# Prioritizing PBT Substances

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## Abstract

The interplay between partial order ranking and Quantitative Structure Activity Relationships (QSARs) constitute a strong decision support tool. By means of partial order ranking it is possible to prioritize and select chemicals for decision-making among a group of substances based on simultaneous evaluation of data related to different endpoints. In the absence of experimental data, QSARs are used to provide estimates. In the present chapter, the identification of chemicals with Persistence and Bioconcentration (PB) potential is used to illustrate the interplay between partial order ranking and QSARs. The endpoints biodegradation and bioconcentration were obtained using the BioWin and BCFWin modules from http://www.epa.gov/oppt/exposure/docs/episuitedl.htm. Partial order theory was used to rank chemicals for PB potential based on QSAR estimates. The proposed approach is suggested as a decision support tool to facilitate pollution prevention activities by regulated and regulatory communities.

## Introduction

Persistent, bioaccumulative and toxic (PBT) substances are chemicals that persist in the environment, accumulate in tissues of biological organisms and cause toxic effects. PBT substances are characterized by having persis-

tence characteristics (e.g., an atmospheric half-life of ≥ 2 days, an aquatic half life of ≥ 60 days or a soil or sediment half life of ≥ 6 months), a bioconcentration factor (BCF) ≥ 5,000 and toxicity potential, e.g., an aquatic organism $LC_{50}$ ≤ 1 mg/L (cf. Carlsen and Walker, 2003 and references therein).

It is advantageous to prioritize chemicals for PBT potential by evaluating several criteria. One method for accomplishing this is to include all criteria into a single criterion (for a discussion please see Brüggemann et al., p. 237). As described in this chapter for substances with P and B characteristics, a more effective method for prioritizing chemicals for P and B potential is by simultaneous evaluation of several criteria using partial order ranking.

## Materials and Methods

## Substances studied

The TSCA Interagency Testing Committee (ITC, http://www.epa.gov/opptintr/itc) screened 8,511 chemicals for PB potential. Walker and Carlsen (2002) described the PB characteristics for 50 of these chemicals (Table 1).

**Table 1.** Bioconcentration factors (BCF) and Biodegradation potentials (BDP) for the 50 chemicals included in the Walker and Carlsen (2002) study. H and M denotes high and medium estimates for both the bioconcentration (B) and Persistence (P) scores

| | CAS RN | Chemical | BCF | BDP | B | P |
|---|---|---|---|---|---|---|
| 1 | 000087-82-1 | Benzene, hexabromo- | 9417 | 1.1644 | H | H |
| 2 | 000118-74-1 | Benzene, hexachloro- | 5153 | 1.3302 | H | H |
| 3 | 000128-69-8 | Perylo[3,4-cd:9,10-c'd']dipyran-1,3,8,10-tetrone | 13200 | 1.5328 | H | H |
| 4 | 000133-14-2 | Peroxide, bis(2,4-dichlorobenzoyl) | 8478 | 1.533 | H | H |
| 5 | 000355-42-0 | Hexane, tetradecafluoro- | 8609 | 0.5777 | H | H |
| 6 | 000375-81-5 | 1-Pentanesulfonyl fluoride, 1,1,2,2,3,3,4,4,5,5,5-undecafluoro- | 29740 | 1.0596 | H | H |
| 7 | 000423-50-7 | 1-Hexanesulfonyl fluoride, 1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluoro- | 7444 | 0.737 | H | H |
| 8 | 000509-34-2 | Spiro[isobenzofuran-1(3H),9'-[9H]xanthen]-3-one, 3',6'-bis(diethylamino)- | 25450 | 1.5815 | H | H |
| 9 | 000596-49-6 | Benzenemethanol, 4-(diethylamino)-.alpha.,.alpha.-bis[4-(diethylamino)phenyl]- | 4292 | 1.1758 | M | H |

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|---|---|---|---|---|---|---|
| 10 | 000678-39-7 | 1-Decanol, 3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro- | 12200 | 0.3357 | H | H |
| 11 | 001568-80-5 | 1,1'-Spirobi[1H-indene]-6,6'-diol, 2,2',3,3'-tetrahydro-3,3,3',3'-tetramethyl- | 13070 | 1.994 | H | M |
| 12 | 001770-80-5 | Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid, 1,4,5,6,7,7-hexachloro-, dibutyl ester | 29340 | 1.2935 | H | H |
| 13 | 002379-79-5 | Anthra[2,3-d]oxazole-5,10-dione, 2-(1-amino-9,10-dihydro-9,10-dioxo-2-anthracenyl)- | 2310 | 1.9347 | M | M |
| 14 | 002475-31-2 | 3H-Indol-3-one, 5,7-dibromo-2-(5,7-dibromo-1,3-dihydro-3-oxo-2H-indol-2-ylidene)-1,2-dihydro- | 3972 | 1.0633 | M | H |
| 15 | 002641-34-1 | Propanoyl fluoride, 2,3,3,3-tetrafluoro-2-[1,1,2,3,3,3-hexafluoro-2-(heptafluoropropoxy)propoxy]- | 1363 | -0.5183 | M | H |
| 16 | 003006-86-8 | Peroxide, cyclohexylidenebis[(1,1-dimethylethyl) | 13560 | 1.9874 | H | M |
| 17 | 003864-99-1 | Phenol, 2-(5-chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)- | 14930 | 1.8338 | H | M |
| 18 | 004051-63-2 | [1,1'-Bianthracene]-9,9',10,10'-tetrone, 4,4'-diamino- | 5198 | 1.8572 | H | M |
| 19 | 004162-45-2 | Ethanol, 2,2'-[(1-methylethylidene)bis[(2,6-dibromo-4,1-phenylene)oxy]]bis- | 7479 | 1.2501 | H | H |
| 20 | 004378-61-4 | Dibenzo[def,mno]chrysene-6,12-dione, 4,10-dibromo- | 6110 | 1.8566 | H | M |
| 21 | 005590-18-1 | 1H-Isoindol-1-one, 3,3'-(1,4-phenylenediimino)bis[4,5,6,7-tetrachloro- | 1916 | 0.0193 | M | H |
| 22 | 013080-86-9 | Benzenamine, 4,4'-[(1-methylethylidene)bis(4,1-phenyleneoxy)]bis- | 39730 | 1.6937 | H | H |
| 23 | 013417-01-1 | 1-Octanesulfonamide, N-[3-(dimethylamino)propyl]-1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro- | 1300 | -0.3446 | M | H |
| 24 | 013680-35-8 | Benzenamine, 4,4'-methylenebis[2,6-diethyl- | 15070 | 1.8689 | H | M |
| 25 | 014295-43-3 | Benzo[b]thiophen-3(2H)-one, 4,7-dichloro-2-(4,7-dichloro-3-oxobenzo[b]thien-2(3H)-ylidene)- | 1461 | 1.3684 | M | H |
| 26 | 015667-10-4 | Peroxide, cyclohexylidenebis[(1,1-dimethylpropyl) | 28610 | 1.9254 | H | M |
| 27 | 016090-14-5 | Ethanesulfonyl fluoride, 2-[1-[difluoro[(trifluoroethenyl)oxy]methyl]-1,2,2,2-tetrafluoroethoxy]-1,1,2,2-tetrafluoro- | 12710 | 0.8345 | H | H |
| 28 | 017527-29-6 | 2-Propenoic acid, 3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl ester | 45320 | 0.8418 | H | H |
| 29 | 024108-89-2 | Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline-1,3,8,10(2H,9H)-tetrone, 2,9-bis(4-ethoxyphenyl)- | 14640 | 0.8899 | H | H |
| 30 | 025637-99-4 | Cyclododecane, hexabromo- | 6211 | 1.9548 | H | M |
| 31 | 026628-47-7 | Spiro[12H-benzo[a]xanthene-12,1'(3'H)-isobenzofuran]-3'-one, 9-(diethylamino)- | 26190 | 1.8829 | H | M |
| 32 | 029512-49-0 | Spiro[isobenzofuran-1(3H),9'-[9H]xanthen]-3-one, 6'-(diethylamino)-3'-methyl-2'-(phenylamino)- | 23790 | 1.5734 | H | H |
| 33 | 031148-95-5 | 1-Phenanthrenecarbonitrile, 1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl-7-(1-methylethyl)-, [1R-(1.alpha.,4a.beta.,10a.alpha.)]- | 13900 | 1.9209 | H | M |
| 34 | 031506-32-8 | 1-Octanesulfonamide,1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-heptadecafluoro-N-methyl- | 2355 | 0.0673 | M | H |

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|---|---|---|---|---|---|---|
| 35 | 040567-16-6 | Butanoyl chloride, 2-[2,4-bis(1,1-dimethylpropyl)phenoxy]- | 19450 | 1.9678 | H | M |
| 36 | 041556-26-7 | Decanedioic acid, bis(1,2,2,6,6-pentamethyl-4-piperidinyl) ester | 1351 | 0.9971 | M | H |
| 37 | 050598-28-2 | 1-Hexanesulfonamide, N-[3-(dimethylamino)propyl]-1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluoro- | 14300 | 0.3006 | H | H |
| 38 | 051461-11-1 | Butanamide, N-(3-amino-4-chlorophenyl)-4-[2,4-bis(1,1-dimethylpropyl)phenoxy]- | 4393 | 1.3375 | M | H |
| 39 | 051772-35-1 | 1-Naphthalenamine, N-[(1,1,3,3-tetramethylbutyl)phenyl]- | 1333 | 1.8096 | M | M |
| 40 | 054079-53-7 | Propanedinitrile, [[4-[[2-(4-cyclohexylphenoxy)ethyl]ethylamino]-2-methylphenyl]methylene]- | 3996 | 1.6579 | M | H |
| 41 | 058798-47-3 | 3H-Indolium, 2-[[(4-methoxyphenyl)methylhydrazono]methyl]-1,3,3-trimethyl-, acetate | 1952 | 1.9594 | M | M |
| 42 | 064022-61-3 | 1,2,3,4-Butanetetracarboxylic acid, tetrakis(2,2,6,6-tetramethyl-4-piperidinyl) ester | 24930 | 0.4125 | H | H |
| 43 | 067584-54-7 | 1-Heptanesulfonamide, N-[3-(dimethylamino)propyl]-1,1,2,2,3,3,4,4,5,5,6,6,7,7,7-pentadecafluoro- | 27380 | -0.022 | H | H |
| 44 | 067584-57-0 | 2-Propenoic acid, 2-[methyl[(tridecafluorohexyl)sulfonyl]amino]ethyl ester | 29550 | 0.636 | H | H |
| 45 | 068084-62-8 | 2-Propenoic acid, 2-[methyl[(pentadecafluoroheptyl)sulfonyl]amino]ethyl ester | 7529 | 0.3134 | H | H |
| 46 | 068259-36-9 | 1-Naphthalenamine, N-phenyl-ar-(1,1,3,3-tetramethylbutyl)- | 1333 | 1.9294 | M | M |
| 47 | 068555-73-7 | 1-Heptanesulfonamide, N-ethyl-1,1,2,2,3,3,4,4,5,5,6,6,7,7,7-pentadecafluoro-N-(2-hydroxyethyl)- | 35110 | 0.4216 | H | H |
| 48 | 068555-76-0 | 1-Heptanesulfonamide, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,7-pentadecafluoro-N-(2-hydroxyethyl)-N-methyl- | 14700 | 0.4526 | H | H |
| 49 | 106246-33-7 | Benzenamine, 4,4'-methylenebis[3-chloro-2,6-diethyl- | 9015 | 1.3034 | H | H |
| 50 | 106917-30-0 | 2,5-Pyrrolidinedione, 3-dodecyl-1-(1,2,2,6,6-pentamethyl-4-piperidinyl)- | 1457 | 1.8888 | M | M |

## QSARs

BCFs were estimated using EPI Suite's BCFWin program (http://www.epa.gov/oppt/exposure/docs/episuitedl.htm). BCFs were estimated from the log octanol-water partition coefficient (log $K_{OW}$) and a series of structural correction factors (Meylan et al., 1999). The ITC uses BCFs of ≥1,000 and ≥ 5,000 to screen chemicals for bioconcentration potential. Chemicals with 1000 ≤ BCF < 5,000 are assigned a medium (M) bioconcentration potential. Chemicals with BCF ≥ 5,000 are assigned a high (H) bioconcentration potential (cf. Table 1).

Persistence predictions were estimated using EPI Suite's BioWin program (http://www.epa.gov/oppt/exposure/docs/episuitedl.htm). The ultimate aerobic biodegradation probabilities (BDPs) from the ultimate survey model in BioWin were used to predict persistence potential. These predictions were based on expert opinions that different structural groups could be used to estimate a chemical's biodegradation potential (Boethling et al, 1994). The ITC uses BDPs of < 2 and < 1.75 as surrogates for chemicals that are likely to persist for approximately 2 and 6 months, respectively. Chemicals with BDP < 2 were associated with a medium (M) persistence potential. Chemicals with BDP < 1.75 were assigned a high (H) persistence potential (cf. Table 1).

## Partial Order Ranking

The theory of partial order ranking has been presented in previous papers (Carlsen et al. 2001, Brüggemann et al. 2001a, Carlsen et al. 2002). In brief, Partial Order Ranking is a simple principle, which a priori includes "□" as the only mathematical relation. If a system is considered, which can be described by a series of descriptors $p_i$, a given compound A, characterized by the descriptors $p_i(A)$ can be compared to another compound B, characterized by the descriptors $p_i(B)$, through comparison of the single descriptors, respectively. Thus, compound A will be ranked higher than compound B, i.e., B □ A, if at least one descriptor for A is higher than the corresponding descriptor for B and no descriptor for A is lower than the corresponding descriptor for B. If, on the other hand, $p_i(A) > p_i(B)$ for descriptor i and $p_j(A) < p_j(B)$ for descriptor j, A and B will be denoted incomparable. In mathematical terms this can be expressed as

$$B \leq A \Leftrightarrow p_i(B) \leq p_i(A) \text{ for all i} \quad (1)$$

In partial order ranking – in contrast to standard multidimensional statistical analysis - neither assumptions about linearity nor any assumptions about distribution properties are made. Partial order ranking may be considered as a parameter-free method. Thus, there is no preference among the descriptors. The graphical representation of the partial ordering is typically given in a so-called Hasse diagram (Halfon and Reggiani 1986, Brüggemann et al. 2001b, Brüggemann et al. 1995, Hasse 1952), where comparable elements are connected with lines, whereas incomparable elements appear as unconnected. Substances being ranked identically, i.e. these substances cannot be distinguished by the partial order ranking are located in the same levels in the diagram. Thus, substances that on a cumulative basis are ranked, as the most hazardous, are located in level 1.

Note that the enumeration of levels follows convention. In other chapters of this book the enumeration begins with the bottom level. Patil & Taillie, 2005 introduce in that context the concepts level and co-level. In the present study, the QSAR derived estimates for persistence and bioconcentration were descriptors for the construction of the Hasse diagrams using the WHASSE software (Brüggemann et al., 1995).

## Results

Partial order ranking of the substances was made using the 50 BCF and BDP estimates (cf. Table 1) and applying the WHASSE software (Fig. 1).

Fig. 1 consists of 11 levels, 4 maximal elements, i.e., only those connected to lower-ranked elements (15, 28, 43, 47) and 5 minimal elements, i.e., only those connected to higher-ranked elements (11, 23, 41, 39, 46), respectively.

## Discussion

Ranking the 4 chemicals in level 1 based on BCF alone (Table 1) would be 28 > 47 > 43 >> 15. However, based only on BDP just the opposite ranking would occur, viz., 15 > 43 > 47 > 28. However, partial order ranking allows both descriptors to be taken into account simultaneously leading to the conclusion that all 4 compounds 15, 28, 43 and 47 apparently are the environmentally more problematic. In the case of compound 15, displaying only a medium level bioaccumulation, the high ranking is associated with a very high environmental persistence.

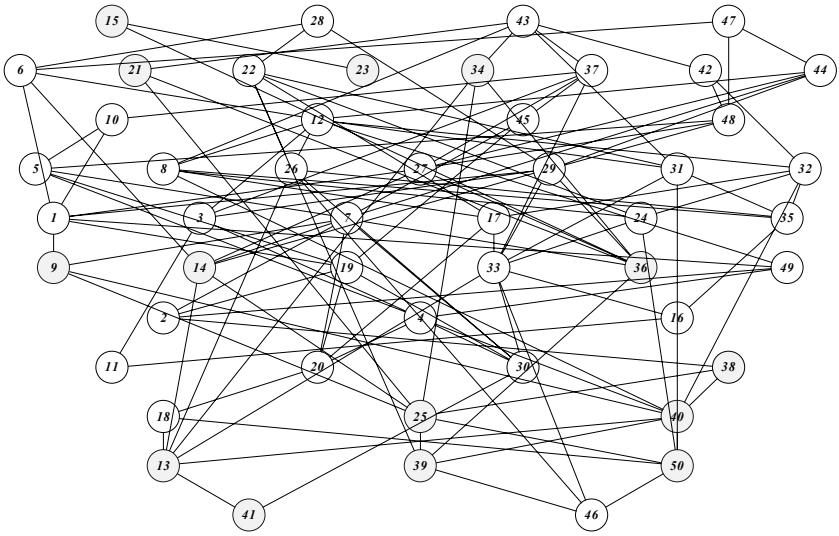


**Fig. 1.** Hasse Diagram displaying the partial order ranking of the substances studied using the BCF and BDP estimates as descriptors

## Conclusions

The present study has demonstrated that substances can be prioritized or ranked using a partial order ranking technique, e.g., based on their PB characteristics. Simple "yes/no" classification or total linear ranking can be obtained based on QSARs alone with reference to selected PB criteria. However, partial order ranking provides more valuable information with regard to which substances are environmentally hazardous because it simultaneously takes into account the persistence and bioaccumulation of the substances under investigation. As such, the combination of QSAR modelling and partial order ranking constitute an effective decision support tool that could be used to facilitate pollution prevention activities by regulated and regulatory communities.

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