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Hansen Solubility Parameters as descriptors of adverse persistence and bioaccumulation properties of substances
Part 1: overview

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1. Executive summary

This report is intended for anyone interested in regulation of persistent and bioaccumulative chemicals, from discovery chemists through to regulators. Hansen Solubility Parameters (HSP) are highly relevant to persistence, bioaccumulation, and toxicity (PBT) assessment. HSP describe the nature and strength of intermolecular forces, which are the fundamental basis of understanding chemical interactions.

The emphasis in this report is, for simplicity, on the “legacy pollutants” and analogues in comparison to a set of around 9700 substances.

Comparison to methods of screening based on measurement of bioconcentration and stability is made. HSP gives insights into the bioaccumulation process.

HSP has a sound basis in chemical thermodynamics, which gives weight to the new insights in the study of PBT issues. HSP can be determined very easily and could be a much better initial screen than the current methods. There may be a case that some substances should be re-examined in respect of PBT. However, it is unlikely that the regulatory authorities will move away from the present criteria.

The strongest benefit of the use of HSP over study of bioconcentration factor (BCF) is that these parameters have been utilised in many research and development programmes relating to technical performance. Bringing the environmental and performance themes together, it can be stated clearly that there are regions of HSP space that are best avoided by chemistry researchers, due to the risk of a substance having as-yet-undiscovered adverse PBT properties. Adverse properties and desired properties can be examined using the same molecular descriptors. This benefit does not apply to screening based on BCF.

2. Introduction

The regulatory concerns over substances which are persistent, bioaccumulative and toxic are well known and do not need to be set out here. Substances named within the Stockholm Convention have been identified by the authorities, on the basis of their presence in the environment and higher organisms. The challenge has been, for

many years now, to predict whether a substance could, after prolonged use, also be found in the food chain. The screening for this has largely been based on laboratory tests of bioconcentration factor (BCF) and biodegradability.

Prediction of BCF has been made commonly using the octanol-water partition coefficient.[1]

The main purpose of the present report is not to try to find new methods to predict BCF but to examine the HSP values of the legacy pollutants (LPs) to find out whether there is any pattern in relationship to HSP. The intention is not to criticise current regulatory approaches, but to show that the use of the HSP can be used for screening for PBT in parallel with its long-established place as an important research tool.

Part 2 of the report will deal with a detailed analysis of several relevant chemical structural classes using HSP, in comparison to more detailed consideration of persistence and bioaccumulation.

3. Why use HSP?

Introduction to HSP

For an introduction go to https://www.hansen-solubility.com/HSP-science/basics.php which describes how cohesive energy of a molecule in solution can be described in terms of a solubility parameter broken down into three terms: dispersion, polarity and hydrogen bonding. These are referred to as δD, δP and δH.

Values of these properties for many molecules have been measured, and can be calculated for others.

HSP were originally developed as a method to explore solubility properties of polymers but since then they have been found to be useful for solubility in general and then have been applied to a wide range of other chemical phenomena involving interactions between molecules.

Molecular descriptors such as solvatochromic parameters have been described in the literature for the examination of bioconcentration and partition. They have some benefits as tools but suffer from a lack of accessibility, as they must be measured empirically, and their relative complexity makes them more difficult to visualise than HSP.

Applicability to PBT issues

The starting point is to consider bioaccumulation. In its simplest expression, bioconcentration of a substance from an aqueous environment into an organism can be related to the relative affinity of a molecule for water and the lipids, proteins and membranes of which the organism consists. Therefore it can easily be imagined that the HSP could relate to bioaccumulation; in particular, high dispersion energy might relate to van der Waals' bonding to non-polar substrates, and hydrogen bonding will relate to affinity to water. Additionally, strong polar interactions with proteins found in cells and cellular membranes can also lead to slow elimination of a xenobiotic from an organism.

However, bioaccumulation potential also depends on metabolic elimination of the molecule, if it occurs. Any possible link between HSP and degradation has not been examined here.

It is interesting to note that HSP are under investigation by other workers as useful predictors of skin and eye irritation.

[1] There are many scientific reasons why laboratory measurements such as BCF are not wholly adequate as predictors of bioaccumulation in the environment. However, it is beyond the scope of this report to address those.

Shortcomings of current methods to screen for bioaccumulation

Why is there any need to examine HSP? Is it not sufficient to examine octanol-water partition coefficient (K_{ow}) as a predictor of the BCF? There are several shortcomings with this approach. These can be summarised:

- K_{ow} does not give detailed insight into intermolecular forces, and in particular the polar forces. This shortcoming can be illustrated in several ways, but one example is that two substances can have the same K_{ow} value but completely different affinities for water (or octanol) i.e. K_{ow} is a dimensionless relative property.
- K_{ow} is an equilibrium measure but the environment is not in equilibrium (this comment is also relevant to HSP)
- K_{ow} cannot be determined for surfactants.

Although HSP does not address all these points, there are sufficient reasons to investigate alternatives to K_{ow} as a surrogate for BCF.[2]

Bioaccumulation, as explained above, also depends on metabolic elimination. HSP might give some insights into that, which K_{ow} certainly does not. Of course, a laboratory BCF study using fish does give an indication of rates of uptake and elimination. However, for ethical and cost reasons good alternatives to testing with fish are needed.

4. Methods

Access to HSP

HSP values were obtained from the HSPiP version 5.3.02 (https://www.hansen-solubility.com/HSPiP/).

Typical values of the HSP values[3] of organic molecules are:

δD: 11 to 23; the lowest numbers are typically for low molecular weight and /or certain atoms;
δP: 0 to 30, with 0 representing molecules of very high symmetry and no π bonds;
δH: 0 to 35, with 0 representing molecules containing no functionalities.

Listing substances of concern

LPs and close analogues listed in the Stockholm Convention or ECHA's list of authorised substances and its candidate list as PBT/vPvB were assembled into a database[4]. Some are present in both sources. One substance (Coal tar pitch, CAS 65996-93-2) was excluded because it is a UVCB. The short-chain chlorinated paraffins (CAS 85535-84-8) were represented by a nominal structure with 55% m/m chlorine. The complete list studied here, including SMILES and HSP values is given in Annex 1, Table A1.

Categorisation of 9700 substances

The HSPiP software contains a list of around 9700 substances with HSP parameters (and many other properties). These were examined and categorised as

A LPs and analogues (53 substances), as in Table A1;
B isomers of substances in list A (a further 100 substances);
C structural analogues of list A (40 substances).
others

Annex 2 comments briefly on the usefulness of the set of 9700 for the current study. As will be described in section 5, the main emphasis of the investigation was on substances with δD $\geq$19, of which there are over 1800 in the set of 9700.

[2] For these reasons, it is not of interest to examine whether HSP can be related to K_{ow}. There is a relationship but there is no great gain in looking at K_{ow} when it is a surrogate for the properties of real concern.
[3] For simplicity the HSP are given without their dimensions; they are absolute thermodynamic and not relative properties, and they all possess the unit $(Joules/cm^3)^{½}$.
[4] The use of this list does not mean that the author agrees with the PBT assignation made by the authorities.

The database of substances can be provided on request.

5. Findings

Applicability to LPs currently subject to regulatory control

The δD, δP and δH values of the substances in groups A, B and C were examined. δD was seen to be important in that these substances usually have high values of it. δP and δH both tended to be at the low end of the range, but usually >0. When a wider range of substances were examined, both parameters were useful, but for ease of visualisation it was (arbitrarily) decided to take an average of the two. Other combinations were examined but gave no particularly different insight.

Therefore, HSP properties of regulated substances (group A) are displayed in Figure 1. It should be remembered that the vast majority of organic molecules would not be within the ranges displayed in the graph (see Figure 2).

Examination of Table A1 shows a strong tendency for the LPs to have δD >19, and generally the average δP and δH is less than 8 but more than 1. There are, however, substances with δD <19, and these are listed in Table 1 with some comments.

It should be noted that the basis of assignation as PBT varies between substances: some have very high BCF, but others are named simply because they have been found high in the food chain despite having BCF below the threshold. That has not been reviewed here in any detail.

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Figure 1: HSP values of regulatory-listed LPs

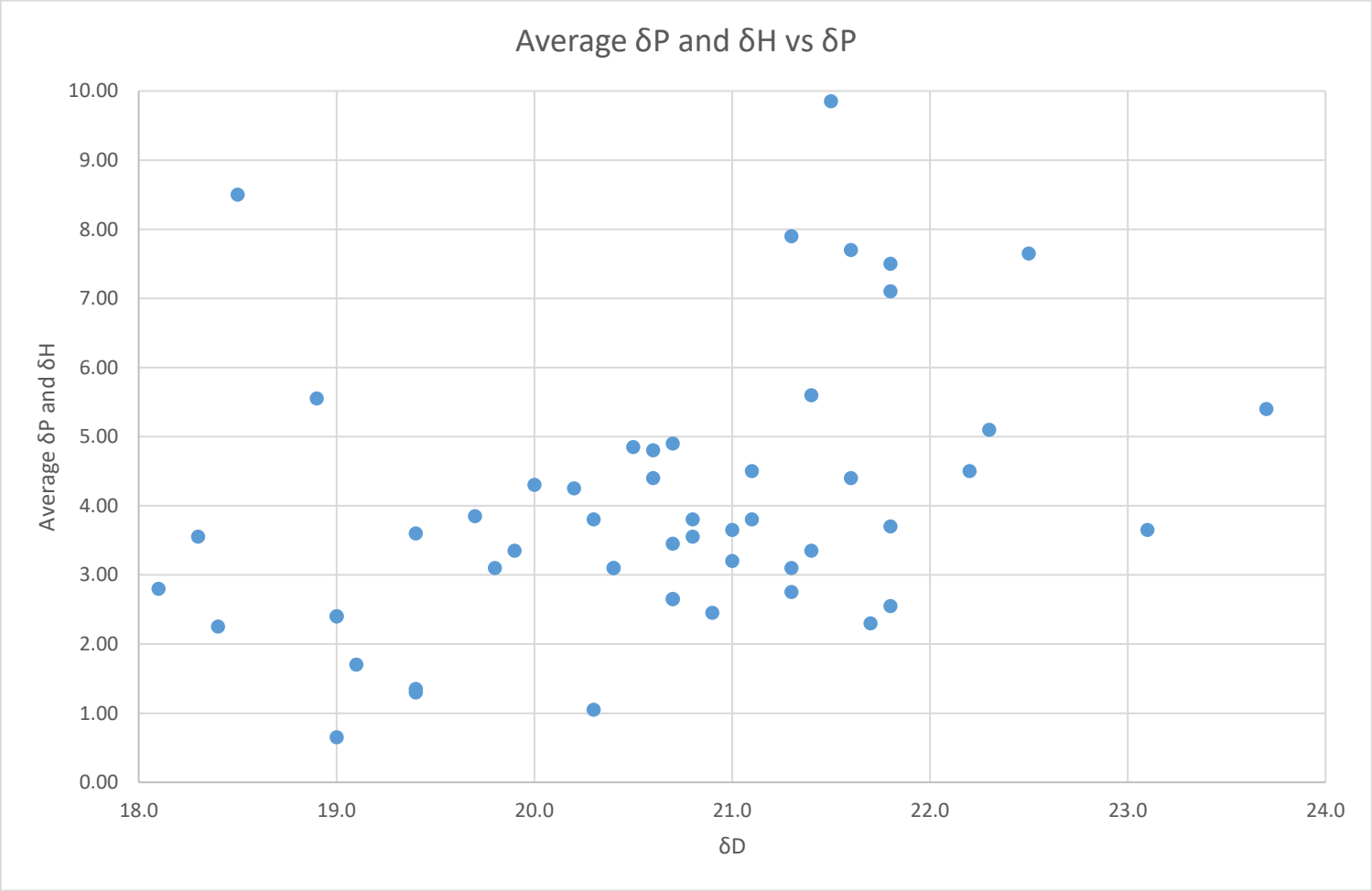

Table 1: LPs that are regulatory listed but have δD <19

Name	CAS	Comment
Terphenyl, hydrogenated	61788-32-7	It is surprising that this substance meets the persistence criteria.
Hexachlorobutadiene	87-68-3	Given the number of atoms the δD value is surprisingly low. This will be further investigated.
1,1,2,2,3,3-Hexabromocyclododecane	25637-99-4	An unusual structure that should be re-examined in respect of HSP.

HSP properties of the members of the set of 9700 substances

The regulated substances suggest that δD >19 should be a definite area of interest for the next stage of this study. An examination of δD <19 was made and no further relevant substances beyond those in Table 1 that seemed likely to be PBT-suspects emerged.

Therefore, substance with δD >19 were extracted from the 9700 substances found in the HSPiP software. As explained above, these were put into four groups, but for simplicity of inspection groups A, B and C are merged. These are shown in Figure 2, with the two sets (A+B+C, and 'others') distinguished subjectively.

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Figure 2: HSP values of ca. 1850 substances with δD ≥19

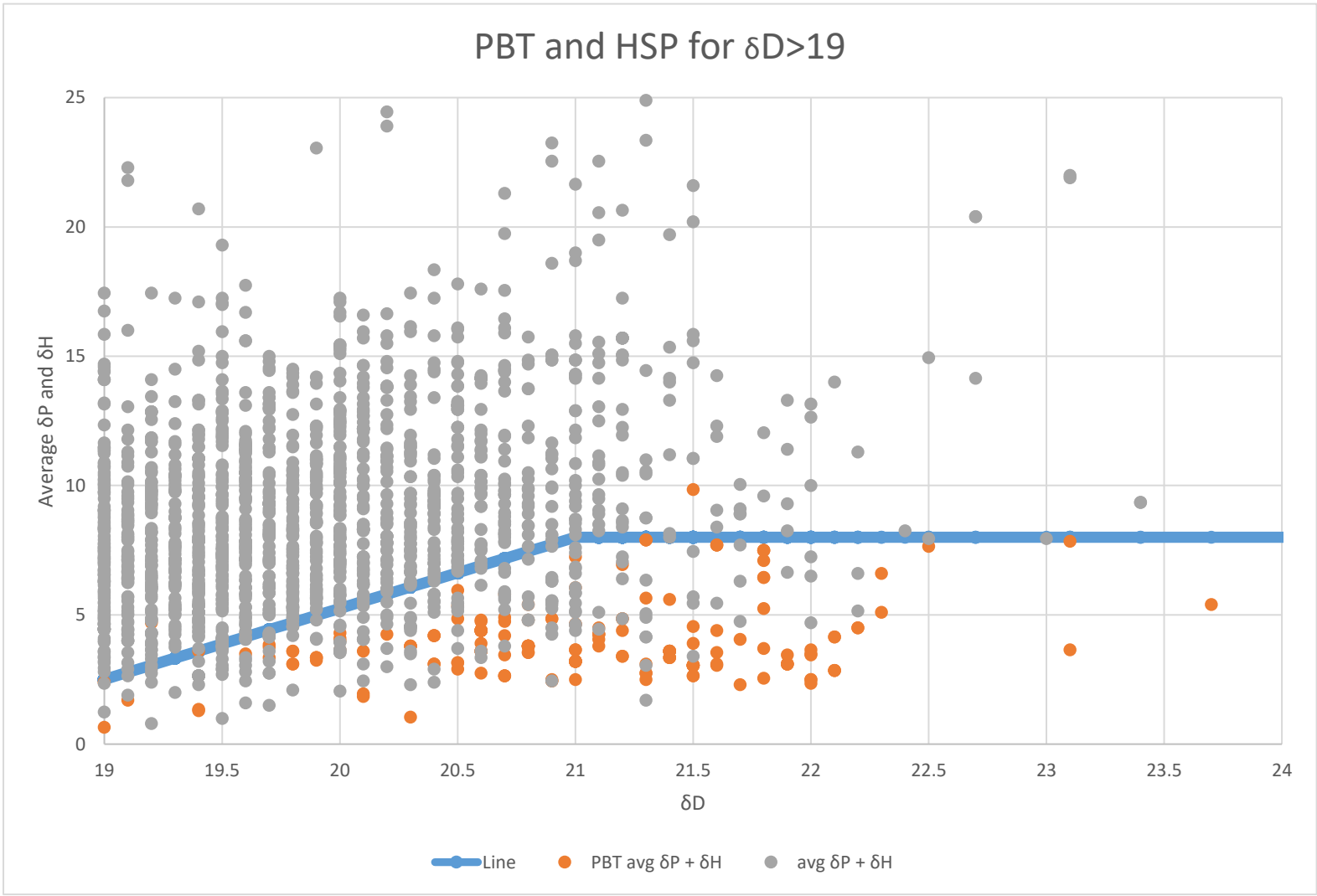

Figure 2 shows two zones:

A zone with high values of the average δP and δH where no PBT candidates are seen;

A zone where many, but not all, the substances are PBT candidates.

It will be useful in future for the Hansen space of δD, δP and δH that distinguishes 'PBT' from 'not PBT' to be defined in a non-subjective way, and without merging of δP and δH.

6. Discussion

Are any LP analogues not identified by the proposed criteria?

The following were missed:

Name	δD	avg δP + δH	Comment
Trichlorobiphenyl	19.2	4.70	Marginal as to whether this is a concern
Pentachlorophenol	21.5	9.85	Possible that the high acidity affects the calculation.

The number is relatively small.

Are there substances which meet the proposed criteria but have not been identified before by the regulatory authorities?

This is a relative large group of about 200 'false negatives' (if they are false!) Substance types which seem to have been picked up but are unlikely PBT candidates are:

Type	Comment
Alkylated aromatics	Usually these would be biodegradable and therefore not PBT.
Thiophenols	Perhaps the HSP need to be reconsidered?
Isocyanates	The HSP did not pick up their rapid hydrolysis

Substances which could require further investigation by the authorities include:

Type	Comment
Chlorinated styrene	
Several polyaromatics	Note that many other polyaromatics are identified by the authorities
Substances with short alkyl chains which are heavily substituted by aryl groups	
Various chlorinated aromatics	

The full list of potential PBT candidates that are LP analogues but which have not been identified as such before is available on request.

Can HSP have a place in the screening and determination of PBT concerns?

The use of BCF and biodegradation data, alongside environmental concentrations, have been used for over 50 years to screen for chemicals which may accumulate in food chains. The reliance on BCF and K_{ow} as screening criteria is misplaced. New types of contaminant are being uncovered. Use of HSP as a new screening tool could

be useful. It could also contribute to weight of evidence discussions around substances which meet the traditional criteria but which do not behave like the legacy pollutants.

7. Conclusions

Hansen Solubility Parameters (HSP) have a fundamental basis in the physical chemistry of intramolecular forces in the liquid state, and this report applies that insight to the interactions which occur between molecules and their surroundings in the environment.

The relevance of HSP is that the tendency for a molecule to be absorbed by lipids, proteins and membranes is quantified. Furthermore, HSP may relate to the potential for biodegradation, although that has not been explicitly studied yet. However, **in the HSP domain of δD, δP and δH, substances with adverse PBT properties are generally found clustered together**.

Some LP analogues considered as PBT by current methods were not found in the main cluster. The reasons for that are analysed. Some substances found in the HSP space of concern are not as yet identified as PBT by the regulatory authorities. These have also been discussed. There may be a case that these substances should be re-examined.

The overall conclusion is that determination of HSP can provide a clear indication of the chance that a new substance could have PBT concerns.

A more in-depth assessment of some specific chemical classes will be made in Part 2.

The strongest benefit of the use of HSP is that these parameters have been utilised in many research and development programmes relating to technical performance. A review of the use of the parameters is outside the scope of this document, but the main use has been in understanding solubility of substances, including polymers and in mixtures. Solvent designers routinely rely on HSP.

Bringing the environmental and performance themes together, it can be stated clearly that there are regions of HSP space that are best avoided by researchers, due to the risk of a substance having as-yet-undiscovered adverse PBT properties. HSP are unlikely to relate to chronic mammalian toxicological data, although they do give insights into uptake and distribution in the body. They do relate to ecotoxicological effects driven by narcosis, and that will be discussed in Part 2.

8. Acknowledgements

My thanks to Professor Steven Abbott, Dr Anna Zhenova and Dr James Sherwood for their insightful observations on the draft report.

Annex 1: substances of regulatory concern for PBT properties

Table A1: Substances present in regulatory lists, listed in δD order

Name	CAS	Also known as	SMILES	δD	δP	δH	Average dP dH
Terphenyl, hydrogenated	61788-32-7		C1CC=CC(C1)C2=CC=C(C=C2)C3CCC=CC3	18.3	3.1	4.0	3.55
Hexachlorobutadiene	87-68-3	HCBD)	C(=C(Cl)Cl)(C(=C(Cl)Cl)Cl)Cl	18.4	4.0	0.5	2.25
1,1,2,2,3,3-Hexabromocyclododecane	25637-99-4	(HBCDD)	C1CCCCC(C(C(CCCC1)(Br)Br)(Br)Br)(Br)Br	18.9	6.1	5.0	5.55
Toxaphene	8001-35-2		ClC2(Cl)C1(Cl)C(/C(=C)C(Cl)(C1(Cl)Cl)C2(Cl)Cl)(C)C	19.0	1.2	0.1	0.65
Dieldrin	60-57-1		ClC1=C(Cl)[C@@]2(Cl)[C@H]3[C@@H]([C@]1(C2(Cl)Cl)Cl)[C@H]5C[C@@H]3[C@@H]4O[C@H]45	19.0	3.9	0.9	2.40
Endrin	72-20-8		ClC1=C(Cl)C2(Cl)C4C(C1(C2(Cl)Cl)Cl)C5C3OC3C4C5	19.0	3.9	0.9	2.40
Aldrin	309-00-2		C1C2C=CC1C3C2C4(C(=C(C3(C4(Cl)Cl)Cl)Cl)Cl)Cl	19.1	2.5	0.9	1.70
Lindane	58-89-9	Gamma HCH	C1(C(C(C(C(C1Cl)Cl)Cl)Cl)Cl)Cl	19.2	21.0	2.9	11.95
Chlordane	5566-34-7		Cl/C1=C(\Cl)C2(Cl)C(Cl)(Cl)C1(Cl)C3C2CC(Cl)(Cl)C3	19.4	2.3	0.3	1.30
Dechlorane	13560-89-9		Cl\C2=C(/Cl)C3(Cl)C1CCC4C(CCC1C2(Cl)C3(Cl)Cl)C5(Cl)C(\Cl)=C(\Cl)C4(Cl)C5(Cl)Cl	19.4	2.5	0.2	1.35
Heptachlor	76-44-8		C1=CC(C2C1C3(C(=C(C2(C3(Cl)Cl)Cl)Cl)Cl)Cl)Cl	19.4	5.9	1.3	3.60
Endosulfan	115-29-7		Cl\C1=C(/Cl)C3(Cl)C(Cl)(Cl)C1(Cl)C2C3COS(=O)OC2	19.7	6.5	1.2	3.85

Name	CAS	Also known as	SMILES	δD	δP	δH	Average dP dH
2,2'-Dichlorobiphenyl	13029-08-8		Clc2ccccc2c1c(Cl)cccc1	19.8	3.6	2.6	3.10
1,4-Dichloronaphthalene	1825-31-6		ClC1=CC=C(Cl)C2=C1C=CC=C2	19.9	2.5	4.2	3.35
DDT	50-29-3	DDT	ClC(Cl)(Cl)C(C2=CC=C(Cl)C=C2)C1=CC=C(Cl)C=C1	20.0	5.5	3.1	4.30
1,2,3,4-Tetrachloronaphthalene	20020-02-4		ClC1=C(C(=C(C2=C1C=CC=C2)Cl)Cl)Cl	20.2	4.6	3.9	4.25
Hexachlorobenzene	118-74-1	HCB)	ClC(C(Cl)=C(Cl)C(Cl)=C1Cl)=C1Cl	20.3	2.1	0.0	1.05
2,2',4-Trichlorobiphenyl	37680-66-3		Clc2cc(Cl)ccc2c1c(Cl)cccc1	20.3	4.6	3.0	3.80
Anthracene	120-12-7		C12=CC=CC=C1C=C3C(C=CC=C3)=C2	20.4	1.4	4.8	3.10
Phenanthrene	85-01-8		C1(C(C=CC=C3)=C3C=C2)=C2C=CC=C1	20.4	1.4	4.8	3.10
3,6-Dichlorodibenzofuran	74918-40-4		Clc3ccc1c(oc2c1cccc2Cl)c3	20.5	5.6	4.1	4.85
2,3-Dichlorodibenzo-p-Dioxin	29446-15-9		Clc2cc1Oc3c(Oc1cc2Cl)cccc3	20.6	4.7	4.9	4.80
2,2',3,3'-Tetrachloro-1,1'-Biphenyl	38444-93-8		Clc2c(c1cccc(Cl)c1Cl)cccc2Cl	20.6	5.4	3.4	4.40
Fluoranthene	206-44-0		C24=C(C=CC=C4)C1=CC=CC3=C1C2=CC=C3	20.7	1.3	4.0	2.65
Chrysene	218-01-9		C12=C(C=CC3=C2C=CC4=C3C=CC=C4)C=CC=C1	20.7	1.3	4.0	2.65
Dicofol	115-32-2		Clc1ccc(cc1)C(O)(c2ccc(Cl)cc2)C(Cl)(Cl)Cl	20.7	4.1	5.7	4.90
Pentachlorobenzene	608-93-5		ClC(C(Cl)=CC(Cl)=C1Cl)=C1Cl	20.7	4.1	2.8	3.45
2,3,6,7-Tetrachlorodibenzofuran	57117-39-2		Clc3cc1c(oc2c1ccc(Cl)c2Cl)cc3Cl	20.8	4.0	3.1	3.55

Name	CAS	Also known as	SMILES	δD	δP	δH	Average dP dH
2,2',3,3',5-Pentachlorobiphenyl	60145-20-2		Clc2c(c1cccc(Cl)c1Cl)cc(Cl)cc2Cl	20.8	4.6	3.0	3.80
Benzo[k]fluoranthene	207-08-9		c4c3c1cccc2c1c(ccc2)c3cc5ccccc45	20.9	0.1	4.8	2.45
Benz[a]anthracene	56-55-3		C12=C(C=CC=C3)C3=CC=C1C=C4C(C=CC=C4)=C2	21.0	2.5	4.8	3.65
2,2',3,3',4,6'-Hexachlorobiphenyl	38380-05-1		Clc2ccc(c1c(Cl)ccc(Cl)c1Cl)c(Cl)c2Cl	21.0	3.8	2.6	3.20
1,2,3,4-Tetrachlorodibenzo-p-Dioxin	30746-58-8		Clc2c1Oc3ccccc3Oc1c(Cl)c(Cl)c2Cl	21.1	3.8	3.8	3.80
1,2,4-Trichlorodibenzo[B,E][1,4]Dioxin	39227-58-2		Clc2c1Oc3ccccc3Oc1c(Cl)c(Cl)c2	21.1	4.5	4.5	4.50
1,2,3,4,6,7-Hexachlorodibenzofuran	79060-60-9		Clc3ccc1c(oc2c1c(Cl)c(Cl)c(Cl)c2Cl)c3Cl	21.3	3.3	2.2	2.75
2,2',3,4,5,5',6'-Heptachloro-1,1'-Biphenyl	52712-05-7		Clc1c(c(Cl)c(Cl)c(Cl)c1Cl)c2cc(Cl)ccc2Cl	21.3	4.0	2.2	3.10
2,2',4,4'-Tetrabromodiphenyl Ether	5436-43-1	BDE 47	BrC1=CC(=C(C=C1)OC2=C(C=C(Br)C=C2)Br)Br	21.3	8.4	7.4	7.90
1,2,3,7,8-Pentachlorodibenzofuran	57117-41-6		Clc2cc1oc3cc(Cl)c(Cl)c(Cl)c3c1cc2Cl	21.4	3.8	2.9	3.35
1,3,7-Trichloronaphthalene	55720-37-1		Clc1ccc2c(c1)c(Cl)cc(Cl)c2	21.4	6.5	4.7	5.60
Pentachlorophenol	87-86-5		OC1=C(Cl)C(Cl)=C(Cl)C(Cl)=C1Cl	21.5	6.9	12.8	9.85
1,2,3,7,8-Pentachlorodibenzo-p-Dioxin	40321-76-4		Clc2cc1Oc3cc(Cl)c(Cl)c(Cl)c3Oc1cc2Cl	21.6	4.4	4.4	4.40
2,2',4,4',5-Pentabromodiphenyl Ether	60348-60-9	BDE 99	Brc2cc(Oc1ccc(Br)cc1Br)c(Br)cc2Br	21.6	7.8	7.6	7.70
1,2,3,4,5,6,7,8-Octachlorodibenzofuran	39001-02-0		Clc1c2oc3c(c2c(Cl)c(Cl)c1Cl)c(Cl)c(Cl)c(Cl)c3Cl	21.7	3.2	1.4	2.30
Benzo[ghi]perylene	191-24-2		c36ccc2ccc1cccc4c1c2c3c5c4cccc5cc6	21.8	2.7	4.7	3.70

Name	CAS	Also known as	SMILES	δD	δP	δH	Average dP dH
1,2,3,4,6,7,8-Heptachlorodibenzofuran	67562-39-4		Clc3cc1c(oc2c1c(Cl)c(Cl)c(Cl)c2Cl)c(Cl)c3Cl	21.8	3.1	2.0	2.55
Decabromodiphenyl ether	1163-19-5	DBDPE	BrC1=C(Br)C(=C(Br)C(=C1Br)Br)OC2=C(Br)C(=C(Br)C(=C2Br)Br)Br	21.8	6.4	7.8	7.10
2,2',3,4,4',5'-Hexabromodiphenyl Ether	182677-30-1	BDE138	Brc2ccc(Oc1cc(Br)c(Br)cc1Br)c(Br)c2Br	21.8	7.1	7.9	7.50
Benzo[a]pyrene	50-32-8		C1=CC=C4C3=C1C=CC2=C5C(=CC(=C23)C=C4)C=CC=C5	22.2	4.3	4.7	4.50
Pyrene	129-00-0		C1(C=CC3=CC=C4)=CC=CC2=CC=C4C3=C12	22.3	4.6	5.6	5.10
2,2',3,4,4',5',6-Heptabromodiphenyl ether	207122-16-5	BDE 183	Brc2cc(Br)c(Br)c(Br)c2Oc1cc(Br)c(Br)cc1Br	22.5	7.0	8.3	7.65
Mirex	2385-85-5		C12(C3(C4(C5(C3(C(C1(C5(C2(C4(Cl)Cl)Cl)Cl)Cl)Cl)(Cl)Cl)Cl)Cl)Cl)Cl	23.1	7.2	0.1	3.65
Chlordecone	143-50-0	Kepone	C13(Cl)C([C@]4(Cl)C2([C@@]5(C(C([C@]12Cl)([C@]3(C45Cl)Cl)Cl)(Cl)Cl)Cl)Cl)=O	23.7	10.7	0.1	5.40

Annex 2: usefulness of the 9700 substance set from HSPiP

The 9700 substance set in HSPiP was used for the overview study due to the data being available and verified by the software developers. It covers a wide range of substances, covering simple molecules through to common pesticides and pharmaceuticals. All major chemical structural types are well represented. It includes 948 substances of molecular weight (MW) less than 100 g/mol, 5996 in the range 100 to 199 g/mol, 2164 in the range 200 to 299 g/mol, and 661 with MW from 300 up to about 1000 g/mol.

Figure 2 shows the 9700 substances displayed in a similar way to the subset described in the report. It can be seen that very few substances have both δP and δH = 0, and very few of these are for δD >18. All atoms contribute something to δD, so δP and δH probe more the significance of functionalities.

Figure 2: HSP values of 9700 substances