **300 mg/kg bw/day:** *Clinical signs:* increased incidence of emesis *Body weight*: ↓ in week 4 males 3.9%, females 2.4% less than starting weight *Food consumption:* ↓ males 23.5%, females 27.9% **100 mg/kg bw/day:** *Clinical signs:* occasional emesis *Body weight gain:* ↓ in males overall gain 1.8% v 9.8% in control *Food consumption:* ↓ males 23.5% **30 mg/kg bw/day:** *Clinical signs:* occasional emesis *Body weight gain:* generally lower than control *Food consumption:* ↓ males 19.3%, females 16.6% NOAEL: 100 mg/kg bw/d	R-4689 Study 1 (1987)
Chronic oral toxicity OPPTS 83-1 GLP Dog, Beagle 5/sex/group	Captan technical (WRC 4921-26-15; purity 90.4%) Oral (capsule) Doses: 0, 12.5, 60 and 300 mg/kg bw/day 52 weeks	**300 mg/kg bw/day:** *Clinical signs*: ↑ incidence of emesis and soft/mucoid faeces ↑ liver weight ↑ AP in females, ↑ total protein and albumin in males **60 mg/kg bw/day**: No treatment-related effects	R-5284 Study 2 (1988)

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, route of exposure, dose levels, duration of exposure**	**Results**	**Reference**
Sub-acute dermal toxicity US FIFRA 82-2 GLP Deviations: occlusive dressing Rabbit, New Zealand White 5/sex/group	Captan technical (Lot/batch: not reported; purity: not reported) Dermal application (occlusive dressing) Dose levels: 0, 12.5, 110 and 1000 mg/kg bw/day. 21 days (5 days per week)	**1000 mg/kg bw/day:** *Clinical observations:* very slight erythema (2 animals on day 4, 1 animal on days 8 and 15); very slight erythema and oedema and slight desquamation in 5-8 animals on days 18 and 21, moderate desquamation 1 animal on day 21, slight atonia in 1 animal on day 18. *Body weight*: ↓ females 13% day 22 *Food consumption*: ↓ males 35% week 2, females ~ 33% weeks 2 and 3 *Microscopic pathology*: akanthosis (5 males, 5 females), hyperkeratosis (5 males, 5 females), dermatitis (2 females) **110 mg/kg bw/day:** *Clinical observations:* slight desquamation in 2 animals on day 21. *Microscopic pathology*: akanthosis (5 males, 4 females), hyperkeratosis (5 males, 4 females), dermatitis (1 male, 2 females). **12.5 mg/kg bw/day:** *Clinical observations:* slight desquamation in 1 animal on day 21. *Microscopic pathology*: akanthosis (5 males, 4 females), hyperkeratosis (5 males, 4 females), dermatitis (1 female). NOAEL (systemic): 110 mg/kg bw/d NOAEL (local): 12.5 mg/kg bw/d	R-4666 Study 3 (1987)

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
Subchronic inhalation toxicity USEPA 82-4 GLP Rat, Alpk:APfSD strain 20/sex/group control and high dose, 10/sex/group intermediate groups	Captan technical (Batch/lot: 11240-37-1; purity 88.7%) Inhalation (nose-only) Dose levels: 0, 0.13, 0.60, 5.06, 12.98 µg/L 90 days exposure six hours per day, 5 days per week, plus 4 week recovery period control and high dose	**12.98 µg/L:** *Mortality:* 5 males were found dead or killed *in extremis*. *Microscopic pathology*: lung – sub-epithelial cellular necrosis (2 males, 1 female), attenuated bronchial epithelium (6 males, 9 females), submucosal gland formation (1 male, 1 female); larynx – squamous metaplasia (6 males, 9 females), ulceration (1 male, 1 female), squamous hyperplasia (6 males, 9 females), parakeratosis (2 males, 3 females), vacuolar degeneration of squamous epithelium (4 males, 7 females); nasal cavity – rhinitis (3 males, 2 females), degeneration/atrophy olfactory epithelium dorsal meatus (3 males, 4 females). All effects in the lung and nasal passages had resolved in the 4 week recovery period. Squamous hyperplasia and squamous hyperplasia in the larynx persisted in the recovery period. **5.06 µg/L:** *Microscopic pathology*: lung – sub-epithelial cellular necrosis (6 males, 2 female), attenuated bronchial epithelium (8 males, 9 females, hyperplasia bronchial epithelium (2 males); larynx – squamous metaplasia (9 males, 7 females), ulceration (3 females), squamous hyperplasia (9 males, 8 females), parakeratosis (2 males, 2 females), vacuolar degeneration of squamous epithelium (3 males, 4 females); nasal cavity – rhinitis (1 male), necrosis squamous epithelium (1 male). **0.60 µg/L:** *Microscopic pathology*: larynx –squamous hyperplasia (5 males, 7 females); nasal cavity – rhinitis (1 male), degeneration/atrophy olfactory epithelium dorsal meatus (1 female). **0.13 µg/L:** *Microscopic pathology*: larynx –squamous hyperplasia (1 male, 4 females); nasal cavity –degeneration/atrophy olfactory epithelium dorsal meatus (1 female). The pathological findings were consistent with exposure to an irritant particulate. NOAEC (systemic): 0.6 µg/L LOAEC (local): 0.13 µg/L	R-5603 Study 4 (1989)

Table 50: Summary table of human data on STOT RE

Type of data/report	Test substance	Route of exposure Relevant information about the study (as applicable)	Observations	Reference
No relevant data				

Table 51: Summary table of other studies relevant for STOT RE

Type of study/data	Test substance	Observations	Reference
Combined Chronic Toxicity/ Carcinogenicity Study Guideline not reported but consistent with OECD 453 (1981). No major deviations. GLP Rat: Charles River CD 50/sex/group for carcinogenicity 10/sex/group interim kill after 12 months 10/sex/group interim kill after 18 months	Captan technical, (batch: SX944; purity: 89%) 0, 25, 100 and 250 mg/kg bw/day in diet For up to 2 years	**250 mg/kg bw/day** ↓ Body weight: mean 20.1% males, 19.4% females ↑ Liver weight: 36% males 18 months ↑ Hepatocellular hypertrophy: 10/10 males, 8/10 females 18 months (0/10 controls) **100 mg/kg bw/day** ↓ Body weight: mean 11.9% males, 18.9% females **25 mg/kg bw/day** No treatment-related findings	R-9282 Section 8.9 Study 1 (1982)
Carcinogenicity study Guideline not reported but consistent with OECD 451 (1981). No major deviations. GLP Rat: Cpb:WU Wistar random. 50/sex/group	Merpan technical, (batch and purity not reported). 0, 125, 500 and 2000 ppm in diet (eq. to 0, 5, 24 and 98 mg/kg bw/day). For 130 weeks	**2000 ppm (98 mg/kg bw/day)** ↓ Body weight: 7.8 and 8.8% males after 364 and 728 days respectively, 10.0 and 10.2% females after 364 and 728 days respectively ↓ Food consumption: 11.9% males, 10.0% females overall mean to day 252 ↓ Food utilisation efficiency: 0.293 g growth/g food/week males week 1 (control 0.416); 0.286 females week 1 (control 0.371) ↑ Liver weight: 15% relative to body weight males **500 ppm (24 mg/kg bw/day)** No treatment-related findings **125 ppm (5 mg/kg bw/day)** No treatment-related findings	R-3608 Section 8.9 Study 2 (1983)

Type of study/data	Test substance	Observations	Reference
Carcinogenicity study Guideline not reported but consistent with OECD 451 (1981). No major deviations but increased number of animals per group. GLP Mouse: CD-1 (ICR derived). 80/sex/group	Captan technical, (batch: SX-944; purity: 90.7%) 0, 2000, 6000, and 10000 ppm in diet weeks 1-4. 0, 6000, 10000 and 16000 ppm in diet weeks 5-113	**16000 ppm (1890/1880 mg/kg bw/day in males/females)** ↓ Survival: males 68% week 75 [control 83%] ↓ Body weight: 21.9% males, 20.3% females week 52 ↓ Food consumption: 17.6% males;16.5% females week 52 ↑ Duodenum mucosal hyperplasia: 24/75 males and 34/76 females [control 3/74 and 6/72] **10000 ppm (1030/1080 mg/kg bw/day in males/females)** ↓ Body weight: 9.0% males, 12.2% females week 52 ↓ Food consumption: 10.3% males; 6.1% females week 52 ↑ Duodenum mucosal hyperplasia: 36/72 males and 37/76 females [control 3/74 and 6/72] **6000 ppm (599/634 mg/kg bw/day in males/females)** ↓ Body weight: 2.9% males, 8.7% females week 52 ↓ Food consumption: 7.5% males; 6.6% females week 52 ↑ Duodenum mucosal hyperplasia: 39/73 males and 33/78 females [control 3/74 and 6/72]	R-8292 Section 8.9 Study 3 (1981)

Type of study/data	Test substance	Observations	Reference
Carcinogenicity study Guideline not reported but design based on OECD 451 (1981). Deviations: tissues examined limited to GI tract, lungs and grossly abnormal tissues, increased number of animals per group. Duodenal sections re-evaluated in 1994. GLP Mouse: CD-1 (ICR derived). 100/sex/group	Captan technical, (batch: SX-1086; purity: 89%) 0, 100, 400, 800 and 6000 ppm in diet. For 94 weeks (22 months)	**6000 ppm (924.8/1042.7 mg/kg bw/day in males/females)** ↑ Mortality: males 35% 14 months [control 15%] ↓ Body weight: approx. 5% males in first year; approx. 7% females weeks 1-94 ↑* Duodenum focal mucosal hyperplasia: 12/84 males and 20/91 females [control 4/91 and 11/85] ↑* Duodenum lymphoid proliferation: 23/84 males and 18/91 females [control 9/91 and 10/85] **800 ppm (122.8/141.9 mg/kg bw/day in males/females)** ↓ Body weight: 6.9% males week 1 only ↑* Duodenum lymphoid proliferation: 18/81 females [control 10/85] **400 ppm (60.9/70.4 mg/kg bw/day in males/females)** No significant treatment-related findings **100 ppm (15.1/17.7 mg/kg bw/day in males/females)** No significant treatment-related findings * All microscopic incidences of findings in the duodenum from Robinson (1994)	R-7995/ R-9775a Section 8.9 Study 4 (1983/1982/1994)

9.12.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

Repeated dose toxicity was assessed in the rat, mouse and dog in oral, dermal and inhalation studies lasting 4 weeks to 2 years.

In a four week dose range-finding oral toxicity study in the dog (Study 1, 1987, Table 49) the only effects seen were emesis in all animals at 300 mg/kg bw/day and above, reduced food consumption and body weight loss/reduced body weight gain throughout the study. One male at 1000 mg/kg bw/day showed fatty changes in the liver and the collecting tubules of the kidneys. However, due to small number of animals per group, the toxicological significance of this finding was equivocal. No similar findings were noted in longer term studies.

Similarly, in the one year oral toxicity study in the dog (Study 2, 1988) treatment-related observations were limited to a higher incidence of emesis and soft/mucoid faeces predominantly at doses ≥ 300 mg/kg bw/day.

In a 13-week inhalation (nose only) study in the rat (Study 4, 1989) treatment-related effects were confined to the respiratory tract and might be consistent with exposure to an irritant particulate. Effects in the lungs resulted in the death of five males at the highest exposure concentration of 12.98 µg/L. These mortalities occurred not earlier than week 5. Following a 4-week recovery period in the 13 week inhalation exposure captan study the lung and nasal passage effects had resolved, but the laryngeal effects (squamous metaplasia and squamous hyperplasia) were still present in the high dose group (low and mid dose groups were not examined). Effects in the larynx (squamous hyperplasia) and nasal cavity (degeneration/atrophy olfactory epithelium) were present from ≥ 0.13 µg/L. Folpet, which has the same toxicophore, results in similar observations in the available 28-day inhalation study in the respiratory tract. However, in this study no mortality was observed.

Similar to folpet, the observations might be in-line with the exposure towards an irritant particle. In addition, rhinitis, laryngitis, bronchitis and alveolitis have all been diagnosed in the rat inhalation study packages for both folpet and captan.

It is generally accepted that the rat is very sensitive with respect to inhalation toxicity. Particularly, squamous metaplasia is often considered to have no toxicological relevance for human health. The extreme sensitivity of the rat larynx to irritant particulates is considered to arise from anatomical, airflow, epithelial cell type and possibly clearance rates. In rat larynx, the cartilage associated with the ventral pouch is U-shaped and larynx and trachea form a relatively straight line from the nasal turbinates, which enhances the deposition of aerosols. In contrast, in humans the U-shaped pouch is absent, and the larynx is more sharply angled to the oro-nasal cavity. Often degeneration of the original epithelial cells with subsequent regeneration hyperplasia and squamous metaplasia occurs, which was observed in the available study package for captan, which on the one hand could be considered as an adaptive response to inhalation of irritants. On the other hand, laryngeal effects (squamous metaplasia and squamous hyperplasia) were still present in the recovery period in the 13 week inhalation exposure study and mortalities were observed at a dose level of 12.98 µg/L.

In Kluxen and Koenig (2021 accepted for publication), comparisions in acute LC50 and cumulative exposure are provided. The lowest concentration resulting in 50% mortality was observed at 12.98 µg/L, or 0.013 mg/L, which is 52 times lower than the LC50 of 0.67 mg/L. However, here the animals in the repeated study were exposed a total of 62 times and 50% longer per day and the repeat exposure ratio is similar to the single dose ratio. It may be questioned, whether adverse effects caused by irritation observed in repeated exposure studies are specific target organ toxicity distinct from acute effects or whether they occur due to the same aetiology, being already covered by classification for irritation and acute toxicity.

However, no repeated dose inhalation ADME studies are available proving this assumed cumulative toxicity of captan in the respiratory tract. Furthermore, oral ADME studies show that > 75% of Captan was excreted within 24 hours and half-life of captan in blood (*in vitro*) was extremely short (seconds) raising the level of uncertainty towards exposure to cumulated captan deposits in the respiratory tract.

According to the ECHA "Guidance on the Application of the CLP Criteria" (2017) one way to distinguish if the severe effect is a reflection of true repeated exposure toxicity or whether it is in fact just acute toxicity (i.e. corrosivity) is to consider the dose level which causes the toxicity. If the dose is more than half an order of magnitude lower than that mediating the evident acute toxicity (corrosivity) then it could be considered to be a repeated-dose effect distinct from the acute toxicity.

Currently captan is classified as Eye Dam. Cat. 1 and Acute Tox. Cat. 3 (inhalation) (LC50 = 0.67 mg/L in females) (i.e. Study 2). Clinical signs were noted in animals exposed to 0.23 mg/L (lowest dose) in the same acute inhalation study. There is no information on the irritation/corrosive potential of captan at lower dose levels. However, there is a factor of > 15 between the dose causing mortalities in the repeated dose inhalation toxicity study and the dose level causing clinical signs in acute inhalation toxicity studies. Therefore, the effects (including mortalities) observed during the repeated dose inhalation toxicity study could be considered relevant for considering classification as STOT-RE.

In a sub-acute dermal toxicity study in the rabbit (Study 3, 1987) decreased body weight gain and food consumption and evidence of mild skin irritation were seen at a dose of 1000 mg/kg bw/day. There were no clinical signs of toxicity or effects on body weight or food consumption at lower dose levels (12.5 and 110 mg/kg bw/day) and evidence of dermal irritation was minimal.

In two, carcinogenicity studies in the rat (Section 8.9 Study 1, 1982 and Study 2, 1983) effects were limited to reduced body weight gain, lower food consumption and evidence of liver hypertrophy (increased weight and/or hepatocellular hypertrophy) at doses ≥ 98 mg/kg bw/day.

Similarly, in the mouse carcinogenicity studies (Section 8.9 Study 3, 1981; Study 4, 1983) the only in-life findings were decreases in body weight, sometimes accompanied by reduced food consumption at dose levels of 122.8 mg/kg bw/day and above. In addition, there was evidence of duodenal damage due to captan degradation in the duodenum starting at a dose level of 123 mg/kg bw/d (see 8.9.1). Captan degradation in the duodenum results in the formation of the irritant thiophosgene, leading to villus cell damage and irritation and as a result there is enhanced cell replication. This in turn leads to crypt cell hyperplasia, adenoma and ultimately carcinoma.

Table 52: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days

Study reference	Effective dose (mg/kg/d)	Length of exposure	Extrapolated effective dose when extrapolated to 90-day exposure	Classification supported by the study
Study 1, 1987	300, 600, 1000 oral dog	28 days	900, 1800, 3000	Not classified, no specific organ toxicity
Study 3, 1987	100, 1000 dermal rabbit	21 days	433, 4333	Not classified, no specific organ toxicity
Study 2, 1988	300 oral dog	12 months	75	Not classified, no specific organ toxicity
Study 4, 1983, section 3.9.1.4	924.8 males, 141.9 females oral mouse	22 months	126.1 males, 16.3 females	Covered by classification proposal Carc. 2
Study 3, 1981, section 3.9.1.3	1890 males, 1880 females oral mouse	113 weeks	217.4 males, 216.3 females	Not classified, no specific organ toxicity

9.12.2 Comparison with the CLP criteria

Substances are classified as specific target organ toxicants following repeated exposure on the basis of "significant" or "severe" toxicity. In this context "significant" means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. "Severe" effects are generally more profound or serious than "significant" effects and are of a considerably adverse nature which significantly impact on health.

The effects of captan following repeated dosing by the oral or dermal route were effects on body weight and food consumption and evidence of irritation. Irritation was evident in the skin in the dermal study. In the mouse irritation in the duodenum resulting in mucosal hyperplasia of the duodenum and subsequent tumour formation occurs in both males and females. This has been attributed to the localised production of the metabolite phosgene and is covered by the classification proposal for carcinogenicity.

The effects of inhalation exposure might be also indicative of an irritant effect. However, exposure of rats for 90 days to captan aerosols at atmospheric concentrations of 0.13, 0.60, 5.06 and 12.98 µg/L captan resulted in five treatment-related mortalities in males exposed to the highest concentration, triggering classification for STOT RE 1 – H372 ("Causes damage to organs through prolonged or repeated exposure if inhaled.") due to significant toxic effects (mortality) occurring at concentrations below the guidance value of 0.02 mg/L/6h/day for 90-day inhalation toxicity studies in rats exposed to dust/mist/fume, according to Regulation (EC) No 1272/2008.

As regards neurotoxicity, data on functional observations (as required in a 90-day oral toxicity study) are missing for captan as they were not examined in the available 1-year dog and the 2-year rat studies. However, there is no indication of potential neurotoxicity of captan from the available data. Captan does not induce specific indications of potential neurotoxicity, neurological signs or neuropathological lesions in toxicity studies at dose levels not associated with marked general toxicity. Captan does also not have a neurotoxic mode of pesticidal action. Furthermore, captan is not structurally similar or related to structures that are capable of inducing neurotoxicity.

The potential for immunotoxicity following administration of captan has been assessed (position paper by Anonymous, 2018). There are no toxicological alerts from subchronic and chronic mammalian studies with

captan that suggest an immunologic mode of action. Similarly, there are no such alerts for the structural analog of captan, folpet.

9.12.3 Conclusion on classification and labelling for STOT RE

Captan is proposed to be classified for STOT-RE Category 1.

9.13 Aspiration hazard

This hazard class not assessed in this dossier.

10 EVALUATION OF ENVIRONMENTAL HAZARDS

10.1 Rapid degradability of organic substances

Table 53: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
Hydrolysis, [trichloromethyl-^{14}C] Captan USEPA 161-1	DT50 (pH 5, 25 °C): 18.4 h DT50 (pH 7, 25 °C): 4.8 h DT50 (pH 9, 25 °C): 7.8 min Relevant for classification regarding degradability in aquatic environment → rapidly degradable in the aquatic environment: DT50 < 16 d and degradation products do not meet the criteria for classification as hazardous to the aquatic environment – please see point 9.4 to 9.7.	Study considered valid.	Annex I, fate and behaviour in water and sediment, study 1, 1989a
Hydrolysis, [ring-1-^{14}C] Captan USEPA 161-1	Captan: DT50 (pH 5, 25 °C): 11.7 h DT50 (pH 7, 25 °C): 4.6 h DT50 (pH 9, 25 °C): 8.1 min Metabolite THCP: DT50 (pH 5, 25 °C): 15.1h DT50 (pH 7, 25 °C): 8.1 h DT50 (pH 9, 25 °C): 12 min Relevant for classification regarding degradability in aquatic environment → rapidly degradable in the aquatic environment: DT50 < 16 d and degradation products do not meet the criteria for classification as hazardous to the aquatic environment – please see point 9.4 to 9.7.	Study considered valid.	Annex I, fate and behaviour in water and sediment, study 2, 1989b
Hydrolysis Metabolite THPI OECD 111	Metabolite THPI: DT50 (pH 4, 25 °C): stable DT50 (pH 7, 25 °C): 152 d DT50 (pH 9, 25 °C): 3.2 d	Study considered valid.	Annex I, fate and behaviour in water and sediment, study 3, 2002a
Hydrolysis Metabolite THPAM OECD 111	Metabolite THPAM: DT50 (pH 4, 25 °C): 4 d DT50 (pH 7, 25 °C): 360 d DT50 (pH 9, 25 °C): stable	Study considered valid.	Annex I, fate and behaviour in water and sediment, study 4, 2002b

Method	Results	Remarks	Reference
Photolysis [trichloromethyl-^{14}C] Captan USEPA 161-2	DT_{50} : 9.9 h (pH 5, 48 h, 25°C) irradiated, DT_{50}: 10.1 h in the dark control No photolytic degradation products.	Study considered valid.	Annex I, fate and behaviour in water and sediment, study 5, 1986b
Photolysis THPI SETAC (March 1995), OECD guidance document (97)21	THPI: Stable at pH 7 and 22°C	Study considered valid.	Annex I, fate and behaviour in water and sediment, study 6, 2002a
Photolysis THPAM SETAC (March 1995), OECD guidance document (97)21	THPAM: Stable at pH 7 and 22°C	Study considered valid.	Annex I, fate and behaviour in water and sediment, study 7, 2002b
Biological degradation [carboximide-^{14}C]Captan OECD 301 B / CO_2 Evolution Test (Modified Sturm)	Captan is not readily biodegradable in the 10-days window and within 28 days. Relevant for classification regarding degradability in aquatic environment → not rapidly degradable in the aquatic environment	Study considered valid.	Annex I, fate and behaviour in water and sediment, study 8, 2015
Aerobic mineralisation in surface water OECD 309	DT50 < 1 h Relevant for classification regarding degradability in aquatic environment → rapidly degradable in the aquatic environment: DT50 < 16 d and degradation products do not meet the criteria for classification as hazardous to the aquatic environment – please see point 9.4 to 9.7.	Study considered valid.	Annex I, fate and behaviour in water and sediment, study 9-13, 2016b and 2016 and 2017
Water/Sediment Study [cyclohexene 1,2-^{14}C]-Captan GD not specified, but complies with the SETAC guideline	Captan: Water: DT50: < 1 d DT90: < 1 d Whole system: DT50: < 1 d DT90: < 1 d Mineralization: 49-53 % CO_2 90 d after application Metabolite THPI: Whole system: DT50: 4.7 d DT90: 15.5 d	Study considered valid.	Annex I, fate and behaviour in water and sediment, study 14, 1993

Method	Results	Remarks	Reference
	Metabolite THPAM: Whole system: DT50: 13.6 d DT90: 45.1 d Relevant for classification regarding degradability in aquatic environment →rapidly degradable in in the aquatic environment: total system DegT50<16 days and degradation products do not meet the criteria for classification as hazardous to the aquatic environment – please see point 9.4 to 9.7.		

10.1.1 Ready biodegradability

Results of a new readily biodegradability study (OECD 301 B / CO2 Evolution Test (Modified Sturm)) indicate that captan is not readily biodegradable. For more detailed information on the study (Anonymous, 2015), please refer to Annex I Fate (Fate and behaviour in water and sediment, Study 8) and section Vol.3 B.8.2.2.1.

10.1.2 BOD_5/COD

No data were submitted.

10.1.3 Hydrolysis

The hydrolysis of [trichloromethyl-^{14}C] captan was investigated in the dark at a temperature of 25°C in sterile aqueous buffer solutions at pH 5, 7 and 9. Captan exhibited rapid first-order hydrolysis at all pH values in sterile water with half-lifes of 18.4 hr, 4.8 hr and 7.8 min at pH values of 5, 7 and 9.

The hydrolysis of [ring-1-^{14}C] captan was investigated in the dark at a temperature of 25°C in sterile aqueous buffer solutions at pH 5, 7 and 9. The mean first-order hydrolysis rates for captan were 11.7 hr, 4.6 hr and 8.1 min at pH values of 5, 7 and 9 respectively.

The hydrolysis of non-radiolabelled metabolite THPI was investigated in sterile aqueous buffer solutions at pH values of 4.0, 7.0 and 9.0 at 50°C. The metabolite THPI was stable to hydrolysis at pH 4 in sterile aqueous buffer solutions at 25°C. At pH values of 7 and 9, hydrolysis proceeded with pseudo-first order half lives of 152 and 3 days, respectively.

The hydrolysis of non-radiolabelled THPAM was investigated in sterile aqueous buffer solutions at pH values of 4.0, 7.0 and 9.0 at 50°C. The metabolite THPAM was stable to hydrolysis at pH 9 in sterile aqueous buffer solutions at 25°C. At pH values of 4 and 7, hydrolysis proceeded with pseudo-first order half lives of 4 and 360 days respectively.

For more detailed information on the studies, please refer to Annex I Fate (Fate and behaviour in water and sediment, Study 1-4) and section Vol.3 B.8.2.1.1.

10.1.4 Other convincing scientific evidence

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

No data relevant for C&L were provided.

10.1.4.2 Inherent and enhanced ready biodegradability tests

No data were submitted.

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

A new study on aerobic mineralisation of captan in surface water was performed with [cyclohexene-^{14}C] captan under aerobic conditions in the dark at 20 ± 3°C at pH 8.0-8.1 for 60 days. Captan rapidly degraded and was not detectable after 1 hour of incubation. Thus, the DT50-value can be assumed to be < 1 h. For more detailed information on the study, please refer to Annex I Fate (Fate and behaviour in water and sediment, study 9-13) and section Vol.3 B.8.2.2.2.

The degradation of [cyclohexene 1,2- ^{14}C]-captan was studied in two aerobic natural water/sediment systems under laboratory conditions in the dark at 20°C up to 90 days. Captan degraded very rapidly to THPI and was not detected one day after application. THPI was further degraded to THPAM and THPAI. The pathway fitting for the whole system provided DT_{50} and DT_{90} values for THPI of 4.7 d and 15.5 d and for THPAM of 13.6 d and 45.1d. For more detailed information on the study, please refer to Annex I Fate (Fate and behaviour in water and sediment, study 14) and section Vol.3 B.8.2.2.3.

The DT50 values of captan determined in 4 soils in laboratory studies are in the range of 0.5 to 5.7 days. The maximum DT_{50} value of 5.7 days is used for captan PEC_{Soil} modelling, whereas the geomean of 3.8 days is used for the calculations of the predicted concentrations in groundwater and surface water for captan. The DT50 values of the metabolite THPI determined in 4 soils in laboratory studies are in the range of 3.3 to 15.6 days. The maximum DT50 value of 15.6 days (persistence endpoints) is used for THPI PEC_{Soil} modelling, whereas the geomean of 6.85 days is used for the calculations of the predicted concentrations in groundwater and surface water for THPI. The DT50 values of the metabolite THPAM determined in 4 soils in laboratory studies are in the range of 2.0 to 11.2 days. The maximum DT50 value of 11.2 days (persistence endpoints) is used for THPAM PEC_{Soil} modelling, whereas the geomean of 5.38 days is used for the calculations of the predicted concentrations in groundwater and surface water for THPAM. For more detailed information on the studies, please refer to Annex I Fate (Fate and behaviour in soil, study 1-8) and section Vol.3 B.8.1.1.2.1.1. and Vol.3 B.8.1.1.2.1.2.

10.1.4.4 Photochemical degradation

Aquatic photolysis of captan was investigated in sterile aqueous buffer solution at pH 5 (the pH at which captan is most stable to chemical hydrolysis) using [trichloromethyl - ^{14}C] – captan. The test system was continuously irradiated with a black light fluorescent lamp (> 290 nm) for 48 hours at 25 °C. Captan degraded rapidly in the irradiated samples and in the dark controls. The half-life in the irradiated solution was 9.9 hours, and the half-life of the dark control almost identical at 10.1 hours, respectively. These results indicate that the chemical hydrolysis is the principal route of degradation and that photolysis is a very minor route of degradation. Therefore, no photolytic degradation products were determined.

The aqueous photolysis of non-radiolabelled THPI was investigated in sterile buffer solution at pH 7 and a temperature of 22.4°C using an artificial light source. The solutions were continuously irradiated with a xenon lamp (> 290 nm) for a period of 15 days. No significant degradation was observed in both the irradiated samples and the dark controls. THPI was shown to be stable to photolysis in aqueous solutions at a pH 7.

The aqueous photolysis of non-radiolabelled THPAM was investigated in sterile buffer solution at pH 7 and a temperature of 22.3°C using an artificial light source. The solutions were continuously irradiated with a xenon lamp (> 290 nm) for a period of 15 days. The extent of degradation was similar for both the exposed samples and dark controls indicating that THPAM is not significantly photo-degraded. THPAM was shown to be stable to photolysis in aqueous solutions at a pH 7.

For more detailed information on the studies, please refer to Annex I Fate (Fate and behaviour in water and sediment, study 5-7) and section Vol.3 B.8.2.1.2.

10.2 Environmental transformation of metals or inorganic metals compounds

Not relevant.

10.2.1 Summary of data/information on environmental transformation

Not relevant.

10.3 Environmental fate and other relevant information

Not relvant.

10.4 Bioaccumulation

Table 54: Summary of relevant information on bioaccumulation

Method	Test substance	Results	Remarks	Reference
USEPA Test Method CG-1400 (shake flask)	Captan Batch: S-31 (518) Purity: 98.95%	pH 7 log P_{OW} = 2.57 (25°C)	Acceptable EU agreed endpoint DAR 2003 GLP: No	Anonymous (1987e)
EEC A.8 OECD 107	Captan Batch: ASJ10097-01S Purity: 99.8%	pH 5 log P_{OW} = 2.5 (20°C)	Acceptable EU agreed endpoint DAR 2003 GLP: Yes	Anonymous (1995b)
Fish bioaccumulation test In-house method	[^{14}C]- Captan Batch: J42893 Purity: not reported	*Lepomis macrochirus* $BCF_{steady\text{-}state}$ = 140 (measured) $BCF_{steady\text{-}state}$ = 250 (estimated) CT_{50} = 3-7 d (edible) CT_{50} = 1-3 d (non-edibel, whole fish) Depuration after 14 days greater than 72% (edible), 92% (non-edible) and 89% (whole fish)	Acceptable EU agreed endpoint DAR 2003 GLP: Yes	Anonymous (1988a)
Fish bioaccumulation test In-house method	Cyclohexane [^{14}C]-Captan Batch: 2099-252 Purity: not reported	*Lepomis macrochirus* $BCF_{steady\text{-}state}$ = 113 (measured) $BCF_{steady\text{-}state}$ = 134 (estimated) CT_{50} = 0-3 d Depuration after 14 days greater than 94%	Acceptable EU agreed endpoint DAR 2003 GLP: Yes	Anonymous (1988b)
EEC A.8 OECD 107 (shake flask)	1.2.3.6-Tetrahydrophthalamic acid (THPAM) Batch: 469-121-00 Purity: 99.2%	pH 4.23 log P_{OW} = -0.40 (22.3°C)	Acceptable GLP: Yes	Anonymous (2015a)
EEC A.8 OECD 117 (HPLC)	1.2.3.6-Tetrahydrophthalimide (THPI) Batch: 279-071-02 Purity: 98.5%	log P_{OW} = 0.22 (20°C)	Acceptable GLP: Yes	Anonymous (2015b)

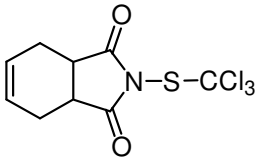
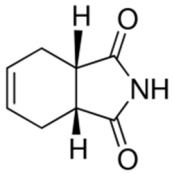
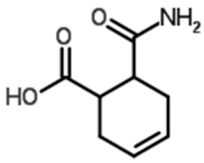
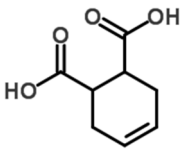
10.4.1 Estimated bioaccumulation

For the active substance captan and the metabolites THPI and THPAM (information on the structure of the active substance captan and its metabolites see Table 55) experimental data on log P_{OW} and the BCF are available.

However, no experimentally determined log P_{OW} was available for the metabolite THPAI (sediment). Hence, the log P_{OW} was determined using the US EPA softwate KOWWIN (EPIWEB 4.1).

Information on the structure of the active substance and the environmental relevant metabolites used for the estimation of the log P_{OW} and BCF is provided in Table 55: Substances and metabolites of environmental relevance (structure, synonyms and codes)

Table 55: Substances and metabolites of environmental relevance (structure, synonyms and codes)

Codes and synonyms	Description (IUPAC)	Compound found in	Structure
Captan	N-(trichloromethylthio)cyclohex-4-ene-(1,2 14C)-1,2-dicarboxyimide	All matrices	
THPI	cis-4-cyclohexane-1.2-dicarboximide	Environment (soil, groundwater, surface water, sediment), plant, rat	
THPAM	3-cyclohexene-1-carboxylic acid-6-(aminocarbonyl)	Environment (soil, groundwater, surface water), rat	
THPAI	4-cyclohexene-1,2-dicarboxylic acid	Environment (sediment)	

Considering the structure of the metabolite THPAI the log P_{OW} for the metabolite was estimated to be about 0.74. Detailed information on the estimation using KOWWIN (EPIWEB 4.1.) is provided in Table 56.

Table 56: Log P_{OW} estimation using EPIWEB

KOWWIN Program (v1.68) Results:

Log Kow(version 1.68 estimate): 0.74

SMILES : OC(=O)C1CC=CCC1C(=O)(O)
CHEM :
MOL FOR: C8 H10 O4
MOL WT : 170.17

TYPE	NUM	LOGKOW FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	2	-CH2- [aliphatic carbon]	0.4911	0.9822
Frag	2	-CH [aliphatic carbon]	0.3614	0.7228
Frag	2	=CH- or =C< [olefinc carbon]	0.3836	0.7672
Frag	2	-COOH [acid, aliphatic attach]	-0.6895	-1.3790
Factor	1	Multi-aliphatic carboxylic acids	-0.5865	-0.5865
Const		Equation Constant		0.2290
			Log Kow =	0.7357

An estimation of the BCF value for captan was conducted even though experimentally measured BCF values are available (Anonymous, 1988a and b).

However, the experimentally measured BCF values were questioned during the peer-review of the active substance captan because the studies were conducted according to no agreed test guidelines (in-house methods) and several deficiencies were identified challenging the reliability of the results.

However, as additional information and taking into account the identified deficiencies an estimation of the BCF value of captan was conducted using the US EPA software BCFBAF (EPIWEB 4.1) taking into account the chemical structure and a measured log P_{OW} of 2.52 as well as the estimated log P_{OW} of 2.85 (using KOWWIN). The BCF considering the measured log P_{OW} and the estimated log P_{OW} values were estimated to be 21.4 L/kg wet wt and 35.3 L/kg wet wt, respectively.

Further details on the estimation based on the measured log P_{OW} see Table 57.

Table 57: BCF estimation using EPIWEB

```
SMILES : c1ccc2c(c1)C(=O)N(C2(=O))SC(CL)(CL)CL
CHEM   :
MOL FOR: C9 H4 CL3 N1 O2 S1
MOL WT : 296.56
---------------------------------- BCFBAF v3.01 ----------------------------------
Summary Results:
  Log BCF (regression-based estimate):  1.33  (BCF = 21.4 L/kg wet-wt)
  Biotransformation Half-Life (days) :  2.49  (normalized to 10 g fish)
  Log BAF (Arnot-Gobas upper trophic):  1.54  (BAF = 34.8 L/kg wet-wt)

============================
BCF (Bioconcentration Factor):
============================
Log Kow  (estimated)  :  2.84
Log Kow (experimental):  2.85
Log Kow used by BCF estimates:  2.52 (user entered)

Equation Used to Make BCF estimate:
   Log BCF = 0.6598 log Kow - 0.333 + Correction

      Correction(s):                    Value
       No Applicable Correction Factors

   Estimated Log BCF =  1.330  (BCF = 21.36 L/kg wet-wt)

============================================================
Whole Body Primary Biotransformation Rate Estimate for Fish:
============================================================
------+-----+-----------------------------------------+---------+---------
 TYPE | NUM | LOG BIOTRANSFORMATION FRAGMENT DESCRIPTION |  COEFF  |  VALUE
------+-----+-----------------------------------------+---------+---------
 Frag |  3  |  Aliphatic chloride   [-CL]               |  0.3608 |  1.0823
 Frag |  1  |  Carbon with 4 single bonds & no hydrogens | -0.2984 | -0.2984
 Frag |  4  |  Aromatic-H                               |  0.2664 |  1.0655
 Frag |  1  |  Number of fused acyclic rings            |  0.6477 |  0.6477
 Frag |  1  |  Number of fused 6-carbon aromatic rings  | -0.5779 | -0.5779
 L Kow|  *  |  Log Kow =   2.52 (user-entered   )       |  0.3073 |  0.7745
 MolWt|  *  |  Molecular Weight Parameter               |         | -0.7605
 Const|  *  |  Equation Constant                        |         | -1.5371
============+===========================================+=========+=========
   RESULT   |        LOG Bio Half-Life (days)           |         |  0.3961
   RESULT   |            Bio Half-Life (days)           |         |    2.49
   NOTE     |  Bio Half-Life Normalized to 10 g fish at 15 deg C  |
============+===========================================+=========+=========

Biotransformation Rate Constant:
 kM (Rate Constant):  0.2784 /day (10 gram fish)
 kM (Rate Constant):  0.1566 /day (100 gram fish)
 kM (Rate Constant):  0.08804 /day (1 kg fish)
 kM (Rate Constant):  0.04951 /day (10 kg fish)

Arnot-Gobas BCF & BAF Methods (including biotransformation rate estimates):
   Estimated Log BCF (upper trophic) =  1.542  (BCF = 34.81 L/kg wet-wt)
   Estimated Log BAF (upper trophic) =  1.542  (BAF = 34.81 L/kg wet-wt)
   Estimated Log BCF (mid trophic)   =  1.365  (BCF = 23.15 L/kg wet-wt)
   Estimated Log BAF (mid trophic)   =  1.365  (BAF = 23.17 L/kg wet-wt)
   Estimated Log BCF (lower trophic) =  1.310  (BCF = 20.42 L/kg wet-wt)
   Estimated Log BAF (lower trophic) =  1.311  (BAF = 20.46 L/kg wet-wt)

Arnot-Gobas BCF & BAF Methods (assuming a biotransformation rate of zero):
   Estimated Log BCF (upper trophic) =  1.560  (BCF = 36.27 L/kg wet-wt)
   Estimated Log BAF (upper trophic) =  1.582  (BAF = 38.21 L/kg wet-wt)
```

10.4.2 Measured partition coefficient and bioaccumulation test data

The octanol-water-partitioning coefficient (log P_{OW}) for the active substance captan and its relevant metabolites THPAM (soil, surface water) and THPI (soil, surface water) were experimentally determined. The measured log P_{OW} values were considered acceptable. The log P_{OW} of the active substance captan was determined to be between 2.50 and 2.52. The measured log P_{OW} values were shown to be comparable to the estimated log P_{OW} for captan (2.85, further detailed see 10.4.1).

The log P_{OW} determined for the metabolite THPAM and THPI were – 0.40 and 0.22, respectively.

No experimentally determined log P_{OW} was available for the metabolite THPAI (sediment). Hence, the log P_{OW} was determined using the US EPA softwate KOWWIN (EPIWEB 4.1). Log P_{OW} for the metabolite THPAI see 10.4.1.

Even though the log P_{OW} of captan is below 3 two fish bioconcentrations studies (Anonymous, 1988a and b) were conducted in which the bioconcentrations fator and the bioaccumulation potential of [^{14}C]-labelled captan were measured in bluegill (*Lepomis macrochirus*). The steady-state bioconcentrations factors (BCF) were estimed in whole fish was 250 (Anonymous, 1988a). Uptake residues were rapidly and nearly 89 to 94% elimated from whole fish within the 14-day depuration phase.

However, during the peer-review of the active substance the validity and reliability of the fish bioconcentration studies (Anonymous, 1988 a and b) were challenged because of several deficiencies identified in the studies.

In the fish bioconcentration study by Anonymous (1988a) the validity criterium according to the current test guideline (OECD 305, 2012) regarding the stability of the test substance during the uptake phase was not met. Further, the study was conducted with only one test concentration instead of two test concentrations. Further deficiencies were the lack of information on the lipid content of the fish and the lack of detailed information on the environmental test conditions (temperature, pH, dissolved oxygen) and information on residues and metabolites.

In the fish bioconcentration study by Anonymous (1988b) all validity criteria according to the current test guideline (OECD 305, 2012) were met. However, the study was conducted with only one test concentration instead of two test concentrations. Further deficiencies were the lack of information on the lipid content of the fish and the lack of detailed information on the environmental test conditions (temperature, pH, dissolved oxygen) and information on residues and metabolites.

The studies were considered valid and reliable and it was agreed on a $BCF_{steady\text{-}state}$ of 250 for the active substance captan.

Overall, the results of the studies ($BCF_{stead\text{-}state}$ = 250) and the log P_{OW} of < 3 indicate a low concern on the bioaccumulation of captan in aquatic animals. The information derived from the BCF estimation (see 10.4.1) confirm this conclusion.

10.5 Acute aquatic hazard

Robust study summaries (all studies submitted) are provided in Annex II (Ecotoxicology AS and PPP) to this CLH report.

Table 58: Summary of relevant information on acute aquatic toxicity

Method	Species	Test material	Test condition	Exposure time	Results [1] [mg a.s./L]	Remarks	Reference
OECD 203 (1992)	*Salmo trutta* Brown trout	Captan Batch #: 94138737 Purity: 95.6%	Static	4 h 24 h 96 h	LC_{50} = 0.0511 mm LC_{50} = 0.0246 mm LC_{50} = 0.0913 im	The brown trout was identified to be the most sensitive fish species. The acute fish study was not considered valid and reliable because no appropriate exposure throughout the test duration was maintained. For the higher risk assessment (refined exposure) a 96 h LC_{50} was calculated based on initial measured concentration. In addition, for classification purposes a 4 h and 24 h LC_{50} based on geometric mean measured concentrations were derived.	Anonymous (2016a)
OECD 203 (1984)	*Oncorhynchus mykiss* Rainbow trout	83% WP formulation Batch #: A00634 Purity: 84.62%	Flow-through	96 h	LC_{50} > 0.036 mm	The acute fish toxicity study was conducted with an 83% WP formulation.	Anonymous (1993a)
OECD 203 (1992)	*Oncorhynchus mykiss* Rainbow trout	83% WP formulation Batch #: 720977 Purity: 83%	Flow-through	96 h	LC_{50} = 0.0147 mm	The acute fish toxicity study was conducted with an 83% WP formulation.	Anonymous (1995)
OECD 203 (1992)	*Oncorhynchus mykiss* Rainbow trout	Metabolite THPI Purity: 96%	Static	96 h	LC_{50} > 120 nom	-	Anonymous (1994)
OECD 203 (1992)	*Oncorhynchus mykiss* Rainbow trout	Metabolite THPAM Purity: 95%	Semi-static	96 h	LC_{50} > 120 nom	-	Anonymous (1995)
OECD 202 (1984)	*Daphnia magna* Waterflea	Merpan 80 WDG Batch #: 4722 AA Purity: 79.6%	Semi-static	48 h	EC_{50} = 0.289 mm	The acute toxicity study with daphnids was conducted with an 80% WDG formulation.	Anonymous (1996)
OECD 202 (1984)	*Daphnia magna* Waterflea	Metabolite THPI Purity: 96%	Static	48 h	EC_{50} > 120 nom	-	Anonymous (1994)
OECD 202 (1984)	*Daphnia magna* Waterflea	Metabolite THPAM Purity: 95%	Static	48 h	EC_{50} = 220 nom	-	Anonymous (1995)

OECD 201 (2011) EC C.3 (2009)	*Raphidocelis subcapitata* Green algae	Captan Batch #: 95138738 Purity: 95.8%	Static	72 h	E_rC_{50} = 0.660 $_{mm}$ E_yC_{50} = 0.432 $_{mm}$	-	Anonymous (2016c)
OECD 201 (2011) EC C.3 (2009)	*Raphidocelis subcapitata* Green algae	Captan 80 WDG Batch #: 95131119/3 Purity: 79.1%	Static	72 h	E_rC_{50} = 0.780 $_{mm}$ E_yC_{50} = 0.440 $_{mm}$	The algae toxicity study was conducted with an 80% WDG formulation	Anonymous (2016d)
OECD 201 (1984)	*Raphidocelis subcapitata* Green algae	83% WP formulation Batch #: A00634 Purity: 84.62%	Static	72 h	E_rC_{50} = 0.316 $_{mm}$ E_yC_{50} = 0.154 $_{mm}$	The algae toxicity study was conducted with an 80% WDG formulation	Anonymous (1994)
OECD 201 (1984)	*Selenastrum capricornutum* Green algae	Metabolite THPI Purity: 96%	Static	72 h	E_rC_{50} > 180 $_{nom}$ E_yC_{50} > 180 $_{nom}$	-	Anonymous (1994)
OECD 201 (1984)	*Raphidocelis subcapitata* Green algae	Metabolite THPI Batch #: 279-071-02 Purity: 98.5%	Static	72 h	E_rC_{50} > 100 $_{nom}$ E_yC_{50} > 100 $_{nom}$	-	Anonymous (2016a)
OECD 201 (1984)	*Selenastrum capricornutum* Green algae	Metabolite THPAM Batch #: 15184-161 Purity: 95%	Static	72 h	E_rC_{50} = 41 $_{nom}$ E_yC_{50} = 33 $_{nom}$	-	Anonymous (1995)
OECD 201 (1984)	*Raphidocelis subcapitata* Green algae	Metabolite THPAM Batch #: 516-156-00 Purity: 98.1%	Static	72 h	E_rC_{50} = 154 $_{mm}$ E_yC_{50} = 107 $_{mm}$	-	Anonymous (2016b)

[1] Indicate if the results are based on mean measured (mm), initial measured (im) or on nominal (nom) concentrations.

10.5.1 Acute (short-term) toxicity to fish

Based on the available acute toxicity data the fish were identified to be the most sensitive group of aquatic organisms. The active substance captan has an acute toxic mode-of-action in fish, i.e. mortality of fish due to the irritation of the gill membranes.

Acute toxicity studies with several different fish species were submitted by the applicant. The 96 h acute tests were conducted under static test conditions to take into account more realistic exposure conditions due to the rapid degradation of captan in the water sediment system. Taking into account the available studies the trouts (i.e. the brown trout) were observed to be the most sensitive fish species.

However, the fish acute toxicity tests were not considered valid and reliable because of the instability of the test substance. The active substance captan degrades rapidly in the water sediment system. The hydrolysis of captan is highly dependent on the pH value and the temperature of the test medium. The DT_{50} of captan was determined to be between 3.6 and 8.3 minutes at pH 9 (20°C), and between 11.0 and 18.8 hours at pH 5 (20 °C). At a neutral pH value, the DT_{50} is in a range of 2.6 and 49 hours (20 °C).

While it was agreed that the exposure to aquatic organisms is short-time due to the fast hydrolysis of captan, the acute toxicity studies were evaluated to be not valid and reliable because the exposure of the test substance was not maintained throughout the test period. Further, the analytical measurments were not sufficient to express the endpoints in terms of mean measured concentrations as recommended according to the OECD test guideline 203. Hence, in the absence of analytically measured concentrations at least at the start and end of test, no valid interpretation can be made and hence the test should be considered as invalid for classification purposes.

Hence, no valid Tier 1 acute toxicity study with the active substance captan is available for classification purposes. However, acute toxicity studies with the rainbow trout (*Oncorhynchus mykiss*) conducted with an 83% WP formulation are available. The studies were conducted under flow-through test conditions and the endpoints were expressed in terms of mean measured concentraitons. The relevant Tier 1 endpoint based on the acute toxicity study by Anonymous (1995), resulting in a 96 h LC_{50} of 0.0147 mg a.s./L $_{mm}$.

In addition, the acute fish study by Anonymous (2016a) was considered reliable to be used in a higher tier risk assessment. In the study conducted with the sensitive species the brown trout (*Salmo trutta*) the concentrations of the active substance captan in the test medium was analysed at 0 h and after 4 h of exposure. For one test concentration samples were taken at several sampling dates within 24 hours. Samples were analysed at test start (0 h), after 0.5 h, 1 h, 4 h, 10 h and 24 hours. Based on these analytical measurments an exposure profile could be determined for the acute study.

Based on the available information LC_{50} values after 4 h, 24 h and 96 h of exposure were calculated. Considering the static test regime and the rapid degradation of the active substance captan no reliable 96 h LC_{50} value based on geomean measured concentrations could be calculated because of the lack of appropriate analytical measurments. However, it was agreed during the peer-review to base the 96 h LC_{50} on initial measured concentrations and to use the study as a refined exposure study (Tier 2C). Hence, for the risk assessment a 96 h LC_{50} of 0.0913 mg a.s./L (based on initial measured concetrations) was used.

However, for classification purposes this endpoint is not considered reliable because no appropriate exposure throughtout the test duration was maintainted. Hence, a 4 h and 24 h LC_{50} value was calculated based on the available analytical measurements.

The 4 h LC_{50} was determined based on the geometric mean concentrations after 0 h and after 4 h of exposure. The measured concentrations after 4 h were greater than the LOQ.

The 24 h LC_{50} was determined based on the geometric mean cocentrations after 0 h and 24 h of exposure. However, analytical measurements for 24 h are only available for one test concentration (i.e. 66.1 µg a.s./L). Therefore, the measured concentrations after 24 hours were calculated taking into account the degradation of captan observed in the 66.1 µg a.s./L treatment group. Detailed information on the analytical measurments see Table 59 and Table 60.

Table 59: Analytical mesaurments for the treatment rate 66.1 µg a.s./L (Anonymous, 2016a)

Nominal concentrations [µg ai/L]	Measured concentrations of captan [µg ai/L], (% of nominal concentrations)				
	0.5 h	1 h	4 h	10 h	24 h
66.1	78.8 (119%)	74.8 (113%)	38.7 (59%)	12.0 (18%)	2.55 (3.9%)

Table 60: Geometric mean measured concetrations (Anonymous, 2016a)

0h [µg ai/L]	4h [µg ai/L]	24h [µg ai/L]*	Geomean concentrations [µg ai/L]
15.7	10.6	0.6	4.64
36.8	24.6	1.4	10.82
66.9	38.7	2.5	18.64
129	60.1	4.9	33.62
278	163	10.6	78.32

* Assuming 3.9% of the initial measured concentrations (0 h)

Based on the geometric mean measured concentrations a 4 h LC_{50} of 0.051 mg a.s./L was determined. However, the reliability of the endpoint is low considering that no confidence interval could be calculated due to the steep dose response. However, it can be assumed that the 4 h LC_{50} is greater than 0.034 mg a.s./L (0% mortality) and smaller than 0.078 mg a.s./L (100% mortality).

The 24 h LC_{50} was determined based on predicted mean measured concentrations based on the degradation observed in one test concentration. The 24 h LC_{50} was calculated to be 0.025 mg a.s./L (95% C.I. 0.020776 – 0.029636 mg a.s./L).

While this endpoints are not considered appropriate to be used in the risk assessment, they might be considered as additional information for classification purposes.

10.5.2 Acute (short-term) toxicity to aquatic invertebrates

Acute toxicity tests with *Daphnia magna* were conducted with the active substance captan. However, the studies were assessed to be not reliable because of the rapid degradation of captan in the test medium, an exposure throughout the study duration could not be maintained.

Further acute toxicity test with *Daphnia magna* were conducted with the formulation Merpan 80 WDG (Anonymous, 1996) and an 83% WP formulation (Anonymous, 1993). For both studies no reliable endpoint could be derived due to the lack of analytical verification of the active substance.

However, for the study by Anonymous (1996), which was conducted under semi-static test conditions an endpoint was derived based on the availbale data. Analytical measurments were only conducted in three of the nine test concentrations (see Table 61).

Table 61: Measured concentrations of captan (Anonymous, 1996)

Nominal [mg/L]	0 h [mg ai/L]	24 h (old) [mg ai/L]	24 h (new) [mg ai/L]	48 h (old) [mg ai/L]	Geomean [mg ai/L]	% nominal
0.064	0.065	0.001	0.060	0.001	0.007	10.383
0.501	0.433	0.004	0.470	0.002	0.036	7.130
3.980	3.860	0.060	4.070	0.150	0.613	15.407
					Mean:	**10.97**

Even though the analytical measurments were not conducted according to the OECD test guideline, a 48 h endpoint based on geomtetric mean measured concentrations was calculated. The endpoint was determined taking into account predicted mean measured concentrations based on the available analytical measurements was determined (see Table 62).

Table 62: Predicted concentrations of captan (Anonymous, 1996)

Nominal [mg ai/L]	Geomean measured [mg ai/L]
0.032	0.003
0.064	0.007 *
0.127	0.014
0.247	0.027
0.501	0.036 *
0.995	0.109
1.990	0.218
3.980	0.613 *
7.960	0.873

* Measured values

Based on the predicted geometric mean concentrations of captan an endpoint of 0.289 mg a.s./L was derived.

Overall, no reliable acute endpoint for aquatic organisms despite of the formulation study by Anonymous (1996) with *Daphnia magna* is available. However, there are also some uncertainties considering the reliability of the study by Anonymous (1996). Further, it has to be taken into account that the endpoint derived form the study by Anonymous (1996) was not discussed during the peer-review of the active substance captan.

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

Toxicity studies with the green algae *Raphidocelis subcapitata* were conducted with the active substance captan and the formulation Captan 80 WDG and a 83% WP formulation. The studies were conducted under static test conditions; hence, no appropriate exposure could be maintained throughout the study duration of 72/96 hours.

Due to the lack of analytical verification of the test substance it was agreed during the peer-reivew of the active substance captan to express the endpoint based on geometric mean measured concentrations. As a pragmatic approach it was agreed to use the LOQ/2 to calculate the mean measured concentrations for the test concentrations below the LOQ.

The lowest endpoint for algae of 0.316 mg a.s./L (72 h E_rC_{50}) was derived from a study with the 83% WP formulation (Anonymous, 1994). For the active substance captan the lowest endpoint relevant for classification purposes was derived form a study by Anonymous (2016c). The 72 h E_rC_{50} for the green algae was 0.660 mg a.s./L, based on mean measured concentrations.

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

No toxicity data are available on other groups of aquatic organisms.

10.6 Long-term aquatic hazard

Robust study summaries (all studies submitted) are provided in Annex II (Ecotoxicology AS and PPP) to this CLH report.

Table 63: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Test condition	Exposure time	Results [mg a.s./] [1]	Remarks	Reference
OECD 210 (2013) US EPA OPPTS 850.1400	*Oncorhynchus mykiss* Rainbow trout	Captan 80 WDG Batch #: 94131283 Purity: 81.2%	Pulsed exposure (12 dosing events, 7 d interval)	95 d	NOEC = 0.2 $_{nom}$	The study was conducted with an 80% WDG formulation. No EC_{10} or EC_{20} values were determined considering that the reduction of hatchability, fry survival and growth was < 10% for all treatment groups.	Anonymous (2016)
OECD 211 (2012)	*Daphnia magna* Waterflea	Captan Batch #: 94138737 Purity: 95.8%	Pulsed exposure (4 dosing events, 7 d interval)	28 d	NOEC = 0.4 $_{nom}$	No EC_{10} or EC_{20} values were determined considering that the reduction of hatchability, fry survival and growth was < 10% for all treatment groups.	Anonymous (2017)
OECD 201 (2011) EC C.3 (2009)	*Raphidocelis subcapitata* Green algae	Captan Batch #: 95138738 Purity: 95.8%	Static	72 h	NOE_rC = 0.217 $_{mm}$ NOE_yC = 0.217 $_{mm}$	-	Anonymous (2016c)
OECD 201 (2011) EC C.3 (2009)	*Raphidocelis subcapitata* Green algae	Captan 80 WDG Batch #: 95131119/3 Purity: 79.1%	Static	72 h	NOE_rC = 0.293 $_{mm}$ NOE_yC < 0.293 $_{mm}$	The algae toxicity study was conducted with an 80% WDG formulation	Anonymous (2016d)
OECD 201 (1984)	*Raphidocelis subcapitata* Green algae	83% WP formulation Batch #: A00634 Purity: 84.62%	Static	72 h	NOE_rC = 0.077 $_{mm}$ NOE_yC = 0.077 $_{mm}$	The algae toxicity study was conducted with an 80% WDG formulation	Anonymous (1994)

[1] Indicate if the results are based on mean measured (mm), initial measured (im) or on nominal (nom) concentrations.

10.6.1 Chronic toxicity to fish

A refined exposure early life stage fish study (Anonymous, 2016) conducted with the rainbow trout (*Oncorhynchus mykiss*) was conducted to address the long-term risk to fish.

In the study, conducted with a 80% WDG formulation early life stages of fish were exposed to 12 dosing events, each separated by 7 days. Taking into account possible adverse effects on behaviour, growth and reproduction a NOEC of 0.2 mg a.s./L (based on nominal concentrations) was determined. During the test, the concentrations of captan were measured in test solution samples collected on day 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, 69, and 76. Additionally, on day 21, samples were collected approximately 1, 2, 4, and 10 hours after dosing. The rate captan concentrations declined immediately after a dosing event was established on Day 21.

In the study report the endpoint was expressed in terms of nominal concentrations which was considered acceptable as the the study was used as a refined exposure study in a higher tier risk assessment.

However, this endpoint (Tier 2C) is not considered appropriate for classification purposes as for classification standard Tier 1 endpoints should be taken into account. According to the OECD 210 test guideline the endpoint should be expressed relative to the geometric mean of the measured concentrations when the measured concentrations do not remain within 80-120% of the nominal concentrations. No Tier 1 endpoint based on geometric mean measured concentrations was provided in the study report.

10.6.2 Chronic toxicity to aquatic invertebrates

A refined exposure reproduction study (Anonymous, 2017) conducted with the *Daphnia magna* was conducted to address the long-term risk to aquatic invertebrates.

In the study, conducted with the active substance daphnids were exposed to 4 dosing events, each separated by 7 days. Taking into account possible adverse effects on reproduction and immobilisation a NOEC of 0.4 mg a.s./L (based on nominal concentrations) was determined.

During the d test, the concentrations of captan were measured in test solution samples collected on day 0, 7, 14, 21 and 28. Additionally, on day 7, samples were collected approximately 0.5, 1, 4, 10 and 24 hours after dosing. The rate captan concentrations declined immediately after a dosing event was established on Day 7.

In the study report the endpoint was expressed in terms of nominal concentrations which was considered acceptable as the the study was used as a refined exposure study in a higher tier risk assessment.

However, this endpoint (Tier 2C) is not considered appropriate for classification purposes as for classification standard Tier 1 endpoints should be taken into account. According to the OECD 211 test guideline the endpoint should be expressed in terms of the time-weighted mean when the measured concentrations do not remain within 80-120% of the nominal concentrations. No Tier 1 endpoint based on time-weighted mean was provided in the study report.

10.6.3 Chronic toxicity to algae or other aquatic plants

Toxicity studies with the green algae *Raphidocelis subcapitata* were conducted with the active substance captan and the formulation Captan 80 WDG and a 83% WP formulation. The studies were conducted under static test conditions; hence, no appropriate exposure could be maintained throughout the study duration of 72/96 hours.

Due to the lack of analytical verification of the test substance it was agreed during the peer-reivew of the active substance captan to express the endpoint based on geometric mean measured concentrations. As a pragmatic approach it was agreed to use the LOQ/2 to calculate the mean measured concentrations for the test concentrations below the LOQ.

The lowest endpoint for algae of 0.077 mg a.s./L (72 h NOE_rC) was derived from a study with the 83% WP formulation (Anonymous, 1994). For the active substance captan the lowest endpoint relevant for classification

purposes was derived form a study by Anonymous (2016c). The 72 h NOE_rC for the green algae was 0.217 mg a.s./L, based on mean measured concentrations.

10.6.4 Chronic toxicity to other aquatic organisms

No toxicity data are available on other groups of aquatic organisms.

10.7 Comparison with the CLP criteria

10.7.1 Acute aquatic hazard

- The most sensitive endpoint for fish is LC_{50} = 0.0147 mg/L for *Oncorhynchis mykiss*. The study was conducted with a 83% WP formulation under flow-through conditions. Reliable fish acute tocixity test with the active substance captan are not available; but a 24 h LC_{50} of 0.0246 mg a.s./L was determined for the most sensitive fish species, the brown trout (*Salmo trutta*).

  The most sensitive endpoint for aquatic invertebrates was *Daphnia magna* with an EC_{50} of 0.289 mg/L. The study was conducted with a 80% WDG formulation under semi-static conditions.

  The most sensitive endpoint for algae was derived for green algae (*Raphidocelis subcapitata*) conducted with a 83% WP formulation under static conditions. The E_rC_{50} was determined to be 0.316 mg a.s./L. Further, an algae study with active substance captan was available. The 72 h E_rC_{50} for the green algae *Raphidocelis subcapitata* was 0.660 mg a.s./L.

  Information on the composition of the formulations are provided in the confidential annex to the CLH report.

  Aquatic toxicity studies with the relevant metabolites THPI and THPAM are available but are not considered to be relevant for classification (LC_{50}/EC_{50} clearly > 1 mg/L).

- Based on the acute toxicity of captan to fish, daphnids and algae, the active substance is classified as acute aquatic hazard, category 1 (CLP criteria $LC_{50}/EC_{50} \leq 1$ mg/L). A M-factor of 10 is derived considering the high acute toxicity to fish.

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

- Based on the fish bioaccumulation study (Anonymous, 1988a) with *L. macrochirus* a BCF (whole fish) of 250 was determined, which indicate a low potential to bioaccumulate in the aquatic food chain. The substance Captan does not meet the CLP criterion (BCF ≥ 500) based on the measured fish BCF.
  In addition, the log P_{OW} of Captan is 2.5 which is below the CLP criterion of log P_{OW} > 4.

- The active substance is not readily biodegradable (Anonymous, 2015) in the 10 days window and within 28 days. Further, it was shown that captan is also not rapidly degradable based on the aerobic mineralisation in the surface water (DT_{50} < 1 h) and the results derived from the water sediment studies. In the water-sediment studies conducted in two aerobic natural systems under laboratory conditions it was shown that captan degraded very rapidly (DT_{50} < 1 d) to the metabolites THPI (DT_{50} = 4.7 d) and THPAM (DT_{50} = 13.6 d). Overall, in the water-sediment studies a DT_{50} of 1 day (geomean) was determined for the whole system. For the metabolites THPI and THPAM whole system DT_{50} values of 4.7 and 13.6 d were determined, respectively. The $DegT_{50}$ for the active substance captan and its metabolites THPI and THPAM is < 16 days; hence, the active substance and its metabolites THPI and THPAM are considered raoidly degradable in the aquatic environment.

- No reliable chronic toxicity data with the most sensitive species are available. According to the Regulation (EU) No 1272/2008 substances for which no adequate chronic toxicity data are available should be classified based on the acute toxicity data. Even though the 96 h LC_{50} for fish is below 1 mg/L no chronic classification is foreseen considering the rapdidly degredation of the active substance in the water-sediment system and the low potential for bioaccumulation (BCF ≤ 500, log $K_{OW} \leq 4$).

However, taking into account the available data on captan and the similar active substance folpet a precautionary chronic classification is proposed considering the following argumentation.
- A classification according to chronic aquatic hazard, category 3 (CLP criteria for rapidly degradable substances NOEC ≤ 0.1 mg/L) was determined based on the toxicity of captan to algae (*Raphidocelis subcapitata*, NOEC = 0.217 mg a.s./L).
- Taking into account the data for the similar (structure, acute toxicity, mode of action) active substance folpet a chronic classification for captan should be assumed. Folpet is classified as chronic aquatic hazard, cat. 1 (H410) based on a valid and reliable fish early life stage study conducted under flow-through test conditions (NOEC = 0.00881 mg folpet/L, CLP criteria for rapidly degradable substances NOEC ≤ 0.01 mg/L). A M-factor of 1 is derived considering the chronic toxicity to fish.
To further confirm the assumption of similarity between captan and folpet a read-across assessment was conducted using the QSAR Toolbox (OECD, vers. 4.5, 2021). A detailed overview of the read-across assessment is provided in the Annex of the CLH report (Category report, Prediction report, Data matrix). In the following a summary of the read-across assessment is provided.

Methodology:

A read-across assessment between captan and folpet was conducted using the OECD QSAR Toolbox (ver. 4.5.).

A a starting point captan (CAS No. 133-06-2) was considered as target substance. As target endpoints the acute and chronic toxicity endpoints for fish (standard fish species) were identified.

For profiling the following methods were considered:

Suitable methods	**Plausible methods**
Acute aquatic toxicity classification by Verhaar (modified)	Chemical elements
Acute aquatic toxicity MOA by OASIS	Groups of elements
Aquatic toxicity classification by ECOSAR	Hydrolysis half-life, Ka and Kb, pH 7-8 (Hyrodwin)
US-EPA New Chemical Categories	Hydrolysis half-life, pH 6.5-7.4
	Ionization at pH 1, 4, 7.4 and 9
	Lipinski Rule OASIS
	OECD HPV Chemical Categories
	Organic functional groups (nested, US EPA, Norbert Haider)
	Protein binding by OASIS, OECD
	Protein binding potency GSH
	Structural similarity
	Substance type

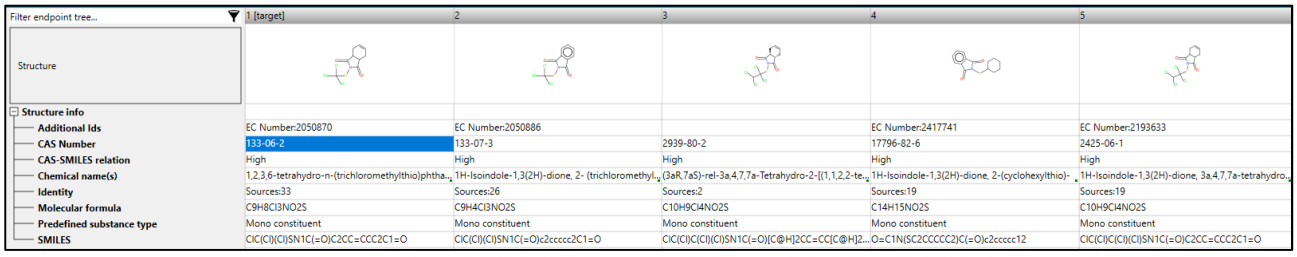
For data gathering the following databases were used:

Physical Chemical properties	ECHA REACH
Environmental Fate and Transport	ECHA REACH ECOTOX
Ecotoxicological Information	Aquatic ECETOC Aquatic Japan MoE Aquatic OASIS ECHA REACH ECOTOX Food TOX Hazard EFSA
Human Health Hazards	ECHA REACH ECOTOX

	Food TOX Hazard EFSA ToxCastDB ToxRefDB US-EPA

For the category definition the aquatic toxicity classification by ECOSAR was considered and as target categories the chemical categories “Imides” and “Thiophthalimides” were chosen.

In total four substances with a similar profile were identified, including folpet (CAS No. 133-07-3).



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Structure					
Structure info					
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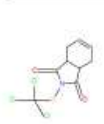
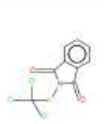
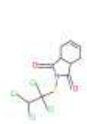
CAS Number	133-06-2	133-07-3	2939-80-2	17796-82-6	2425-06-1
CAS-SMILES relation	High	High	High	High	High
Chemical name(s)	1,2,3,6-tetrahydro-n-(trichloromethylthio)phtha...	1H-Isoindole-1,3(2H)-dione, 2- (trichloromethyl...	(3aR,7aS)-rel-3a,4,7,7a-Tetrahydro-2-[(1,1,2,2-te...	1H-Isoindole-1,3(2H)-dione, 2-(cyclohexylthio)-	1H-Isoindole-1,3(2H)-dione, 3a,4,7,7a-tetrahydro...
Identity	Sources:33	Sources:26	Sources:2	Sources:19	Sources:19
Molecular formula	C9H8Cl3NO2S	C9H4Cl3NO2S	C10H9Cl4NO2S	C14H15NO2S	C10H9Cl4NO2S
Predefined substance type	Mono constituent	Mono constituent	Mono constituent	Mono constituent	Mono constituent
SMILES	ClC(Cl)(Cl)SN1C(=O)C2CC=CCC2C1=O	ClC(Cl)(Cl)SN1C(=O)c2ccccc2C1=O	ClC(Cl)C(Cl)(Cl)SN1C(=O)[C@H]2CC=CC[C@H]2...	O=C1N(SC2CCCCC2)C(=O)c2ccccc12	ClC(Cl)C(Cl)(Cl)SN1C(=O)C2CC=CCC2C1=O

For the substances a number of data for fish are available (5 chemical and 149 data points). However, based on tha available data points a predition of an chronic endpoint is not feasable considering that most of the chronic endpoints were derived from acute or short-term toxicity studies; hence, a prediction would mainl be based on toxicity data from acute exposure.

Results:

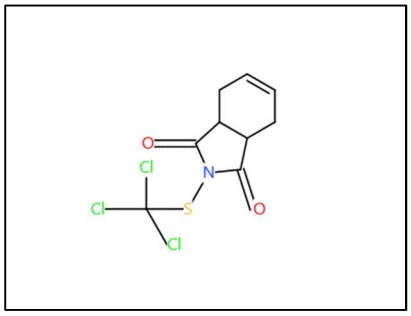
Taking into account the results from the read-across the substances were analysed considering different subcategories.

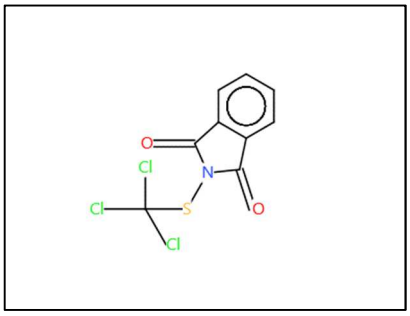
Filter endpoint tree...		1 [target]	2	4	5
Structure					
Structure info					
Additional Ids		EC Number:2050870	EC Number:2050886	EC Number:2417741	EC Number:2193633
CAS Number		133-06-2	133-07-3	17796-82-6	2425-06-1
CAS-SMILES relation		High	High	High	High
Chemical name(s)		1,2,3,6-tetrahydro-n-(t...	1H-Isoindole-1,3(2H)-...	1H-Isoindole-1,3(2H)-...	1H-Isoindole-1,3(2H)-...
Identity		Sources:33	Sources:26	Sources:19	Sources:19
Molecular formula		C9H8Cl3NO2S	C9H4Cl3NO2S	C14H15NO2S	C10H9Cl4NO2S
Predefined substance type		Mono constituent	Mono constituent	Mono constituent	Mono constituent
SMILES		ClC(Cl)(Cl)SN1C(=O)C...	ClC(Cl)(Cl)SN1C(=O)c2...	O=C1N(SC2CCCCC2)C...	ClC(Cl)C(Cl)(Cl)SN1C(=...
Parameters					
Physical Chemical Properties	2/27	M: 1.8 µm		M: ≥50÷≤50.5 µm	
Environmental Fate and Transport	2/35	M: 13 %		M: 16 %	
Ecotoxicological Information	4/2816	M: 600 mg/kg bdwt/d	M: 0.012 mg/L	M: 0.093 mg/L	M: 540÷3.48E+03 mg/...
Human Health Hazards	4/1246	M: 10 mg/kg bdwt/d	M: 9 mg/kg bdwt/d	M: 30 mg/kg bdwt/d	M: 0.54 mg/kg bdwt/d
Profiling					
Predefined					
OECD HPV Chemical Categories		Not categorized	Not categorized	Not categorized	Not categorized
Substance type		Discrete chemical	Discrete chemical	Discrete chemical	Discrete chemical
US-EPA New Chemical Categories		Imides (Acute toxicity)	Imides (Acute toxicity)	Imides (Acute toxicity)	Imides (Acute toxicity)
General Mechanistic					
Hydrolysis half-life (Ka, pH 7)(Hydrowi...		No value	No value	No value	No value
Hydrolysis half-life (Ka, pH 8)(Hydrowi...		No value	No value	No value	No value
Hydrolysis half-life (Kb, pH 7)(Hydrow...		No value	No value	No value	No value
Hydrolysis half-life (Kb, pH 8)(Hydrow...		No value	No value	No value	No value
Hydrolysis half-life (pH 6.5-7.4)		Extremely fast	Extremely fast	Extremely fast	Extremely fast
Ionization at pH = 1		Acidic [0.000, 10.000)	Acidic [0.000, 10.000)	Acidic [0.000, 10.000)	Acidic [0.000, 10.000)
Ionization at pH = 4		Acidic [0.000, 10.000)	Acidic [0.000, 10.000)	Acidic [0.000, 10.000)	Acidic [0.000, 10.000)
Ionization at pH = 7.4		Acidic [0.000, 10.000)	Acidic [0.000, 10.000)	Acidic [0.000, 10.000)	Acidic [60.000, 70.000)
Ionization at pH = 9		Acidic [0.000, 10.000)	Acidic [0.000, 10.000)	Acidic [0.000, 10.000)	Acidic [90.000, 100.000]
Protein binding by OASIS		Acylation	Acylation	Acylation	Acylation
Protein binding by OECD		Acylation	Acylation	Acylation	Acylation
Protein binding potency GSH		Not possible to classif...	Not possible to classif...	Not possible to classif...	Not possible to classif...
Endpoint Specific					
Acute aquatic toxicity classification by...		Class 5 (Not possible t...	Class 5 (Not possible t...	Class 5 (Not possible t...	Class 5 (Not possible t...
Acute aquatic toxicity MOA by OASIS		Basesurface narcotics	Basesurface narcotics	Basesurface narcotics	Basesurface narcotics
Aquatic toxicity classification by ECOS...		Imides	Imides	Imides	Imides
Empiric					
Chemical elements		Group 14 - Carbon C	Group 14 - Carbon C	Group 14 - Carbon C	Group 14 - Carbon C
Groups of elements		Halogens	Halogens	Non-Metals	Halogens
Lipinski Rule Oasis		Bioavailable	Bioavailable	Bioavailable	Bioavailable
Organic functional groups		Alkene moiety	Alkyl halide	Aryl	Alkene moiety
Organic functional groups (nested)		Alkyl halide	Alkyl halide	Benzamide	Overlapped groups
Organic functional groups (US EPA)		Aliphatic Carbon [C]	Aliphatic Carbon [C]	Aliphatic Carbon [CH]	Aliphatic Carbon [C]
Organic functional groups, Norbert Ha...		Alkene	Alkyl chloride	Aromatic compound	Alkene
Structure similarity		[90%,100%]	[70%,80%)	[60%,70%)	[90%,100%]

Based on the profiling data it could be shown that captan and folpet are similar considering the US EPA Chemical Categories (Imides), the general mechanistic properties (protein binding, Ioinizitation and hydrolysis half-life) and the endpoint specific properties like acute aquatic toxicity MoA (basesurface narcotics or aquatic toxicity classification). Regarding the empiric data there are similarities in organic functional groups, chemical elements and groups of elements. The structural similarity (based on

PubChem features) of folpet does not reach the target structural similarity of > 90% but was shown to be > 70%.

Captan: Folpet:





Conclusion:

The similarity between captan and folpet regarding mechanistic properties, endpoint specific properties (MoA) and empiric properties is considered to be sufficient, even though the structural similarity is only 70-80% compared to captan. However, the observed differences in the structur of captan and folpet (cyclic compound) are not considered to have an impact on the toxicity of the active substance considering the MoA as basesurface narcotic.

Overall, captan is considered to be similar to folpet considering the MoA and the chemical elements and groups of elements; hence, the study used for chronic classification of folpet might also be considered for captan for which no appropriate chronic data with fish are available. Therefore, a classification according to chronic aquatic hazard, category 1 (410) based on the read-across assessment is proposed.

CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Hazard pictogram		Environment
Hazard class and category:	Hazardous to the aquatic environment Acute Hazard Category 1, M-factor = 10 Chronic Hazard Category 1, M-factor = 1	
Signal word	Warning!	
Hazard statement:	H400	Very toxic to aquatic life
	H410	Very toxic to aquatic life with long lasting effects
Precautionary statements - Prevention	P273	Avoid release to the environment
Precautionary statements - Response	P391	Collect spillage
Precautionary Statement Disposal	P501	Proper disposal of contents/container

11 EVALUATION OF ADDITIONAL HAZARDS

11.1 Hazardous to the ozone layer

Hazard class not assessed in this dossier.

11.1.1 Short summary and overall relevance of the provided information on ozone layer hazard

11.1.2 Comparison with the CLP criteria

11.1.3 Conclusion on classification and labelling for hazardous to the ozone layer

No harmonised classification is proposed by the RMS due to data lacking.

Captan is not listed in the Annexes to the Montreal Protocol. Therefore, a classification is not possible regarding the hazards to the ozone layer.

12 ADDITIONAL LABELLING

None.

13 REFERENCES

Reference list with unpublished studies is provided in a separate confidential annex to this CLH report.

Arce G T, Gordon E B, Cohen S M, and Singh P, 2010. Genetic toxicology of folpet and captan. Critical Reviews in Toxicology 40 (6):546-574.

Becker R A, Ankley G T, Edwards S W, Kennedy S W, Linkov I, Meek B, Sachana M, Segner H, Van der Burg B, Villeneuve D L, Watanabe H and Barton-Maclaren T S, 2015. Increasing scientific confidence in adverse outcome pathways: application of tailored Bradford-Hill considerations for evaluating weight-of-evidence. Regulatory Toxicology and Pharmacology, 72, 514-537.

Berthet A, Bouchard M, and Danuser B, 2012b. Toxicokinetics of captan and folpet biomarkers in orally exposed volunteers. Journal of Applied Toxicology, Vol. 32, 194-20. (Company file: R-31005).

Berthet A, Bouchard M, Vernez D, 2011. Toxicokinetics of captan and folpet biomarkers in dermally exposed volunteers. Journal of Applied Toxicology, 32, 202-209. (Company file: R-29191).

Berthet A, Heredia-Ortiz R, Vernez D, Danuser B and Bouchard M, 2012a. A detailed urinary excretion time course study of captan and folpet biomarkers in workers for the estimation of dose, main route-of-entry and most appropriate sampling and analysis strategies. Ann. Occup. Hyg., Vol. 56(7), 815-828.

Bhat VS, Cohen SM, Gordon EB, Wood CE, Cullen JM, Harris MA, Proctor DM, Thompson CM. An adverse outcome pathway for small intestinal tumors in mice involving chronic cytotoxicity and regenerative hyperplasia: a case study with hexavalent chromium, captan, and folpet. Crit Rev Toxicol. 2020 Sep;50(8):685-706.

Carere A, Ortali V A, Cardamone G, Torracca A M and Raschetti R, 1978. Microbiological mutagenicity studies of pesticides *in vitro*. Instituto Superiore di Sanita, Italy. Mutation Research, 57, 277 - 286. (Company file: R-2615/TMN-806).

Chappell, G. A., Rager, J. E., Wolf, J., Babic, M., LeBlanc, K. J., Ring, C. L., Harris, M. A. and Thompson, C. M. Comparison of gene expression responses in the small intestine of mice following exposure to 3 carcinogens using the S1500+ gene set informs a potential common adverse outcome pathway. Toxicol Pathol. 2019;47(7):851-64.

Chidiac P and Goldberg M T, 1986. Lack of inductions of nuclear aberrations by captan in mouse duodenum. Environmental mutagenesis 9, 297-306 (Company file: R-6346/TMN-0833).

Collins T F X, 1972. Dominant lethal assay. I. Captan. *Food Cosmet. Toxicol* **10**, 353-361.

EFSA et al, 2020, Peer review of the pesticide risk assessment of the active substance captan. EFSA Journal 10.2903/j.efsa.2020.6230

Epstein S S, Arnold E, Andrea, J, Bass W and Bishop Y, 1972. Detection of mouse mutagens by dominant lethal assay in the mouse. Toxicology and Applied Pharmacology, ***23****, 288-235.*

Feng J and Lin B, 1987. Cytogenetic effects of an agricultural antibiotic, captan, on mouse bone marrow and testicular cells. Environmental Research 43, 359 - 363.

Fry S M and Ficsor G, 1978. Cytogenetic test of captan in mouse bone marrow. Mutation Research 58, 111-114.

Heredia-Ortiz R, Bouchard M, 2012. Toxicokinetic modelling of captan fungicide and its tetrahydrophthalimide biomarker of exposure in humans. Toxicology Letters, Vol. 213(1), 27-34.

Kluxen F.M., Koenig C.M., 2021. Inhalation Toxicity of Captan and Folpet accepted manuscript submitted to Regulatory Toxicology and Pharmacology

O'Neill P J, Forbes N L and Hsie AW, 1981. Cytotoxicity and mutagenicity of the fungicides captan and folpet in cultured mammalian cells (CHO/HGPRT system). Oak Ridge National Laboratory. Environmental Mutagenesis 3, 233 - 237 (Company file: R-3487/TMN-0810).

Tezuka H, Teramoto S, Kaneda M, Henmi R, Murakami N and Shirasu Y. 1978: Cytogenetic and dominant lethal studies on captan. Institute of Environmental Toxicology, Tokyo, Japan. Mutation Research (1978) 57, pp 201-207. (Company file: R-1666/TMN-0824).

Tezuka H, Ando N, Suzuki R, Terahata M, Moriya M and Shirasu Y, 1980: Sister-chromatid exchanges and chromosomal aberrations in cultured Chinese hamster cells treated with pesticides positive in microbial reversion assays. Mutation Research (1980) 78, pp 177-191. (Company file: R-2715/TMN-0816).

Thompson, C. M., Wolf, J. C., McCoy, A., Suh, M., Proctor, D. M., Kirman, C. R., Haws, L. C. and Harris, M. A. Comparison of toxicity and recovery in the duodenum of B6C3F1 mice following treatment with intestinal carcinogens captan, folpet, and hexavalent chromium. Toxicol Pathol. 2017;45(8):1091-101.

Wagner Palshaw M, 1980. An epidemiologic study of mortality within a cohort of captan workers. Stauffer Chemical Company. (Company file: R-4641/TMN-0881). Unpublished.

Wagner Palshaw M, 1987. An epidemiologic study of mortality within a cohort of captan workers. Addendum I. Stauffer Chemical Company Report No. 87-2 (Company file: R-4641/TMN-0881). Unpublished.

14 ANNEXES

Annex I: Human Health

Annex II: Ecotoxicology (AS) and (PPP)

Annex I: Fate

Confidential Annex

QSAR (Read-Across): Category Report