

Development and assessment of risk profiles for pharmaceuticals

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It is no longer enough to develop actives, a number of wider 'acceptability' criteria need to be considered. Their properties in respect of effects on the environment need to be understood. A method of setting priorities for action or research in respect of environmental effects of pharmaceuticals is described.

Many substances can be compared on a uniform basis. The poster also sets out a general discussion of the properties that influence risk to the aquatic environment. The method of calculating a 'critical release' gives a very high level of differentiation between substances.

INTRODUCTION

Current approach to risk assessment: substance by substance

At present substances are individually prioritised for detailed risk assessment. This substance-by-substance approach is thorough, but slow.

Risk Profiling concept

An alternative method, which applies some simple defaults and assumptions across the board, allows a range of substances with similar applications and emission routes to be compared in a preliminary screening assessment.

In terms of chemicals in general, an assessor could investigate one industrial sector at a time. Then within that sector, many substances can be considered at once, with a range of properties, effects and use patterns being explored.

A generic exposure model is compiled from knowledge of likely release levels and patterns and the influence of key chemical properties. It is possible to model the combinations which result in a conclusion of risk.

This type of approach is termed 'risk profiling'. Past experience from full risk assessments can be used to 'calibrate' the profiling.

A brief and simple investigation has been undertaken for a range of pharmaceutical active substances to illustrate this concept.

RISK PROFILING: AN ALTERNATIVE APPROACH TO ENVIRONMENTAL RISK ASSESSMENT

Risk profiling uses the current regulatory risk assessment techniques to inform about which data give rise to acceptable or unacceptable outcomes, for a specific use, and can be applied to all substances with that use, comparable routes of release (e.g. via domestic waste water or industrial emission) and those properties.

The main potential advantage of this approach is that substances can be rapidly screened and prioritised. There is also scope to communicate a lot of information to non-specialists.

The risk profile would thus be a combination of factors, already familiar to risk assessors:

- Use pattern
- Distribution and degradation
- Effects

Using risk profiling, it is possible to derive PEC values and/or RCRs as a function of those chemical properties and commercial factors that affect it.

In addition, the capacity of risk profiling to show these outcomes as functions of parameters (i.e. properties and exposure patterns) that are potentially controllable, as well as those that are not, may help identify appropriate courses of action.

Nobody sets out to make substances which possess undesirable hazardous properties such as adverse effects on the environment. Some properties are essential to the intended function. Pharmaceuticals in particular are designed to be biologically active and some have low environmental effect concentrations.

Critical release concept

A particularly useful method associated with this approach is the ability to derive a 'Critical release' – the level of release at which the substance becomes a probable risk to the environment.

If typical release rates can be estimated this can be taken through to an evaluation of the market. An assessor can calculate the tonnage of a substance that could be on the market for a particular application which gives an RCR of 1, as a function of the substance properties, given typical release rates.

In terms of industrial sites, there is some control possible over the tonnage in use at one site, and release rates may be controllable in some industry sectors.

This could also guide the user to the maximum tonnage that could safely be used for that release rate.

Critical release calculation method

Consider the question "What release rate is going to give PEC/PNEC above 1 for the aquatic compartment?"

If the rate of release of the substance is R kg/d, then PEC_{local} in mg/l is given by:

$$PEC_{local} (mg/l) = \frac{\text{rate of release to waste} \times \text{fraction passing to water in WWTP } (F_w)**}{\text{total flow of WWTP in l/d} \times \text{DILUTION}} + PEC_{reg}$$

**using the SimpleTreat model

total flow of WWTP in l/d = CAPACITY x WASTEWinhab

Therefore

$$PEC (mg/l) = (R \times 10^6 \times F_w / (\text{CAPACITY} \times \text{WASTEWinhab} \times \text{DILUTION})) + PEC_{reg}$$

We know that when PEC/PNEC = 1 and the critical release rate is **R_c** then

$$R_c = (\text{PNEC} - PEC_{reg}) (\text{CAPACITY} \times \text{WASTEWinhab} \times \text{DILUTION}) / (10^6 \times F_w)$$

This is only valid if PNEC > PEC_{reg}.

Therefore the Critical release in the region is R_c x (number of days) / fmls

The expression for R_c is an explicit function of known values.

Critical release can be expressed in terms of the total tonnage e.g. of an industrial chemical, or as kg/d passing to an individual waste water treatment plant of a standard size. This latter approach is used in the investigation described in the poster.

The two figures show the general relationship of critical tonnage for a particular industrial use, as a function of two key input properties.

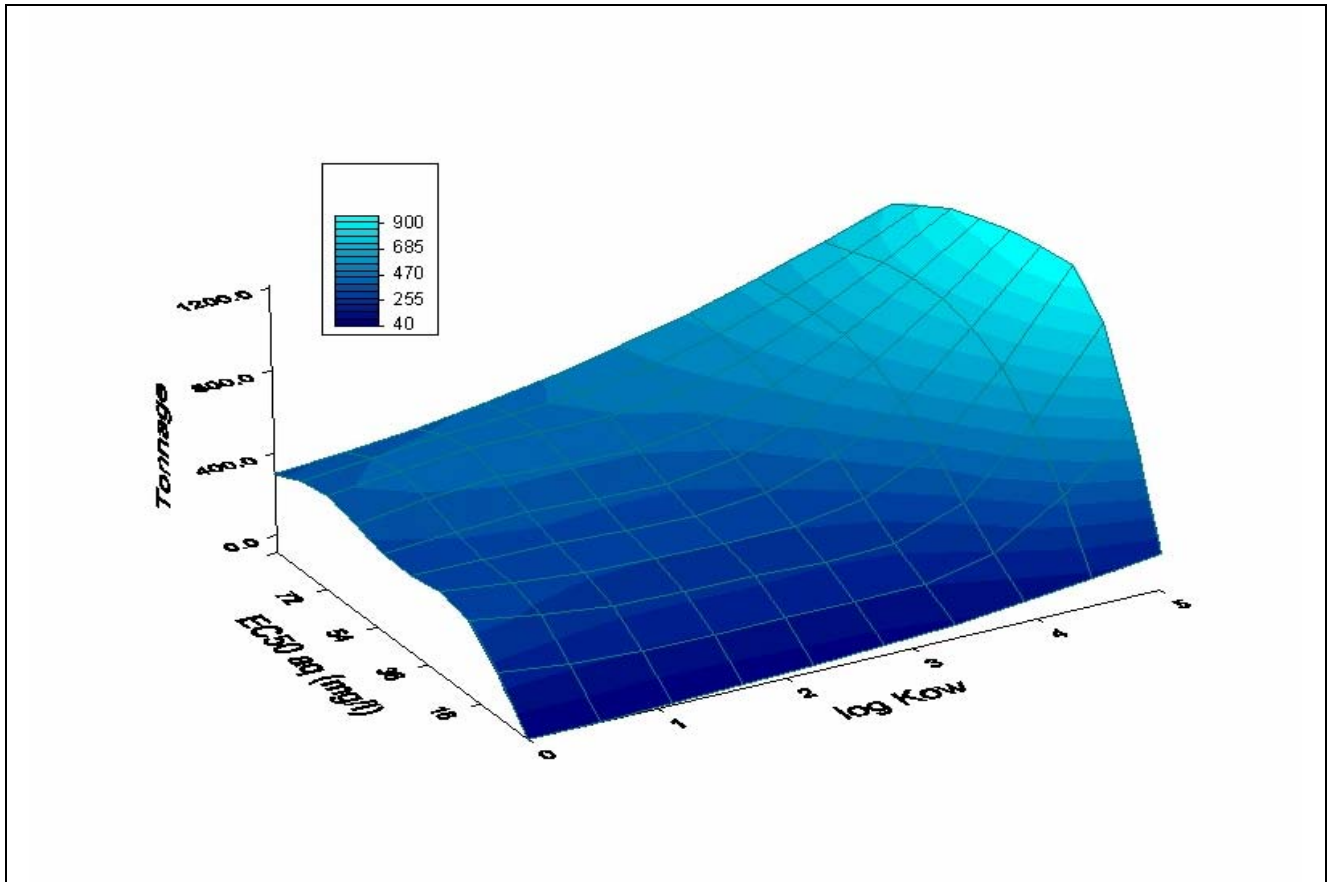


Figure 1: This graph shows how in the aquatic compartment, Critical release varies in relation to log K_{ow} and EC_{50} water, for non-biodegradable substances (or assuming zero biodegradation).

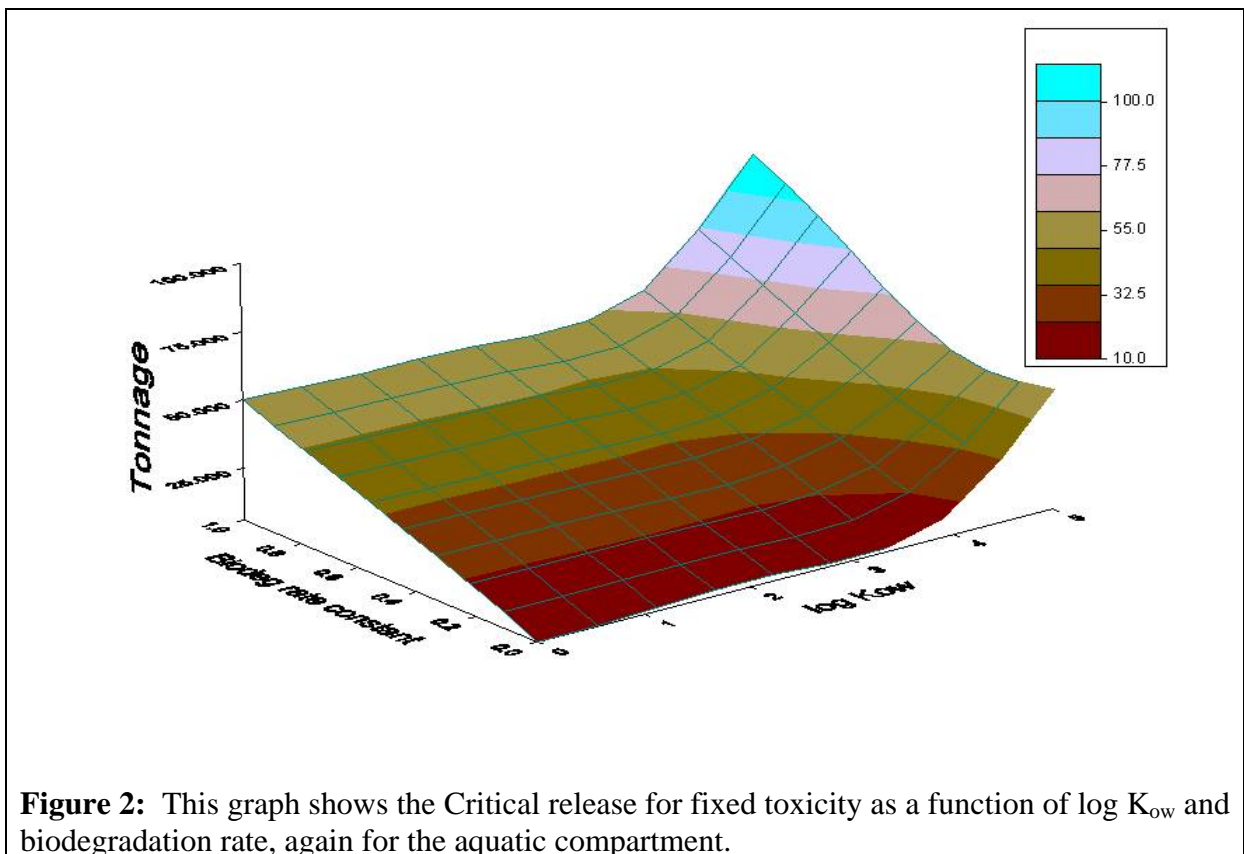


Figure 2: This graph shows the Critical release for fixed toxicity as a function of log K_{ow} and biodegradation rate, again for the aquatic compartment.

DATA REQUIREMENTS

Key property data for environmental risk assessment include physicochemical data, persistence data and ecotoxicity data.

1. Molecular weight
2. Vapour pressure
3. Water solubility
4. Log K_{ow}
5. Biodegradation rates
6. EC_{50} and NOEC values

RISK ASSESSMENT OF PHARMACEUTICALS

Phase I of environmental risk assessment is a simple assessment of PEC_{surfacewater}. It is assumed that the only potential source of environmental exposure is via human excretion, and is released to municipal sewage treatment, that no degradation takes place in the STP and that there is no metabolism of the parent drug in the patient. The amount of product used each year is predicted, and it is assumed that use is evenly distributed both geographically and throughout the year.

$$PEC_{surfacewater} = (DOSE_{ai} * F_{pen}) / (WASTE_{winhab} * DILUTION * 100)$$

The resulting PEC is compared to the so-called “action limits”:

If $PEC_{surfacewater} > 0.01 \mu\text{g/l}$ then the assessment proceeds to Phase II.

If $PEC_{surfacewater} < 0.01 \mu\text{g/l}$, in general no further assessment is required.

In Phase II, Tier B, $PEC_{surfacewater}$ for pharmaceuticals is evaluated in essentially the same way as for general chemicals, using the following information:

- Excretion route and qualitative and quantitative information on excreted compounds
- Adsorption to sewage sludge
- Biodegradation in surface water
- Ready biodegradability
- Abiotic degradation by hydrolysis or photolysis

Although expressed slightly differently, $PEC_{surfacewater}$ is calculated using the same method as the TGD i.e. using the SIMPLETREAT model to determine the fraction directed to water in the STP, taking adsorption to suspended matter into account:

$$PEC = (E_{localwater} * F_w) / (WASTE_{winhab} * CAPACITY_{stp} * FACTOR * DILUTION)$$

$$\text{Where } E_{localwater} = (DOSE_{ai} * F_{excreta} * F_{pen} * CAPACITY_{stp}) / 100$$

USE OF RISK PROFILING IN RESEARCH AND DEVELOPMENT

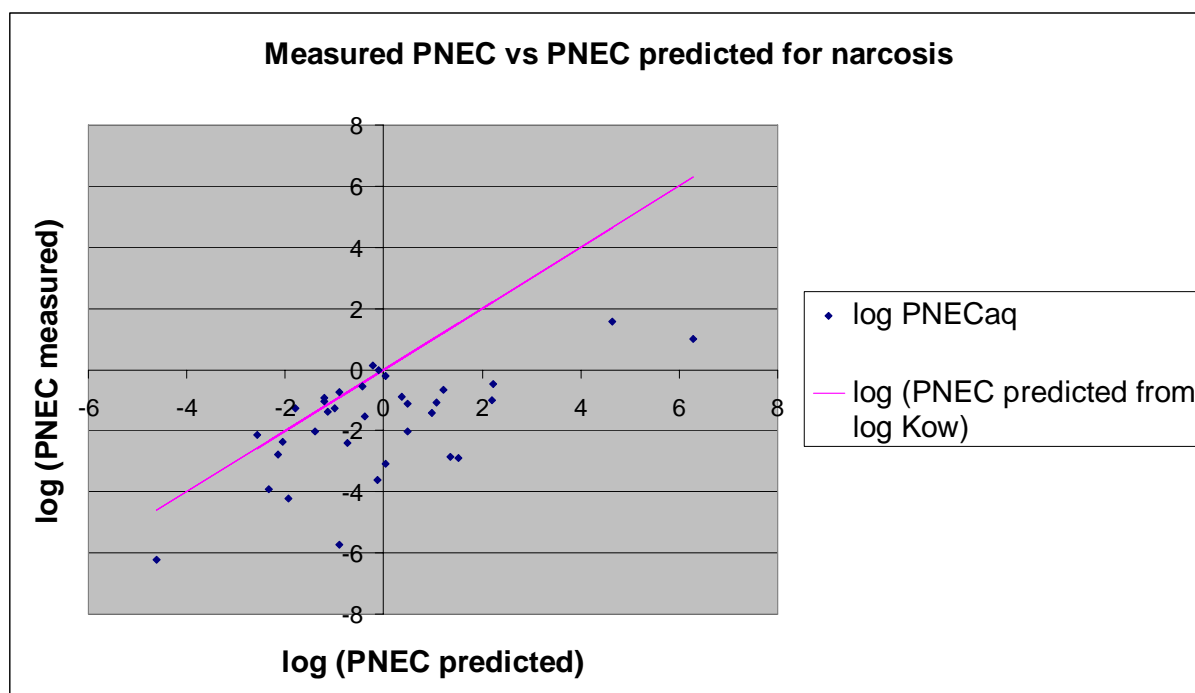
The R and D process for pharmaceuticals is complex and expensive, and it cannot be expected that environmental criteria will be taken into account as a reason to prioritise one candidate over another. However, it can help in choice of formulation ingredients.

A further use of risk profiling can be to set priorities. For example, if it is necessary to consider which substances are of most urgent need of new data, then the method identifies the most serious cases.

INVESTIGATION OF CRITICAL RELEASES FOR PHARMACEUTICALS

A set of data are available where ecotoxicity test data for at least one of acute fish, *Daphnia* or algae are available. The lowest value has been selected, and a PNEC determined as $EC_{50}/1000$.

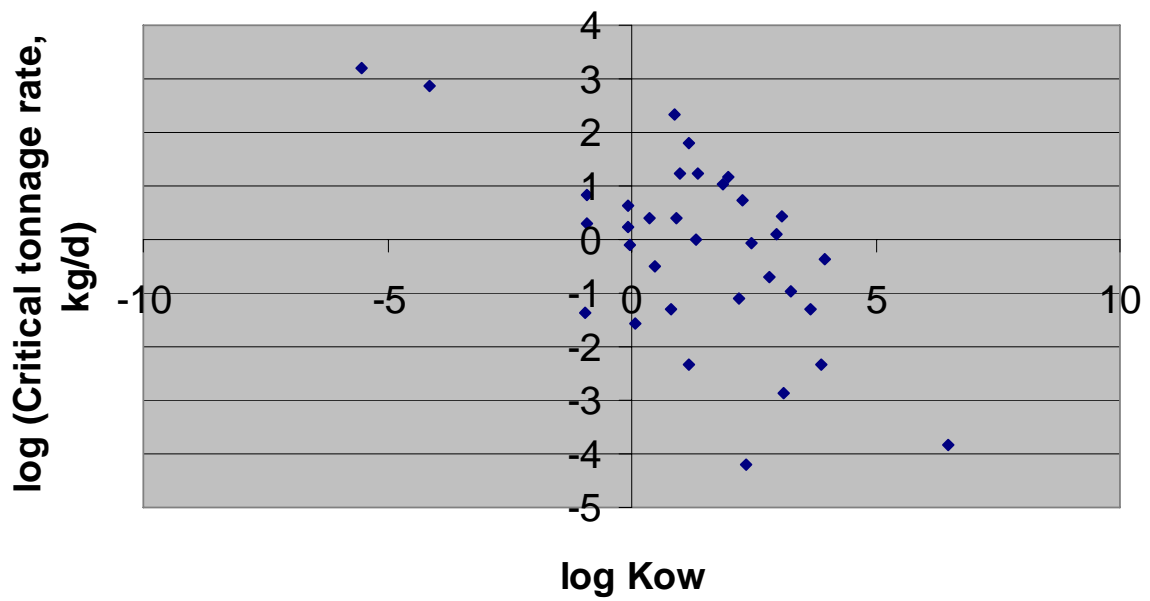
The following graph shows that most of the substances in the data set have more severe ecotoxic effects than would be expected on the basis of narcosis alone.



The table overleaf shows input data and outputs from the approach described.

It can be seen that it is possible for pharmaceutical ingredients to be sufficiently toxic to aquatic organisms that their excretion from human users can give rise to adverse effects on the environment.

**Relationship between Critical Release rate to Drain,
and log Kow**



CONCLUSIONS

The number of pharmaceutical substances for which ecotoxicology data are available is few relative to other types of chemical, although this is growing. The substances exhibit toxicities which are more acute than a simple narcotic effect, due to specific modes of toxic action.

Overall findings of the assessment of substances follow the broad trends that one might expect.

The very wide range of 'Critical release' – (a range of about seven orders of magnitude has been observed) is something of a surprise at first, and makes it a powerful tool. The variation is due in part to the biological activity of these substances leading to very high sensitivity in environmental species and hence very low tolerance limits for ecotoxicity.

Resources to meet the growing demands on regulatory work can be in short supply; priority setting is a key area, for industry and government

Determination of 'Critical release' may be of considerable interest. It can enable decisions to be made, for example within industry consortia or representational groups, without confidential tonnage data having to be shared in detail.

The breadth of possible application of the approach used, from basic research through to setting regulatory priorities, has made it necessary to try to develop versatile tools.

Acronyms and terminology	
PEC	Predicted Environmental Concentration; PEC _{reg} is the regional PEC
PNEC	Predicted No Effect Concentration
RCR	Risk Characterisation Ratio (= PEC/PNEC)
EPI	EPISuite: property prediction programs downloadable from the USEPA web site
R _c	Critical release rate
SimpleTreat	A model which predicts the behaviour of a chemical in a municipal waste water treatment plant
Region	A hypothetical area of mixed urban and agricultural use, population 20 million
EC ₅₀	Ecotoxicity test result: concentration in solution giving 50% effect or mortality to an aquatic organism
(in the equations)	<p>F_w is the fraction passing to water in a waste water treatment plant</p> <p>CAPACITY = Capacity of the WWTP</p> <p>DILUTION = dilution factor = 10 as default</p> <p>f_{mls} is 'fraction of the main local source', representing the fractional of tonnage used in a region going to the default-sized waste water treatment plant. This is 0.002 in standard models.</p> <p>DOSE_{ai} = Maximum daily dose consumed per inhabitant</p> <p>F_{pen} = Percentage of market penetration (i.e. how much of the overall market will the new substance occupy, default = 1%)</p> <p>WASTEWinhab = Amount wastewater per inhabitant per day (default = 200 l/capita/d as TGD)</p>



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	CAS number	MW	Water solubility EPI mg/l	log n-octanol /water partition coefficient	Vapour pressure EPI Pa	Biodegradation rating	fW	PNEC mg/l	Water critical release rate kg/d	mg/head/day to drain
acetylsalicylic acid	50782	180.2	5295	1.19	8.74E-03	Ready deg. outside window	0.325	1	61.5	6149
diethyl ether	60297	74.1	2.32E+04	0.89	7.21E+04	Ready deg. outside window	0.132	1.38	208.6	20861
benzoic acid	65850	122.1	2493	1.87	3.97E-01	Ready deg. outside window	0.323	0.18	11.1	1113
caffeine	58082	194.2	2632	-0.07	9.77E-07	No Biodeg.	1.000	0.087	1.7	174
carbamazepine	298464	236.3	17.66	2.45	1.17E-05	No Biodeg.	0.966	0.043	0.9	89
chloral hydrate	302170	165.4	9225	0.99	1.23E+03	No Biodeg.	0.725	0.63	17.4	1738
chlorhexidine	56951	505.5	0.04746	0.08	2.64E-12	No Biodeg.	1.000	0.0014	0.03	2.8
chlorocresol	1321104	142.6	1522	3.1	5.40E+00	No Biodeg.	0.857	0.00006	0.001	0.1
chloroform	67663	119.4	2096	1.97	2.52E+04	No Biodeg.	0.074	0.054	14.6	1458
chloroxylenol	88040	156.6	434.6	3.27	2.40E-01	No Biodeg.	0.813	0.0045	0.1	11
deanol	108010	89.1	1.00E+06	-0.94	4.37E+02	Inherent deg.	0.591	0.00128	0.04	4.3
diazepam	439145	284.8	58.78	2.82	1.36E-05	No Biodeg.	0.924	0.0091	0.2	20
disulfiram	97778	296.5	63.66	3.88	8.81E-04	No Biodeg.	0.532	0.00012	0.005	0.5
guaiacol	90051	124.1	7226	1.32	1.51E+01	Inherent deg.	0.588	0.0289	1.0	98
ibuprofen	15687271	206.3	41.05	3.97	2.48E-02	Inherent deg.	0.326	0.0071	0.4	44
lactitol	585864	344.3	1.00E+06	-5.53	1.60E-09	Ready deg. inside window	0.127	10	1580.0	158000
malathion	121755	330.4	78.45	2.36	1.65E-02	Inherent deg.	0.577	0.0000018	0.0001	0.006
methenamine	100970	140.2	1.00E+06	-4.15	1.21E+01	No Biodeg.	1.000	36	720.0	72002
nicotine	54115	162.2	1.00E+06	1.17	4.27E+00	No Biodeg.	0.998	0.00024	0.005	0.5
nicotinic acid	59676	123.1	4.82E+04	0.36	1.25E-02	Inherent deg.	0.592	0.077	2.6	260

	CAS number	MW	Water solubility EPI mg/l	log n-octanol /water partition coefficient	Vapour pressure EPI Pa	Biodegradation rating	fW	PNEC mg/l	Water critical release rate kg/d	mg/head/day to drain
nifedipine	21829254	346.3	357.5	2.2	3.51E-06	No Biodeg.	0.981	0.00388	0.1	7.9
paracetamol	103902	151.2	3.04E+04	0.46	2.59E-04	Inherent deg.	0.592	0.0092	0.3	31
permethrin	52645531	391.3	0.009747	6.5	1.10E-04	No Biodeg.	0.082	0.0000006	0.00	0.015
phenethyl alcohol	60128	122.2	2.20E+04	1.36	3.24E+00	Ready deg. outside window	0.325	0.287	17.7	1767
resorcinol	108463	110.1	8.57E+04	0.8	1.60E-02	Ready deg. outside window	0.326	0.0008	0.05	4.9
salicylic acid	69727	138.1	3808	2.26	4.25E-03	Ready deg. outside window	0.320	0.09	5.6	562
terpineol	98555	154.3	371.7	2.98	2.61E+00	No Biodeg.	0.876	0.055	1.3	126
erythromycin	114078	734	0.5168	3.06	2.83E-23	No Biodeg.	0.876	0.121	2.8	277
ethinyl estradiol	57636	296.4	116.4	3.67	2.60E-07	No Biodeg.	0.642	0.0016*	0.05	5.0
metronidazole	443481	171.2	2.57E+04	-0.02	1.75E-05	No Biodeg.	1.000	0.0398	0.8	80
oxytetracycline	79572	460.4	1.00E+06	-0.9	7.20E-15	No Biodeg.	1.000	0.1	2.0	200
sulfadiazine	68359	250.3	2.81E+04	-0.09	7.01E-07	No Biodeg.	1.000	0.221	4.4	442
tetracycline	64755	482.9	2.49E+05	-0.9	1.04E-26	No Biodeg.	1.000	0.34	6.8	680
trimethoprim	738705	290.3	2334	0.91	1.00E-06	No Biodeg.	0.999	0.13	2.6	260

*The PNEC for endocrine-disruption is much lower than this