Miljø- og
Fødevareministeriet
Miljøstyrelsen

Fastsættelse af kvalitetskriterier for vandmiljøet

4,4-Dimethylisoxazolidin-3-on

CAS nr. 81778-07-6

Vandkvalitetskriterium	$VKK_{ferskvand}$	100 µg/l
Vandkvalitetskriterium	$VKK_{saltvand}$	100 µg/l
Korttidsvandkvalitetskriterium	$KVKK_{ferskvand}$	100 µg/L
Korttidsvandkvalitetskriterium	$KVKK_{saltvand}$	100 µg/L
Sedimentkvalitetskriterium	$SKK_{ferskvand}$	Ikke beregnet
Sedimentkvalitetskriterium	$SKK_{saltvand}$	Ikke beregnet
Biota-kvalitetskriterium, sekundær forgiftning	$BKK_{sek.forgiftn.}$	Ikke beregnet
Biota-kvalitetskriterium, sundhed	$BKK_{sundhed}$	Ikke beregnet

December 2020

Indhold

Forord

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

Miljøstyrelsen (MST) udarbejder kvalitetskriterier for kemikalier i vandsøjlen (vandkvalitetskriterium), i sediment og i dyr og planter (biota).

Miljøstyrelsen bruger kvalitetskriterierne som det faglige grundlag til at kunne fastsætte 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 miljøkvalitetskrav 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 23. oktober 2020.

English Summary and conclusions

Derivation of environmental quality standards (EQS) for the aquatic environment is following the EU Guidance Document No. 27. Technical Guidance Document for Deriving Environmental Quality Standards (TGD) (EU, 2018).

4,4-dimethylisoxazolidin-3-one is an intermediate in production of fine chemicals.

Short-term ecotoxicity data have been available for the three marine organisms: *Skeletonema* sp. (algae), *Acartia tonsa* (crustacean) and *Scophthalmus maximus* (fish). Furthermore, data have been supported by QSAR data for freshwater organisms from the Danish (Q)SAR Database (2020) and ECOSAR (2020).

Long-term ecotoxicity data have been available for two marine organisms: the algae *Skeletonema* sp. and the crustacean *Acartia tonsa*.

QS for freshwater and saltwater
According to the TGD (EU, 2018) for datasets with limited data, the deterministic approach using assessment factors shall be used for the derivation of annual average quality standard (AA-QS). Therefore, this approach is followed for derivation of the AA-QS for 4,4-dimethylisoxazolidin-3-one.

The AA-QS is derived for both freshwater organisms and saltwater organisms based on the experimentally determined long-term and short-term data for saltwater organisms. According to TGD (table 4, note b), when the lowest long-term effect value have a higher effect value than the lowest short-term effect value; an assessment factor of 1000 shall be applied to the lowest effect value. The lowest effect value is LC_{50} >100 mg/L for marine fish. This value is conservatively set to 100 mg/L.

The AA-QS for freshwater is derived based on toxicity data of marine species, since no freshwater data is available. This approach is uncertain and therefore an extrapolation factor of 10 is applied to the ordinarily assessment factor for deriving a freshwater AA-QS (100) for deriving the freshwater AA-QS for 4,4-dimethylisoxazolin-3-one. Therefore, the same assessment factor of 1000 is applied for deriving the AA-QS for both freshwater and saltwater:

$AA\text{-}QS_{freshwater}$ = 100 mg/L / 1000 = 0.1 mg/L = 100 µg/L

$AA\text{-}QS_{saltwater}$ = 100 mg/L / 1000 = 0.1 mg/L = 100 µg/L

The maximum acceptable concentration (MAC-QS) is derived for both freshwater organisms and saltwater organisms based on the experimentally determined short-term data for saltwater organisms. There are three short-term effect values for marine species, representing three tropic levels and according to TGD (table 6) an assessment factor of 1000 shall be applied to the lowest short-term effect value. The MAC-QS for freshwater is derived based on toxicity data of marine

species, since no freshwater data is available. This approach is uncertain and therefore an extrapolation factor of 10 is applied to the ordinarily assessment factor for deriving a freshwater AA-QS (100) for 4,4-dimethylisoxazolin-3-one. Therefore, the same assessment factor of 1000 is applied for deriving the MAC-QS for both freshwater and saltwater:

$MAC\text{-}QS_{freshwater}$ = 100 mg/L / 1000 = 0.1 mg/L = 100 µg/L

$MAC\text{-}QS_{saltwater}$ = 100 mg/L / 1000 = 0.1 mg/L = 100 µg/L

QS for sediment
Based on the log K_{ow} < 3 (1) for 4,4-dimethylisoxazolidin-3-one, the QS for sediment shall not be derived according to the TGD (EU, 2018).

QS for secondary poisoning
4,4-dimethylisoxazolidin-3-one has a log K_{ow} < 3 (1) and an estimated bioconcentration factor (BCF), lower than 100 (1.02) indicating a low potential for bioaccumulation and accumulation in the food chain. Therefore, the QS for secondary poisoning shall not be derived according to the TGD (EU, 2018).

EQS for human health
Based on low potential for bioaccumulation and accumulation in the food chain, no QS for human health needs to be developed. At the same time, the substance poses no known hazards for carcinogenic, mutagenic or reprotoxic effects or known risk of irreversible effects.

The following EQS have been derived for 4,4-dimethylisoxazolidin-3-one:

$AA\text{-}QS_{freshwater}$ = 100 µg/L
$AA\text{-}QS_{saltwater}$ = 100 µg/L
$MAC\text{-}QS_{freshwater}$ = 100 µg/L
$MAC\text{-}QS_{saltwater}$ = 100 µg/L
$QS_{sediment,\ freshwater}$ = Not determined
$QS_{sediment,\ saltwater}$ = Not determined
$QS_{biota,\ secondary\ poisoning}$ = Not determined
$QS_{biota,\ human\ health}$ = Not determined

1 Indledning

Identiteten af 4,4-dimethylisoxazolidin-3-on fremgår af tabel 1.1.

Stoffet 4,4-dimethylisoxazolidin-3-on indgår som et intermediat i produktion af kemiske stoffer (ECHA, 2020a). Den årlige tonnage af 4,4-dimethylisoxazolidin-3-on er ukendt (ECHA, 2020a).

Tabel 1.1. Identitet

IUPAC navn	4,4-dimethyl-1,2-oxazolidin-3-on
Strukturformel	
CAS nr.	81778-07-6
EINECS nr.	692-895-5
Kemisk formel	$C_5H_9NO_2$
SMILES	CC1(C)CONC1=O (ECHA, 2020b)

2 Fysisk kemiske egenskaber

De fysisk kemiske egenskaber for 4,4-dimethylisoxazolidin-3-on fremgår af tabel 2.1.

Tabel 2.1. Fysisk kemiske egenskaber for 4,4-dimethylisoxazolidin-3-on

Parameter	**Værdi**	**Reference**
Molekylevægt, M_w ($g \cdot mol^{-1}$)	115,13	DHI, 2020a
Smeltepunkt, T_m (°C)	74,5	CDS, 1984
Kogepunkt, T_b (°C)	224[1]	CDS, 1984
Damptryk, P_v (Pa)	0,693[1]	Danish QSAR Database, 2020
Henry's konstant, H ($pa \cdot m^3 \cdot mol^{-1}$)	Ikke angivet	
Vandopløselighed, S_w ($g \cdot L^{-1}$)	69,9[2]	CDS, 1984
Dissociationskonstant, pK_a	6,86[3]	CDS, 1984
Octanol/vand fordelingskoefficient, log K_{ow}	1,00	Eurofins, 2020
K_{oc} ($L \cdot kg^{-1}$)	29,82[1]	Epi Suite, 2020

[1]Estimeret
[2]Ved 26 °C
[3]Ved 20 °C

3 Skæbne i miljøet

Der er søgt efter data for stoffet 4,4-dimethylisoxazolidin-3-ons skæbne i miljøet i let tilgængelige oversigtsværker:

- ECHA-databasen (ECHA, 2020a, 2020b)
- eChemportal (OECD, 2020) (metadatabase med flere relevante databaser inkluderet ECHA CHEM, ETOX, J-Check, US EPA ECOTOX, OECD SIDS)
- Søgning i det kongelige biblioteks søgetjenester og særsamlinger (https://www.kb.dk/find-materiale) (søgt på 4,4-dimethylisoxazolidin-3-one og 81778-07-6)
- Generel søgning via google (søgt på 4,4-dimethylisoxazolidin-3-one og 81778-07-6)

Der blev ikke fundet eksperimentelle data på skæbne i miljøet, og derfor er der suppeleret med QSAR fra den danske QSAR database (Danish QSAR Database, 2020), som indeholder QSAR fra EPI Suite. QSAR-resultaterne fremgår af i Bilag A.

3.1 Nedbrydelighed

Der foreligger ingen eksperimentel data på nedbrydeligheden af 4,4-dimethylisoxazolidin-3-on. Via QSAR programmet BIOWIN (v4.10) er nedbrydeligheden af stoffet estimeret til ikke let bionedbrydelig (Danish QSAR Database, 2020).

3.2 Bioakkumulering

Da 4,4-dimethylisoxazolidin-3-on har en log K_{ow} på 1, anses stoffet ikke for at være bioakkumulerende. Via QSAR programmet BCFBAF (v.3.01) forudsiger beregningerne (Danish QSAR Database, 2020) en BCF-værdi på 3,16 L/kg vådvægt og en BCF Arnot-Gobas inklusiv biotransformering på 1,016 L/kg vådvægt, hvilket underbygger, at stoffet har et lavt potentiale for at bioakkumulere.

3.3 Naturlig forekomst

Stoffet forventes ikke at forekomme naturligt.

4 Giftighedsdata

To forsøgsrapporter med økotoksikologisk karakterisering af 4,4-dimethylisoxazolidin-3-on (DHI; 2020a, 2020b) har været tilgængelige for udarbejdelse af miljøkvalitetskriterier.

Derudover er der søgt data i let tilgængelige oversigtsværker og sammenfattende rapporter:

- ECHA-database (ECHA, 2020a, 2020b)
- eChemportal (OECD, 2020) (metadatabase med flere relevante databaser inkluderet ECHA CHEM, ETOX, J-Check, US EPA ECOTOX, OECD SIDS)
- Søgning i det kongelige biblioteks søgetjenester og særsamlinger (https://www.kb.dk/find-materiale) (søgt på 4,4-dimethylisoxazolidin-3-one og 81778-07-6)
- Generel søgning via google (søgt på 4,4-dimethylisoxazolidin-3-one og 81778-07-6)

Der er ikke fundet eksperimentelt data for giftigheden af 4,4-dimethylisoxazolidin-3-on ud over forsøgsrapporterne med økotoksikologisk karakterisering af 4,4-dimethylisoxazolidin-3-on (DHI; 2020a, 2020b). Derfor er data suppleret med QSAR (Danish QSAR Database, 2020), som indeholder QSAR fra EPI Suite. QSAR-resultaterne fremgår af i Bilag A.

4.1 Giftighed over for vandlevende organismer

Den akutte toksicitet af 4,4-dimethylisoxazolidin-3-on er testet på tre marine arter fra tre forskellige taksonomiske grupper: alge (*Skeletonema* sp. (kiselalge)), invertebrat (*Acartia tonsa* (krebsdyr)) og fisk (*Scophthalmus maximus*). Effektkoncentrationerne for akuttest med marine organismer er sammenstillet i tabel 4.1. Studierne med 4,4-dimethylisoxazolidin-3-on indikerer en lav akut toksicitet (L(E)C_{50} > 1000 mg/L) for alge og invertebrat.

Tabel 4.1 Akutte effekter af 4,4-dimethylisoxazolidin-3-on på marine arter

Art	**Varighed**	**Effekt**	**Værdi mg/L**	**Bemærkninger**	**Reference + troværdighed (CRED: 1-4)**
Alger *Skeletonema* sp.	72 t	EC_{50} (Vækst)	>1000		DHI, 2020a (1)
Krebsdyr *Acartia tonsa*	48 t	LC_{50}	>1000	Ingen effekter observeret i den højeste testkoncentration	DHI, 2020a (2)
Fisk *Scophthalmus maximus*	96 t	LC_{50}	>100	Ingen effekter observeret i den højeste testkoncentration	DHI, 2020a (2)

Ud over de tre akutte forsøg, er den kroniske toksicitet testet på to marine arter fra to forskellige taksonomiske grupper: alge (*Skeletonema* sp. (kiselalge)) og invertebrat (*Acartia tonsa* (krebsdyr)). Effektkoncentrationerne for kroniske test med marine organismer er sammenstillet i tabel 4.2.

Tabel 4.2 Kroniske effekter af 4,4-dimethylisoxazolidin-3-on på marine arter

Art	**Varighed**	**Effekt**	**Værdi mg/L**	**Bemærkninger**	**Reference + troværdighed (CRED: 1-4)**
Alger					
Skeletonema sp.	72 t	NOEC (Vækst)	100		DHI, 2020a (1)
Skeletonema sp.	72 t	LOEC (Vækst)	150		DHI, 2020a (1)
Skeletonema sp.	72 t	EC_{10} (Vækst)	1074	Estimeret ud fra probit-analyse	DHI, 2020a (1)
Krebsdyr					
Acartia tonsa	5 d	LC_{10}	250		DHI, 2020b (1)
Acartia tonsa	5 d	EC_{10} (Udvikling)	130		DHI, 2020b (1)
Acartia tonsa	5 d	NOEC (Klæknings succes)	1000	Ingen effekter observeret i den højeste testkoncentration	DHI, 2020b (1)

Væksthæmmende effekter over for den marine alge, *Skeletonema* sp., er undersøgt i henhold til ISO standard testguidelinen 10253 (2016). Effektkoncentrationerne er usikre grundet lave væksthæmmende effekter, og derfor er EC_{10} estimeret via probit-analyse til 1074 mg/L. Der blev observeret en statistisk signifikant (Dunnett's test, $p < 0,05$) hæmning af væksten ved 150, 320, 470, 690 og 1000 mg/L, men ikke ved 220 mg/L (DHI, 2020a). Derfor er den laveste observerede effektkoncentration (LOEC) bestemt til 150 mg/L, hvilket betyder at den højeste testkoncentration, som ikke er statistisk signifikant forskellig fra kontrollen (NOEC) er bestemt til 100 mg/L. EC_{50} er >1000 mg/L.

Da *Skeletonema* sp. er cirka en faktor otte mindre sensitiv end *A. tonsa*, ved sammenligning af kroniske effekter, hvor EC_{10} er 130 mg/L og 1074 mg/L for hhv. *A. tonsa* og *Skeletonema* sp, vurderes det, at studiet med *Skeletonema* sp. kan betragtes som et kronisk studie. Hvis *Skeletonema* sp. og *A. tonsa* var omtrent lige sensitive, skulle der foreligge et yderligere studie på en anden algeart, som vil underbygge algers sensitivitet (EU, 2018, s. 39).

Den akutte toksicitet over for den marine invertebrat, *Acartia tonsa*, er undersøgt i henhold til ISO standard testguidelinen 14669 (1999), hvor der for den observerede dødelighed ikke var statistisk signifikant ($p > 0,05$) forskel mellem kontrollen og de eksponerende grupper (100, 180, 320, 560 og 1000 mg/L). Individerne af *A. tonsa* var voksne eller i det sidste copepodidstadie (stadie V). LC_{50} sættes konservativt til 100 mg/L, da der ikke er andet tilgængeligt akutdata for invertebrater.

Den kroniske toksicitet er undersøgt i henhold til ISO standard testguidelinen 16778 (2015), hvor æg af *A. tonsa* blev eksponerede for 4,4-dimethylisoxazolidin-3-on (0, 100, 180, 320, 560 og 1000 mg/L). Eksponeringstiden er fastsat ud kriteriet, at mindst 60 % af individerne i kontrollen, skal udvikle sig til copepoditlarver, og derfor kan eksponeringstiden varierer fra fem til syv dage (DHI, 2020b). Udviklingen fra æg til copepoditlarve er det mest følsomme endpoint med en EC_{10}-værdi på 130 mg/L (konfidensinterval: 120-150 mg/L), mens dødeligheden af nauplius- og copepoditlarver er et mindre følsomt endpoint med LC_{10}-værdi på 250 mg/L (konfidensinterval:

230-260 mg/L). Klækningssuccesen blev ikke påvist at være påvirket af 4,4-dimethylisoxazolidin-3-on (NOEC = 1000 mg/L).

Toksiciteten over for den marine fisk, *Scophthalmus maximus* (pigvar), er undersøgt i henhold til OECD testguideline 203 (2019) og OSPAR kommission (2006), hvor voksne individer blev eksponeret for én testkoncentration (100 mg/L) ud over kontrollen (0 mg/L). Der blev ikke observeret nogen dødelighed i forsøget. Årsagen til at der kun blev anvendt én testkoncentration, skyldes REACH-principper om begrænsning af dyreforsøg (EC/1907/2006, artikel 13). LC_{50} sættes konservativt til 100 mg/L, da der ikke er andet tilgængeligt data for fisk.

4,4-dimethylisoxazolidin-3-on er ikke testet på ferskvandsorganismer, og derfor anvendes QSAR-modeller (ECOSAR, 2020; Danish QSAR Database, 2020) til at estimere toksiciteten over for ferskvandsorganismer (Tabel 4.3). QSAR-modellerne har en lav troværdighed (CRED-score på 3), da modellerne har lave regressionsværdier ($R^2 < 0,8$) eller et lavt antal datapunkter ($n < 20$).

Tabel 4.3 Estimerede akutte effekter af 4,4-dimethylisoxazolidin-3-on på ferskvandsarter

Art	**Varighed**	**Effekt**	**Værdi mg/L**	**Reference + troværdighed (CRED: 1-4)**
Alger				
Grøn alge	96 t	EC_{50}	16,4	ECOSAR, 2020 (3)
Grøn alge	96 t	EC_{50}	12,4	Danish QSAR Database, 2020 (3)
Krebsdyr				
Daphnia sp.	48 t	LC_{50}	219	ECOSAR, 2020 (3)
Daphnia sp.	48 t	EC_{50}	1369	Danish QSAR Database, 2020 (3)
Fisk				
Pimephales promelas	96 t	LC_{50}	194	ECOSAR, 2020 (3)
Pimephales promelas	96 t	LC_{50}	576	Danish QSAR Database, 2020 (3)

Da de estimerede effektværdier har en lav troværdighed, anvendes de ikke direkte i udledningen af vandkvalitetskriterier. De estimerede effektværdier for ferskvandsarter forudsiger at alge er den mest sensitive gruppe, mens det tyder på, fra forsøgsdata for marine arter, at krebsdyr er den mest sensitive gruppe. Det kan ikke konkluderes, hvilken gruppe, som er den mest sensitive, da langtidseffekter i fisk er ukendt, samt datamaterialet er begrænset idet kun én art for hver af de taksonomiske gruppe (alger, krebsdyr (invertebrat) og fisk) er blevet testet. Det er også muligt, at det ikke er den samme taksonomiske gruppe som er den mest følsomme i både det marine og ferske miljø.

4.2 Giftighed over for sedimentlevende organismer

Der er ikke fundet data for giftighed over for sedimentlevende organismer.

4.3 Giftighed over for pattedyr og fugle

Der er ikke fundet data for giftighed over for pattedyr og fugle.

4.4 Giftighed over for mennesker

Der er ikke fundet data for giftighed over for mennesker.

5 Andre effekter

4,4-dimethylisoxazolidin-3-on har ingen harmoniseret klassificering, men stoffet er selvklassificeret med Skin Irrit. 2; forårsager hudirritation (H315) og STOT SE 3; kan forårsage irritation af luftveje (H335) (ECHA 2020a; ECHA 2020b).

Et datablad for 4,4-dimethylisoxazolidin-3-on angiver resultater fra en Ames-test (bakteriologisk metode), som ikke påviste at stoffet har mutagene effekter (CDS, 1984). Stoffet blev testet fra 0,14 til 13,6 mg/petriskål på fem forskellige stammer af bakteriearten *Salmonella typhimurium*.

Der er ikke fundet yderligere oplysninger om andre effekter.

6 Udledning af vandkvalitetskriterium

6.1 Vandkvalitetskriterium (VKK)

Når der er toksicitetsdata på få arter, anvendes den deterministiske metode, som tager udgangspunkt i den laveste pålidelige effektværdi (EU, 2018). Resultater fra QSAR anbefales kun at anvendes som supplerende data til udledningen af VKK (EU, 2018), og derfor anvendes de estimerede værdier i dette datablad (Tabel 4.3) ikke til udledningen af VKK. Dertil er der også usikkerhed om hvilken taksonomisk gruppe, som er den mest sensitive overfor 4,4-dimethylisoxazolidin-3-on.

Der foreligger to marine langtidsstudier for to forskellige trofiske niveauer (alge og invertebrat) for 4,4-dimetylisoxazolidin-3-on. Ved fastsættelse af vandkvalitetskriteriet for saltvand anvendes der jf. tabel 4 og note b i EU-vejledningen (EU, 2018) en usikkerhedsfaktor på 1000 til den laveste akutte effektkoncentration på >100 mg/L for fisken *Scophthalmus maximus*. Kriteriet beregnes på baggrund af akut data, da den laveste kroniske effektkoncentration er højere (EC_{10} = 130 mg/L) end den akutte effektkoncentration, der foreligger, som i dette tilfælde er for en fisk. LC_{50} sættes til 100 mg/L, ud fra forsigtighedsprincippet, og fordi der ikke er andet tilgængeligt data for fisk.

Der foreligger ikke troværdige toksicitetsdata for ferskvandsarter, og vandkvalitetskriteriet for ferskvand udledes derfor ud fra toksicitetsdata for marine arter. Der er usikkerheder forbundet ved denne tilgang, da det er uvist om det er de ferskvandslevende eller marine organismer, som er de mest sensitive. Studier tyder på, at ved anvendelse af en faktor 10 i ekstrapoleringen fra ferskvandslevende organismer til marine organismer, sikres beskyttelsen af de marine organismer (Leung et al, 2001; Wheeler et al, 2002), og dette stemmer overens med EU-vejledningen (EU, 2018). EU-vejledningen angiver ikke en forklaring eller en faktor, hvis der kun foreligger toksicitetsdata på marine organismer, som skal ekstrapoleres til ferskvandslevende organismer. Et studie af Wheeler et al. (2002) tyder på, at en faktor 10 ved ekstrapolering fra marine organismer til ferskvandslevende organismer, vil sikre beskyttelse for de ferskvandslevende organismer. Der er i forvejen inkluderet en ekstrapolering fra ferskvand til marin med en faktor 10 i usikkerhedsfaktoren på 1000 (EU, 2018, s. 48). Derfor anvendes en usikkerhedsfaktor på 1000 til vandkvalitetskriteriet for både ferskvand og saltvand:

$VKK_{ferskvand}$ = 100 mg/L / 1000 = 0,1 mg/L = 100 µg/L

$VKK_{saltvand}$ = 100 mg/L / 1000 = 0,1 mg/L = 100 µg/L

6.2 Korttidsvandkvalitetskriterium (KVKK)

Et korttidsvandkvalitetskriterium (KVKK) fastsættes ud fra resultater fra akutte forsøg, hvor der for stoffet 4,4-dimethylisoxazolidin-3-on foreligger akutte studier for *Skeletonema* sp (alge), *Acartia tonsa* (invertebrat) og *Scophthalmus maximus* (fisk). De akutte studier for *Skeletonema* sp , *A. tonsa* og *S. maximus* angiver hhv. en $L(E)C_{50}$ på >1000 mg/L, >1000 mg/L og >100 mg/L. Større end værdier bør ifølge EU-vejledningen ikke anvendes som udgangspunkt til udledningen af miljøkvalitetskriterier (EU, 2018, s. 144), men da der ikke er andre akutte studier tilgængelige for alger, invertebrater og fisk, sættes $L(E)C_{50}$ konservativt til 1000, 1000 og 100 mg/L for hhv.

Skeletonema sp, *A. tonsa* og *S. maximus*. Ved fastsættelse af korttidsvandskvalitetskriterium anvendes tabel 6 i EU-vejledningen (EU, 2018), hvor en usikkerhedsfaktor på 1000 anvendes til den laveste akutte effektkoncentration. Med samme argumentation som beskrevet i udledning af VKK, anvendes samme usikkerhedsfaktor til KVKK for både ferskvand og saltvand:

$KVKK_{ferskvand}$ = 100 mg/L / 1000 = 0,1 mg/L = 100 µg/L

$KVKK_{saltvand}$ = 100 mg/L / 1000 = 0,1 mg/L = 100 µg/L

6.3 Kvalitetskriterium for sediment (SKK)

4,4-dimethylisoxazolidin-3-on har et lavt potentiale for at bioakkumulere (log K_{ow} = 1) og adsorbere i jord (K_{oc} = 29,82, log K_{oc} = 1,47), og derfor opfylder stoffet ikke kriteriet ($K_{oc} \geq 100$ eller log $K_{ow} \geq 3$) til udarbejdelse af et sedimentkvalitetskriterium ifølge EU-vejledningen (EU, 2018).

6.4 Kvalitetskriterium for biota (BKK)

4,4-dimethylisoxazolidin-3-on har et lavt potentiale for at bioakkumulere (log K_{ow} = 1 og BCF = 1,016 L/Kg), og derfor opfylder stoffet ikke kriteriet (BCF ≥ 100 eller log $K_{ow} \geq 3$), til udarbejdelse af et biotakvalitetskriterium ifølge EU-vejledningen (EU, 2018).

6.5 Kvalitetskriterium for human konsum af vandlevende organismer (HKK)

4,4-dimethylisoxazolidin-3-on er ikke klassificeret som kræftfremkaldende, mutagent eller reproduktionstoksisk, og derfor opfylder stoffet ikke kriteriet til udarbejdelse af et humankonsumkvalitetskriterium ifølge EU-vejledningen (EU, 2018).

7 Konklusion

Der er stor usikkerhed forbundet med nedenstående miljøkvalitetskriterier grundet begrænset datamængde for 4,4-dimethylisoxazolidin-3-on, derfor er miljøkvalitetskriterierne for stoffet konservativt fastsat til følgende:

$VKK_{ferskvand}$ = 100 µg/L

$VKK_{saltvand}$ = 100 µg/L

$KVKK_{ferskvand}$ = 100 µg/L

$KVKK_{saltvand}$ = 100 µg/L

SKK: Ikke beregnet

$BKK_{sek.\ forg.}$: Ikke beregnet

$BKK_{sundhed}$: Ikke beregnet

SKK, $BKK_{sek.\ forg.}$ og $BKK_{sundhed}$ er ikke udledt, da 4,4-dimethylisoxazolidin-3-on har lavt potentiale for bioakkumulering (log K_{ow} = 1 og BCF = 1,016 L/Kg) og adsorbering i jord (log K_{oc} = 1,47), og derfor opfylder stoffet ikke kriterierne for behov for udledning af SKK og BKK ifølge EU-vejledning (EU, 2018).

8 Referencer

CDS (1984): Chemical data sheet of 4,4-dimethyloxazolidin-3-on, FMC Corporation.

DHI (2020a): Ecotoxicity characterisation of 4,4-Dimethylisoxazolidin-3-one, acute toxicity testing with *Skeletonema sp*., *Acartia tonsa* and *Scophthalmus maximus* (Turbot), accredited test report No. BWL190, unpublished.

DHI (2020b): Ecotoxicity characterisation of 4,4-Dimethylisoxazolidin-3-one, chronic toxicity testing with the marine crustacean *Acartia tonsa*, accredited test report No. BWL198, unpublished.

ECHA (2020a): REACH registreringsdossier af 4,4-dimethyl-1,2-oxazolindin-3-on, CAS nr.: 81778-07-6 (https://echa.europa.eu/da/registration-dossier/-/registered-dossier/7410).

ECHA (2020b): Brief profile, 4,4-dimethyl-1,2-oxazolidin-3-on (https://echa.europa.eu/da/brief-profile/-/briefprofile/100.221.217).

ECOSAR (2020): The Ecological Structure Activity Relationship Class Program, v.2.0, United States Environmental Protection Agency, Washington, DC, USA, (anvendt log K_{ow} = 1).

EPI Suite (2020): Estimation Programs Interface Suite™ for Microsoft® Windows, v 4.11. United States Environmental Protection Agency, Washington, DC, USA, (anvendt log K_{ow} = 1).

EU (2000): Europa-Parlamentets og Rådets Direktiv 2000/60/EF om fastsættelse af en ramme for fællesskabets vandpolitiske foranstaltninger af 23. oktober 2000.

EU (2008): ECHA: Guidance on information requirements and chemical safety assessment Chapter R.10: Characterisation of dose [concentration]-response for environment (https://echa.europa.eu/documents/10162/13632/information_requirements_r10_en.pdf/bb902be7-a503-4ab7-9036-d866b8ddce69).

EU (2018): Common Implementation Strategy for the Water Framework Directive (2000/60/EC). Guidance Document No. 27. Technical Guidance Document for Deriving Environmental Quality Standards.

Eurofins (2020): Test report: Partition coefficient (n-octanol/water), unpublished.

Leung, K., Morritt, D., Wheeler, J., Whitehouse, P., Sorokin, N., Toy, R., Holt, M and Crane, M. (2001): Can saltwater toxicity be predicted from freshwater data? Marine Pollution Bulletin, 42, 1007-1013.

Miljøstyrelsen (2004): Principper for fastsættelse af vandkvalitetskriterier for stoffer i overfladevand. Vejledning fra Miljøstyrelsen nr. 4, 2004.

OECD (2020): eChemPortal (https://www.echemportal.org/echemportal/substance-search).

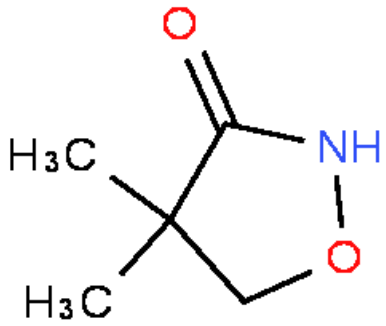
Wheeler, J., Leung, K., Morritt, D., Sorokin, N., Rogers, H., Toy, R., Holt, M., Whitehouse, P. and Crane, M. (2002): Freshwater to saltwater toxicity extrapolation using species sensitivity distributions. Environmental Toxicology and Chemistry, 21, 2459-2467.

Bilag A: Non-test data

Danish (Q)SAR Database, http://qsar.food.dtu.dk Date: 23-10-2020

(Q)SAR predicted profile

- **Structure (as used for QSAR prediction):**



SMILES (used for QSAR prediction): C1(=O)C(C)(C)CON1

- **ID**

REACH EC Number (pre-registration, by 2013)		REACH EC Number (registration, by Dec. 2019)	692-895-5
Registry Number	81778-07-6	PubChem CID	
EU CLP Harmonized Classification*		DK-EPA / DTU QSAR-based CLP Advisory Classification	Aquatic Chronic 3
REACH registration cumulated minimum annual tonnage			
Molecular Formula	C5 H9 N1 O2	Molecular weight (g/mole)	115.13
Chemical Name			

(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)	71.95	Melting Point Experimental (deg C)	
Boiling Point (deg C)	261.86	Boiling Point Experimental (deg C)	
Vapour Pressure (atm)	EPI.Estimated_VP_atm	Vapour Pressure Experimental (atm)	EPI.Exp_VP_atm
Vapour Pressure (mm Hg)	0.0052	Vapour Pressure Experimental (mm Hg)	
Vapour Pressure (Pa)	0.6933	Vapour pressure Subcooled Liquid (Pa)	1.92

EPI MPBPVP models

- **Henry's Law Constant**

HLC Bond Method (atm-m3/mole)	5.574E-009	HLC Group Method (atm-m3/mole)	
HLC Via VP/WSol (atm-m3/mole)	1.354E-008	HLC Via VP/WSol (Pa-m3/mole)	0.001372
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)	58180	Water solubility from Fragments (mg/L)	338420
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	12
- Standard deviation (±)	0.8
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	-0.09	-0.09	-0.09	-0.09	-0.09	-0.09	

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	6.943	Log Kaw	-6.643

EPI KOAWIN models

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

Log Kow	0.3		
Log Kow Exp		Log Kow Exp Ref	

EPI WSKOW model

LogKow: log octanol-water partition coefficient

Kp (m3/ug) Mackay-based	1.56E-006	Kp (m3/ug) Koa-based	2.15E-006
Phi Junge-Pankow-based	5.64E-005	Phi Mackay-based	0.000125
Phi Koa-based	0.000172		

EPI AEROWIN models

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

Koc from MCI (L/kg)	29.06	Log Koc from MCI	1.4633
Koc from Kow (L/kg)	12.23	Log Koc from Kow	1.0872

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 (%)	0.0547	26.2	73.7	0.0861
Half-Life (hr)	36.8	900	1800	8100
Emissions (kg/hr)	1000	1000	1000	0

EPI Level III Fugacity Model

Persistence time (hr)	1310
Persistence time (days)	

EPI Level III Fugacity Model

- **Level III Fugacity Environmental Partitioning, emission only to water**

	Air	Water	Soil	Sediment
Mass Amount (%)	1.21E-005	99.7	0.00754	0.328
Half-Life (hr)	36.8	900	1800	8100
Emissions (kg/hr)	0	1000	0	0

EPI Level III Fugacity Model

Persistence time (hr)	567
Persistence time (days)	23.625

EPI Level III Fugacity Model

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

	Total removal	Biodegradation	Sludge Adsorption	Volatilization
(%)	1.85	0.09	1.76	0

EPI STPWIN model

- **Atmospheric oxidation (25 deg C)**

	OH	Ozone
Half-Life (d)	1.532	0
Half-Life (hr)	18.387	
Overall Rate Const. (OH: E-12 cm3/molecule-sec and OZ: E-17 cm3/molecule-sec)	6.9804	

EPI AOPWIN models

- **Biodegradation**

Biowin1 (linear model) Probability of Rapid Biodegradation	0.5088
Biowin2 (non-linear model) Probability of Rapid Biodegradation	0.4135
Biowin3 Expert Survey Ultimate Biodegradation	2.7326
Biowin3 Expert Survey Ultimate Timeframe	weeks-months
Biowin4 Expert Survey Primary Biodegradation	3.5282
Biowin4 Exp. Survey Primary Timeframe	days-weeks
Biowin5 (MITI linear model) Biodegradation Probability	0.4578
Biowin6 (MITI non-linear model) Biodegradation Probability	0.4691
Biowin7 (Anaerobic Linear) Biodegradation Probability	0.2227
Petroleum Hydrocarbon Biodegradation Half-Life (days)	

EPI BIOWIN models

Biowin1 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)		NEG_OUT	INC_OUT	NEG_OUT	NEG_IN

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)	0.03526
BCF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	1.016
BCF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	1.105
BAF Arnot-Gobas (upper trophic) Including Biotransformation (L/kg wet-wt)	1.016
BAF Arnot-Gobas (upper trophic) Zero Biotransformation (L/kg wet-wt)	1.108

EPI BCFBAF models

BCF: Bioconcentration factor, BAF: Bioaccumulation factor

- **Aquatic toxicity**

Exp	Battery	Leadscope	SciQSAR
Fathead minnow 96h LC50 (mg/L)		175.4844	2132.498
Domain	OUT	OUT	OUT
Daphnia magna 48h EC50 (mg/L)		32.54158	372.9825
Domain	OUT	OUT	OUT
Pseudokirchneriella s. 72h EC50 (mg/L)		94.89175	376.1737
Domain	OUT	OUT	OUT

DTU-developed models

	Fish 96h	Daphnid 48h	Green Algae 96h
LC50 (Fish) or EC50 (Daphnid and Algae) for Most Toxic Class (mg/L)	567.302	1368.5	12.357
Max. Log Kow for Most Toxic Class	>8.5	>8.5	>8
Most Toxic Class	Amides	Amides	Amides
Note			

EPI ECOSAR models

ECOSAR Classes: Amides

- **Oral absorption**

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

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)

EPI DERMWIN model

- **Brain/blood Distribution**

Log brain/blood partition coefficient	

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)		NEG_OUT	INC_OUT	NEG_OUT	NEG_IN
CYP2D6 substrates (Human clinical data)		NEG_OUT	INC_OUT	NEG_OUT	NEG_IN

DTU-developed models

- **Acute toxicity in Rodents**

	LD50 (mg/kg/d)	Reliability Index
Rat Oral	1500	0.36
Rat Intraperitoneal	650	0.64
Mouse Oral	2900	0.67
Mouse Intraperitoneal	370	0.46
Mouse Intravenous	290	0.45
Mouse Subcutaneous	960	0.76

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	NEG_IN	NEG_OUT	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		NEG_OUT	INC_OUT	POS_OUT	NEG_IN
Allergic Contact Dermatitis in Guinea Pig and Human*	N/A	NEG_OUT	INC_OUT	NEG_OUT	NEG_IN
Respiratory Sensitisation in Humans		POS_OUT	INC_OUT	POS_OUT	POS_IN

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%) >> No protein binding alert
- 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%) >> No protein binding alert
- 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	Not possible to classify according to these rules (GSH)

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	INC_OUT	NEG_OUT	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_OUT	INC_OUT	NEG_OUT	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_OUT	INC_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_OUT	NEG_OUT	NEG_OUT	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_OUT	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			18415.71	1954.154	
- μM			159955.8	16973.45	
- Positive for IC_{50} ≤ 10 μM					
- Positive for IC_{50} ≤ 100 μM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			0.482157	55.07043	
- μM			4.187935	478.3326	
- Positive for IC_{50} ≤ 10 μM					
- Positive for IC_{50} ≤ 100 μM					
- Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	INC_OUT	N/A
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	INC_OUT	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	NEG_IN	POS_OUT	NEG_IN	NEG_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	INC_OUT	N/A
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
Constitutive Androstane Receptor (CAR) Activation at max. 20 μM (*in vitro*)		N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 μM (*in vitro*)		N/A	N/A	NEG_IN	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	INC_OUT	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)		N/A	N/A	INC_OUT	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	INC_OUT	N/A

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, non cyclic structure
- metabolites from Rat liver S9 metabolism simulator only	
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	

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	POS_OUT	INC_OUT	INC_OUT	POS_IN

DTU-developed models based on commercial training set

- **Genotoxicity - Structural Alerts for DNA Reactivity**

	Battery	CASE Ultra	Leadscope	SciQSAR
Ashby Structural Alerts	NEG_OUT	INC_OUT	NEG_OUT	NEG_IN
DTU-developed models based on commercial training set				
DNA binding by OASIS, alerts in:				
- parent only	No alert found			
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*)		INC_OUT	NEG_OUT	NEG_OUT	NEG_OUT
*Direct Acting Mutagens (without S9)	N/A	POS_OUT	INC_OUT	POS_OUT	POS_IN
*Base-Pair Ames Mutagens	N/A	INC_OUT	INC_OUT	POS_OUT	INC_OUT
*Frameshift Ames Mutagens	N/A	NEG_OUT	INC_OUT	NEG_OUT	NEG_IN
*Potent Ames Mutagens, Reversions ≥ 10 Times Controls	N/A	INC_OUT	INC_OUT	NEG_OUT	INC_OUT

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.

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	No alert found

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_OUT	INC_OUT	INC_OUT	NEG_IN
Chromosome Aberrations in Chinese Hamster Lung (CHL) Cells		INC_OUT	INC_OUT	INC_OUT	INC_OUT
Mutations in Thymidine Kinase Locus in Mouse Lymphoma Cells		INC_OUT	INC_OUT	INC_OUT	NEG_OUT
Mutations in HGPRT Locus in Chinese Hamster Ovary (CHO) Cells		INC_OUT	INC_OUT	NEG_OUT	POS_OUT
Unscheduled DNA Synthesis (UDS) in Rat Hepatocytes		NEG_OUT	INC_OUT	NEG_OUT	NEG_IN
Syrian Hamster Embryo (SHE) Cell Transformation		NEG_OUT	INC_OUT	INC_OUT	NEG_IN

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_OUT	INC_OUT	INC_OUT	NEG_IN
Micronucleus Test in Mouse Erythrocytes		NEG_OUT	INC_OUT	NEG_OUT	NEG_IN
Dominant Lethal Mutations in Rodents		POS_OUT	INC_OUT	NEG_OUT	POS_IN
Sister Chromatid Exchange in Mouse Bone Marrow Cells		NEG_OUT	INC_OUT	POS_OUT	NEG_IN
Comet Assay in Mouse		NEG_OUT	INC_OUT	POS_OUT	NEG_IN

DTU-developed models

In vivo mutagenicity (Micronucleus) alerts by ISS, alerts in:	
- parent only	H-acceptor-path3-H-acceptor

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	INC_OUT	INC_OUT
FDA RCA Cancer Female Rat	INC_OUT	INC_OUT
FDA RCA Cancer Rat	INC_OUT	NEG_OUT
FDA RCA Cancer Male Mouse	POS_OUT	INC_OUT
FDA RCA Cancer Female Mouse	INC_OUT	INC_OUT
FDA RCA Cancer Mouse	POS_OUT	NEG_OUT
FDA RCA Cancer Rodent	INC_OUT	INC_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	No alert found
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		NEG_OUT	POS_OUT	NEG_OUT	NEG_IN

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/