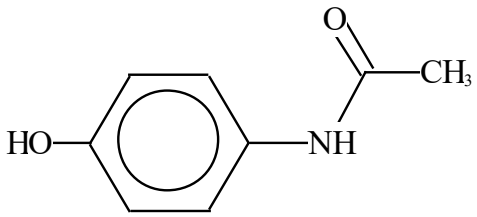
Miljøministeriet
Miljøstyrelsen

Fastsættelse af kvalitetskriterier for vandmiljøet

Paracetamol

CAS nr. 103-90-2



Vandkvalitetskriterium	$VKK_{ferskvand}$	24,4 µg/l
Vandkvalitetskriterium	$VKK_{saltvand}$	2,44 µg/l
Korttidsvandkvalitetskriterium	$KVKK_{ferskvand}$	1 390 µg/l
Korttidsvandkvalitetskriterium	$KVKK_{saltvand}$	139 µg/l
Sedimentkvalitetskriterium	$SKK_{ferskvand}$	Ikke relevant
Sedimentkvalitetskriterium	$SKK_{saltvand}$	Ikke relevant
Biota-kvalitetskriterium, sekundær forgiftning	$BKK_{sek.forgiftn.}$	Ikke relevant
Biota-kvalitetskriterium, human konsum	HKK	Ikke relevant

Juni 2024

Indholdsfortegnelse

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, i sediment, i dyr og planter (biota) og for human konsum.

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 07/02-2024.

English Summary and conclusions

Paracetamol is a synthetic pain reliever and antipyretic pharmaceutical used for mild conditions of headache, muscle pain etc. Paracetamol is one of the most sold over-the-counter pharmaceuticals in the EU.

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

Valid experimental values for the toxicity of paracetamol are available in the literature for short-term tests on 21 freshwater species (Algae: *Chlamydomonas reinhardtii, Chlorella vulgaris, Pseudokirchneriella subcapitata, Scenedesmus subspicatus*; Ciliates: *Tetrahymena pyriformis*; Cyanobacteria: *Cylindrospermopsis raciborskii*; Crusteaceans: *Ceriodaphnia silvestrii, Daphnia longispina, Daphnia magna, Daphnia pulex, Moina macrocopa*; Fish: *Brachydanio rerio, Danio rerio, Oryzias latipes, Pimephales promelas*; Water plants: *Lemna gibba, Lemna minor*; Molluscs: *Corbicula fluminea*; Polyp: *Hydra vulgaris*; Flatworm: *Dugesia japonica*; Amphibian: *Xenopus laevis*). Furthermore, valid experimental values are available for long-term tests on 7 freshwater species (Crusteaceans: *Daphnia magna*, *Ceriodaphnia silvestrii, Daphnia longispina, Moina macrocopa,* Fish: *Oryzias latipes,* Molluscs: *Corbicula fluminea,* Polyp: *Hydra vulgaris*). Three valid short-term tests have been found for saltwater species (Algae: *Phaeodactylum tricornutum*; Crusteaceans: *Artemia salina*; Bacteria: *Vibrio fischeri*), and one long-term test have been found for saltwater organisms (Algae: *Phaeodactylum tricornutum*).

The dataset is listed in Appendix A.

AA-EQS for water

According to the TGD (EU, 2018), when not enough data is available to use the SSD (Species Sensitivity Distribution) method the deterministic approach using uncertainty factors, UF, shall be used for the derivation of EQS. Therefore, this approach is followed for derivation of the AA-EQS for paracetamol.

In the chronic dataset, crustaceans exhibit the greatest sensitivity towards paracetamol and the aggregated chronic NOEC (reproduction) value of 1.22 mg/L is used for the derivation of the AA-EQS as this dataset contains the lowest effect value. Since there are two available chronic studies (EC_{10} or NOEC) for two trophic levels, an UF of 50 can be used on the lowest EC_{10}/NOEC value, according to TGD (EU, 2018). $AA\text{-}EQS_{freshwater}$ is calculated:

$AA\text{-}EQS_{freshwater}$ = 1.22 mg/L / 50 = 0.0244 mg/L = 24.4 µg/L

Since no chronic studies are available for saltwater organisms, the $AA\text{-}EQS_{saltwater}$ is based on the same chronic test data as for the freshwater. An additional UF factor is applied compared to the

freshwater AA-EQS, so an UF of 500 is used to the NOEC value of 1.22 mg/L. AA-$EQS_{saltwater}$ is calculated:

AA-$EQS_{saltwater}$ = 1.22 mg/L / 500 = 0.00244 mg/L = 2.44 µg/L

MAC-EQS for water

In the short-term dataset, crustaceans exhibit the greatest sensitivity towards paracetamol and the aggregated acute EC_{50} (immobile) value of 13.9 mg/L is used for the derivation of the MAC-EQS as this dataset contains the lowest effect value. According to the TGD (EU, 2018) an UF of 10 can be applied to the lowest E(L)C_{50} value, when short-term data are available for three trophic levels with the most sensitive species included in the dataset and the mode of action is known. The mode of action of paracetamol is known and possible toxic effects stems from an accumulated metabolite of paracetamol in the body. Because of this mode of action, it is expected that crustaceans and/or fish are most sensitive towards paracetamol, which is also observed. Thus, it seems acceptable to use an UF of 10 on the lowest EC_{50} value. MAC-$EQS_{freshwater}$ is calculated:

MAC-$EQS_{freshwater}$= 13.9 mg/L / 10 = 1.39 mg/L = 1,390 µg/L

Since limited short-term studies are available for saltwater organisms, the MAC-$EQS_{saltwater}$ is based on the same acute test data as for the freshwater. An additional UF factor is applied compared to the freshwater MAC-EQS, so an UF of 100 is used to the EC_{50} value of 13.9 mg/L. MAC-$EQS_{saltwater}$ is calculated:

MAC-$EQS_{saltwater}$ = 13.9 mg/L / 100 = 0.139 mg/L = 139 µg/L

QS for sediment

No evidence of high toxicity to aquatic and/or sediment-dwelling organisms or evidence of accumulation in sediments from monitoring have been found for the substance. In combination with the Log K_{ow} < 3 (1.098) and Log Koc < 3 (1.32) for paracetamol, the QS for sediment shall not be derived according to the TGD (EU, 2018).

QS for secondary poisoning

There are no valid values for the bioaccumulation potential (BMF or BCF (BAF)) of paracetamol. Therefore, whether a QS for secondary poisoning ($QS_{sec.\ pois.}$) is relevant is determined using Log K_{ow}. According to the TGD (EU, 2018), it is relevant to derive $QS_{sec.\ pois.}$ for a substance when Log K_{ow} ≥3. ECHA (2024) indicates a Log K_{ow} = 1.098, from which it is concluded that a derivation of a $QS_{sec.\ pois.}$ is not relevant.

QS for human health

According to TGD (EU, 2018), a QS for human health of fishery products is relevant if the substance has relevant human hazard properties. Paracetamol is not considered to have such properties and a criterion for human consumption is not relevant.

QS_{water} based on $QS_{sec.\ pois.}$ and $QS_{human\ health}$

A QS for secondary poisoning and human health has not been derived. Considering the lack of bioaccumulating properties and human health hazards it is realistic to assume that the EQS for water also covers biota and human consumption.

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

$AA\text{-}EQS_{freshwater}$	= 24.4 µg/l
$AA\text{-}EQS_{saltwater}$	= 2.44 µg/l
$MAC\text{-}EQS_{freshwater}$	= 1,390 µg/l
$MAC\text{-}EQS_{saltwater}$	= 139 µg/l
$QS_{sediment,\ freshwater}$	Not relevant
$QS_{sediment,\ saltwater}$	Not relevant
$QS_{sec.\ pois.}$	Not relevant
$QS_{human\ health}$	Not relevant

1 Indledning

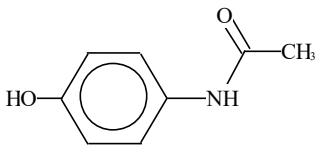
Nærværende datablad vedrører paracetamol med CAS nr. 103-90-2.

Identiteten af paracetamol fremgår af Tabel 1.1.

Paracetamol er et syntetisk smertestillende og febernedsættende lægemiddelstof, som anvendes mod milde smerter som f.eks. hovedpine og muskelsmerter eller ved feber. Da paracetamol generelt set har få bivirkninger, er det det præparat, der oftest bruges ved milde til moderate smerter (Sundhedsstyrelsen).
Paracetamol sælges i de fleste EU-lande både som receptpligtigt og håndkøbsmedicin. I EU bliver der på pr. indbygger basis solgt mellem 4-5 tons/million og op til 30-50 tons/million (Moore & Moore, 2016).

Stoffet har ingen harmoniseret CLP-klassificering, men har én selvklassificering for miljøet; Aquatic Chronic 3 (H412) (baseret på 142 C&L notifikationer). Stoffet har yderligere, som del af REACH registreringsdossieret, selvklassificeringerne Acute Tox. 4 (H302) (142 C&L notifikationer) og STOT SE 2 (H371) (2 C&L notifikationer), som er relevant for humant konsum (ECHA, 2024).

Tabel 1.1. Identitet af paracetamol

IUPAC navn	N-(4-hydroxyphenyl)acetamide
Strukturformel	
CAS nr.	103-90-2
EINECS nr.	203-157-5
Kemisk formel	$C_8H_9NO_2$
SMILES	O=C(Nc(ccc(O)c1)c1)C
Harmoniseret klassificering	Ingen
Selvklassificering	Acute Tox. 4, H302 (farlig ved indtagelse) Aquatic Chronic 3, H412 (skadelig for vandlevende organismer, med langvarige virkninger) STOT SE 2, H371 (kan forårsage organskader)

2 Fysisk kemiske egenskaber

De fysisk kemiske egenskaber for paracetamol fremgår af Tabel 2.1.

Tabel 2.1. Fysisk kemiske egenskaber for paracetamol

Parameter	**Værdi**	**Reference**
Molekylevægt, M_w ($g \cdot mol^{-1}$)	151,17	EPI Suite, 2023, se Bilag B
Smeltepunkt, T_m (ºC)	165,6	ECHA, 2024
Kogepunkt, T_b (ºC)	>250	ECHA, 2024
Damptryk, P_v (Pa)	$1{,}00 \times 10^{-3}$ [1]	ECHA, 2024
Henry's konstant, H ($Pa \cdot m^3 \cdot mol^{-1}$)	$2{,}80 \times 10^{-6}$ [2]	EPI Suite, 2023, se Bilag B
Vandopløselighed, S_w ($g \cdot L^{-1}$)	19 (pH 5,8) [3]	ECHA, 2024
Dissociationskonstant, pK_a	7,28 [4]	ECHA, 2024
Octanol/vand fordelingskoefficient, log K_{ow}	1,098 [1]	ECHA, 2024
Sediment/vand fordelingskoefficient, normaliseret til organisk karbon, K_{oc} ($L \cdot kg^{-1}$)	20,844 [5]	ECHA, 2024

[1]Estimeret værdi for 25 °C
[2]Eksperimentiel værdi fra database ved 25 °C
[3]ved 28 °C
[4]ved 26 °C
[5]ved 20 °C

3 Skæbne i miljøet

3.1 Nedbrydelighed

I REACH registreringen er paracetamol vurderet som biologisk let nedbrydeligt i vand under aerobe forhold (ECHA, 2024). Vurderingen er foretaget på baggrund af en "vægtning af data" tilgang (Weight of Evidence) baseret på videnskabelige publikationer, herunder et studie udført efter OECD 301F, samt (Q)SAR.

Under anaerobiske forhold fandt Edrees *et al.* (2017), at 90% af paracetamol nedbrydes efter 6 måneder i slam ved pH 7,0.

(Q)SAR forudsigelser ved brug af BIOWIN v4.10 (EPI Suite) vurderer dog generelt paracetamol som værende ikke let-bionedbrydelig under anaerobe forhold (EPI Suite, 2023) (se Bilag B).

Ved brug af BIOWIN v4.10 (EPI Suite) er paracetamol vurderet som ikke-persistent i jord, da den estimerede halveringstid (DT_{50}) af paracetamol i jord er 30 dage ved 25 °C (ECHA, 2024). Resultatet understøttes af paracetamols lave affinitet for organisk materiale i jord (K_{OC} på 20,8), der indikerer, at stoffet er meget mobilt i jord.

Henry's lov konstant (H) på $2{,}80\times10^{-6}$ $Pa\cdot m^3\cdot mol^{-1}$ angiver en lav flygtighedsrate for paracetamol og derved må det antages, at fordampning af paracetamol ikke spiller en væsentlig rolle for stoffet i miljøet (EPI Suite, 2023).

Samlet set kan paracetamol således karakteriseres som let-bionedbrydelig i vand under aerobe forhold og potentielt nedbrydelig under anaerobe forhold. Yderligere forventes paracetamol at blive i vandfasen og vil ikke akkumulere i jord eller sediment (ECHA, 2024).

3.2 Bioakkumulering

Der er ikke fundet eksperimentelle data for bioakkumulering af paracetamol. Stoffets affinitet for sorption til organisk materiale er lav (eksperimentel log K_{OW} på 1,098 (ECHA, 2024)), og derfor forventes stoffet ikke at ophobes i organisk væv. EPI Suite beregning baseret på en estimeret log K_{OW} på 0,46 estimerer en BCF på 3,2 L/kg vådvægt (EPI Suite, 2023, se Bilag B), hvilket understøtter, at stoffet ikke forventes at være bioakkumulerende.

3.3 Naturlig forekomst

Paracetamol fremstilles ved kemisk syntese og findes ikke naturligt i miljøet.

Størstedelen af indtaget af paracetamol bliver omdannet i kroppen til ikke-giftige stoffer, men en lille andel forbliver uændret og udskilles med urinen, hvor størstedelen forventes af blive omsat i avanceret (MBNDK) renseanlæg. For mekaniske renseanlæg er der dog kun målt en reduktion af

paracetamol på 19% fra indløb til udløb (Miljøstyrelsen, 2021), hvorfor forekomsten af paracetamol i miljøet herved sker via udløb fra renseanlæg. Hertil er der detekteret miljøkoncentrationer af paracetamol i bl.a. overfladevand med koncentrationer på >65 µg/L i Tyne floden i England og >78 µg/L i Donau floden. Gennemsnitskoncentrationer på 5 ng/L er fundet i overfladevand (Żur *et al.*, 2018). En median koncentration på 343 ng/L er fundet for europæiske floder, hvor der er målt efter bl.a. paracetamol ved 344 lokationer i et globalt studie fra Wilkinson *et al.,* (2022).

4 Toksicitetsdata

De anvendte studier og deres troværdighed fremgår af bilag A. Troværdigheden af studierne er vurderet ved tildelingen af en Klimisch score fra 1 til 4 (Klimisch *et al.,* 1997). Score 1 angiver, at studiet kan anvendes uden forbehold, mens score 2 angiver at studiet kan anvendes med forbehold, f.eks. at der er tilstrækkelige oplysninger, selvom studiet ikke er udført i forhold til guideline. Studier, som ikke er tilstrækkeligt beskrevet, tildeles score 3 eller 4, hvor score 4 tildeles studier, hvor det ikke er muligt at vurdere kvaliteten og dermed troværdigheden. Estimerede værdier tildeles score 3, da de ikke bør anvendes direkte i udledningerne af miljøkvalitetskriterier jf. TGD (EU, 2018).

4.1 Toksicitet over for vandlevende organismer

Der er fundet akutte og kroniske effektværdier for både ferskvands- og saltvandsorganismer. Effektkoncentrationer for organismer er sammenstillet i Bilag A. Krebsdyr er den mest følsomme organisme med en aggregeret NOEC-værdi på 1,22 mg/L, samt en aggregeret EC_{50}-værdi på 13,9 mg/L.

Der er fundet troværdige akutte toksicitetsdata for 21 forskellige arter (Alger: *Chlamydomonas reinhardtii, Chlorella vulgaris, Pseudokirchneriella subcapitata, Scenedesmus subspicatus*; Ciliater: *Tetrahymena pyriformis*; Cyanobakterier: *Cylindrospermopsis raciborskii*; Krebsdyr: *Ceriodaphnia silvestrii, Daphnia longispina, Daphnia magna, Daphnia pulex, Moina macrocopa*; Fisk: *Brachydanio rerio, Danio rerio, Oryzias latipes, Pimephales promelas*; Vandplanter: *Lemna gibba, Lemna minor*; Bløddyr: *Corbicula fluminea*; Polyp: *Hydra vulgaris*; Fladorm: *Dugesia japonica*; Padder: *Xenopus laevis*) fordelt på tre trofiske niveauer: primærproducenter, primærkonsumenter og sekundærkonsumenter, og som repræsenterer 10 taksonomiske grupper. Dertil er der fundet troværdige akutte toksicitetsdata for tre saltvandsarter (Alger: *Phaeodactylum tricornutum*; Krebsdyr: *Artemia salina*; Bakterier: *Vibrio fischeri*), som repræsenterer tre taksonomiske grupper).

Det kroniske datasæt for ferskvand består af eksperimentelle data fra troværdige langtidstest på 7 arter (Krebsdyr: *Daphnia magna*, *Ceriodaphnia silvestrii, Daphnia longispina, Moina macrocopa*; Fisk: *Oryzias latipes*; Bløddyr: *Corbicula fluminea*; Polyp: *Hydra vulgaris*) fordelt på to trofiske niveauer: primærkonsumenter og sekundærkonsumenter, der repræsenterer fire taksonomiske grupper. Studierne med algearterne beskrevet for akutte effektværdier for ferskvandsorganismer kan ikke understøtte kroniske effektværdier, da der ikke foreligger EC_{10}/NOEC-værdier på algestudierne.

4.2 Toksicitet over for sedimentlevende organismer

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

4.3 Toksicitet over for pattedyr og fugle

Der er ikke søgt efter data for giftighed over for pattedyr og fugle. Ifølge TGD (EU, 2018) skal der udledes et biota-kvalitetskriterie for stoffer med potentiale for bioakkumulering eller høj toksicitet over for pattedyr og fugle. Paracetamol vurderes ikke at være potentiel bioakkumulerbar. Paracetamol har selvklassificeringerne; farlig ved indtagelse (H302) samt kan forårsage organskader (H371). H302-klassifceringen henviser til en fysisk fare ved indtagelse af lægemidlet, og H371-klassificeringen henviser til risiko for organskade ved overforbrug af lægemidlet. Dette er ikke et niveau, man forventer at observere i miljøet, hvorfor det er realistisk at antage, at vandkvalitetskriteriet også sikrer beskyttelse over for fugle og pattedyr.

4.4 Toksicitet over for mennesker

Der er ikke søgt efter data for giftighed over for mennesker, idet udledning af et kvalitetskriterie for humant konsum (af fisk) ikke er relevant. Jævnfør TGD (EU, 2018) er dette relevant at udlede, hvis stoffet har relevante human fareegenskaber. Som nævnt ovenfor har paracetamol selvklassificeringerne H302 og H371, men da det ikke er harmoniserede klassificeringer og stoffet ydermere ikke betragtes som en alvorlig fare ved indtag, vurderes paracetamol ikke at være farlig over for mennesker ved eksponering via miljøet. Ifølge Sundhedsstyrelsen kan der dog forekomme leverskader, hvis der indtages højere doser af paracetamol end den maksimale daglige dosis på 4 g dagligt (Sundhedsstyrelsen, n.d.).

5 Andre effekter

Det er vurderet, at paracetamol ikke har andre relevante effekter, da stoffet ikke er listet på aktuelle lister, inklusiv lister over hormonforstyrrende stoffer (CoRAP, EASIS, EDLIST, EDSP, PACT og TEDX)[1] samt ikke har en relevant klassificering, der antyder endokrine eller andre effekter end anført i databladet.

[1] CoRAP: Community Rolling Action Plan (https://echa.europa.eu/da/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table); EASIS: Endocrine Active Substances Information System (https://easis.jrc.ec.europa.eu/iuclid6-web/browser/raw/SUBSTANCE); EDLIST: Endocrine Disruptor List (https://edlists.org/the-ed-lists); EDSP: Endocrine Disruptor Screening Program (https://www.epa.gov/endocrine-disruption/endocrine-disruptor-screening-program-edsp-estrogen-receptor-bioactivity); PACT: Public Activities Coordination Tool (https://echa.europa.eu/da/pact); TEDX: The Endocrine Disruption Exchange (https://endocrinedisruption.org/interactive-tools/tedx-list-of-potential-endocrine-disruptors/search-the-tedx-list)

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)

Der er ikke tilstrækkelige data og taksonomiske grupper nok repræsenteret til at anvende SSD (Species Sensitivity Distribution) metoden, som jf. TGD (EU, 2018) kræver minimum 10 forskellige arter fordelt på minimum 8 taksonomiske grupper. Derfor anvendes den deterministiske metode med anvendelse af usikkerhedsfaktorer til udledning af vandkvalitetskriterier for paracetamol.

Det kroniske datasæt for ferskvand består af eksperimentelle data fra langtidstest på to trofiske niveauer: primærkonsument og sekundærkonsument med de fire taksonomiske grupper: krebsdyr, muslinger, ferskvandspolypper og fisk. Studierne med algearterne beskrevet for akutte effektværdier for ferskvandsorganismer kan ikke understøtte kroniske effektværdier, da der ikke foreligger EC_{10}/NOEC-værdier på algestudierne.

6.1.1 Ferskvand

For det kroniske datasæt udviser muslingen *Corbicula fluminea* den største følsomhed. Det er dog ikke angivet, hvilken effekt NOEC-værdien er målt på. Det vurderes derfor, at studiet ikke kan benyttes som udslagsgivende. I stedet vurderes det, at krebsdyrene udviser den største følsomhed, når der ses bort fra *Corbicula fluminea,* og den aggregerede kroniske NOEC-værdi på 1,22 mg/L anvendes til udledning af $VKK_{ferskvand}$. Da der er flere tilgængelige datasæt for samme organisme (*Daphnia magna*) og samme effekt (reproduktion), er der beregnet en aggregeret værdi. NOEC (reproduktion) for *Daphnia magna* er valgt som effekt, da den laveste effektværdi er fundet under dette endpoint. Da der er kroniske resultater (EC_{10} eller NOEC) tilgængelige for arter repræsenterende to trofiske niveauer kan der, jf. TGD (tabel 3 i EU, 2018), anvendes en usikkerhedsfaktor (UF) på 50 på den laveste EC_{10}/NOEC-værdi. Herved beregnes $VKK_{ferskvand}$:

$VKK_{ferskvand}$ = 1,22 mg/L / 50 = 0,0244 mg/L = 24,4 µg/L

6.1.2 Saltvand

Der er fundet ét studie med kronisk data for saltvandsalger, men der mangler data for krebsdyr og fisk for at fuldende basissættet. Vandkvalitetskriteriet for saltvand findes derfor ved anvendelse af en yderligere UF på 10 i forhold til ferskvand, jf. TGD (tabel 4 i EU, 2018). $VKK_{saltvand}$ beregnes til:

$VKK_{saltvand}$ = 1,22 mg/L / 500 = 0,00244 mg/L = 2,44 µg/L

6.2 Korttidsvandkvalitetskriterium (KVKK)

Det akutte datasæt for ferskvand består af eksperimentelle data fra korttidstest på de tre trofiske niveauer: primærproducenter, primærkonsumer og sekundærkonsumer med en række arter repræsenteret indenfor de følgende taksonomiske grupper: alger, cyanobakterier, ciliater, krebsdyr, polypper, bløddyr (muslinger), padder, fladorme, hjuldyr, vandplanter og fisk.

6.2.1 Ferskvand

For det akutte datasæt udviser fisken *D. rerio* den største følsomhed. Varigheden af studiet er dog angivet som hpf (hours post fertilisation), hvilket ikke er en standard angivelse for varighed. Det vurderes derfor, at studiet ikke kan benyttes som udslagsgivende. I stedet vurderes det, at krebsdyrene udviser den største følsomhed, når der ses bort fra *D. rerio*, og den aggregerede akutte EC_{50}-værdi på 13,9 mg/L anvendes til udledning af $KVKK_{ferskvand}$, da der er flere tilgængelige datasæt for samme organisme (*Daphnia magna*) og samme effekt (immobilisering). EC_{50} (immobilitet) for *Daphnia magna* er valgt som den kritiske værdi, da den laveste effektværdi er fundet under dette endpoint. Jævnfør TGD (EU, 2018) skal der anvendes en UF på 100 på den laveste $E(L)C_{50}$-værdi ved data tilgængeligt for korttidstest på mindst tre trofiske niveauer af basissættet: fisk, krebsdyr og alger. Der er mulighed for at ændre denne til 10, hvis standardafvigelsen på de log10 transformerede data for de forskellige trofiske niveauer er mindre end 0,5 eller stoffet har en kendt virkemekanisme og hvis den mest følsomme gruppe er inkluderet i datasættet. Når paracetamol indtages, konjugeres det med co-faktorer og danner ikke-toksiske metabolitter, der bliver udskilt. Ved nogle tilfælde kan de dannede metabolitter dog akkumulere i kroppen og udøve toksiske virkninger på organismen, hvor det vil forventes, som det også er observeret, at krebsdyr og/eller fisk er den mest følsomme organismegruppe (Nunes *et al.,* 2014). Derfor vurderes det, at det er acceptabelt at anvende en usikkerhedsfaktor på 10 på den lavest EC_{50}-værdi. Herved beregnes $KVKK_{ferskvand}$:

$KVKK_{ferskvand}$ = 13,9 mg/L / 10 = 1,39 mg/L = 1390 µg/L

6.2.2 Saltvand

Basissættet er ikke fuldendt for det akutte datasæt for saltvandsorganismer, da der ikke er fundet data for fisk. Vandkvalitetskriteriet for saltvand findes derfor ved anvendelse af en yderligere UF på 10 i forhold til ferskvand, jf. TGD (EU, 2018). $KVKK_{saltvand}$ beregnes til:

$KVKK_{saltvand}$ = 13,9 mg/L / 100 = 0,139 mg/L = 139 µg/L

6.3 Kvalitetskriterium for sediment (SKK)

Jævnført TGD (EU, 2018) er det relevant at udlede sedimentkvalitetskriterier for et stof, når log $K_{OW} \geq 3$ eller log $K_{OC} \geq 3$. Paracetamol har en Log K_{OW} = 1,098 og en Log K_{OC} = 1,32 (ECHA, 2024). Der er ikke fundet anden relevant data (evidens for høj toksicitet mod vand- og/eller sedimentlevende organismer eller evidens for akkumulering i sedimenter fra monitering) for stoffet, hvoraf det konkluderes, at et sedimentkriterie for paracetamol ikke er relevant.

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

Der foreligger ikke valide værdier for paracetamols bioakkumulerbarhed (BMF eller BCF (BAF)), og hvorvidt et biotakriterie for sekundær forgiftning ($BKK_{sek.forgiftn.}$) er relevant afgøres derfor alene på baggrund af Log K_{OW}. Jævnfør vejledningen (EU, 2018) er det relevant at udlede BKK for et stof, når Log $K_{OW} \geq 3$. I ECHA's registreringsdatabase angives en Log $K_{OW} = 1{,}098$ (ECHA, 2024), hvoraf det vurderes, at udledning af en $BKK_{sek.forgiftn.}$ ikke er relevant.

6.5 Kvalitetskriterium for human konsum af vandlevende organismer (HKK)

Et kvalitetskriterie for human konsum af fiskeriprodukter (HKK) er i følge vejledningen (EU, 2018) relevant at udlede, hvis stoffet har relevante humane fareegenskaber (nærmere specificeret i vejledningen afsnit 2.4.3.2). Stoffer, som forårsager effekter på reproduktion, fertilitet og udvikling er af særlig vigtighed, da disse er langsigtede effekter på populationsniveau. Paracetamol vurderes ikke at have sådanne egenskaber, hvorfor et kriterie for human konsum ikke er relevant.

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

Der er ikke udledt $BKK_{sek.forgiftn.}$ og HKK, jævnfør ovenfor. På baggrund af manglende potentiale for bioakkumulering og humanfareegenskaber er det realistisk at antage, at vandkvalitetskriteriet også sikrer beskyttelse af biota- og human konsum.

7 Konklusion

Følgende kvalitetskriterier for vandmiljøet er udregnet for paracetamol:

Vandkvalitetskriterium

$VKK_{ferskvand}$	24,4 µg/l
$VKK_{saltvand}$	2,44 µg/l

Korttidsvandkvalitetskriterium

$KVKK_{ferskvand}$	1.390 µg/l
$KVKK_{saltvand}$	139 µg/l

Sedimentkvalitetskriterium

$SKK_{ferskvand}$	Ikke relevant
$SKK_{saltvand}$	Ikke relevant

Biotakvalitetskriterium, sekundær forgiftning

$BKK_{sek.forgiftn.}$	Ikke relevant

Biotakvalitetskriterium, human konsum

HKK	Ikke relevant

8 Referencer

Boulassel, A., Djebar, M. R., Rouabhi, R. & Djebar, H. (2013). Physiological and biochemical changes observed in alternative cellular model: Paramecuim tetraurelia treated with paracetamol. *International Journal of Biosciences, 3*(9), 132-141. doi: http://dx.doi.org/10.12692/ijb/3.9.132-141

Brandão, F. P., Pereira, J. L., Gonçalves, F. & Nunes, B. (2014). The Impact of Paracetamol on Selected Biomarkers of the Mollusc Species *Corbicula fluminea*. *Environmental Toxicology*, *29*(1), 74-83. DOI: 10.1002/tox.20774

Broderius, S. J., Kahl, M. D. & Hoglund, M. D. (1995). Use of Joint Toxic Response to Define the Primary Mode of Toxic Action for Diverse Industrial Organic Chemicals. *Environmental Toxicology and Chemistry, 14*(9), 1591-1605.

Brun, G. L., Bernier, M., Losier, R., Doe, K., Jackman, P. & Lee, H.-B. (2006). Pharmaceutically Active Compounds in Atlantic Canadian Sewage Treatment Plant Effluents and Receiving Waters, and Potential for Environmental Effects as Measured by Acute and Chronic Aquatic Toxicity, *Environmental Toxicology and Chemistry, 25*(8), 2163-2176. DOI: 10.1897/05-426r.1

Calleja, M. C., Persoone, G. & Geladi, P. (1994). Human acute toxicity prediction of the first 50 MEIC chemicals by a battery of ecotoxicological tests and physicochemical properties. *Food and Chemical Toxicology, 32*(2), 173-187. https://doi.org/10.1016/0278-6915(94)90180-5

Castro, B. B., Freches, A. R., Rodrigues, M., Nunes, B. & Antunes, S. C. (2018). Transgenerational Effects of Toxicants: An Extension of the Daphnia 21-Day Chronic Assay?, *Archives of Environmental Contamination and Toxicology, 74*(4): 616-626. DOI: 10.1007/s00244-018-0507-0

Chabchoubi, I. B., Bouchhima, R. A., Louhichi, N., Baanannou, A., Masmoudi, S. & Hentati, O. (2023). Short-term effects of various non-steroidal anti-inflammatory drugs (NSAIDs) on Danio rerio embryos. *MethodsX, 10*, 102215. DOI: 10.1016/j.mex.2023.102215

Claessens, M., Vanhaecke, L., Wille, K. & Janssen, C. R. (2013). Emerging contaminants in Belgian marine waters: Single toxicant and mixture risks of pharmaceuticals, *Marine Pollution Bulletin, 71*(1-2), 41–50. DOI: 10.1016/j.marpolbul.2013.03.039

Daniel, D., Dionísio, R., de Alkimin, G. D. & Nunes, B. (2018). Acute and chronic effects of paracetamol exposure on *Daphnia magna*: how oxidative effects may modulate responses at distinct levels of organization in a model species. *Environmental Science and Pollution Research International, 26*(4), 3320–3329. DOI: 10.1007/s11356-018-3788-y

de Oliveira, L. L. D., Antunes, S. C., Gonçalves, F., Rocha, O. & Nunes, B. (2015). Acute and chronic ecotoxicological effects of four pharmaceuticals drugs on cladoceran *Daphnia magna*. *Drug and Chemical Toxicology, 39*(1), 13-21. DOI: 10.3109/01480545.2015.1029048

de Oliveira, L. L. D., Nunes, B., Antunes, S. C., Campitelli-Ramos, R. & Rocha, O. (2018). Acute and Chronic Effects of Three Pharmaceutical Drugs on the Tropical Freshwater *Cladoceran Ceriodaphnia silvestrii*. *Water Air and Soil Pollution, 229*(4), 116. https://doi.org/10.1007/s11270-018-3765-6

Du, J., Mei, C-F., Ying, G-G. & Xu, M-Y. (2016). Toxicity Thresholds for Diclofenac, Acetaminophen and Ibuprofen in the Water Flea *Daphnia magna*. *Bulletin of Environmental Contamination and Toxicology*, *97*(1), 84-90. DOI: 10.1007/s00128-016-1806-7

ECHA (2024). ECHA registreringsdossier for paracetamol CAS 103-90-2. Data hentet februar 2024. https://echa.europa.eu/da/substance-information/-/substanceinfo/100.002.870

Edrees, W., Abdullah, Q., Al-kaf, A. & Naji, K. (2017). A Review On Comparative Study Between The Physicochemical And Biological Processes For Paracetamol Degradation. *Universal Journal of Pharmaceutical Research. 2.* 18-29.

EPI Suite (2023), December 2023. EPI-Suite calculation (EPIWEB version 4.11 US-EPA).

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. (https://circabc.europa.eu/sd/a/ba6810cd-e611-4f72-9902-f0d8867a2a6b/Guidance%20No%2027%20-%20Deriving%20Environmental%20Quality%20Standards%20-%20version%202018.pdf)

Fort, D. J., Rayburn, J. R. & Bantle, J. A. (1992). Evaluation of acetaminophen-induced developmental toxicity using fetax. *Drug and Chemical Toxicology, 15*(4), 329-350. https://doi.org/10.3109/01480549209014161

Gomez, D. A. M. (2012). A Survey of Selected Pharmaceuticals and Personal Care Products in a Binational River and Their Effects on a Member of Its Zooplankton Community, *Plationus patulus* (Rotifera). M.S. Thesis, *The University of Texas at El Paso*, TX:113 p.

Gómez-Oliván, L. M., Neri-Cruz, N., Galar-Martínez, M., Islas-Flores, H. & García-Medina, S. (2014). Binary mixtures of diclofenac with paracetamol, ibuprofen, naproxen, and acetylsalicylic acid and these pharmaceuticals in isolated form induce oxidative stress on Hyalella azteca. *Environmental Monitoring and Assessment, 186*(11), 7259–7271. DOI: 10.1007/s10661-014-3925-0

Guk, H. H., Hor, G. H. & Sang, D. K. (2006). Ecotoxicological Risk Of Pharmaceuticals From Wastewater Treatment Plants In Korea: Occurrence And Toxicity To *Daphnia Magna*, *Environmental Toxicology and Chemistry*, *25*(1), 265–271. DOI: 10.1897/05-193r.1

Henschel, K. P., Wenzel, A., Diedrich, M. & Fliedner, A. (1997). Environmental Hazard Assessment of Pharmaceuticals. *Regulatory Toxicology and Pharmacology, 25*(3), 220–225.

Huang, S. S. Y., Benskin, J. P., Chandramouli, B., Butler, H., Helbing, C. C. & Cosgrove, J. R. (2016). Xenobiotics Produce Distinct Metabolomic Responses in Zebrafish Larvae (*Danio rerio*). *Environmental Science and Technology, 50*(12), 6526-6535.

J-CHECK (2013). Short-term toxicity to aquatic invertebrate, Results of Ecotoxicity tests of chemicals conducted by Ministry of the Environment in Japan (- March 2013).

Kaza, M., Nalecz-Jawecki, G. & Sawicki, J. (2007). The Toxicity of Selected Pharmaceuticals to the Aquatic Plant *Lemna minor*, *Fresenius Environmental Bulletin, 16*(5), 524-531.

Kim, J., Park, J., Kim, P-G., Lee, C. & Choi, K. (2010). Implication of global environmental changes on chemical toxicity-effect of water temperature, pH, and ultraviolet B irradiation on acute toxicity of several pharmaceuticals in *Daphnia magna*. *Ecotoxicology, 19*(4), 662–669. DOI: 10.1007/s10646-009-0440-0

Kim, P., Park, Y., Ji, K., Seo, J., Lee, S., Choi, K., Kho, Y., Park, J. & Choi, K. (2012). Effect of Chronic Exposure to Acetaminophen and Lincomycin on Japanese Medaka (*Oryzias latipes*) and Freshwater Cladocerans *Daphnia magna* and *Moina macrocopa*, and Potential Mechanisms of Endocrine Disruption. *Chemosphere*, *89*(1), 10-18. DOI: 10.1016/j.chemosphere.2012.04.006

Kim, Y., Choi, K., Jung, J., Park, S., Kim, P-G. & Park, J. (2007). Aquatic Toxicity of Acetaminophen, Carbamazepine, Cimetidine, Diltiazem and Six Major Sulfonamides, and Their Potential Ecological Risks in Korea, *Environment International*, *33*(3), 370-375. DOI: 10.1016/j.envint.2006.11.017

Klimisch H., Andreae M. & Tillmann U. (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharm., 25, 1-5. DOI: 10.1006/rtph.1997.1102

Kühn, R., Pattard, M., Pernak, K-D. & Winter, A. (1989). Results of the Harmful Effects of Selected Water Pollutants (Anilines, Phenols, Aliphatic Compounds) to *Daphnia Magna*. *Water Research, 23*(4), 495-499. DOI:10.1016/0043-1354(89)90141-3

Li, M. H. (2013). Acute Toxicity of 30 Pharmaceutically Active Compounds to Freshwater Planarians, *Dugesia japonica. Toxicological and Environmental Chemistry, 95*(7), 1157-1170.

Lilius, H., Hästbacka, T. & Isomaa, B. (1995). Short Communication: A comparison of the toxicity of 30 reference chemicals to Daphnia Magna and Daphnia Pulex. *Environmental Toxicology and Chemistry, 14*(12), 2085-2088. https://doi.org/10.1002/etc.5620141211

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

Miljøstyrelsen (2021). Nøgletal for miljøfarlige forurenende stoffer i spildevand fra renseanlæg. Opdatering på baggrund af data fra det nationale overvågningsprogram for punktkilder 1998-2019. NOVANA Marts 2021.

Minguez, L., Pedelucq, J., Farcy, E., Ballandonne, C., Budzinski, H. & Halm-Lemeille, M. (2014). Toxicities of 48 pharmaceuticals and their freshwater and marine environmental assessment in northwestern France. *Environmental Science Pollution Reseach*, *23*(6), 4992–5001. DOI: 10.1007/s11356-014-3662-5

Moore R. A, Moore, N. (2016). Paracetamol and pain: the kiloton problem. *European Journal of Hospital Pharmacy, 23,* 187-188. https://doi.org/10.1136/ejhpharm-2016-000952

National Institute of Technology and Evaluation (2016). Long-term toxicity to aquatic invertebrates, J check National Institute of Technology and Evaluation (NITE) Chemical Risk Information Platform (CHRIP)2016 Results of ecotoxicity test of chemicals conducted by ministry of the environment in japan(-March 2013).

Nunes, B., Antunes, S. C., Santos, J., Martins, L. & Castro, B. B. (2014). Toxic potential of paracetamol to freshwater organisms: A headache to environmental regulators?. *Ecotoxicology and Environmental Safety*, *107*, 178-185. DOI: 10.1016/j.ecoenv.2014.05.027

Pascoe, D., Karntanut, W. & Muller, C. T. (2003). Do Pharmaceuticals Affect Freshwater Invertebrates? A Study with the Cnidarian *Hydra vulgaris*, *Chemosphere*, *51*(6), 521-528. DOI: 10.1016/S0045-6535(02)00860-3

Pino, M. R., Muniz, S., Val, J. & Navarro, E. (2016). Phytotoxicity of 15 Common Pharmaceuticals on the Germination of *Lactuca sativa* and Photosynthesis of *Chlamydomonas reinhardtii*, *Environmental Science Pollution Research International, 23*(22): 22530-22541. DOI: 10.1007/s11356-016-7446-y

Pino, M. R., Val, J., Mainar, A. N., Zuriaga, E., Español, C. & Langa, E. (2015). Acute toxicological effects on the earthworm *Eisenia fetida* of 18 common pharmaceuticals in artificial soil, *Science of the Total Environment, 15*(518–519), 225–237. DOI: 10.1016/j.scitotenv.2015.02.080

Rhee, J. S., Jeong, C. B., Kim, B. M. & Lee, J. S. (2012). P-Glycoprotein (P-gp) in the Monogonont Rotifer, *Brachionus koreanus*: Molecular Characterization and Expression in Response to Pharmaceuticals. *Aquatic Toxicology, 114/155,* 104-118.

Rosas-Ramírez, J. R., Orozco-Hernández, J. M., Elizalde-Velázquez, G. A., Raldúa, D., Islas-Flores, H. & Gómez-Oliván, L. M. (2022). Teratogenic effects induced by paracetamol, ciprofloxacin, and their mixture on *Danio rerio* embryos: Oxidative stress implications. *Science of the Total Environment, 806*(2), 150541

Solé, M., Shaw, J. P., Frickers, P. E., Readman, J. W. & Hutchinson, T. H. (2010). Effects on Feeding Rate and Biomarker Responses of Marine Mussels Experimentally Exposed to Propranolol and Acetaminophen. *Analytical and Bioanalytical Chemistry*, *396*(2), 649-656. DOI: 10.1007/s00216-009-3182-1

Sundhedsstyrelsen (n.d.). FAQ om smertestillende håndkøbspræparater til voksne. Indsatser for Rationel Farmakoterapi (IRF). (https://www.sst.dk/-/media/Viden/Laegemidler/Smerter/FAQ-haandkoebspraeparatet.ashx?.la=da%26amp;hash=62436B78E62BBFCE75167DA4AA0075C92166AEDB)

Touliabah, H.E., El-Bassat, R. A., El-Shimy, A. & Harisa, G. I. (2008). Oxidative Stress of Plankton Community and Some Isolated Species During Paracetamol Toxicity Test. *Journal of Biological Sciences, 8*(1), 13-23. DOI:10.3923/jbs.2008.13.23

Wilkinson, J. L., Boxall, A. B. A., Kolpin, D. W., Leung, K. M. Y., Lai, R. W. S., Galbán-Malagón, C., Adell, A. D., Mondon, J., Metian, M., Marchant, R. A., Bouzas-Monroy, A., Cuni-Sanchez, A., Coors, A., Carriquiriborde, P., Rojo, M., Gordon, C., Cara, M., Moermond, M., Luarte, T., Petrosyan, V., … Teta, C. (2022). Pharmaceutical pollution of the world's rivers. *Proceedings of the National Academy of Sciences of the United States of America*, *119*(8), e2113947119. https://doi.org/10.1073/pnas.2113947119

Żur, J., Piński, A., Marchlewicz, A., Hupert-Kocurek, K., Wojcieszyńska, D., & Guzik, U. (2018). Organic micropollutants paracetamol and ibuprofen-toxicity, biodegradation, and genetic background of their utilization by bacteria. *Environmental science and pollution research international, 25*(22), 21498–21524. https://doi.org/10.1007/s11356-018-2517-x

Bilag A

Toksicitet over for vandorganismer (EC_x, LC_x, NOEC, osv.)

Ferskvandsorganismer

Akut toksicitet

	Form/salt	**Målt**	**Varighed**	**Effekt**	**Værdi mg/l**	**Reference**	**Troværdighed (1-4)**
Alger	Paracetamol						
Chlamydomonas reinhardtii		Nej	72 timer	E_rC_{50} (vækst)	2286 ± 16	Pino *et al.,* 2016	1[1]
Chlorella vulgaris		Nej	72 timer	E_rC_{50} (vækst)	112,66	ECHA, 2024 (Guidelinestudie i registreringsdossier for paracetamol, 2016)	2[2]
Pseudokirchneriella subcapitata		Nej	72 timer	E_rC_{50} (vækst)	317,4	Nunes *et al.,* 2014	1[1]
Pseudokirchneriella subcapitata		Nej	72 timer	E_rC_{50} (vækst)	>100[7]	Minguez *et al.,* 2014	1[1]
Scenedesmus subspicatus			72 timer	E_rC_{50} (vækst)	134	Henschel *et al.,* 1997	2[3]
Ciliater	Paracetamol						
Paramecuim tetraurelia			2 timer	I_rC_{50} (vækst)	5	Boulassel *et al.,* 2013	3[4]
Tetrahymena pyriformis			48 timer	E_rC_{50} (vækst)	112	Henschel *et al.,* 1997	2[3]
Vorticella convallaria		Nej	48 timer	LC_{50} (densitet)	2	Touliabah *et al.,* 2008	3[4]
Cyanobakterier	Paracetamol						
Cylindrospermopsis raciborskii		Nej	72 timer	E_rC_{50} (vækst)	192,9	Nunes *et al.,* 2014	1[1]
Oscellatoria		Nej	24 timer	LC_{50} (densitet)	4	Touliabah *et al.,* 2008	3[4]
Krebsdyr, Malacostraca	Paracetamol						
Hyalella azteca			72 timer	LC_{50}	7,7	Gómez-Oliván *et al.,* 2014	3[4]
Krebsdyr, Branchiopoda	Paracetamol						
Ceriodaphnia silvestrii		Nej	48 timer	EC_{50} (immobil)	40,3	de Oliveira *et al.,* 2018	1[1]
Daphnia longispina		Nej	48 timer	EC_{50} (immobil)	65,9	Nunes *et al.,* 2014	1[1]

Daphnia magna		Nej	48 timer	EC_{50} (immobil)	2,99[6]	Daniel *et al.,* 2018	2[3]
Daphnia magna			48 timer	EC_{50}	3,5	J-CHECK (2013)	3[5]
Daphnia magna		Nej	48 timer	EC_{50} (immobil)	4,68[6]	Castro *et al.,* 2018	1[1]
Daphnia magna		Nej	48 timer	EC_{50} (immobil)	4,7[6]	Nunes *et al.,* 2014	1[1]
Daphnia magna		Nej	48 timer	EC_{50} (immobil)	9,2[6]	Kühn *et al.,* 1989	2[3]
Daphnia magna			48 timer	EC_{50} (mortalitet)	11,85[6]	Kim *et al.,* 2012	2[3]
Daphnia magna		Nej	48 timer	EC_{50} (immobil), pH 7,4	12,7[6]	Kim *et al.,* 2010	2[3]
				EC_{50} (immobil), pH 8,3	8,3		
Daphnia magna		Nej	48 timer	EC_{50} (immobil)	30,1[6]	Kim *et al.,* 2007	2[3]
Daphnia magna		Nej	48 timer	EC_{50} (immobil)	34,99[6]	Minguez *et al.,* 2014	1[1]
Daphnia magna			48 timer	EC_{50} (immobil)	50[6]	Henschel *et al.,* 1997	2[3]
Daphnia magna			24 timer	LC_{50}	269,153	Calleja *et al.,* 1994	3[4]
Daphnia magna		Nej	48 timer	LC_{50}	>0,032[7]	Brun *et al.,* 2006	2[3]
Daphnia magna			48 timer	LC_{50}	20,1[6]	Guk *et al.,* 2006	2[3]
Daphnia magna		Ja	48 timer	LC_{50}	40,0[6]	Du *et al.,* 2016	2[3]
Daphnia magna, aggregeret, N=11			48 timer	EC_{50} (immobil)	13,9		
Daphnia pulex			24 timer	EC_{50}	136,053	Lilius *et al.,* 1995	2[3]
Moina macrocopa			48 timer	EC_{50} (mortalitet)	56,34	Kim *et al.,* 2012	2[3]
Fisk	Paracetamol						
Brachydanio rerio			48 timer	LC_{50}	378	Henschel et al., 1997	2[3]
				EC_{50} (pulsrate)	920		
Danio rerio		Nej	48 timer	EC_{50} (mortalitet)	378	Henschel et al., 1997	2[3]
Danio rerio		Nej	96 timer	LC_{50}	>100[7]	ECHA, 2024 (Guidelinestudie i registreringsdossier for paracetamol, 2016)	2[2]
Danio rerio			96 hpf[3]	LC_{50}	0,7369	Rosas-Ramírez *et al.,* 2022	2[3]
				EC_{50} (malformation)	0,4388		
Danio rerio		Nej	120 hpf[2]	LC_{50}	3,27	Chabchoubi *et al.,* 2023	2[3]
Oryzias latipes		Nej	96 timer	LC_{50}	>160[7]	Kim *et al.,* 2007	2[3]

[2] hpf: hours post fertilisation (timer efter befrugtning)

Pimephales promelas			96 timer	LC_{50}	814	Broderius *et al*., 1995	2[3]
Vandplanter	Paracetamol						
Lemna gibba		Nej	7 dage	E_rC_{50} (vækst)	>1000[7]	Nunes *et al.,* 2014	1[1]
Lemna minor			7 dage	EC_{50} (antal blade)	>200[7]	Kaza *et al.,* 2007	1[1]
Lemna minor		Nej	7 dage	E_rC_{50} (vækst)	429,9	Nunes *et al.,* 2014	1[1]
Bløddyr - Musling	Paracetamol						
Corbicula fluminea		Nej	96 timer	LC_{50}	>532.78[7]	Brandão *et al.,* 2014	2[3]
Polyp	Paracetamol						
Hydra vulgaris		Nej	7 dage	$L(E)C_{50}$ (mortalitet, malformation)	>10[7]	Pascoe *et al.,* 2003	2[3]
Fladorm	Paracetamol						
Dugesia japonica		Nej	96 timer	LC_{50}	150.8	Li, 2013	2[3]
Hjuldyr	Paracetamol						
Plationus patulus		Nej	48 timer	LC_{50}	319	Gomez, 2013	3[3]
				LC_{50}	121		
Padder	Paracetamol						
Xenopus laevis			96 timer	EC_{50} (malformation)	49,6	Fort *et al*., 1992	2[3]
				LC_{50}	20,1		

[1]Klimisch score 1: ikke guideline studie, men udført efter tilsvarende guidelines uden manglende information

[2] Klimisch score 2: summary af guideline studie med tilstrækkelige oplysninger, men mangler original studierapport

[3] Klimisch score 2: ikke guideline studie, men tilstrækkelige oplysninger

[4] Klimisch score 3: ikke guideline studie og få tilstrækkelige oplysninger

[5] Klimisch score 3: guideline studie, men ikke detaljeret dokumentation

[6] Værdi benyttet til beregning af EC50 (immobil) for *Daphnia magna*, aggregeret. Den aggregerede værdi er beregnet som et geometrisk gennemsnit.

[7] Højeste koncentration testet

Ferskvandsorganismer
Kronisk toksicitet

	Form/salt	Målt	Varighed	Effekt	Værdi mg/l	Reference	Troværdighed (1-4)
Krebsdyr	Paracetamol						
Ceriodaphnia silvestrii		Nej	8 dage	EC_{50} (reproduktion)	0,8989	de Oliveira et al., 2018	1[1]
Daphnia longispina		Nej	21 dage	EC_{50} (reproduktion)	12,2	Nunes *et al.,* 2014	1[1]
Daphnia magna		Ja	21 dage	EC_{10} (ægproduktion) EC_{10} (antal afkom)	0,64 1,35	Du *et al.,* 2016	2[2]
Daphnia magna			21 dage	NOEC (immobil)	1,25[6]	de Oliveria *et al.,* 2015	2[3]
Daphnia magna		Nej	21 dage	NOEC (mortalitet, reproduktion, population)	5,72[5, 6]	Kim *et al.,* 2012	2[2]
Daphnia magna		Nej	21 dage	NOEC (reproduktion)	0,08[5, 6]	Daniel *et al.,* 2018	2[2]
Daphnia magna			21 dage	NOEC (reproduktion)	0,46	ECHA, 2024 (National Institute of Technology and Evaluation, 2016)	3[4]
Daphnia magna		Nej	21 dage	NOEC (reproduktion)	4[5, 6]	Castro *et al.,* 2018	1[1]
Daphnia magna		Nej	21 dage	EC_{50} (reproduktion)	>4,0[6]	Nunes *et al.,* 2014	1[1]
Daphnia magna, aggregeret, N=3			21 dage	NOEC (reproduktion)	1,22[6]		
Moina macrocopa		Nej	7 dage	LOEC (mortalitet) LOEC (reproduktion)	25,74 0,95	Kim *et al.,* 2012	2[2]
Fisk	Paracetamol						
Oryzias latipes			90 dage	NOEC (vækst, reproduktion)	9,5[6]	Kim *et al.,* 2012	2[2]
Bløddyr - Musling	Paracetamol						
Corbicula fluminea		Nej	28 dage	NOEC	0.06195[6]	Brandão *et al.,* 2014	2[2]
Polyp	Paracetamol						
Hydra vulgaris		Nej	17 dage	NOEC (reproduktion)	10[6]	Pascoe *et al.,* 2003	2[2]

[1]Klimisch score 1: ikke guideline studie, men udført efter tilsvarende guidelines uden manglende information

[2] Klimisch score 2: ikke guideline studie, men tilstrækkelige oplysninger

[3] Klimisch score 3: guideline studie, men ikke detaljeret dokumentation

[4] Klimisch score 3: ikke guideline studie og få tilstrækkelige oplysninger

[5] Værdi benyttet til beregning af NOEC (reproduktion) *Daphnia magna*, aggregeret. Den aggregerede værdi er beregnet som et geometrisk gennemsnit.

[6] Højeste koncentration testet

Saltvandsorganismer
Akut toksicitet

	Form/salt	Målt	Varighed	Effekt	Værdi mg/l	Reference	Troværdighed (1-4)
Alger	Paracetamol						
Phaeodactylum tricornutum			72 timer	E_rC_{50} (vækst)	265,8	Claessens *et al.,* 2013	2[2]
Krebsdyr	Paracetamol						
Artemia salina		Nej	48 timer	EC_{50} (immobil)	>100[5]	Minguez *et al.,* 2014	1[1]
Bakterier	Paracetamol						
Vibrio fischeri		Nej	5 min	EC_{50} (lysblokering)	92,2	Nunes *et al.,* 2014	1[1]
Vibrio fischeri		Nej	15 min	EC_{50} (lysblokering)	567,5	Kim *et al.,* 2007	2[2]
Vibrio fischeri		Nej	15 min	IC_{50} (lysblokering)	>0,437[5]	Brun *et al.,* 2006	2[2]
Vibrio fischeri			30 min	EC_{50} (lysblokering)	650	Henschel *et al.,* 1997	2[2]
Hjuldyr	Paracetamol						
Brachionus koreanus		Ja	24 timer	LC_{50}	185,4	Rhee *et al.,* 2012	3[3]
				NOEC (mortalitet)	92,5		
Bløddyr - Musling	Paracetamol						
Mytilus galloprovincialis		Ja	10 dage	NOEC (madindtagelse)	0,403	Solé *et al.,* 2010	4[4]

[1]Klimisch score 1: ikke guideline studie, men udført efter tilsvarende guidelines uden manglende information

[2] Klimisch score 2: ikke guideline studie, men tilstrækkelige oplysninger

[3] Klimisch score 3: ikke guideline studie og få tilstrækkelige oplysninger

[4] Klimisch score 4: ikke guideline studie og endpoint ikke valid

[5] Højeste koncentration testet

Saltvandsorganismer
Kronisk toksicitet

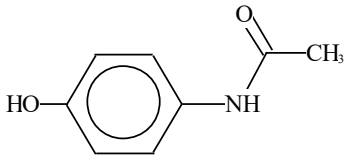
	Form/salt	Målt	Varighed	Effekt	Værdi mg/l	Reference	Troværdighed (1-4)
Alger	Paracetamol						
Phaeodactylum tricornutum			72 timer	E_rC_{10} (vækst)	96,7	Claessens *et al.,* 2013	2[1]

[1] Klimisch score 2: ikke guideline studie, men tilstrækkelige oplysninger

Bilag B

EpiSuite-beregninger for paracetamol

EPI Suite Results For CAS 103-90-2




```
SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
------------------------------ EPI SUMMARY (v4.11) --------------------------
Physical Property Inputs:
Log Kow (octanol-water):   ------
Boiling Point (deg C)  :   ------
Melting Point (deg C)  :   ------
Vapor Pressure (mm Hg) :   ------
Water Solubility (mg/L):   ------
Henry LC (atm-m3/mole) :   ------

KOWWIN Program (v1.68) Results:
===============================

Log Kow(version 1.69 estimate): 0.27

Experimental Database Structure Match:
Name     :  ACETAMIDE, N-(4-HYDROXYPHENYL)
CAS Num  :  000103-90-2
Exp Log P:  0.46
Exp Ref  :  SANGSTER (1994)

SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
-------+-----+-----------------------------------------+---------+--------
TYPE   | NUM |        LOGKOW FRAGMENT DESCRIPTION      |  COEFF  |  VALUE
-------+-----+-----------------------------------------+---------+--------
Frag   |  1  |  -CH3    [aliphatic carbon]             | 0.5473  |  0.5473
Frag   |  6  |  Aromatic Carbon                        | 0.2940  |  1.7640
Frag   |  1  |  -OH     [hydroxy, aromatic attach]     |-0.4802  | -0.4802
Frag   |  1  |  -N    [aliphatic N, one aromatic attach]|-0.9170  | -0.9170
Frag   |  1  |  -C(=O)N  [aliphatic attach]            |-0.5236  | -0.5236
```

```
Factor|  1  |  Ring reaction ->  -N< / -OH  (non-ortho)  |-0.3510  | -0.3510
Const |     |  Equation Constant                         |         |  0.2290
-------+-----+--------------------------------------------+---------+--------
Log Kow   =   0.2685



MPBPVP (v1.43) Program Results:
===============================
Experimental Database Structure Match:
Name     :  ACETAMIDE, N-(4-HYDROXYPHENYL)
CAS Num  :  000103-90-2
Exp MP (deg C):  170
Exp BP (deg C):  ---
Exp VP (mm Hg):  ---

SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
------------------------ SUMMARY MPBPWIN v1.44 --------------------


Boiling Point:  340.65 deg C (Adapted Stein and Brown Method)

Melting Point:  258.63 deg C (Adapted Joback Method)
Melting Point:   85.25 deg C (Gold and Ogle Method)
Mean Melt Pt :  171.94 deg C (Joback; Gold,Ogle Methods)
Selected MP:  119.92 deg C (Weighted Value)

Vapor Pressure Estimations (25 deg C):
(Using BP: 340.65 deg C (estimated))
(Using MP: 170.00 deg C (exp database))
VP:  9.63E-007 mm Hg (Antoine Method)
:  0.000128 Pa  (Antoine Method)
VP:  1.94E-006 mm Hg (Modified Grain Method)
:  0.000259 Pa  (Modified Grain Method)
VP:  1.58E-005 mm Hg (Mackay Method)
:  0.00211 Pa  (Mackay Method)
Selected VP:  1.94E-006 mm Hg (Modified Grain Method)
:  0.000259 Pa (Modified Grain Method)
Subcooled liquid VP:  6.12E-005 mm Hg (25 deg C, Mod-Grain method)
:  0.00815 Pa  (25 deg C, Mod-Grain method)

-------+-----+--------------------+----------+---------
TYPE   | NUM |  BOIL DESCRIPTION  |  COEFF   |  VALUE
-------+-----+--------------------+----------+---------
Group |  1  |  -CH3              |   21.98  |   21.98
Group |  1  |  -OH (phenol)      |   70.48  |   70.48
Group |  4  |  CH (aromatic)     |   28.53  |  114.12
Group |  2  |  -C (aromatic)     |   30.76  |   61.52
Group |  1  |  -C(=O)NH-         |  225.09  |  225.09
*   |     |  Equation Constant |          |  198.18
============+====================+==========+=========
RESULT-uncorr|  BOILING POINT in deg Kelvin  |  691.37
RESULT- corr |  BOILING POINT in deg Kelvin  |  613.81
|  BOILING POINT in deg C       |  340.65
---------------------------------------------------------
```

```
-------+-----+--------------------+----------+---------
TYPE   | NUM |  MELT DESCRIPTION  |  COEFF   |  VALUE
-------+-----+--------------------+----------+---------
Group |  1  |  -CH3              |   -5.10  |   -5.10
Group |  1  |  -OH (phenol)      |   82.83  |   82.83
Group |  4  |  CH (aromatic)     |    8.13  |   32.52
Group |  2  |  -C (aromatic)     |   37.02  |   74.04
Group |  1  |  -C(=O)NH-         |  225.00  |  225.00
*   |     |  Equation Constant |          |  122.50
============+====================+==========+=========
RESULT    |  MELTING POINT in deg Kelvin  |  531.79
|  MELTING POINT in deg C       |  258.63
-----------------------------------------------------


Water Sol from Kow (WSKOW v1.42) Results:
=========================================

Water Sol: 3.035e+004 mg/L

Experimental Water Solubility Database Match:
Name     :  ACETAMIDE, N-(4-HYDROXYPHENYL)
CAS Num  :  000103-90-2
Exp WSol :  1.4E+004 mg/L (25 deg C)
Exp Ref  :  YALKOWSKY,SH & HE,Y (2003)

SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
---------------------------------- WSKOW v1.43 Results -----------------------
Log Kow  (estimated)  :  0.27
Log Kow (experimental):  0.46
Cas No: 000103-90-2
Name  : ACETAMIDE, N-(4-HYDROXYPHENYL)
Refer : SANGSTER (1994)
Log Kow used by Water solubility estimates:  0.46

Equation Used to Make Water Sol estimate:
Log S (mol/L) = 0.796 - 0.854 log Kow - 0.00728 MW + Correction
(used when Melting Point NOT available)

Correction(s):         Value
--------------------   -----
No Applicable Correction Factors

Log Water Solubility  (in moles/L) :  -0.697
Water Solubility at 25 deg C (mg/L):  3.035e+004



WATERNT Program (v1.01) Results:
================================

Water Sol (v1.01 est): 2.3665e+005 mg/L

Experimental Water Solubility Database Match:
Name     :  ACETAMIDE, N-(4-HYDROXYPHENYL)
CAS Num  :  000103-90-2
```

```
Exp WSol :  1.4E+004 mg/L (25 deg C)
Exp Ref  :  YALKOWSKY,SH & HE,Y (2003)

SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
-------+-----+-----------------------------------------+----------+---------
TYPE   | NUM |    WATER SOLUBILITY FRAGMENT DESCRIPTION   |  COEFF   |  VALUE
-------+-----+-----------------------------------------+----------+---------
Frag   |  1  |  -CH3    [aliphatic carbon]                |-0.3213   | -0.3213
Frag   |  4  |  Aromatic Carbon  (C-H type)               |-0.3359   | -1.3435
Frag   |  1  |  -OH     [hydroxy, aromatic attach]        | 1.6578   |  1.6578
Frag   |  1  |  -N    [aliphatic N, one aromatic attach]  | 1.2749   |  1.2749
Frag   |  1  |  -C(=O)N  [aliphatic attach]               |-0.2426   | -0.2426
Frag   |  2  |  Aromatic Carbon  (C-substituent type)     |-0.5400   | -1.0799
Const  |     |  Equation Constant                         |          |  0.2492
-------+-----+-----------------------------------------+----------+---------
Log Water Sol (moles/L) at 25 dec C  =    0.1946
Water Solubility (mg/L) at 25 dec C  =2.3665e+005


ECOSAR Program (v1.11) Results:
==============================
ECOSAR Version 1.11 Results Page

SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
CAS Num:
ChemID1:
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
Log Kow: 0.269      (EPISuite Kowwin v1.68 Estimate)
Log Kow:            (User Entered)
Log Kow: 0.46       (PhysProp DB exp value - for comparison only)
Melt Pt:            (User Entered for Wat Sol estimate)
Melt Pt: 170.00     (deg C, PhysProp DB exp value for Wat Sol est)
Wat Sol: 4190       (mg/L, EPISuite WSKowwin v1.43 Estimate)
Wat Sol:            (User Entered)
Wat Sol: 1.4E+004   (mg/L, PhysProp DB exp value)


-------------------------------------
Values used to Generate ECOSAR Profile
-------------------------------------
Log Kow: 0.269      (EPISuite Kowwin v1.68 Estimate)
Wat Sol: 1.4E+004   (mg/L, PhysProp DB exp value)


-------------------------------------
ECOSAR v1.11 Class-specific Estimations
-------------------------------------
Phenols
Amides
Phenol Amines
Predicted
ECOSAR Class                  Organism            Duration  End Pt   mg/L (ppm)
============================  ==================  ========  ======   ==========
Phenols                     : Fish                96-hr     LC50      543.711
```

Phenols	: Daphnid	48-hr	LC50	75.717
Phenols	: Green Algae	96-hr	EC50	412.065
Phenols	: Fish		ChV	42.594
Phenols	: Daphnid		ChV	14.445
Phenols	: Green Algae		ChV	197.874
Phenols	: Fish (SW)	96-hr	LC50	336.890
Phenols	: Earthworm	14-day	LC50	716.911
Phenols	: Lemna gibba	7-day	EC50	597.957
Amides	: Fish	96-hr	LC50	781.539
Amides	: Daphnid	48-hr	LC50	1910.838
Amides	: Green Algae	96-hr	EC50	16.916
Amides	: Fish		ChV	0.479
Amides	: Daphnid		ChV	34.175
Amides	: Green Algae		ChV	7.654
Amides	: Fish (SW)	96-hr	LC50	678.316
Amides	: Mysid (SW)	96-hr	LC50	24.844
Phenol Amines	: Fish	96-hr	LC50	30.253
Phenol Amines	: Daphnid	48-hr	LC50	1.652
Phenol Amines	: Green Algae	96-hr	EC50	14.165
Phenol Amines	: Fish		ChV	2.745 !
Phenol Amines	: Daphnid		ChV	1.239
Phenol Amines	: Green Algae		ChV	1.817
Neutral Organic SAR	: Fish	96-hr	LC50	4457.745
(Baseline Toxicity)	: Daphnid	48-hr	LC50	2157.158
: Green Algae	96-hr	EC50	829.658	
: Fish		ChV	360.840	
: Daphnid		ChV	134.818	
: Green Algae		ChV	152.187	

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported.

NOTE: ! = exclamation designates: The toxicity value was estimated through application of acute-to-chronic ratios per methods outlined in the ECOSAR Methodology Document provided in the ECOSAR Help Menu.

Class Specific LogKow Cut-Offs

If the log Kow of the chemical is greater than the endpoint specific cut-offs presented below, then no effects at saturation are expected for those endpoints.

Phenols:

Maximum LogKow: 7.0 (Fish 96-hr LC50, Daphnid LC50)
Maximum LogKow: 6.4 (Earthworm, Lemna)
Maximum LogKow: 7.0 (Green Algae EC50
Maximum LogKow: 8.0 (ChV)
Maximum LogKow: 5.0 (Fish (SW) 96-hr LC50, Mysid)
Amides :

Maximum LogKow: >8.5 (LC50)

Maximum LogKow: >8.0 (EC50,ChV)

Phenol Amines :

Maximum LogKow: 5.0 (Fish 96-hr LC50)
Maximum LogKow: 7.0 (Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50
Maximum LogKow: 8.0 (ChV)

Baseline Toxicity SAR Limitations:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)

HENRYWIN (v3.20) Program Results:
==========

Bond Est : 6.42E-013 atm-m3/mole (6.51E-008 Pa-m3/mole)
Group Est: Incomplete

SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
---------- HENRYWIN v3.21 Results ----------

Experimental Database Structure Match:
Name : ACETAMIDE, N-(4-HYDROXYPHENYL)
CAS Num : 000103-90-2
Exp HLC : 2.76E-11 atm-m3/mole (2.8E-006 Pa-m3/mole)
Temper : 25 deg C
Exp Ref : VP/WSOL

CLASS	BOND CONTRIBUTION DESCRIPTION	COMMENT	VALUE
HYDROGEN	3 Hydrogen to Carbon (aliphatic) Bonds		-0.3590
HYDROGEN	4 Hydrogen to Carbon (aromatic) Bonds		-0.6172
HYDROGEN	1 Hydrogen to Oxygen Bonds		3.2318
HYDROGEN	1 Hydrogen to Nitrogen Bonds		1.2835
FRAGMENT	1 C-CO		1.7057
FRAGMENT	6 Car-Car		1.5828
FRAGMENT	1 Car-OH		0.5967
FRAGMENT	1 CO-N		2.4261
FRAGMENT	1 Car-N		0.7304
RESULT	BOND ESTIMATION METHOD for LWAPC VALUE	TOTAL	10.581

HENRYs LAW CONSTANT at 25 deg C = 6.42E-013 atm-m3/mole
= 2.63E-011 unitless
= 6.51E-008 Pa-m3/mole

GROUP CONTRIBUTION DESCRIPTION	COMMENT	VALUE
1 Car (N)(Car)(Car)	ESTIMATE	-0.50

```
|           1  CH3 (X)                              |            | -0.62
|           4  Car-H (Car)(Car)                     |            |  0.44
|           1  Car (Car)(Car)(O)                    |            | -0.43
|           1  O-H (Car)                            |            |  4.45
|              MISSING Value for:  CO (N)(C)
|              MISSING Value for:  NH (Car)(CO)
--------+-------------------------------------------+------------+--------
RESULT |  GROUP ESTIMATION METHOD for LOG GAMMA VALUE  | INCOMPLETE |  3.34
--------+-------------------------------------------+------------+--------


For Henry LC Comparison Purposes:
Exper Database: 2.76E-11  atm-m3/mole  (2.80E-006 Pa-m3/mole)
User-Entered Henry LC:  not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC:  1.271E-011 atm-m3/mole  (1.288E-006 Pa-m3/mole)
VP:   1.94E-006 mm Hg (source: MPBPVP)
WS:   3.04E+004 mg/L (source: WSKOWWIN)



Log Octanol-Air (KOAWIN v1.10) Results:
=======================================

Log Koa: 9.408

SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
--------------------------- KOAWIN v1.10 Results -------------------------

Log Koa (octanol/air) estimate:  9.408
Koa (octanol/air) estimate:  2.556e+009
Using:
Log Kow:  0.46  (exp database)
HenryLC:  2.76e-011  atm-m3/mole (exp database)
Log Kaw:  -8.948  (air/water part.coef.)

LogKow  : 0.46 (exp database)
LogKow  : 0.27 (KowWin estimate)
Henry LC: 2.76e-011 atm-m3/mole (exp database)
Henry LC: 6.42e-013 atm-m3/mole (HenryWin bond estimate)

Log Koa (octanol/air) estimate:  10.851 (from KowWin/HenryWin)



BIOWIN (v4.10) Program Results:
==============================
SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
--------------------------- BIOWIN v4.10 Results ---------------------------

Biowin1 (Linear Model Prediction)    :  Biodegrades Fast
Biowin2 (Non-Linear Model Prediction):  Biodegrades Fast
Biowin3 (Ultimate Biodegradation Timeframe):  Weeks
```

Biowin4 (Primary Biodegradation Timeframe): Days
Biowin5 (MITI Linear Model Prediction)   : Does Not Biodegrade Fast
Biowin6 (MITI Non-Linear Model Prediction): Does Not Biodegrade Fast
Biowin7 (Anaerobic Model Prediction): Does Not Biodegrade Fast
Ready Biodegradability Prediction: NO

TYPE	NUM	Biowin1 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic alcohol [-OH]	0.1158	0.1158
Frag	1	Amide [-C(=O)-N or -C(=S)-N]	0.2102	0.2102
MolWt	*	Molecular Weight Parameter		-0.0720
Const	*	Equation Constant		0.7475
RESULT		Biowin1 (Linear Biodeg Probability)		1.0015

TYPE	NUM	Biowin2 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic alcohol [-OH]	0.9086	0.9086
Frag	1	Amide [-C(=O)-N or -C(=S)-N]	2.6913	2.6913
MolWt	*	Molecular Weight Parameter		-2.1466
RESULT		Biowin2 (Non-Linear Biodeg Probability)		0.9886

A Probability Greater Than or Equal to 0.5 indicates --> Biodegrades Fast
A Probability Less Than 0.5 indicates --> Does NOT Biodegrade Fast

TYPE	NUM	Biowin3 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic alcohol [-OH]	0.0564	0.0564
Frag	1	Amide [-C(=O)-N or -C(=S)-N]	-0.0542	-0.0542
MolWt	*	Molecular Weight Parameter		-0.3341
Const	*	Equation Constant		3.1992
RESULT		Biowin3 (Survey Model - Ultimate Biodeg)		2.8673

TYPE	NUM	Biowin4 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic alcohol [-OH]	0.0397	0.0397
Frag	1	Amide [-C(=O)-N or -C(=S)-N]	0.2054	0.2054
MolWt	*	Molecular Weight Parameter		-0.2181
Const	*	Equation Constant		3.8477
RESULT		Biowin4 (Survey Model - Primary Biodeg)		3.8748

Result Classification: 5.00 -> hours 4.00 -> days 3.00 -> weeks
(Primary & Ultimate) 2.00 -> months 1.00 -> longer

TYPE	NUM	Biowin5 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic alcohol [-OH]	0.0382	0.0382

TYPE	NUM	Biowin5 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Amide [-C(=O)-N or -C(=S)-N]	0.0298	0.0298
Frag	4	Aromatic-H	0.0004	0.0016
Frag	1	Methyl [-CH3]	0.0399	0.0399
MolWt	*	Molecular Weight Parameter		-0.2384
Const	*	Equation Constant		0.5544
RESULT		Biowin5 (MITI Linear Biodeg Probability)		0.4255

TYPE	NUM	Biowin6 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic alcohol [-OH]	0.2723	0.2723
Frag	1	Amide [-C(=O)-N or -C(=S)-N]	0.0424	0.0424
Frag	4	Aromatic-H	0.0342	0.1368
Frag	1	Methyl [-CH3]	0.2351	0.2351
MolWt	*	Molecular Weight Parameter		-2.6152
RESULT		Biowin6 (MITI Non-Linear Biodeg Probability)		0.4338

A Probability Greater Than or Equal to 0.5 indicates --> Readily Degradable
A Probability Less Than 0.5 indicates --> NOT Readily Degradable

TYPE	NUM	Biowin7 FRAGMENT DESCRIPTION	COEFF	VALUE
Frag	1	Aromatic alcohol [-OH]	0.0807	0.0807
Frag	1	Amide [-C(=O)-N or -C(=S)-N]	-0.5679	-0.5679
Frag	4	Aromatic-H	-0.0954	-0.3817
Frag	1	Methyl [-CH3]	-0.0796	-0.0796
Const	*	Equation Constant		0.8361
RESULT		Biowin7 (Anaerobic Linear Biodeg Prob)		-0.1124

A Probability Greater Than or Equal to 0.5 indicates --> Biodegrades Fast
A Probability Less Than 0.5 indicates --> Does NOT Biodegrade Fast

Ready Biodegradability Prediction: (YES or NO)

Criteria for the YES or NO prediction: If the Biowin3 (ultimate survey model) result is "weeks" or faster (i.e. "days", "days to weeks", or "weeks" AND the Biowin5 (MITI linear model) probability is >= 0.5, then the prediction is YES (readily biodegradable). If this condition is not satisfied, the prediction is NO (not readily biodegradable). This method is based on application of Bayesian analysis to ready biodegradation data (see Help). Biowin5 and 6 also predict ready biodegradability, but for degradation in the OECD301C test only; using data from the Chemicals Evaluation and Research Institute Japan (CERIJ) database.

BioHCwin (v1.01) Program Results:

SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM : Acetamide, N-(4-hydroxyphenyl)-

```
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
------------------------- BioHCwin v1.01 Results --------------------------

NO Estimate Possible ... Structure NOT a Hydrocarbon
(Contains atoms other than C, H or S (-S-))



AEROWIN Program (v1.00) Results:
================================
Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled):  0.00816 Pa (6.12E-005 mm Hg)
Log Koa (Koawin est  ): 9.408
Kp (particle/gas partition coef. (m3/ug)):
Mackay model           :  0.000368
Octanol/air (Koa) model:  0.000628
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model     :  0.0131
Mackay model           :  0.0286
Octanol/air (Koa) model:  0.0478


AOP Program (v1.92) Results:
============================
SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
------------------- SUMMARY (AOP v1.92): HYDROXYL RADICALS (25 deg C) --------
Hydrogen Abstraction       =   0.1020 E-12 cm3/molecule-sec
Reaction with N, S and -OH =   0.1400 E-12 cm3/molecule-sec
Addition to Triple Bonds   =   0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds =   0.0000 E-12 cm3/molecule-sec
**Addition to Aromatic Rings =  17.4341 E-12 cm3/molecule-sec
Addition to Fused Rings    =   0.0000 E-12 cm3/molecule-sec

OVERALL OH Rate Constant =  17.6761 E-12 cm3/molecule-sec
HALF-LIFE =     0.605 Days (12-hr day; 1.5E6 OH/cm3)
HALF-LIFE =     7.261 Hrs
.......................  ** Designates Estimation(s) Using ASSUMED Value(s)
------------------- SUMMARY (AOP v1.91): OZONE REACTION (25 deg C) -----------

******  NO OZONE REACTION ESTIMATION ******
(ONLY Olefins and Acetylenes are Estimated)

NOTE: Reaction with Nitrate Radicals May Be Important!

Experimental Database:  NO Structure Matches
Fraction sorbed to airborne particulates (phi):
0.0208 (Junge-Pankow, Mackay avg)
0.0478 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation
KOCWIN Program (v2.00) Results:
===============================
SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
```

```
--------------------------  KOCWIN v2.01 Results  --------------------------

Koc Estimate from MCI:
----------------------
First Order Molecular Connectivity Index  ..........  :  5.182
Non-Corrected Log Koc (0.5213 MCI + 0.60)  ..........  :  3.3009
Fragment Correction(s):
1   Nitrogen to non-fused aromatic ring ...  : -0.5225
1   N-CO-C (aliphatic carbon)  ............  : -1.0277
1   Aromatic Hydroxy (aromatic-OH)  .......  : -0.0966
Corrected Log Koc  ................................  :  1.6541

Estimated Koc:  45.09  L/kg   <===========

Koc Estimate from Log Kow:
--------------------------
Log Kow  (experimental DB)  .........................  :  0.46
Non-Corrected Log Koc (0.55313 logKow + 0.9251)  ....  :  1.1795
Fragment Correction(s):
1   Nitrogen to non-fused aromatic ring ...  : -0.0216
1   N-CO-C (aliphatic carbon)  ............  : -0.0038
1   Aromatic Hydroxy (aromatic-OH)  .......  :  0.1668
Corrected Log Koc  ................................  :  1.3210

Estimated Koc:  20.94  L/kg   <===========



HYDROWIN Program (v2.00) Results:
=================================
SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
--------------------------- HYDROWIN v2.00 Results ---------------------------
Hydrolyzable Function detected:  Amides

-C-C(=O)-N-C-

With the exception of a few halogenated acetamides, most amides
hydrolyze to acids extremely slowly at 25 degC and pH7 with half-lives
measured in centuries. Electronegative groups on carbon or nitrogen
greatly accelerate base catalyzed hydrolysis, but alkyl groups on
nitrogen retard both acid and base catalyzed processes. No neutral
hydrolysis is evident (Mabey and Mill, 1978).  Selected amides
half-lives include:
Half-Live (in years at 25C, pH7)
Acetamide                3950
Chloroacetamide          1.46
Dichloroacetamide        0.73
Trichloroacetamide       0.23
N-Methylacetamide        38000

Additional experimental amide data are available in the HYDRO on-line
User Guide (help file).



BCFBAF Program (v3.01) Results:
```

```
==============================
SMILES : O=C(Nc(ccc(O)c1)c1)C
CHEM   : Acetamide, N-(4-hydroxyphenyl)-
MOL FOR: C8 H9 N1 O2
MOL WT : 151.17
--------------------------------- BCFBAF v3.01 ---------------------------------
Summary Results:
Log BCF (regression-based estimate):  0.50  (BCF = 3.16 L/kg wet-wt)
Biotransformation Half-Life (days) :  0.0108  (normalized to 10 g fish)
Log BAF (Arnot-Gobas upper trophic):  -0.01  (BAF = 0.984 L/kg wet-wt)

Log Kow (experimental):  0.46
Log Kow used by BCF estimates:  0.46

Equation Used to Make BCF estimate:
Log BCF = 0.50

Correction(s):                    Value
Correction Factors Not Used for Log Kow < 1

Estimated Log BCF =  0.500  (BCF = 3.162 L/kg wet-wt)

============================================================
Whole Body Primary Biotransformation Rate Estimate for Fish:
============================================================
------+-----+-----------------------------------------+---------+---------
TYPE | NUM | LOG BIOTRANSFORMATION FRAGMENT DESCRIPTION |  COEFF  |  VALUE
------+-----+-----------------------------------------+---------+---------
Frag |  1  |  Aromatic alcohol  [-OH]                  | -0.4727 | -0.4727
Frag |  1  |  Amide   [-C(=O)-N  or -C(=S)-N]          | -0.5952 | -0.5952
Frag |  4  |  Aromatic-H                               |  0.2664 |  1.0655
Frag |  1  |  Methyl  [-CH3]                           |  0.2451 |  0.2451
Frag |  1  |  Benzene                                  | -0.4277 | -0.4277
L Kow|  *  |  Log Kow =   0.46 (experimental   )       |  0.3073 |  0.1414
MolWt|  *  |  Molecular Weight Parameter               |         | -0.3876
Const|  *  |  Equation Constant                        |         | -1.5371
============+=========================================+=========+=========
RESULT   |        LOG Bio Half-Life (days)            |         | -1.9684
RESULT   |            Bio Half-Life (days)            |         | 0.01075
NOTE     |  Bio Half-Life Normalized to 10 g fish at 15 deg C   |
============+=========================================+=========+=========

Biotransformation Rate Constant:
kM (Rate Constant):  64.45 /day (10 gram fish)
kM (Rate Constant):  36.24 /day (100 gram fish)
kM (Rate Constant):  20.38 /day (1 kg fish)
kM (Rate Constant):  11.46 /day (10 kg fish)

Arnot-Gobas BCF & BAF Methods (including biotransformation rate estimates):
Estimated Log BCF (upper trophic) =  -0.007  (BCF = 0.984 L/kg wet-wt)
Estimated Log BAF (upper trophic) =  -0.007  (BAF = 0.984 L/kg wet-wt)
Estimated Log BCF (mid trophic)   =  0.011  (BCF = 1.025 L/kg wet-wt)
Estimated Log BAF (mid trophic)   =  0.011  (BAF = 1.025 L/kg wet-wt)
Estimated Log BCF (lower trophic) =  0.014  (BCF = 1.032 L/kg wet-wt)
Estimated Log BAF (lower trophic) =  0.014  (BAF = 1.032 L/kg wet-wt)

Arnot-Gobas BCF & BAF Methods (assuming a biotransformation rate of zero):
Estimated Log BCF (upper trophic) =  0.080  (BCF = 1.201 L/kg wet-wt)
Estimated Log BAF (upper trophic) =  0.081  (BAF = 1.206 L/kg wet-wt)
```

Volatilization From Water
==========

Chemical Name: Acetamide, N-(4-hydroxyphenyl)-

Molecular Weight : 151.17 g/mole
Water Solubility : -----
Vapor Pressure : -----
Henry's Law Constant: 2.76E-011 atm-m3/mole (Henry experimental database)

	RIVER	LAKE
Water Depth (meters):	1	1
Wind Velocity (m/sec):	5	0.5
Current Velocity (m/sec):	1	0.05

HALF-LIFE (hours) :	2.608E+007	2.845E+008
HALF-LIFE (days) :	1.087E+006	1.186E+007
HALF-LIFE (years) :	2975	3.246E+004

STP Fugacity Model: Predicted Fate in a Wastewater Treatment Facility
==========
(using 10000 hr Bio P,A,S)
PROPERTIES OF: Acetamide, N-(4-hydroxyphenyl)-

Molecular weight (g/mol)		151.17
Aqueous solubility (mg/l)		0
Vapour pressure (Pa)		0
(atm)	0	
(mm Hg)	0	
Henry 's law constant (Atm-m3/mol)		2.76E-011
Air-water partition coefficient		1.12876E-009
Octanol-water partition coefficient (Kow)		2.88403
Log Kow		0.46
Biomass to water partition coefficient		1.37681
Temperature [deg C]		25

Biodeg rate constants (h^-1),half life in biomass (h) and in 2000 mg/L MLSS (h):

-Primary tank	0.03	27.46	10000.00
-Aeration tank	0.03	27.46	10000.00
-Settling tank	0.03	27.46	10000.00

STP Overall Chemical Mass Balance:
---

g/h	mol/h	percent	
Influent	1.00E+001	6.6E-002	100.00
Primary sludge	2.56E-002	1.7E-004	0.26
Waste sludge	1.51E-001	1.0E-003	1.51
Primary volatilization	1.50E-008	1.0E-010	0.00
Settling volatilization	4.10E-008	2.7E-010	0.00
Aeration off gas	1.01E-007	6.7E-010	0.00
Primary biodegradation	1.76E-003	1.2E-005	0.02
Settling biodegradation	5.27E-004	3.5E-006	0.01
Aeration biodegradation	6.94E-003	4.6E-005	0.07

Final water effluent	9.81E+000	6.5E-002	98.14
Total removal	1.86E-001	1.2E-003	1.86
Total biodegradation	9.23E-003	6.1E-005	0.09

Level III Fugacity Model (Full-Output): MCI Method

Chem Name : Acetamide, N-(4-hydroxyphenyl)-
Molecular Wt: 151.17
Henry's LC : 2.76e-011 atm-m3/mole (Henry database)
Vapor Press : 1.94e-006 mm Hg (Mpbpwin program)
Liquid VP : 1.68e-005 mm Hg (super-cooled)
Melting Pt : 120 deg C (Mpbpwin program)
Log Kow : 0.46 (Kowwin program)
Soil Koc : 45.1 (KOCWIN MCI method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)	
Air	0.000555	14.5	1000	
Water	22.4	360	1000	
Soil	77.6	720	1000	
Sediment	0.0826	3.24e+003	0	

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)	
Air	1.82e-014	0.567	0.119	0.0189	0.00396	
Water	4.37e-016	921	479	30.7	16	
Soil	1.22e-014	1.6e+003	0	53.3	0	
Sediment	3.88e-016	0.378	0.0354	0.0126	0.00118	

Persistence Time: 714 hr
Reaction Time: 849 hr
Advection Time: 4.47e+003 hr
Percent Reacted: 84
Percent Advected: 16

Water Compartment Percents:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)	
Air	0.000555	14.5	1000	
Water	22.4	360	1000	
water	(22.4)			
biota	(3.22e-006)			
suspended sediment	(0.00151)			
Soil	77.6	720	1000	
Sediment	0.0826	3.24e+003	0	

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 14.52
Water: 360
Soil: 720
Sediment: 3240
Biowin estimate: 2.867 (weeks)

Advection Times (hr):
Air: 100

Water: 1000
Sediment: 5e+004

Level III Fugacity Model (Full-Output): EQC Default
==========
Chem Name   : Acetamide, N-(4-hydroxyphenyl)-
Molecular Wt: 151.17
Henry's LC : 2.76e-011 atm-m3/mole (Henry database)
Vapor Press : 1.94e-006 mm Hg (Mpbpwin program)
Liquid VP   : 1.68e-005 mm Hg (super-cooled)
Melting Pt : 120 deg C (Mpbpwin program)
Log Kow   : 0.46 (Kowwin program)
Soil Koc   : 1.18 (EQC Model Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)	
Air	0.000673	14.5	1000	
Water	37.5	360	1000	
Soil	62.4	720	1000	
Sediment	0.0705	3.24e+003	0	

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)	
Air	1.82e-014	0.567	0.119	0.0189	0.00396	
Water	6.05e-016	1.28e+003	663	42.5	22.1	
Soil	3.4e-014	1.06e+003	0	35.4	0	
Sediment	5.53e-016	0.266	0.0249	0.00888	0.00083	

Persistence Time: 589 hr
Reaction Time: 756 hr
Advection Time: 2.66e+003 hr
Percent Reacted: 77.9
Percent Advected: 22.1

Water Compartment Percents:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)	
Air	0.000673	14.5	1000	
Water	37.5	360	1000	
water	(37.5)			
biota	(5.41e-006)			
suspended sediment	(6.66e-005)			
Soil	62.4	720	1000	
Sediment	0.0705	3.24e+003	0	

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 14.52
Water: 360
Soil: 720
Sediment: 3240
Biowin estimate: 2.867 (weeks   )

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004