A QSAR Approach to Physico-Chemical Data for Organophosphates with Special Focus on Known and Potential Nerve Agents

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Abstract

Nerve agents like Sarin, Tabun, Soman, VX, Amiton etc are highly toxic organophosphates (OPs) that exert their toxic effect by inhibition of acetylcholine esterase. These compounds have received considerable interest due their inherent nature as weapons of mass destruction. Since these compounds have been developed for military purposes, data is typically classified material and thus only scarcely available. QSAR modelling is an obvious possibility in order to remedy the lack of data availability. However, a wide variety of structurally related OP insecticides are well known and well characterized. "Noise-deficient" QSARs for physico-chemical properties of nerve agents are based on the use of the EPI Suite. Partial order ranking is an important tool to establish an identity for nerve agents relative to well-know OP insecticides. The development of a simple QSAR model for toxicological properties was unsuccessful.

Method. The results described in the paper are obtained using QSAR modeling based on the EPI Suite in comparison with partial order ranking. The concept of "noise deficient" QSARs is introduced.

Results. "Noise deficient" QSARs can be obtained using EPI Suite generated data in combination with experimental data for the test set, the data subsequently being applied in the ranking exercise. In the present study it is shown that to a certain extent selected insecticides may act as substitutes for nerve agents in preliminary experimental studies

Conclusions. The paper suggests that experimentally well-characterized compounds may be selected as substitutes for highly toxic compounds for preliminary experimental studies.

Availability. The reference manual for the EPI Suite: P2 Manual 6-00.pdf' found at http://www.epa.gov/pbt/framwork.htm, The EPI Suite is available at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm

Keywords. 'Noise-deficient QSARs, Partial Order Ranking, Hasse Diagrams, Organo-phosphates, Nerve agents.

Abbreviations and notations

Collect here in alphabetical order all abbreviations and notations used in the paper
OP, Organo phosphate
QSAR, quantitative structure-activity relationships

1 INTRODUCTION

Organophosphates (OPs) are in general toxic substances that exert their toxic effect by inhibition of acetylcholine esterase. The so-called nerve agents like Sarin, Tabun, Soman, and VX have received considerable interest due their potential use as weapons of mass destruction.

According to the 'Convention for the Prohibition of the Development, Production [1], Stockpiling and Use of Chemical Weapons and their Destruction' major emphasis is given to declaration and destruction of existing stockpiles of chemical weapons as well as of chemical weapons production facilities. The Convention covers both the destruction of chemical weapons

stockpiles and destruction or conversion of chemical weapons production facilities. In both cases there may be a significant risk to environment and human health. Since these compounds have been developed for military purposes data on these compounds are often regarded as classified. However, an excellent review on the sources, fate and toxicity of chemical warfare agent degradation products is available [2]. It should be noted hat this review partly is based on papers and reports that not necessarily is easily obtained.

When assessing environmental or human health effects of these compounds, QSAR modelling can to a certain extent remedy the apparent lack of data. Thus, in the present study physico-chemical properties of nerve agents have been estimated using QSAR models based on the EPI Suite [3]. It should be emphasized that the environmental processes of these substances are no different from other substances. However, for environmental studies the extreme toxicity of the nerve agents obviously must be considered.

Within the frame of the present study, it has not been possible to derive a simple QSAR model for OP toxicity. However, various studies have been devoted to models to the toxicity of OPs [4-7].

The present paper emphasizes the development of "noise-deficient" QSARs that will lead to physico-chemical end-points that subsequently can be used as descriptors in a partial order ranking of OPs with focus on selected nerve agents. The main objective is to find experimentally well-characterized compounds, exhibiting significantly lower toxicity than the nerve agents that can be used as substitutes in experimental studies of the environmental behavior of the nerve agents. Obviously, unique structural elements of the nerve agents may well cause significant differences in the environmental fate of the nerve agents and the OP insecticides. Nevertheless, some insecticides may mimic the nerve agents by, e.g., exhibiting identical volatilization behavior, while others may display similar rates of biodegradation. Based on a partial order ranking, taking several parameters into account simultaneously, it appears possible to give the single nerve agent an identity by comparing to structurally related OP insecticides. These substitutes will, based on an overall viewpoint exhibit analogous environmental characteristics as the nerve agents, and thus be models. Thus, such substitutes may well be used for preliminary experimental studies on the environmental fate of nerve agents, and subsequently constitute the basis of selection of a limited number of necessary experimental studies applied the actual nerve agents in order to perform risk assessment, e.g., in relation to the demilitarization activities.

2 MATERIALS AND METHODS

In the present study the end-points are generated through QSAR modelling, the EPI Suite being the primary tool [3]. Thus, the EPI generated (logarithmic) values for water solubility (log *Sol*), octanol-water partitioning (log K_{OW}), vapour pressure (log *VP*) and Henry's Law constants (log *HLC*) are further treated, i.e., new linear "noise-deficient" QSAR models are built by estimating the

relationships between the EPI generated data and available experimental data for up to 65 OP insecticides, the general formula for the end-points, D_i, to be used being

$$\boldsymbol{D_i = a_i \times D_{EPI} + b_i} \quad (1)$$

D_{EPI} being the EPI generated end-point value and a_i and b_i being constants. The log K_{OW} values generated in this way are subsequently used to generate log *BCF* values according to the Connell formula [8].

$$\log BCF = 6.9\times10^{-3}\times(\log K_{ow})^4 - 1.85\times10^{-1}\times(\log K_{ow})^3 + 1.55\times(\log K_{ow})^2 - 4.18\times\log K_{ow} + 4.72 \quad (2)$$

The model was somewhat modified. Thus, a linear decrease of log *BCF* with log K_{OW} was assumed in the range $1 < \log K_{OW} < 2.33$, the log $BCF = 0.5$ for $\log K_{OW} \leq 1$, the latter value being in accordance with BCFWin [3]. Subsequently data for missing OP insecticides and the nerve agents are calculated based on these formula and the appropriate EPI generated data.

Due to the lack of experimental data for the test set compounds with regard to (logarithmic water-organic carbon partitioning (log K_{OC}) and the ultimate biodegradation potential (*BDP3*), the same procedure was not applicable to these two end-points. Thus, data log K_{OC} and *BDP3* are used as estimated by the appropriate modules in the EPI Suite.

The partial order ranking of the compounds included in this study were made using the WHasse software [9] using the above described "noise-deficient" QSAR generated end-point as descriptors, i.e., log Sol, log K_{OW}, log *VP* and Henry Law constants as generated by the EPI Suite, (log *HLCe*), and by the bond estimation method, (log *HLCb*), organic carbon-water partitioning coefficients (log K_{OC}), and bioconcentration factors (log *BCF*), biodegradation potentials for ultimate degradation (*BDP3*), respectively.

The theory of partial order ranking is presented elsewhere, e.g., [10] and application in relation to QSAR is presented previously [11-14]. Thus, details on the methodology shall not be repeated here. The visualization of the ranking is made through the so-called Hasse Diagrams.

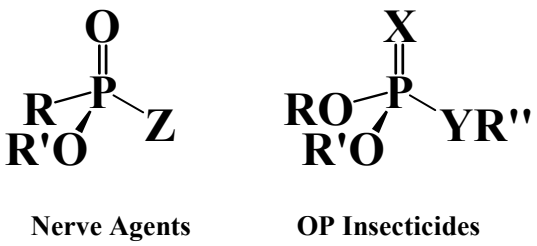
The generation of the average rank of the single compounds in the Hasse diagram is obtained applying the simple empirical relation recently reported by Brüggemann et al [15]. The average rank of a specific compound, $\boldsymbol{c_i}$, can be obtained by the simple relation

$$\boldsymbol{Rk_{av} = (N+1) - (S+1)\times(N+1)/(N+1-U)} \quad (3)$$

where N is the number of elements in the diagram, *S* the number of successors to $\boldsymbol{c_i}$ and *U* the number of elements being incomparable to $\boldsymbol{c_i}$ [15].

2.1 Chemical Data

Even though data on the nerve agents in practice often are unavailable, or at the best scarce (*vide supra*), a wide variety of structurally related compounds are well known and well characterized, i.e., OP insecticides such as parathion, malation, diazinon, etc. with respect to physico-chemical and toxicological characteristics [16].



Generalized formula for the Nerve agents and for OP insecticides

In the present paper up to 65 OP insecticides have been used as test set. Dependent of the single endpoint reduced numbers of OPs may be used, simply reflecting the limitations in experimental data.

The OPs used are summarized in appendix 1. Details on the 16 known and potential nerve agents are given in Appendix 2.

2.2 Computer Software

EPI Suite: The EPI Suite is available from the EPA web-site at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm. The reference manual for the EPI Suite, P2 Manual 6-00.pdf' can be found and downloaded at http://www.epa.gov/pbt/framwork.htm. [3]

WHASSE is described in in Brüggemann et al [9]. The software may be obtained by contacting Dr. R. Brüggemann, Institute of Freshwater Ecology and Inland Fisheries, Berlin

3 RESULTS AND DISCUSSION

The biodegradation potential of the OPs were assessed using the BioWin module of the EPI Suite [3]. In the cases of *BDP3* (ultimate biodegradation) predicted values in the ranges 5.0-4.0, 4.0-3.0, 3.0-2.0, 2.0-1.0 and <1.0 indicate that biodegradation will take place within hours, days, weeks, months or longer than months, respectively. Chemicals with *BDP3* in the interval of 1.75 to 2 are associated with a medium persistence potential, and *BDP3* smaller than 1.75 were assigned a high persistence potential [13]. In Fig. 1 *BDP3* data for the 81 compounds under investigation are summarized.

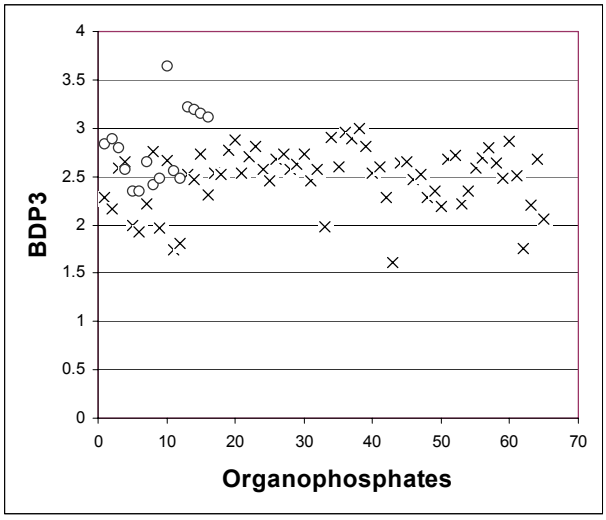


Figure 1. Ultimate biodegradation potential (*BDP3*)of 65 OP insecticides (x) and 16 known or potential nerve agents (o) as derived by BioWin.

Obviously, it is predicted that the biodegradation of the nerve agents are relative fast and as such this should not constitute a problem. However, it should be remembered that if the necessary biological activity is not present significantly longer persistence times might prevail. Thus, half-lives of VX in marine waters and in rivers of up to 1-2 years have been observed [17].

In Fig. 2 – 5 the EPI-based modified QSARs for solubility, octanol-water partitioning, vapor pressure and Henry's Law constants are visualized.

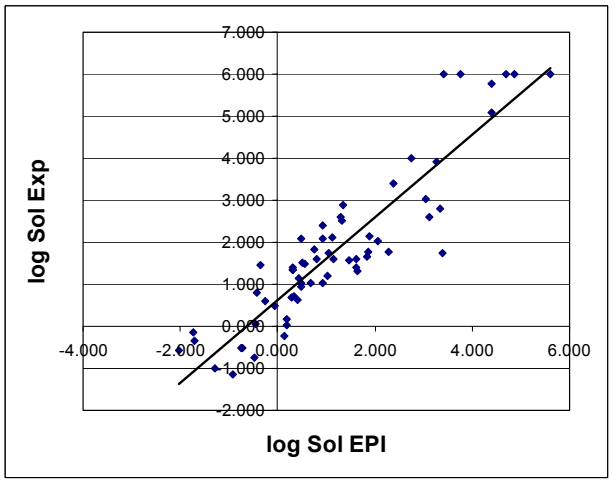


Figure 2 Visualization of the EPI-based modified QSAR modeling of log *Sol* based on 64 OP insecticides

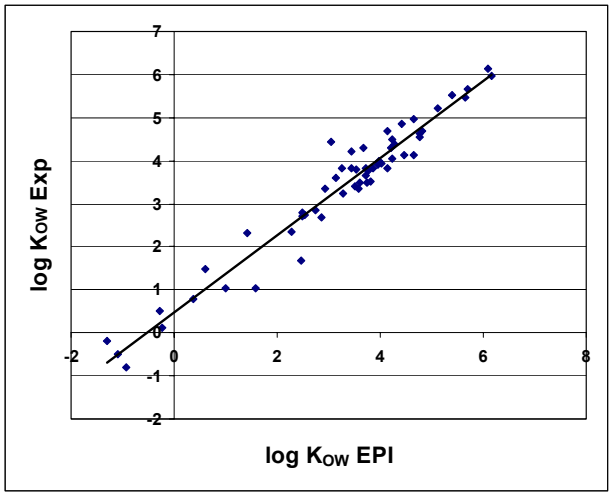


Figure 3. Visualization of the EPI-based modified QSAR modeling of log K_{OW} based on 53 OP insecticides.

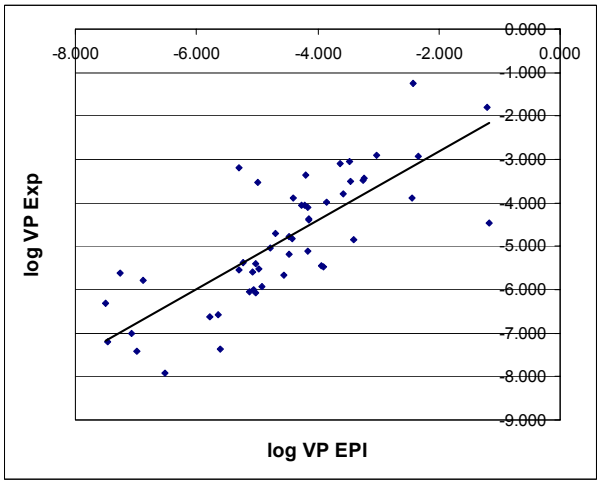


Figure 4. Visualization of the EPI-based modified QSAR modeling of log *VP* based on 51 OP insecticides.

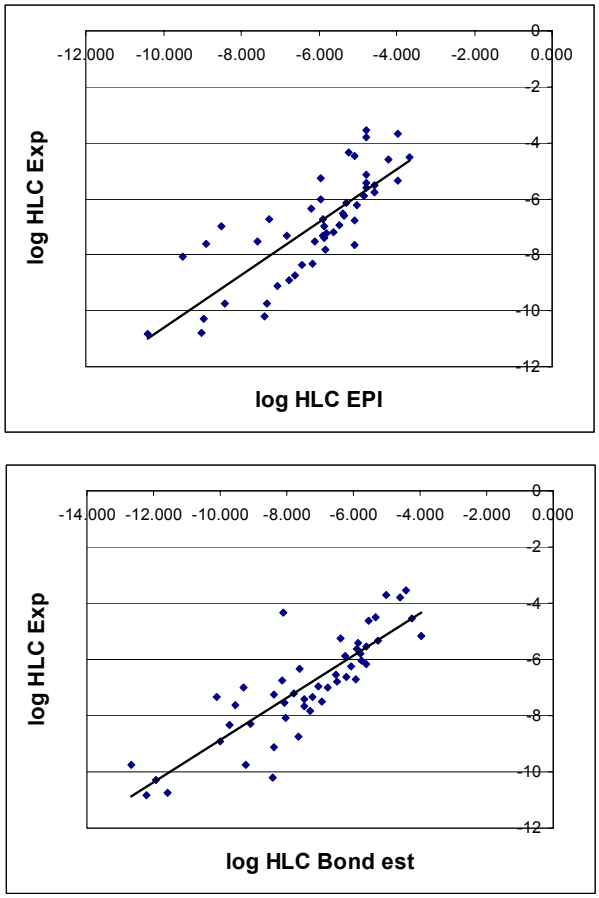


Figure 5. Visualization of the EPI-based modified QSAR modeling of log HLC_e and log HLC_b based on 49 OP insecticides.

The corresponding models are

$$\log Sol = 0.983 \times \log Sol(EPI) + 0.625;\ n = 64,\ r^2 = 0.830 \quad (4)$$

$$\log K_{OW} = 0.894 \times \log K_{OW}(EPI) + 0.487;\ n = 53,\ r^2 = 0.947 \quad (5)$$

$$\log VP = 0.793 \times \log VP(EPI) - 1.229;\ n = 51,\ r^2 = 0.612 \quad (6)$$

$$\log HLC_e = 0.946 \times \log HLCe(EPI) - 1.168;\ r^2 = 0.636 \quad (7)$$

$$\log HLC_b = 0.751 \times \log HLCb(EPI) - 1.371;\ r^2 = 0.727 \quad (8)$$

Although data for nerve agents are scarce some data have been retrieved. These may serve as a validation set for the above models. In Table 1 available experimental data for the "classical" nerve agents, i.e. Tabun, Sarin, Cyclosarin, Soman and VX are given together with the corresponding

values derived based on the above models. Generally a satisfactory agreement can be observed. However, it appears that in the case of vapour pressure there are more significant disagreements. This is due to the fact that the model for estimating vapor pressures is rather poor, as reflected in the regression coefficient r^2 = 0.612. In some case, i.e., for substances exhibiting very low vapour pressures, such as the V-agents, experimental difficulties in the estimation of the vapor pressures may in this case play a role.

Table 1. Experimental data (solubilities, octanol-water partitioning, vapour pressures, Henry's Law constants) compared to model generated data derived by "noise-deficient" QSARs based on the EPI Suite)

	log *Sol* *Exp.*	log *Sol* *Model (eq 4)*	log K_{OW} *Exp.*	log K_{OW} *Model (eq 5)*	log *VP* *Exp.*	log *VP* *Model (eq 6)*	log *HLC* *Exp.*	log *HLCe* *Model (eq 7)*	log *HLCb* *Model (eq 8)*
Tabun	4.99	5.05	0.38	0.74	-1.15	-2.29			
Sarin	6.00	5.21	0.30	0.70	0.46	-0.70			
Cyclosarin	4.30	3.94			-1.22	-1.99			
Soman	4.32	3.78	1.78	1.92	-0.40	-1.54	-5.34	-5.17	-4.88
VX	4.48	4.07	2.09	2.33	-3.15	-3.38	-8.09	-7.47	-7.93

Subsequently the above given models have been applied in estimating physico-chemical data for a broader range of known as well as potential nerve agents. In Table 2 these data are collected together with the corresponding logarithmic bioconcentration factors as derived through the Connell formula (*vide supra*) applying the log K_{OW} values obtained using the model given in eq 5.

Table 2. Physico-chemical data (solubilities, octanol-water partitioning, vapour pressures, Henry's Law constants based on EPI data and bond estimation, respectively, and bioconcentration factors)

for known and potential nerve agents as derived by "noise-deficient" QSARs based on the EPI Suite)

	log *Sol*	log K_{OW}	log *VP*	log *HLCe*	log *HLCb*	log *BCF*
Tabun	5.05	0.74	-2.29	-5.97	-6.97	0.50
Sarin	5.21	0.70	-0.70	-6.94	-7.44	0.50
Cyclosarin	3.94	1.92	-1.99	-6.74	-6.80	1.02
Soman	3.78	1.92	-1.54	-4.64	-4.57	1.02
VX	4.07	2.33	-3.38	-8.11	-10.88	1.25
R-VX	4.03	2.40	-4.14	-8.13	-10.32	1.29
C-VX	3.96	2.46	-4.41	-6.65	-7.68	1.32
EA2192	4.70	1.85	-5.42	-5.69	-5.81	0.98
R/C "EA2192"[a]	5.55	1.09	-5.28	-5.49	-5.73	0.55
VG (Amiton)	4.38	2.01	-4.06	-6.17	-7.91	1.07
Amiton methyl	5.36	1.13	-3.83	-9.46	-8.62	0.57
Vx (EDMM)	5.91	0.71	-3.03	-5.15	-5.55	0.50
VM	4.94	1.59	-3.78	-7.41	-7.13	0.83
VE	4.45	2.02	-4.11	-5.69	-4.82	1.08
VS	3.60	2.77	-4.22	-7.63	-8.97	1.51
S12	2.78	3.48	-3.41	-9.71	-10.07	2.16

[a] Analog to EA2192, however derived from Russian or Chinese VX

The model-generated end-points may subsequently be used as descriptors in ranking the 65 OP insecticides together with the 16 known potential nerve agents. Thus, as in total 81 compounds are included in the subsequent ranking procedure, the resulting Hasse diagrams may seem somewhat confusing. In Fig. 6 the Hasse diagram disclosing the mutual ranking of the compounds due to their combined PB (Persistent and Bioaccumulating) characteristics, i.e., bringing simultaneously the *BDP3* and log *BCF* into play.

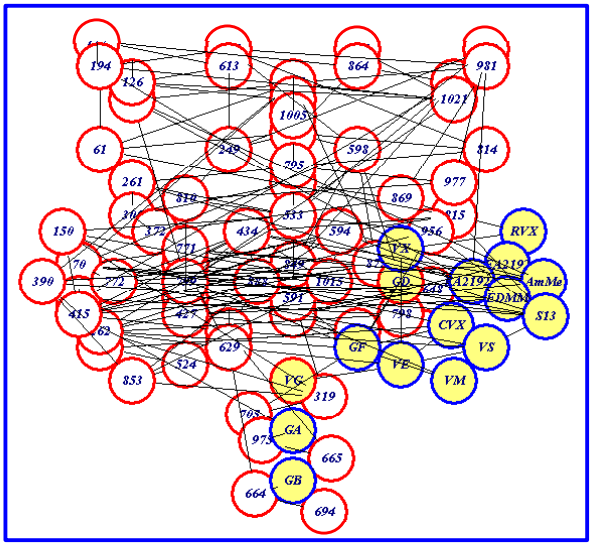


Figure 6. Hasse diagram displaying the PB characteristics of the 65 OP insecticides and 16 nerve agent (hatched), The numbers corresponds to the numbering of the OP insecticides in the FADINAP database.

A priori, compounds located on the same level in the Hasse diagram are assumed to be close in

their overall characteristics based on the set of descriptors used. On this basis, in the above example (Fig. 6) the highly toxic EDMM (LD_{50} (rats, acute, oral) = 0.121 mg/kg) may be substituted by, e.g., compounds No. 71 (Azinphos Methyl; LC_{50} = 4 mg/kg), 312 (Dichlorvos; LC_{50} = 56 mg/kg), 591 (Iprobenfos; LC_{50} = 490 mg/kg) or 648 (Mephosfolan; LC_{50} = 8.9 mg/kg).

However, a further analysis is necessary to disclose how close these compounds actually are. For this analysis we have chosen the concept of average rank [15,18]. Thus, it is assumed that if the average ranks, Rk_{av}, of two compounds are close, the two compounds will on an average basis display similar characteristics as being determined by the set of descriptors applied. In Table 3 the average ranks for the four compounds are compared.

From the values for the average rank (Table 3), that the four possible substitutes for EDMM located on the same level in the Hasse diagram based on average ranks apparently can be regarded as being rather close. Thus, taking the actual toxicities, as expressed through the LC_{50} values into account Dichlorvos appear as the optimal choice as substitute for EDMM in studies where the PB characteristics of the compounds is important, the toxicity associated with the experiments being decreased by a factor close to 500.

Table 3. Average ranks for the PB characteristics as determined by log *BCF* and the biodegradation potential for EDMM, Azinphos Methyl, Dichlorphos, Iprobenfos and Mephosfolan (the compound ID refers to the FADINAP database [16]))

Compound Name	Compound ID	LC_{50} (mg/kg) Rat, acute, oral	Average Rank RK_{av}
EDMM	EDMM	0.121	55.9
Azinphos Methyl	71	4	51.1
Dichlorvos	312	56	55.9
Iprobenfos	591	490	50.6
Mephosfolan	648	8.9	57.9

Similar analyses for other descriptor combinations can obviously be carried out analogously. This is, however, outside the scope of the present paper and is reported elsewhere [19].

The Chemical Weapons Convention [1] obviously covers all the nerve agents. However, as a curiosity it can be noted that the nerve agents, despite their extreme toxicity based on their PB characteristics (cf. Fig. 1 and Table 2) would not immediately qualify to falling into the group of chemicals that requires special authorization in the coming European system for registration, evaluation and authorization of chemicals, REACH, as these compounds would neither be classified as persistent nor as bioaccumulating [20]. This is further substantiated by the placement of all the

16 known or potential nerve agents in the lower half of the Hasse diagram reflecting the combined PB characteristics (Fig. 6). Thus, in cases of extremely toxic compounds, not being covered by, e.g., the Chemical Weapons Convention, it might in addition to the PBT and vPvB (very Persistent and very Bioaccumulating) criteria be relevant to introduce a vT (very Toxic) criteria as well.

4 CONCLUSIONS

The present study has demonstrated that "noise-deficient" QSARs can be generated using the EPI Suite as the modelling onset. Subsequently, the generated physico-chemical end-points can be used as descriptors in a partial order based ranking giving compounds where experimental data are not available an identity by comparing to a test set of experimentally well-characterized, structurally similar compounds.

On this background it has been suggested that experimentally well-characterized compounds may be selected as substitutes for highly toxic compounds, as the nerve agent. Hence, this procedure allows that the environmental behaviour of the latter may be studied experimentally using compounds that from an overall viewpoint exhibit analogous environmental characteristics, however, without exhibiting the extreme toxicity.

Appendix 1

FADINAD No., CAS No. and name for the 65 OPs used as testset.

FADINAD	*CAS No.*	*Name*
61	64249-01-0	Anilofos
69	35575-96-3	Azamethiphos
70	2642-71-9	Azinphos ethyl
71	86-50-0	Azinphos methyl
126	2104-96-3	Bromophos
127	4824-78-6	Bromophos ethyl
139	36335-67-8	Butamifos
150	95465-99-9	Cadusapfos
194	470-90-6	Chlorfenvinphos
201	24934-91-6	Chlormephos
216	2921-88-2	Chlorpyriphos
217	5598-13-0	Chlorpyriphos methyl
249	56-72-4	Coumaphos
261	13067-93-1	Cyanofenphos
262	2636-26-2	Cyanophos
296	10311-84-9	Dialifos
300	333-41-5	Diazinon
312	62-73-7	Dichlorvos
319	141-66-2	Dicrotophos
359	3811-49-2	Dioxabenzofos
372	5131-24-8	Ditalimfos
390	17109-49-8	Edifenphos
415	13194-48-4	Ethoprophos
427	38260-54-7	Etrimfos
434	22224-92-6	Fenamiphos
524	66767-39-3	Fonofos
533	83733-82-8	Fosmethilan
534	98886-44-3	Fosthiazate
558	23560-59-0	Heptonophos
591	26087-47-8	Iprobenfos
594	42509-80-8	Isazofos
598	25311-71-1	Isofenphos
613	18181-70-9	Jodfenphos
629	121-75-5	Malathion
648	950-10-7	Mephosfolan
664	62610-77-9	Methacrifos
665	10265-92-6	Methamidophos
694	7786-34-7	Mevinphos
705	6923-22-4	Monocrotophos
771	56-38-2	Parathion
772	298-00-0	Parathion methyl
795	2310-17-0	Phosalone
796	36519-00-3	Phosdiphen
797	947-02-4	Phosfolan
798	732-11-6	Phosmet
799	13171-21-6	Phosphamidon
810	24151-93-7	Piperophos
814	23505-41-1	Pirimiphos ethyl
815	29232-93-7	Pirimiphos methyl
836	41198-08-7	Profenofos

849	7292-16-2	Propafos
853	31218-83-4	Propetamphos
864	34643-46-4	Prothiofos
869	77458-01-6	Pyraclofos
872	13457-18-6	Pyrazophos
888	13593-03-8	Quinolphos
956	3689-24-5	Sulfotep
959	35400-43-2	Sulphofos
974	3383-96-8	Temephos
975	107-49-3	TEPP
977	13071-79-9	Terbufos
981	22248-79-9	Tetrachlorvinphos
1005	57018-04-9	Tolclofos methyl
1015	24017-47-8	Triazophos
1021	52-68-6	Trichlorfon /Chlorophos

Appendix 2

Details on the 16 known and potential nerve agents

Type	***CAS No.***	***Name/code***	***R***	***R'***	***Z***
CWA (G-agent)	77-81-6	Tabun (GA)	$-N(CH_3)_2$	$-C_2H_5$	-CN
CWA (G-agent)	107-44-8	Sarin (GB)	$-CH_3$	$-CH(CH_3)_2$	-F
CWA (G-agent)	329-99-7	Cyclosarin (GF)	$-CH_3$	$-c\text{-}C_6H_{11}$	-F
CWA (G-agent)	96-64-0	Soman (GD)	$-CH_3$	$-CH(CH_3)C(CH_3)_3$	-F
CWA (V-agent)	50782-69-9	VX	$-CH_3$	$-C_2H_5$	$-SCH_2CH_2(N(CH(CH_3)_2)_2$
CWA (V-agent)	159939-87-4	R-VX	$-CH_3$	$-CH_2CH(CH_3)_2$	$-SCH_2CH_2(N(C_2H_5)_2$
CWA (V-agent)		C-VX	$-CH_3$	$-C_4H_9$	$-SCH_2CH_2(N(C_2H_5)_2$
VX degr. product		EA2192	$-CH_3$	-H	$-SCH_2CH_2(N(CH(CH_3)_2)_2$
RVX degr. product		R/C "EA2192"	$-CH_3$	-H	$-SCH_2CH_2(N(C_2H_5)_2$
Possible V-agent	78-53-5	VG (Amiton)	$-OC_2H_5$	$-C_2H_5$	$-SCH_2CH_2(N(C_2H_5)_2$
Possible V-agent		Amiton methyl	$-OC_2H_5$	$-C_2H_5$	$-SCH_2CH_2(N(CH_3)_2$
Possible V-agent		Vx (EDMM)	$-CH_3$	$-C_2H_5$	$-SCH_2CH_2(N(CH_3)_2$
Possible V-agent		VM	$-CH_3$	$-C_2H_5$	$-SCH_2CH_2(N(C_2H_5)_2$
Possible V-agent		VE	$-C_2H_5$	$-C_2H_5$	$-SCH_2CH_2(N(C_2H_5)_2$
Possible V-agent		VS	$-C_2H_5$	$-C_2H_5$	$-SCH_2CH_2(N(CH(CH_3)_2)_2$
Possible V-agent		S12	$-CH_3$	$-c\text{-}C_5H_9$	$-SCH_2CH_2(N(CH(CH_3)_2)_2$

5 REFERENCES

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