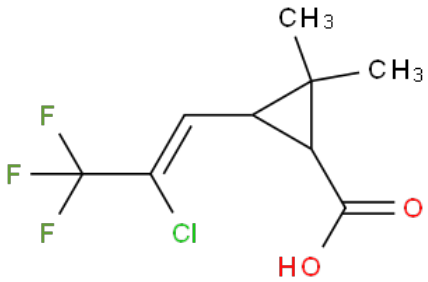
Miljøministeriet
Miljøstyrelsen

Fastsættelse af kvalitetskriterier for vandmiljøet

Cyhalothrinsyre

CAS nr.
76023-99-9 (S-isomer)
72748-35-7 (R-isomer)
68127-59-3 (blanding af S- og R-isomer)

$C_9H_{10}ClF_3O_2$



Vandkvalitetskriterium	$VKK_{ferskvand}$	6,2 µg/l
Vandkvalitetskriterium	$VKK_{saltvand}$	0,62 µg/l
Korttidsvandkvalitetskriterium	$KVKK_{ferskvand}$	62 µg/l
Korttidsvandkvalitetskriterium	$KVKK_{saltvand}$	6,2 µg/l
Sedimentkvalitetskriterium	$SKK_{ferskvand\ EqP}$	0,045 mg/kg tørvægt (5% OC) 0,89 mg/kg tørvægt x foc
Sedimentkvalitetskriterium	$SKK_{saltvand\ EqP}$	0,0045 mg/kg tørvægt (5% OC) 0,089 mg/kg tørvægt x foc
Biota-kvalitetskriterium, sekundær forgiftning	$BKK_{sek.forgiftn.,ferskvand}$	0,544 mg/kg musling, ferskvand, vådvægt
Biota-kvalitetskriterium, human konsum	HKK	4,09 mg/kg vådvægt biota

August 2024

Indholdsfortegnelse

Forord

Et kvalitetskriterium i vandmiljøet er det højeste koncentrationsniveau, ved hvilket der skønnes, ikke at forekomme uacceptable negative effekter på vandøkosystemer.

Miljøstyrelsen udarbejder kvalitetskriterier for miljøfarlige forurenende stoffer i vandsøjlen, i sediment, i dyr og planter (biota) og for human konsum.

Miljøministeriet bruger kvalitetskriterierne som fagligt grundlag for fastsættelsen af miljøkvalitetskrav, hvorved der forstås den endelige koncentration af et bestemt forurenende stof i vand, sediment eller biota, som ikke må overskrides af hensyn til beskyttelsen af miljøet og menneskers sundhed.

Metodikken, der anvendes til udarbejdelse af kvalitetskriterier er harmoniseret i EU og baserer sig på vandrammedirektivet (EU, 2000), EU's vejledning til fastsættelse af kvalitetskriterier i vandmiljøet (EU, 2018) og Miljøstyrelsens vejledning til fastsættelse af vandkvalitetskriterier (Miljøstyrelsen, 2004). Metodikken er endvidere i overensstemmelse med EU's vejledning til risikovurdering under REACH-forordningen (EU, 2008).

Den sidste litteratursøgning er foretaget den 07-05-2024.

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Faglig kvalitetssikring: Hans Sanderson, Institut for Miljøvidenskab, Aarhus Universitet
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English Summary and conclusions

Cyhalothrin (or cyhalothric) acid (CAS no 68127-59-3, 72748-35-7, 76023-99-9) is an intermediate in the formation of lambda and gamma cyhalothrin, which are the active ingredients in a number of current commercial highly potent synthetic pyrethroid insecticide formulations (Bownik et al., 2019; Jvxingchemical (23-04-2023); fluoridealert (23-04-2023)).

Cyhalothrin acid is also a known environmental transformation product of the pyrethroid pesticide tefluthrin (PubChem (Tefluthrin)). EFSA (2010) found cyhalothrin acid (compound Ia (R119890 or PP890): 1R,3R;1S,3S)-3-((Z)-2-chloro3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylic acid) in a water-sediment study. Compound Ia was found in levels up to 22 % of applied radioactivity (AR) in water and 7 % AR in sediment. Compound Ia exhibited low to moderate persistence in soil, and very high to high mobility in soil.

Cyhalothrin acid is registered under the REACH Regulation and is manufactured in and/or imported to the European Economic Area, for intermediate use only. It is used at industrial sites and in manufacturing. Different process categories are stated by ECHA: PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions. PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions. PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities (ECHA 25-04-2023).

No information of produced and used tonnage are available.

Cyhalothrin acid is not naturally occurring in the environment.

Environmental Quality Standards (EQS) for the aquatic environment were calculated for cyhalothrin acid in the water column, sediment, biota and for human health. Derivation of environmental quality standards (EQS) for the aquatic environment follows the EU Guidance Document No. 27. Technical Guidance Document (TGD) for Deriving Environmental Quality Standards (TGD, 2018).

AA-EQS for water and MAC-EQS for water
Experimental data for fresh- and saltwater are combined with QSAR estimates for acute toxicity to fish. This yields a full base set, with at least one short-term LC50/EC50 value for the three trophic levels; fish, invertebrates and algae, in addition to one long-term EC10 for algae. With only one long-term result from algae the short-term data is used to derive both AA-EQS and MAC-EQS. Following the experimental data algae represents to lowest EC50 of 6.2 mg/l.

With an assessment factor (AF) of 1000 and 10,000 AA-EQS was calculated to 6.2 and 0.62 µg/l for freshwater and saltwater, respectively.

And for MAC-EQS an AF of 100 and 1000 was used to calculate the values of 62 and 6.2 µg/l for freshwater and saltwater, respectively.

QS for sediment
There is no evidence of accumulation in the sediment or suspicion of high toxicity to sediment dwelling organisms. However, the mean log Kow value is larger than 3, therefore QS for sediment is calculated with the equilibrium partition (EqP) method, as there are no experimental data for sediment dwelling organisms. The used default values in the TGD (2018) comprise an organic content (foc) of 5 %.

QS for secondary poisoning
The lowest experimental LD50 value of 500 mg/kg bw for rat is used in a deterministic analysis, where the energy normalized toxicity value is calculated from method A, as LD50 is expressed as a dose.

In the study the rats were only administrated once with a dose of either 200 or 2000 mg/kg bw and afterwards observed for 14 days. Therefore, an assessment factor of 100 (TGD, Table 9) was used. With an average bodyweight of 222 g $QS_{sec.\ pois.,freshwater}$ was calculated to 0.544 mg/kg mussel wet weight.

QSAR data on BCF show that cyhalothrin acid does not bioaccumulate, furthermore there is no evidence of biomagnification. Therefore, no specific QS is calculated for the marine environment for the protection of top predators.

QS for human health
According to TGD (2018) (section 2.4.3.2), the hazard statement for CAS No. 76023-99-9 "H302, "Harmful if swallowed", is a trigger for calculating a quality criterion for human consumption of aquatic organisms (HKK) if the substance is also bioaccumulative. The latter criterion is not met. However, the hazard statement H302 and the high log K_{ow} can be used conservatively to calculate a value for human consumption HKK.

Following TGD (2018, page 91 and 73) a $QS_{biota,\ hh\ food}$ was calculated to 4.09 mg/kg wet weight using a NOEAL of 200 mg/kg bw with uncertainty factors of 6 and 10 to extrapolate from sub-acute to chronic and considering large dose spacing, respectively. This was used to calculate a TL_{hh}, since no ADI, TDI or RfD were available.

QS_{water} based on $QS_{sec.\ pois.}$ and $QS_{human\ health}$
Reverse calculation of QS for biota to a water concentration gives a value of 172 µg/l that is higher than AA-EQS and MAC-EQS for water, respectively. The latter values will therefore also protect from secondary poisoning through the food chain.

In conclusion, the following EQS for the aquatic environment have been derived for cyhalothrin acid:

$AA\text{-}EQS_{freshwater}$ = 6.2 µg/l
$AA\text{-}EQS_{saltwater}$ = 0.62 µg/l
$MAC\text{-}EQS_{freshwater}$ = 62 µg/l
$MAC\text{-}EQS_{saltwater}$ = 6.2 µg/l

$QS_{sediment,\ freshwater}$ = 0.045 mg/kg dry weight (5 % OC)
= 0.89 mg/kg x f_{oc}
$QS_{sediment,\ saltwater}$ = 0.0045 mg/kg dry weight (5 % OC)
= 0.089 mg/kg x f_{oc}
$QS_{sec.\ pois.freshwater}$ = 0.544 mg/kg mussels wet weight
$QS_{human\ health}$ = 4.09 mg/kg wet weight

1 Indledning

Cyhalothrinsyre (CAS nr. 68127-59-3, 72748-35-7, 76023-99-9) anvendes til produktion af lambda- og gamma-cyhalothrin, som er aktivstoffer i en række nuværende pyrethroid-insekticid-produkter (Bownik et al., 2019; Jvxingchemical (23-04-2023); Fluoridealert (23-04-2023)).

Cyhalothrinsyre vides endvidere at være et nedbrydningsprodukt i miljøet af pyrethroid-pesticidet tefluthrin (PubChem (Tefluthrin)).

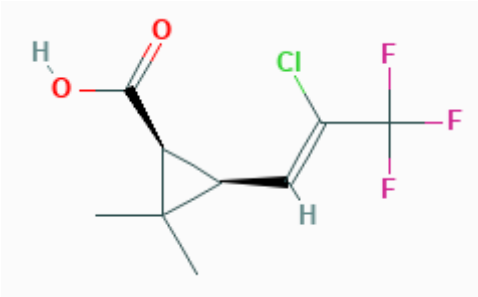
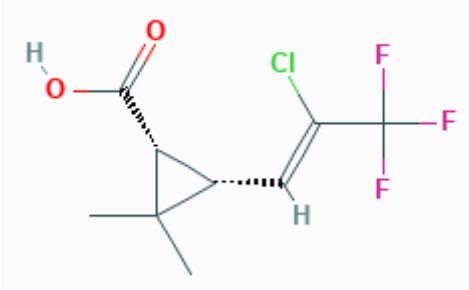
Der foreligger ingen informationer om producerede og anvendte mængder af cyhalothrinsyre.

Cyhalothrinsyre er registreret i REACH's regulering og er produceret i og/eller importeret til det Europæiske Økonomiske Samarbejdsområde (EØS)[1]. Cyhalothrinsyre er registreret udelukkende til anvendelse i følgende kemiske processer og aktiviteter i industrien: i lukkede processer uden sandsynlighed for eksponering i arbejdsmiljøet, i lukkede processer til syntese af kemikalier i dertil indrettet faciliteter. Frigivelse til miljøet kan ske ved industriel anvendelse ved produktion/syntese af andre stoffer (ECHA, 25-04-2023).

Identiteten af cyhalothrinsyre fremgår af tabel 1.1.

[1] Det Europæiske Økonomiske Samarbejdsområde (EØS) omfatter EU's medlemslande samt Island, Liechtenstein og Norge. Aftalen, som trådte i kraft i 1994, giver disse lande adgang til EU's indre marked uden fuldt medlemskab. EØS dækker fri bevægelighed for varer, tjenesteydelser, personer og kapital samt konkurrenceregler (Det Europæiske Økonomiske Samarbejdsområde (EØS), Schweiz og Norden | Faktablade om Den Europæiske Union | Europa-Parlamentet).

Tabel 1.1. Identitet af cyhalothrinsyre

IUPAC navn	**R-isomer og S-isomer:** (1R,3R)-3-[(Z)-2-chloro-3,3,3-trifluoroprop-1-enyl]-2,2-dimethylcyclopropane-1-carboxylic acid https://www.benchchem.com/product/b132028 https://www.benchchem.com/product/b106163
Strukturformel	R-isomer:  S-isomer: 
CAS nr.	68127-59-3, 72748-35-7 (R-isomer), 76023-99-9 (S-isomer)
EINECS nr.	614-283-9
Kemisk formel	$C_9H_{10}ClF_3O_2$
SMILES	CC1(C(C1C(=O)O)C=C(C(F)(F)F)Cl)C
Harmoniseret klassificering	-
Selvklassificering (ECHA)	For CAS nr. 68127-59-3: Sundhed: Skin Irrit. 2 (H315; Forårsager hudirritation) Eye Irrit. 2 (H319; Forårsager alvorlig øjenirritation) STOT SE 3 (H335; Kan forårsage irritation af luftvejene) For CAS nr. 76023-99-9: Sundhed: Acute Tox. 4 (H302; Farlig ved indtagelse) Skin Corr. 1B (H314; Forårsager svære ætsninger af huden og øjenskader) Miljø: Aquatic Chronic 2 (H411; Giftig for vandlevende organismer, med langvarige virkninger)

2 Fysisk kemiske egenskaber

De fysisk kemiske egenskaber for cyhalothrinsyre fremgår af tabel 2.1.

Tabel 2.1. Fysisk kemiske egenskaber for cyhalothrinsyre.

Parameter	**Værdi**	**Reference**
Molekylevægt, M_w ($g \cdot mol^{-1}$)	242,62	ChemNet (25-04-2023)
Smeltepunkt, T_m (ºC)	107-109	ChemNet (25-04-2023)
Kogepunkt, T_b (ºC)	271,6 ved 101.325 Pa	ChemNet (25-04-2023)
Damptryk, P_v (Pa)	0,9613	DK-QSAR (25-04-2023)
Henry's konstant, H ($Pa \cdot m^3 \cdot mol^{-1}$)	6,975	DK-QSAR (25-04-2023)
Vandopløselighed, S_w ($g \cdot l^{-1}$)	0,03344[1]	DK-QSAR (25-04-2023)
Dissociationskonstant, pK_a	4,5 (±0,4)	DK-QSAR (25-04-2023)
Octanol/vand fordelingskoefficient, log K_{ow}	2,44 - 3,41 (model estimater) 2,93 (middelværdi) 2,95 (median) 3,85	CompTox (25-04-2023) DK-QSAR (25-04-2023)
Sediment/vand fordelingskoefficient, normaliseret til organisk karbon, K_{oc} ($l \cdot kg^{-1}$)	Sandy clay loam (3,23 % OC, pH 4,45): 91,9 Sandy loam (2,5, pH 6,05): 13,8 Silt clay loam (0,58 % OC, pH 7,5): 16,2 Fra MCI[2]: 254,5 Fra Kow: 192,9 105	EFSA (2010) EFSA (2010) EFSA (2010) DK-QSAR (25-04-2023) CompTox (25-04-2023)

[1]Estimeret ud fra log Kow på 3,85
[2]MCI: First order Molecular Connectivity Index

3 Skæbne i miljøet

3.1 Nedbrydelighed

Baseret på QSAR-modelestimater er cyhalothrinsyre fundet at være ikke-let-nedbrydeligt i miljøet (ECHA, 04-05-2023; DK-QSAR, 04-05-2023).

OPERA-modellen for bionedbrydning finder en halveringstid på 3,55 dage (CompTox, 25-04-2023).

3.2 Bioakkumulering

Der er ikke fundet eksperimentelle data for bioakkumuleringen af cyhalothrinsyre, så værdierne er estimeret.

BCF er fundet ved QSAR beregninger:

BCF = 3,162 l/kg vådvægt, log BCF = 0,5 l/kg vådvægt (DK QSAR, 25-04-2023).

BCF = 3,74 (CompTox, 25-04-2023).

På baggrund af de QSAR estimerede data af BCF er der ikke forventning om, at cyhalothrinsyre bioakkumulerer.

3.3 Naturlig forekomst

Cyhalothrinsyre forekommer ikke naturlig i miljøet.

4 Toksicitetsdata

Der foreligger ingen EU- eller OECD-risikovurderingsrapporter for stoffet.

Datasøgningen for cyhalothrinsyre er udført i ECOTOX, CompTox, PubChem, ECHA, OECD e-chem, og i den videnskabelige litteratur via Web of Science, samt Google Scholar, med søgeordene: (68127-59-3 OR 72748-35-7 OR 76023-99-9 OR "cyhalothric acid" OR "cyhalothrinsyre" OR "cyhalthrin acid") AND (toxicity OR giftighed OR PNEC OR NOEC). Specifikke søgeord som water/vand, sediment, biota, human, ADI, TDI eller RfV blev også anvendt.

Søgningen giver følgende resultater:

- 3 arter af akvatiske organismer (2 fisk, 1 dafnie) indgår i en vurdering af tefluthrin, udført af EFSA (2009 og 2010), hvor cyhalothrinsyre indgår som et nedbrydningsprodukt.
- En økotoksikologisk undersøgelse af cyhalothrinsyre er udført af DHI (2002) for 3 arter (1 fisk, 1 vandloppe og 1 alge).
- Et rottestudie udført af Safepharm (1999).

Andre mulige relevante studier findes i ECHA's dossier for CAS nr. 68127-59-3 og 76023-99-9. De fleste er dog unavngivne og kan derfor ikke genfindes og kvalitetsvurderes. Nogle er identificeret med et årstal og hovedforfatter navn, men kunne ikke genfindes ved søgning i Web of Science eller Google Scholar. Studieresultaterne fra ECHA's dossier er derfor ikke medtaget i dette datablads vurdering. I Bilag B er resultaterne vist.

4.1 Toksicitet over for vandlevende organismer

I tabel 4.1.1 er vist datasættet for akut og kronisk akvatisk toksicitet baseret på resultaterne i de angivne referencer.

Tabel 4.1.1 Akut og kronisk toksicitet af cyhalothrinsyre på akvatiske organismer.

Arter	Test	Varighed	Effekt	Værdi (mg/l)	Bemærkning	Reference	Troværdighed (Klimisch, 1-4)
Fisk							
Bluegill klumpfisk (*Lepomis macrochirus*)	Laboratorie	96 timer (akut)	Dødelighed LC50 NOEC	 >17 >7,5	Statisk system med nominelle testkoncentrationer: 3,2; 5,6; 10; 18 og 32 mg/l.	Tapp et al. (1987)	2-(3) Ingen test guideline, men der står at det er GLP - har ikke adgang til originalstudiet.
Regnbueørred (*Oncorhynchus mykiss*)	Laboratorie	96 timer (akut)	Dødelighed LC50	 >15,8	Semi-statisk system med nominelle testkoncentrationer: 3,2; 5,6; 7,5; 10 og 18 mg/l.	Hill (1984)	2-(3) Ingen test guideline, men der står at det er GLP - har ikke adgang til originalstudiet.

Marin fisk, pighvar (*Scophthalmus maximus*)	Laboratorie	96 timer (akut)	Dødelighed LC50 LC10 NOEC	 >200 >200 ≥200	Statisk system med testkoncentrationer: 0; 0,1; 1,0; 10; 100 og 200 mg/1.	DHI (2002)	2-(3) Ældre test-guideline og ingen verificering af koncentrationer.
Invertebrater							
Marin vandloppe (*Acartia tonsa*)	Laboratorie	48 timer (akut)	Dødelighed LC50 LC10 NOEC	 55 (45-68) 16 (4,4-25) 10	Statisk system med testkoncentrationer: 0; 2,0; 5,0; 10; 20; 50; 100 og 200 mg/l.	DHI (2002)	2-(3) Ældre test-guideline og ingen verificering af koncentrationer.
Stor dafnie (*Daphnia magna*)	Laboratorie	48 timer (akut)	Immobilisering EC50	105	Statisk system med nominelle testkoncentrationer: 30; 50; 80; 130 og 200 mg/l	Yamauchi et al. (1984)	2-(3) Ingen test-guideline, men der står at det er GLP - har ikke adgang til originalstudiet.
Alger							
Marin kiselalge (*Skeletonema costatum*)	Laboratorie	72 timer (akut og kronisk[a])	Vækstrate EC50 EC10 NOEC	 6,2 (5,5-7,4) 1,8 (1,4-2,2) 1,0	Testkoncentrationer: 0; 0,2; 0,5; 1,0; 2,0; 5,0; 10 og 20 mg/l.	DHI (2002)	2-(3) Ældre test-guideline og ingen verificering af koncentrationer.

[a] Da testen strækker sig over flere generationer alger.

Den laveste akutte værdi er EC50 = 6,2 mg/l (middelværdi) fra algeforsøget, mens den eneste tilgængelige kroniske værdi er fra samme algeforsøg, dvs. EC10 = 1,8 mg/l (middelværdi).

Estimerede data (non-test data) bør ikke anvendes som udslagsgivende værdier (kritiske data) i fastsættelsen af et kvalitetskriterium (TGD, 2018, s. 29, 43 og 120), men kan anvendes som supplerende data, f.eks. i vurderingen af valgte usikkerhedsfaktorer.

For at få et basisdatasæt, dvs. data der omfatter mindst én korttids LC50/EC50, for hver af de tre trofiske niveauer, dvs. fisk, invertebrater og alger (TGD, 2018, s. 41), anvendes Danish (Q)SAR Database (DK-QSAR, 25-04-2023) som grundlag til at fastsætte supplerende korttids LC50/EC50 for fisk.

I tabel 4.1.2 er vist datasættet for akut og kronisk akvatisk toksicitet beregnet med QSARs. Se Bilag A for DK QSAR-dokument for CAS nr. 68127-59-3. Dokumenterne for de andre to CAS-numre er identiske.

Tabel 4.1.2 Værdier for akut og kronisk akvatisk toksicitet beregnet ved QSAR-modeller.

Arter	**LC50/EC50/Andet (mg/L)**		**Varighed (timer)**	**Reference**
Fisk	LC50[1]	4,37	96	DK-QSAR (25-04-2023)
Dafnia	EC50[1]	2,94	48	DK-QSAR (25-04-2023)
Grønalger	EC50[1]	4,44	96	DK-QSAR (25-04-2023)
Fisk	Toxic-3[2]	100-100	-	ECHA (25-04-2023)
Fisk	LC50[3]	68,88	96	ECHA (25-04-2023)

Fisk	ChV	0,523	Kronisk	EPISuite ECOSAR (04-05-2023)
Dafnia	ChV	0,462	Kronisk	EPISuite ECOSAR (04-05-2023)
Grønalger	ChV	1,70	Kronisk	EPISuite ECOSAR (04-05-2023)

[1]EPI ECOSAR-modeller. ECOSAR-klasser: Vinyl/Allyl Halides-syre
[2](SarPy/IRFMN) model i VEGA
[3](KNN/Read-Across) i VEGA

Af Tabel 4.1.2 ses det, at de modellerede LC50/EC50 er i samme størrelsesorden for de tre arter. Dette retfærdiggør valget af EC50 = 6,2 mg/l (middelværdi) fra algeforsøget som repræsentant for den akutte akvatiske toksicitet for vandlevende organismer:

Akut: EC50 = 6,2 mg/l.

Iht. TGD (2018) s. 142 kan EC10 = 1,8 mg/l (middelværdi) fra samme algeforsøg repræsentere den kroniske toksicitet for vandlevende organismer:

Kronisk: ChV = EC10 = 1,8 mg/l.

Grundet begrænset data er det ikke muligt at foretage en statistisk beregning af, om der er forskel på sensitiviteten for salt- og ferskvandsorganismer, derved antages det som udgangspunkt, at salt- og ferskvandsorganismer ikke har forskellig sensitivitet, og derfor, at toksicitetsdata kan kombineres (TGD, 2018, afsnit 3.2.3). Den akutte og den kroniske værdi gælder derfor både for ferskvand og for saltvand.

4.2 Toksicitet over for sedimentlevende organismer

Der er ingen tilgængelige eksperimentelle data for sedimentlevende organismer. Der er heller ingen tilgængelige QSAR-data for sedimentlevende organismer i DK-QSAR (24-05-2023), ECHA (25-04-2023) eller OECD e-chem.

4.3 Toksicitet over for pattedyr og fugle

Der findes ét studie med pattedyr (rotte) med en laveste LD50 = 500 mg/kg lgv og en Klimisch-score på 1 (Safepharm, 1999), se Tabel 4.3.1.

Tabel 4.3.1 LD50-værdi for akut oral toksicitet ved forsøg med rotte.

Arter	Effekt	LD50 (mg/kg lgv)	Varighed (dage)	Bemærkninger	Reference	Troværdighed (score 1-4)
Rotte (*Rattus norvegicus*)	Død eller tydelige tegn på toksicitet.	500-1000	14	Dosis på hhv. 200 og 2000 mg/kg lgv blev givet én gang. Dyrene blev observeret for effekter efter ½, 1, 2 og 4 timer og derefter 1 gang daglig i 14 dage.	Safepharm (1999)	1 Dette er et godt GLP-studie.

4.4 Toksicitet over for mennesker

I Tabel 1.1 er selvklassificering af fare for mennesker angivet for cyhalothrinsyre. CAS nr. 76023-99-9 er selvklassificeret som farlig ved indtagelse (H302) og forårsager svære ætsninger af huden og øjenskader (H314). CAS nr. 68127-59-3 er selvklassificeret som: forårsager hudirritation (H315), alvorlig øjenirritation (H319), og kan forårsage irritation af luftvejene (H335).

Der er ikke fundet nogen fastsatte grænseværdier for mennesker i form af referencedosis (Rdf), TDI- (tolerabel daglig dosis) eller ADI- (acceptable daglig dosis) værdier for cyhalothrinsyre. DK-QSAR (Bilag A) finder en maksimum anbefalet daglig dosis i farmaceutiske kliniske tests, hvor oral indtag er den primære eksponeringsvej på ≤ 2,69 mg/kg kropsvægt/dag.

5 Andre effekter

QSAR viser desuden enkelte positive fund (POS_IN) på effekter, som er fremhævet med gult i Bilag A og listet nedenfor:

- Severe Skin Irritation in Rabbit.
- In vitro Genotoxicity - Bacterial Reverse Mutation Test (Ames test): Tre ud af fire modeller indikerer mekanismer eller potentiale for, at Ames test-modellerne er positive.
- Other in vitro Genotoxicity Endpoints: Mutations in Thymidine Kinase Locus in Mouse Lymphoma Cells, and Mutations in HGPRT Locus in Chinese Hamster Ovary (CHO) Cells.
- In vivo Genotoxicity Endpoints: Comet Assay in Mous

6 Udledning af vandkvalitetskriterium

Kvalitetskriterierne er fastsat i overensstemmelse med EU's Guidance Document no. 27: Technical Guidance Document (TGD) for Deriving Environmental Quality Standards (EU, 2018).

6.1 Vandkvalitetskriterium (VKK) og Korttidsvandkvalitetskriterium (KVKK)

EC50 = 6,2 mg/l (middelværdi) fra algeforsøget, repræsenterer den akutte akvatiske toksicitet for vandlevende organismer.

Et basissæt udgøres af data for akut toksicitet for tre trofiske niveauer, dvs. for fisk, dafnia og alger. Basissættet er opfyldt, når supplerende QSAR-estimater for EC50/LC50 for fisk anvendes, se afsnit 4.1.

Med et fuldt basissæt og kun én kronisk værdi, dvs. for alger, kan UF (usikkerhedsfaktor) findes af tabel 3, 4, 5 og 6. Iht. TGD (2018) s. 41 nederst kan algedata alene ikke anvendes til at fastsætte den kroniske værdi. I dette tilfælde skal UF anvendes med den lavest målte akutte EC50 fra basissættet, dvs. EC50 = 6,2 mg/l, til bestemmelse af både VKK og KVKK.

Som nævnt i afsnit 4.1. kombineres data for fersk- og saltvand. Dette giver følgende vandkvalitetskriterier, VKK, for hhv. ferskvand og saltvand, idet der anvendes en UF på hhv. 1000 (TGD, 2018, Tabel 3) og 10.000 (TGD, 2018, Tabel 4):

$VKK_{ferskvand}$ = EC50/ UF = 6,2 mg/l/1000 = 6,2 µg/l

$VKK_{saltvand}$ = EC50/ UF = 6,2 mg/l/10.000 = 0,62 µg/l

Korttidsvandkvalitetskriteriet KVKK for ferskvand og saltvand beregnes ved at anvende en UF på hhv. 100 (TGD, 2018, Tabel 5) og 1000 (TGD, 2018, Tabel 6):

$KVKK_{ferskvand}$ = EC50/ UF = 6,2 mg/l/100 = 62 µg/l

$KVKK_{saltvand}$ = EC50/ UF = 6,2 mg/l/1000 = 6,2 µg/l

6.2 Kvalitetskriterium for sediment (SKK)

QSAR-estimerede Koc værdier er 254,5 L/kg eller lavere (svarende til log Koc ≤ 2,4). Middelværdien af de tre estimerede log K_{ow} værdier fra CompTox (25-04-23) og den QSAR-estimerede log K_{ow} værdi (DK-(Q)SAR (25-04-2023)), dvs. 2,44, 2,95, 3,41 og 3,85 (Tabel 2.1), er 3,16.

Der foreligger ikke evidens for akkumulation i sediment eller mistanke om høj toksicitet over for sedimentlevende organismer. Men da middelværdien for log K_{ow} er større end 3, kan det tale for at beregne et SKK jf. s. 20 i TGD (EU, 2018). Da der ikke er fundet eksperimentelle data for sedimentlevende organismer, kan SKK beregnes ved equilibrium partition (EqP) metoden (TGD, 2018, s. 102-106).

Ligning 6 til 8 s. 104 i TGD (2018) giver følgende udtryk for sedimentkvalitetskriteriet for ferskvand:

$$SKK_{ferskvand\ EqP\ tørvægt} = \frac{RHO_{sed}}{Fsolid_{sed} \cdot RHOsolid} \cdot \frac{K_{sed-water}}{RHO_{sed}} \cdot QS_{fw,eco} \cdot 1000 \text{ (Ligning 1)}$$

hvor $QS_{fw,eco}$ sættes til langtidskvalitetskriteriet for ferskvand ($VKK_{ferskvand}$) (TGD, 2018, afsnit 5.2.1).

$K_{sed\text{-}water}$ er fordelingskoefficienten mellem sediment og vand. Den beregnes af ligning 2 og 4 på s. 102 og 103 i TGD (2018). Hertil skal anvendes Koc = 112 l/kg, som er middelværdien af de seks Koc-værdier i Tabel 2.1. For alle øvrige parametre anvendes default-værdier fra s. 103 og 104 i TGD (2018). Det giver følgende kvalitetskriterium for sediment i ferskvand:

$SKK_{ferskvand\ EqP\ tørvægt}$ = 7,2 × $VKK_{ferskvand}$ (mg/l) = 7,2 × 0,0062 = 0,045 mg/kg tørvægt (5 % OC)
$SKK_{ferskvand\ EqP\ tørvægt}$ = 0,89 mg/kg tørvægt × f_{oc}

Sedimentkvalitetskriteriet for saltvand, fås ved at indsætte langtidskvalitetskriteriet for saltvand ($VKK_{saltvand}$) i ligning 1:

$SKK_{saltvand\ EqP\ tørvægt}$ = 7,2 × $VKK_{saltvand}$ (mg/l) = 7,2 × 0,00062 = 0,0045 mg/kg tørvægt (5 % OC)
$SKK_{saltvand\ EqP\ tørvægt}$ = 0,089 mg/kg tørvægt × f_{oc}

Default-værdierne, der er anvendt i TGD (2018), omfatter et organisk stof indhold (foc) på 5 %.

6.3 Kvalitetskriterium for biota, sekundær forgiftning ($BKK_{sek.forgiftn.,ferskvand}$)

Cyhalothrinsyre har en QSAR-estimeret BCF på 3,162 l/kg vådvægt (afsnit 3.2) og en QSAR-estimeret log K_{ow} værdi på 3,16 (afsnit 6.2). Da log K_{ow} > 3, berettiger det en beregning af $BKK_{sek.\ forgiftn.,ferskvand}$.

Den laveste LD50-værdi på 500 mg/kg lgv for rotteforsøget (Tabel 4.3.1) indgår i en deterministisk analyse, hvor der beregnes en energinormaliseret toksicitetsværdi ud fra metode A, idet LD50 er udtrykt som en dosis (TGD, 2018, afsnit 4.4.5 til 4.4.8).

Tabel 6.3.1 BKK-værdier beregnet med metode A for rottestudie med Klimisch-score på 1 (se tabel 4.2.1). Gennemsnitslegemsvægten er 222 g.

Arter	Omregnet LD50 (mg/kJ)[1]	$Konc_{musling}$ (mg/kg musling,vådvægt)	$Konc_{fisk}$ (mg/kg fisk,vådvægt)	UF1 (kronisk/sub-kronisk/sub-akut/akut) (tabel 9 i EU, 2018)	UF2 (ekstrapolering til forskellige niveauer) (tabel 10 i EU, 2018)	BKKsek. forgiftn., musling, ferskvand (mg/kg musling,vådvægt)	BKKsek. forgiftn., fisk, ferskvand (mg/kg fisk,vådvægt)
Rotte (*Rattus norvegicus*)	0,364	4,158	14,935	100 (akut)[2]	10	0,544	1,96

[1] Ligningen for pattedyr på s. 85 i TGD (2018) er anvendt.
[2] UF1 = 100 gælder for fugle ifølge Tabel 9 i TGD (2018). Værdien antages at gælde også for pattedyr.

Som nævnt i afsnit 3.2 er der på baggrund af de QSAR-estimerede data af BCF ikke forventning om, at cyhalothrinsyre bioakkumulerer, og der er heller ikke data eller evidens for biomagnifikation af cyhalothrinsyre. Der beregnes derfor ikke et særskilt BKK for det marine miljø med det formål at beskytte toppredatorer.

Det kritiske fødeemne bestemmes ud fra stoffets biomagnificerende egenskaber (TGD, 2018 s. 77). Da cyhalothrinsyre ikke er biomagnificerende, vælges muslinger. Det beregnede kriterium for musling i tabel 6.3.1 sættes derfor som det endelige biotakvalitetskriterium for sekundær forgiftning ($BKK_{sek.\ forgiftn.,ferskvand}$):

$BKK_{sek.\ forgiftn.,ferskvand}$ = 0,544 mg/kg musling, ferskvand, vådvægt (deterministisk metode)

6.4 Kvalitetskriterium for human konsum af vandlevende organismer (HKK)

Iht. TGD (2018) (afsnit 2.4.3.2) er faresætningen for CAS nr. 76023-99-9, "H302; Farlig ved indtagelse", en trigger til at skulle beregne et kvalitetskriterium for human konsum af vandlevende organismer (HKK), hvis stoffet samtidig er bioakkumulerbart.

Disse kriterier er ikke opfyldt. Imidlertid kan faresætningen H302 og den høje log K_{ow} anvendes som argument for, at der konservativt beregnes en værdi for human konsum, HKK.

Da der ikke er fundet nogen EFSA fastsatte værdier for et tolerabelt daglig indtag (TDI) eller et acceptabelt dagligt indtag (ADI) eller øvrige referenceværdier, bestemmes her en referenceværdi (TL_{hh}) ud fra den laveste dosis (sættes lig $NOAEL_{min}$) anvendt i Safepharm (1999). Derved kan HKK bestemmes som følgende ud fra ligningen på s. 91 i TGD (2018):

HKK (mg/kg vådvægt biota) = (0,2 × TL_{hh}) / 0,00163

Hvor:

TL_{hh} = $NOAEL_{min}$ / 100 (s. 73 i TGD, 2018)

Laveste dosis (200 mg/kg lgv) administreret i studiet af Safepharm (1999) vælges som værdi for $NOAEL_{min}$, da der ikke blev observeret en dødelighed eller øvrige synlige effekter ved denne dosis. Det bemærkes, at dosis kun blev administreret en enkelt gang, samt at studiet er et sub-akutstudie.

Ved ekstrapolation fra et sub-akut studie til et kronisk studie, anvendes en UF1 på 6 ihht. tabel R.8-5 i ECHA R.8. Yderligere anvendes en høj UF2 på 10 i hht. tabel R.8-19 (ECHA R.8) for at tage højde for en stor afstand mellem dosis i testen.

Dette giver en beregnet kronisk $NOAEL_{min}$ på:

$NOAEL_{min}$ = 200 mg/kg lgv/(UF1 * UF2) = 200 mg/kg lgv/(6 * 10) = 3,33 mg/kg lgv

Kvalitetskriteriet for human konsum af vandlevende organismer kan nu beregnes til:

HKK = 0,2 × 3,33 mg/kg lgv / 100 / 0,00163 = 4,09 mg/kg vådvægt biota

6.5 Vandkvalitetskriterium baseret på $BKK_{sek.forgiftn.}$ og HKK

Ifølge TGD (2018) vil en tilbageregning fra biotakvalitetskriterierne ($BKK_{sek.forgiftn.}$ og HKK) til en vandkoncentration vise, om vandkvalitetskriteriet fastsat for direkte effekter også beskytter mod sekundær forgiftning gennem fødekæden.

Da biotakvalitetskriteriet for pattedyr er lavere end for human konsum, anvendes $BKK_{sek.forgiftn.,ferskvand}$ = 0,544 mg/kg musling, ferskvand, vådvægt, i tilbageregningen. Tilbageregningen til en vandkoncentration for biota bliver (s. 95 i TGD, 2018):

$BKK_{vand,\ sek.\ forgiftn.} = BKK_{sek.\ forgiftn.,ferskvand} / BAF$

Ifølge afsnit 3.2 er der ikke forventning om, at cyhalothrinsyre bioakkumulerer, og BAF kan derfor sættes lig med BCF (s. 95 i TGD, 2018):

$BKK_{vand,\ sek.\ forgiftn.}$ = $BKK_{sek.\ forgiftn.,ferskvand}$ / BCF = 0,544 mg/kg musling, ferskvand, vådvægt / 3,162 l/kg vådvægt = 0,172 mg/l = **172 µg/l**

hvor BCF = 3,162 l/kg vådvægt er estimeret af DK (Q)SAR (25-04-2023), se afsnit 3.2.

Ved tilbageregning til koncentrationer i vand fra $BKK_{sek.\ forgiftn.,ferskvand}$ fås en vandkoncentration, der er højere end vandkvalitetskriterierne hhv. VKK og KVKK.

Vandkvalitetskriterierne VKK og KVKK, beregnet i afsnit 6.1, vil derfor også beskytte mod sekundær forgiftning gennem fødekæden.

7 Konklusion

Kvalitetskriterier er beregnet for cyhalothrinsyre (CAS nr. 68127-59-3, 72748-35-7 og 76023-99-9) for vand, sediment, biota og human konsum af vandlevende organismer.

Metodikken er baseret på EU's vejledning til fastsættelse af kvalitetskriterier i vandmiljøet (TGD, 2018) og Miljøstyrelsens vejledning til fastsættelse af vandkvalitetskriterier (Miljøstyrelsen, 2004).

Følgende kvalitetskriterier for vandmiljøet er udregnet for cyhalothrinsyre:

Vandkvalitetskriterier:

$VKK_{ferskvand}$ = 6,2 µg/l

$VKK_{saltvand}$ = 0,62 µg/l

Korttidsvandkvalitetskriterier:

$KVKK_{ferskvand}$ = 62 µg/l

$KVKK_{saltvand}$ = 6,2 µg/l

Sedimentkvalitetskriterier:

$SKK_{ferskvand\ EqP\ tørvægt}$ = 0,045 mg/kg tørvægt (5% OC)
= 0,89 mg/kg tørvægt × f_{oc}

$SKK_{saltvand\ EqP\ tørvægt}$ = 0,0045 mg/kg tørvægt (5% OC)
= 0,089 mg/kg tørvægt × f_{oc}

Biotakvalitetskriterium, sekundær forgiftning:
$BKK_{sek.\ forgiftn.,ferskvand}$ = 0,544 mg/kg musling, ferskvand, vådvægt

Biotakvalitetskriterium, human konsum:
HKK = 4,09 mg/kg vådvægt biota

Ved tilbageregning til koncentrationer i vand fra $BKK_{sek.\ forgiftn.,ferskvand}$ fås en vandkoncentration, der er højere end vandkvalitetskriterierne hhv. VKK og KVKK. Vandkvalitetskriterierne VKK og KVKK vil derfor også beskytte mod sekundær forgiftning gennem fødekæden.

8 Referencer

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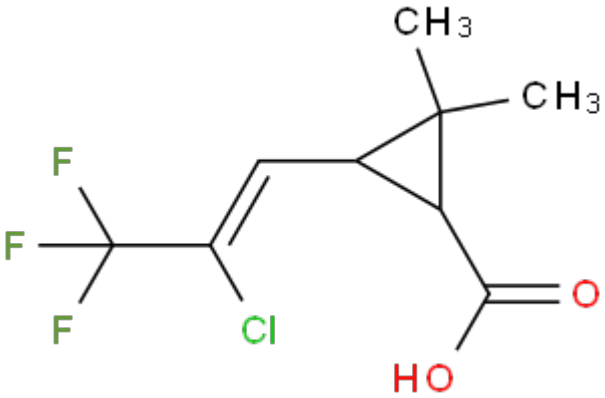
Bilag A Danish (Q)SAR Database document

(Q)SAR predicted profile

Structure (as used for QSAR prediction):



SMILES (used for QSAR prediction): C(F)(F)(F)C(Cl)=CC1C(C)(C)C1C(=O)O

ID

Registry Number	68127-59-3	PubChem CID	
REACH EC Number (pre-registration, by 2013)	614-283-9	REACH EC Number (registration, 2019 or 2022)	614-283-9
REACH registration (2022)	Yes	REACH registration cumulated minimum annual tonnage (2022)	
EU CLP Harmonized Classification*		DK-EPA / DTU QSAR-based CLP Advisory Classification	Acute Tox. 3; Aquatic Chronic 2
EU Biocide active substances		EU Pesticide active substances	
EU EFSA Botanical substances		US TSCA (Oct. 2021)	Yes
Tox21 (2019)		ToxCast (Oct. 2021)	
Molecular Formula	C9 H10 CL1 F3 O2	Molecular weight (g/mole)	242.63
Chemical Name	Cyclopropanecarboxylic acid, 3-[(1Z)-2-chloro-3,3,3-trifluoro-1-propen-1-yl]-2,2-dimethyl-, (1R,3R)-rel-		

(Annex VI to CLP up to and including the 9th ATP, and including Nordic Council of Minister SPIN list for group entries)

Melting point, Boiling point and Vapour pressure

Melting Point (deg C)	60.61	Melting Point Experimental (deg C)	
Boiling Point (deg C)	260.53	Boiling Point Experimental (deg C)	
Vapour Pressure (atm)		Vapour Pressure Experimental (atm)	
Vapour Pressure (mm Hg)	0.00721	Vapour Pressure Experimental (mm Hg)	
Vapour Pressure (Pa)	0.9613	Vapour pressure Subcooled Liquid (Pa)	2.06

EPI MPBPVP models

Henry's Law Constant

HLC Bond Method (atm-m3/mole)	8.744E-006	HLC Group Method (atm-m3/mole)	
HLC Via VP/WSol (atm-m3/mole)	6.883E-005	HLC Via VP/WSol (Pa-m3/mole)	6.975
Henrys Law Const. Exp db (Pa-m3/mole)		Henrys Law Const. Exp db (atm-m3/mole)	

EPI HENRYWIN models

Water Solubility

Water solubility from Kow (mg/L)	33.44	Water solubility from Fragments (mg/L)	49.712
Water solubility Exp (mg/L)		Water solubility Exp Ref	

EPI WATERNT model

Hydrolysis

Hydrolysis Ka half-life pH 7	Hydrolysis Kb half-life pH 7
Hydrolysis Ka half-life pH 8	Hydrolysis Kb half-life pH 8

EPI HYDROWIN model

pKa

pKa Acid	4.5
- Standard deviation (±)	0.4
pKa Base	-999
- Standard deviation (±)	0

ACDLabs model

pKa estimate 999: no acidic moiety found. pKa estimate -999: no basic moiety found.

Partition coefficients

pH	1	4	5	6	7	8	9
LogD	3.24	3.13	2.65	1.77	0.79	-0.13	-0.7

Minimum LogD in the pH interval 4-9	-0.7	Maximum LogD in the pH interval 4-9	3.13

ACDLabs models

LogD: Log octanol-water partition coefficient, which for ionizable compounds varies with the pH-dependent amounts of neutral and ionized species

Log Koa	7.297	Log Kaw	-3.447

EPI KOAWIN models

Koa: octanol-air partition coefficient. Kaw: air-water partition coefficient.

Log Kow	3.85		
Log Kow Exp		Log Kow Exp Ref	

EPI WSKOW model

LogKow: log octanol-water partition coefficient

Kp (m3/ug) Mackay-based	1.45E-006	Kp (m3/ug) Koa-based	4.86E-006
Phi Junge-Pankow-based	5.24E-005	Phi Mackay-based	0.000116
Phi Koa-based	0.000389		

EPI AEROWIN models

Kp: particle-gas partition coefficient. Phi: fraction of substance sorbed to atmospheric particulates

Koc from MCI (L/kg)	254.5	Log Koc from MCI	2.4057
Koc from Kow (L/kg)	192.9	Log Koc from Kow	2.2853

EPI KOCWIN models

Koc: soil adsorption coefficient of organic compounds. Kow: octanol-water partition coefficient. MCI: first order Molecular Connectivity Index

Level III Fugacity Environmental Partitioning, emission to air, water and soil

	Air	Water	Soil	Sediment
Mass Amount (%)	0.481	17.4	81.9	0.271
Half-Life (hr)	15.7	1440	2880	13000
Emissions (kg/hr)	1000	1000	1000	0

EPI Level III Fugacity Model

Persistence time (hr)	1400
Persistence time (days)	58.33333

EPI Level III Fugacity Model

Level III Fugacity Environmental Partitioning, emission only to water

	Air	Water	Soil	Sediment
Mass Amount (%)	0.154	98.2	0.156	1.53
Half-Life (hr)	15.7	1440	2880	13000
Emissions (kg/hr)	0	1000	0	0

EPI Level III Fugacity Model

Persistence time (hr)	650
Persistence time (days)	27.08333

EPI Level III Fugacity Model

Sewage Treatment Plant (STP) overall chemical mass balance using 10,000 hr

	Total removal	Biodegradation	Sludge Adsorption	Volatilization
(%)	24.04	0.27	23.4	0.37

EPI STPWIN model

Atmospheric oxidation (25 deg C)

	OH	Ozone
Half-Life (d)	0.7214	7.045
Half-Life (hr)	8.657	
Overall Rate Const. (OH: E-12 cm3/molecule-sec and OZ: E-17 cm3/molecule-sec)	14.8265	0.162663

EPI AOPWIN models

Biodegradation

Biowin1 (linear model) Probability of Rapid Biodegradation	-0.111
Biowin2 (non-linear model) Probability of Rapid Biodegradation	0.0001
Biowin3 Expert Survey Ultimate Biodegradation	2.1293
Biowin3 Expert Survey Ultimate Timeframe	months
Biowin4 Expert Survey Primary Biodegradation	3.3548
Biowin4 Exp. Survey Primary Timeframe	days-weeks
Biowin5 (MITI linear model) Biodegradation Probability	0.3242
Biowin6 (MITI non-linear model) Biodegradation Probability	0
Biowin7 (Anaerobic Linear) Biodegradation Probability	0.5202
Petroleum Hydrocarbon Biodegradation Half-Life (days)	

EPI BIOWIN models
SkinBiowin1 and Biowin2: ≥0.5: "Rapid" <0.5: "Slow"
Biowin3 and Biowin4: 5 ~ hours; 4 ~ days; 3 ~ weeks; 2 ~ months; 1 ~ years.
Biowin5 and Biowin6: ≥0.5: "Readily", <0.5: "Not readily".
Biowin7: ≥0.5: "Fast", <0.5: "Slow"

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Not Ready Biodegradability (POS=Not Ready)		POS_OUT	POS_OUT	POS_IN	NEG_OUT

DTU-developed models

Bioaccumulation

BCF (L/kg wet-wt)	3.162
Log BCF (L/kg wet-wt)	0.5
Whole Body Primary Biotransformation Fish Half-Life (days)	5.241
BCF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	551.8
BCF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	734.8
BAF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	556.7
BAF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	1400

EPI BCFBAF models

BCF: Bioconcentration factor, BAF: Bioaccumulation factor

Aquatic toxicity

Exp	Battery	Leadscope	SciQSAR
Fathead minnow 96h LC50 (mg/L)	23.41768	21.24098	25.59438
Domain	IN	IN	IN
Daphnia magna 48h EC50 (mg/L)	1.049939	1.54425	0.5556285
Domain	IN	IN	IN
Pseudokirchneriella s. 72h EC50 (mg/L)	74.71098	116.9996	32.42235
Domain	IN	IN	IN

DTU-developed models

	Fish 96h	Daphnid 48h	Green Algae 96h
LC50 (Fish) or EC50 (Daphnid and Algae) for Most Toxic Class (mg/L)	4.373	2.945	4.44
Max. Log Kow for Most Toxic Class	5	5	6.4
Most Toxic Class	Neutral Organic SAR	Neutral Organic SAR	Neutral Organic SAR
Note			

EPI ECOSAR models

ECOSAR Classes: Vinyl/Allyl Halides-acid

Oral absorption

Lipinski's Rule-of-five score (bioavailability)	0
Absorption from gastrointestinal tract for 1 mg dose (%)	100
Absorption from gastrointestinal tract for 1000 mg dose (%)	90

Leadscope model on Lipinski's Rule-of-five. Equation from literature on GI abs.

Lipinski scores of 0 or 1: The substance may be bioavailable. Lipinski scores of 2, 3 or 4: The substance may not be bioavailable.

Skin absorption

Dermal absorption (mg/cm2/event)	0.0027

EPI DERMWIN model

Brain/blood Distribution

Log brain/blood partition coefficient	0.461

Equation from literature

Partitioning between the two tissues at equilibrium. >1: high, >0 to <1: medium, >-1 to <0, fair, <-1: low.

Metabolism

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
CYP2C9 substrates (Human clinical data)		INC_OUT	NEG_OUT	NEG_OUT	INC_OUT
CYP2D6 substrates (Human clinical data)		INC_OUT	NEG_OUT	NEG_OUT	NEG_OUT

DTU-developed models

Acute toxicity in Rodents

	LD50 (mg/kg/d)	Reliability Index
Rat Oral	150	0.65
Rat Intraperitoneal	300	0.65
Mouse Oral	1300	0.3
Mouse Intraperitoneal	88.16	0.24
Mouse Intravenous	100	0.6
Mouse Subcutaneous	3000	0.37

ACDLabs models

Reliability index: <0.3 = Not reliable prediction quality; 0.3-0.5 = borderline prediction quality; 0.5-0.75 = moderate prediction quality; >0.75 = high prediction quality.

MRDD in Humans

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
MRDD in Humans ≤ 2.69 mg/kg-bw/d		NEG_IN	INC_OUT	NEG_IN	NEG_IN

DTU-developed models

Model based on data on pharmaceuticals. Maximum recommended daily dose in pharmaceutical clinical trials employing primarily oral route of exposure and daily treatments, usually for 3-12 months.

Irritation and Sensitization

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Severe Skin Irritation in Rabbit		INC_OUT	POS_OUT	**POS_IN**	NEG_IN
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based (open data only)				INC_OUT	
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based (open data and REACH-registrations)	N/A			NEG_IN	
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based, only negative predictions (open data only)				N/A	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based (open data only)				INC_OUT	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based (open data and REACH-registrations)	N/A			NEG_IN	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based, only positive predictions (open data and REACH-registrations)	N/A			N/A	
Allergic Contact Dermatitis in Guinea Pig and Human*	N/A	NEG_IN	INC_OUT	NEG_IN	NEG_IN
Respiratory Sensitisation in Humans		INC_OUT	INC_OUT	INC_OUT	POS_OUT

DTU-developed models

**Based on commercial training set*

Protein binding by OASIS, alerts in:	
- parent only	No alert found
- metabolites from skin metabolism simulator only	
- metabolites from auto-oxidation simulator only	
Protein binding by OECD, alerts in:	
- parent only	No alert found
- metabolites from skin metabolism simulator only	
- metabolites from auto-oxidation simulator only	
Protein binding potency Cys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> Non-Conjugated carboxylic acids and esters (non reactive)
- metabolites from skin metabolism simulator only	
- metabolites from auto-oxidation simulator only	
Protein binding potency Lys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> Non-Conjugated carboxylic acids and esters (non reactive)
- metabolites from skin metabolism simulator only	
- metabolites from auto-oxidation simulator only	
Keratinocyte gene expression, alerts in:	
- parent only	Not possible to classify according to these rules
- metabolites from skin metabolism simulator only	
- metabolites from auto-oxidation simulator only	
Protein binding potency GSH, alerts in:	
- parent only	

OECD QSAR Toolbox v.4.1 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_OUT	NEG_OUT	NEG_OUT	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		INC_OUT	NEG_OUT	POS_OUT	NEG_OUT
Estrogen Receptor α Activation (Human *in vitro*)		NEG_OUT	NEG_OUT	NEG_OUT	NEG_IN
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Sodium/iodide symporter (NIS), higher sensitivity		N/A	N/A	POS_OUT	N/A
Sodium/iodide symporter (NIS), higher specificity		N/A	N/A	POS_OUT	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L				954.6725	
- μM				3934.684	
- Positive for IC_{50} ≤ 10 μM					
- Positive for IC_{50} ≤ 100 μM					
- Domain				OUT	
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L				45.24334	
- μM				186.4705	
- Positive for IC_{50} ≤ 10 μM					
- Positive for IC_{50} ≤ 100 μM					
- Domain				OUT	
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	INC_OUT	NEG_OUT	INC_OUT	NEG_OUT
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	NEG_IN	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	NEG_OUT	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)		N/A	N/A	NEG_OUT	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
DTU-developed models					

Estrogen Receptor Binding, alerts in:	
- parent only	Non binder, without OH or NH2 group
- metabolites from *in vivo* Rat metabolism simulator only	Non binder, without OH or NH2 group
- metabolites from Rat liver S9 metabolism simulator only	Non binder, without OH or NH2 group
rtER Expert System - USEPA, alerts in:	
- parent only	No alert found
- metabolites from *in vivo* Rat metabolism simulator only	No alert found
- metabolites from Rat liver S9 metabolism simulator only	No alert found

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

Developmental Toxicity

	Battery	CASE Ultra	Leadscope	SciQSAR
Teratogenic Potential in Humans	INC_OUT	INC_OUT	NEG_OUT	POS_OUT

DTU-developed models based on commercial training set

Genotoxicity - Structural Alerts for DNA Reactivity

	Battery	CASE Ultra	Leadscope	SciQSAR
Ashby Structural Alerts	INC_OUT	INC_OUT	INC_OUT	NEG_OUT

DTU-developed models based on commercial training set

DNA binding by OASIS, alerts in:	
- parent only	Geminal Polyhaloalkane Derivatives
DNA binding by OECD, alerts in:	
- parent only	No alert found

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

In vitro Genotoxicity - Bacterial Reverse Mutation Test (Ames test)

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Ames test in S. typhimurium (*in vitro*)		NEG_OUT	POS_OUT	NEG_OUT	NEG_IN
*Direct Acting Mutagens (without S9)	N/A	POS_OUT	INC_OUT	**POS_IN**	NEG_OUT
*Base-Pair Ames Mutagens	N/A	INC_OUT	INC_OUT	**POS_IN**	NEG_IN
*Frameshift Ames Mutagens	N/A	NEG_IN	INC_OUT	NEG_IN	NEG_IN
*Potent Ames Mutagens, Reversions ≥ 10 Times Controls	N/A	INC_OUT	INC_OUT	**POS_IN**	NEG_IN

DTU-developed models

* The four models (Direct Acting mutagens (without S9), Base-Pair Ames Mutagens, Frameshift Ames Mutagens, Potent Ames Mutagens) should not be used to determine if substances are Ames mutagens, but can be used for indication of mechanism or potency for cases where the main Ames model (Ames test in S. typhimurium (*in vitro*)) is **POS_IN**.

	VEGA	Mut. / Non-mut. scores	Used models
Mutagenicity consensus	NEG	0.1 / 0.3	4

Mutagenicity (Ames) consensus model version 1.0.2 contained in VEGA version 1.1.4 with calculation core version 1.2.4

Prediction: POS = Mutagenic, NEG = Non-mutagenic.

VEGA

ISS	CAESAR	SarPy	KNN
POS_Low	NEG_Mod	POS_Low	NEG_Mod

Four individual models in mutagenicity consensus model version 1.0.2 contained in VEGA version 1.1.4 with calculation core version 1.2.4

Prediction: POS = Mutagenic, NEG = Non-mutagenic, SUSP.POS = Suspected mutagenic, POSS.NEG = Possible Non-mutagenic, Exp = experimental value, Good = Good reliability, Mod = Moderate reliability, Low = Low reliability.

DNA alerts for AMES by OASIS, alerts in:	
- parent only	No alert found
In vitro mutagenicity (Ames test) alerts by ISS, alerts in:	
- parent only	Monohaloalkene

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

Other in vitro Genotoxicity Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells*	N/A	NEG_IN	INC_OUT	NEG_IN	NEG_IN
Chromosome Aberrations in Chinese Hamster Lung (CHL) Cells		NEG_OUT	INC_OUT	POS_OUT	NEG_IN
Mutations in Thymidine Kinase Locus in Mouse Lymphoma Cells		INC_OUT	INC_OUT	**POS_IN**	NEG_IN
Mutations in HGPRT Locus in Chinese Hamster Ovary (CHO) Cells		INC_OUT	INC_OUT	NEG_IN	**POS_IN**
Unscheduled DNA Synthesis (UDS) in Rat Hepatocytes		NEG_OUT	NEG_OUT	NEG_IN	INC_OUT
Syrian Hamster Embryo (SHE) Cell Transformation		INC_OUT	INC_OUT	POS_OUT	NEG_OUT

DTU-developed models
**Based on commercial training set*

HGPRT: Hypoxanthine-guanine phosphoribosyltransferase

DNA alerts for CA and MNT by OASIS, alerts in:	
- parent only	No alert found
Protein binding alerts for Chromosomal aberration by OASIS, alerts in:	
- parent only	No alert found

OECD QSAR Toolbox v.4.2 profilers
CA: Chromosomal aberration, MNT: Micronucleus test
Profiler predictions are supporting information to be used together with the relevant QSAR predictions

In vivo Genotoxicity Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Sex-Linked Recessive Lethal (SLRL) Test in Drosophila m.		NEG_IN	INC_OUT	NEG_IN	NEG_IN
Micronucleus Test in Mouse Erythrocytes		NEG_OUT	INC_OUT	NEG_IN	INC_OUT
Dominant Lethal Mutations in Rodents		NEG_IN	POS_OUT	NEG_IN	NEG_IN
Sister Chromatid Exchange in Mouse Bone Marrow Cells		INC_OUT	INC_OUT	POS_OUT	INC_OUT
Comet Assay in Mouse		INC_OUT	INC_OUT	NEG_IN	**POS_IN**

DTU-developed models

In vivo mutagenicity (Micronucleus) alerts by ISS, alerts in:	
- parent only	Monohaloalkene

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

Carcinogenicity

	E Ultra	Leadscope
FDA RCA Cancer Male Rat	NEG_OUT	INC_OUT
FDA RCA Cancer Female Rat	NEG_OUT	NEG_OUT
FDA RCA Cancer Rat	POS_OUT	INC_OUT
FDA RCA Cancer Male Mouse	INC_OUT	NEG_IN
FDA RCA Cancer Female Mouse	NEG_OUT	NEG_IN
FDA RCA Cancer Mouse	POS_OUT	NEG_OUT
FDA RCA Cancer Rodent	POS_OUT	POS_OUT

Commercial models from CASE Ultra and Leadscope

FDA RCA: Data from US Food and Drug Administration as part of Research Cooperation Agreement

Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:	
- parent only	Monohaloalkene (Genotox); Structural alert for genotoxic carcinogenicity
Oncologic Primary Classification, alerts in:	
- parent only	Not classified

OECD QSAR Toolbox v.4.2 profilers

Profiler predictions are supporting information to be used together with the relevant QSAR predictions

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		INC_OUT	POS_OUT	NEG_OUT	INC_OUT

DTU-developed models

Abbreviations

INC: inconclusive. A definite call within the defined applicability domain could not be made.

NEG: negative

POS: positive

IN: inside applicability domain

OUT: outside applicability domain

Exp: Experimental values, from EpiSuite experimental databases or DK DTU QSAR models training sets.

N/A: Not applicable, either because training set data cannot be released for commercial or proprietary models / training sets, or because the model was not developed in a given QSAR software (i.e. a given prediction is not available as the model version does not exist).

Important notes

This is an automatically generated report from the Danish (Q)SAR Database, http://qsar.food.dtu.dk.

For predictions from CASE Ultra, Leadscope, SciQSAR as well as the Acute toxicity in rodent from ACDLabs information on the software versions can be found in the QMRFs. For the other predicted properties the software versions are:

EPI MPBPWIN v1.43

EPI HENRYWIN v3.20

EPI WSKOW v1.42

EPI WATERNT v1.01

EPI KOAWIN v1.10

EPI AEROWIN v1.00

EPI KOCWIN v2.00

EPI Level III Fugacity Model (EPI Suite v4.11)

EPI STPWIN (EPI Suite v4.11)

EPI AOPWIN v1.92

EPI BIOWIN v4.10

EPI BCFBAF v3.01

EPI ECOSAR v1.11

EPI DERMWIN v2.02

ACD/ ToxSuite 2.95.1 Ionization\pKa

ACD/ ToxSuite 2.95.1 Ionization\ LogD

ACD/ ToxSuite 2.95.1

It is recommended to run the latest version of the EPI Suite Programs in preference of the predictions given in this document when these endpoints are of importance and new versions have been released from the United States Environmental Protection Agency in comparisons. EPI Suite can be downloaded from the US EPA homepage: http://www.epa.gov/oppt/exposure/pubs/episuitedl.htm

For further information on the applied systems, see the following homepages:

Case Ultra: http://www.multicase.com/case-ultra

Leadscope: http://www.leadscope.com/

SciQSAR: http://lhasa-llc.com/

ToxSuite: http://www.acdlabs.com/

Bilag B Studier fra ECHA's dossier

Studierne indeholder målte toksicitets data. Studierne kan dog ikke genfindes og kan derfor ikke bruges til udledning af kvalitetskriterier.

Toksicitet over for vandlevende organismer:

CAS 76023-99-9:
ECHA Registration Dossier - ECHA (europa.eu) (se unnamed studie (2002) resultater her): Short-term toxicity to fish:
LC50 (Scophthalmus maximus) (96 h): >200 mg/L
i.e. Key value for chemical safety assessment: Marine water fish:
Effect concentration: 200 mg/L

ECHA Registration Dossier - ECHA (europa.eu) (se unnamed studie (2002) resultater her): Short-term toxicity to aquatic invertebrates:
LC50 (Acartia tonsa) (48 h): 55 mg/L
i.e. Key value for chemical safety assessment: Marine water invertebrates:
Effect concentration: 55 mg/L

ECHA Registration Dossier - ECHA (europa.eu) (se unnamed studie (2002) resultater her): Toxicity to aquatic algae and cyanobacteria:
EC50 (Sk. costatum) (72 h): 6.2 mg/L
i.e. Key value for chemical safety assessment:
EC50 for freshwater algae: 6.2 mg/L

ECHA opsummering for CAS 68127-59-3.: Registration Dossier - ECHA (europa.eu)
Data were available for two trophic levels: freshwater fish and invertebrates. Of these, fish is the most sensitive species however the data obtained from all studies on fish are not suitable for the purpose of classification and labelling.

The key value for the classification is given by the acute toxicity study on daphnia magna.

The acute EC50 of the test substance to the daphnia (Daphnia pulex) was estimated to be 182 (164 - 202) mg/L at 24 hours and 105 (95 - 116) mg/L at 48 hours of exposure. The study report is relevant, adequate and reliable for risk assessment, classification and labelling.

As a result the substance does not meet the criteria for classification as Dangerous for the environment, according to Directive 2001/59/EC as well as the current criteria for classification as Hazardous to the aquatic environment, according to Regulation (EC) No. 1272/2008.

CAS 68127-59-3:
ECHA Registration Dossier - ECHA (europa.eu) (se unnamed (1987) studie resultater her): Short-term toxicity to fish: The acute LC50 of the test substance to the bluegill sunfish (Lepomis macrochirus) was estimated to be > 17 mg/L at 24, 48, 72, and 96 hr of exposure (> 14 mg/L in a first run at lower temperature). Confidence limits could not be calculated. The study report is relevant and reliable with restrictions **but not adequate for** classification and labeling.

ECHA: Registration Dossier - ECHA (europa.eu) (se unnamed (1984) studie resultater her): Short-term toxicity to fish: The acute LC50 of the test substance to the rainbow trout (Oncorhynchus mykiss, reported as Salmo gairdneri) was estimated to be > 15.8 mg/L at approximately 24, 48, 72, and 96 hr of exposure. Confidence

limits could not be calculated. The study report is relevant and reliable with restrictions **but not adequate** for classification and labeling.

ECHA: Registration Dossier - ECHA (europa.eu) (se unnamed (1984) studie resultater her): Short-term toxicity to aquatic invertebrates: The acute EC50 of the test substance to the daphnia (Daphnia pulex) was estimated to be 182 (164 - 202) mg/L at 24 hours and 105 (95 - 116) mg/L at 48 hours of exposure. The study report is **relevant, adequate and reliable** for risk assessment, classification and labeling.
Fresh water invertebrates: Effect concentration: 105 mg/L

EC50 (24-h): 182 mg/L (C.I. 164-202), EC50 (48-h): 105 mg/L (C.I. 95-116), static, daphnia, method equivalent to OECD 202, Yam auchi 1984b

ECHA: Registration Dossier - ECHA (europa.eu) (se unnamed (2018) studie resultater her):
Toxicity to aquatic algae and cyanobacteria: The influence of the test item on the growth ofthe freshwater green algae Raphidocelis subcapitata was assessed in a static concentration-response test.The 96-hours ErC50 value was calculated to be >189 mg test item/L, the 96-hours EbC50was calculated to be 72.9 mg test item/L and the 96-hours EyC50 was calculated to be 83.8 mg test item/L. The 96-hours NOErC was determined to be 5.40 mg/L and the associated 96-hours LOErC was 17.7 mg/L. The 96-hours NOEbC was determined to be 1.65 and the associated 96-hours LOEbC was 5.40 mg/L. The 96-hour NOEyC was determined to be 5.40 ml/L and the associated 96-hour LOEyC was 17.7 mg/L.
EC50 for freshwater algae: 200 mg/L
EC10 or NOEC for freshwater algae: 1.65 mg/L

Toksicitet over for pattedyr og fugle

CAS 76023-99-9:
ECHA Registration Dossier - ECHA (europa.eu) (se unnamed studie (1999) resultater her): Acute toxicity: via oral route:
LD50 (rat, oral): 500-1000 mg/kg bodyweight

CAS 68127-59-3:
ECHA: Registration Dossier - ECHA (europa.eu) Acute toxicity:

Oral: LD50 > 4990 mg/kg bw, male/female, rat, method similar to OECD401, Southwood 1984b
Dermal: LD50 > 2000 mg/kg bw, male/female, rat, method similar to OECD401, Southwood 1984b
Inhalation: LC50 > 1.1 mg/L, male/female, rat, method similar to OECD401, Leah & Mould 1987

Given the deviations in the study on acute inhalation toxicity (no attempt to reach the recommended concentration of 2 mg/L, tested substance with particle size with a Mass median aerodynamic diameter of aerosols >4 micrometer) its results are **not considered to be adequate** for classification and labelling purpose.

Both available studies on acute oral and dermal toxicity are **considered adequate and reliable** for the purposes classification and labelling.

Studies are unnamed, men i den grå boks ovenfor står forfatterne.
Study 1984: The acute oral LD50 of the test substance was estimated to be greater than 4990 mg/kg bw to male and female rats. Confidence limits could not be calculated. The study report is **relevant, reliable** with restrictions and adequate for risk assessment, classification and labeling.
Study 1984: The acute dermal LD50 of the test substance was estimated to be greater than 2000 mg/kg bw to male and female rats. Confidence limits could not be calculated (limit test). The study report is **relevant, reliable** with restrictions and adequate for risk assessment, classification and labeling.

Study 1987: The acute inhalation LC50 of the test substance was estimated to be greater than 1.1 mg/L to male and female rats. Confidence limits could not be calculated. The study report is relevant, but **not adequate and reliable** for classification and labeling.

Toksicitet over for mennesker

CAS 68127-59-3:
ECHA: Registration Dossier - ECHA (europa.eu)
Genetic toxicity:
IKKE RELEVANT: Ames test (bacterial reverse mutation in vitro): Negative

Only a single study conducted under GLP according to a method equivalent to guideline OECD 471 is available (**Callander 1984**). The study is considered to be relevant, reliable with restrictions and adequate for the purposes of risk assessment, classification and labelling. No increase in the incidence of revertant colonies was elicited in strains S. typhimurium TA1535, TA1537, TA1538, TA 98, and TA 100, with and without metabolic activation, with one exception (strain TA98 without S9-mix, test/control ratios up to 2.4). The latter result showed no dose relation, was not reproducible in two further experiments, and was thus considered an artefact (due to exceptionally low background values). Under the conditions of the assay, the test material gave an unequivocal negative (non-mutagenic) response.

Chromosome aberration: Negative

Only a single study (in vitro cytogenetic test in human lymphocytes) conducted according to guideline OECD 473 and under GLP is available (**Fox 1995**). The study is considered to be relevant, reliable and adequate for the purposes of risk assessment, classification and labelling. Two independent experiments were performed with lymphocytes of two different donors (male and female), over a wide range of concentrations. Clear signs of cytotoxicity (reduction of mitotic index) were elicited by the test substance at higher doses. No statistically or biologically significant increase in the incidence of specific chromosomal aberrations was observed, with and without metabolic activation. The test material is not clastogenic to cultured human lymphocytes, under the conditions of the test.

Justification for selection of genetic toxicity endpoint
No study was selected since the results in both studies in vitro were negative.

Short description of key information:
IKKE RELEVANT: Ames test: negative (non-mutagenic), S. typhimurium TA1535, TA1537, TA1538,TA98, and TA100, with + without metabolic activation, OECD 471**, Callander 1984**
Chromosome aberration: negative (non-clastogenic), human lymphocytes, with + without metabolic activation, OECD 473, **Fox 1995**

Endpoint Conclusion: No adverse effect observed (negative)

ECHA
IKKE RELEVANT: Unnamed study 2017 Registration Dossier - ECHA (europa.eu) in vitro gene mutation study in bacteria:

Conclusion:

In conclusion, it can be stated that during the described mutagenicity tests and under the experimental conditions reported, thte test material did not induce gene mutations by base pair changes or frameshifts in the genome of the strains used. Therefore the test material is considered to be non-mutagenic in the *Salmonella typhimurium* and *Escherichia coli* reverse mutation assay.

Andre effekter

CAS 68127-59-3:

ECHA: Registration Dossier - ECHA (europa.eu)

Skin irriration, rabbit: slightly irritating, method similar to OECD 404, Southwood 1984a
Eye irriration, rabbit: moderately irritating, method similar to OECD 405, Southwood 1984a

Sensitisation: no adverse effect observed (not sensitising)