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PBT screening profile of chemical warfare agents (CWAs)

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Abstract

Chemical warfare agents (CWAs) have been used and disposed of in various fashions over the past decades. Significant amounts have been dumped in the Baltic Sea following the disarmament of Germany after World War II causing environmental concerns. There is a data gap pertaining to chemical warfare agents, environmental properties not the least their aquatic toxicities. Given this gap and the security limitations relating to working with these agents we applied Quantitative Structure–Activity Relationship ((Q)SAR) models in accordance with the European Technical Guidance Document (2003) to 22 parent CWA compounds and 27 known hydrolysis products. It was concluded that conservative use of EPI Suite (Q)SAR models can generate reliable and conservative estimations of chemical warfare agents acute aquatic toxicity. From an environmental screening point of view the organoarsenic chemical warfare agents Clark I and Adamsite comprise the most problematic of the screened CWA compounds warranting further investigation in relation to a site specific environmental risk assessment. The mustard gas agents (sulphur and nitrogen) and the organophosphorous CWAs (in particular Sarin and Soman) are a secondary category of concern based upon their toxicity alone. The undertaken approach generates reliable and conservative estimations for most of the studied chemicals but with some exceptions (e.g. the organophosphates).

Keywords: Chemical weapon agents; (Q)SAR; Environmental toxicity; EU TGD; Marine toxicity

1. Introduction

Chemical warfare agents (CWAs) cover, among other, nerve-gases, blistering agents, pulmonary, blood agents and vomiting agents [1]. CWAs have been used in several armed conflicts worldwide, starting with German attacks during World War I [2]. As a result of the disarmament of Germany following the Second World War, and subsequent general disarmament with respect to CWAs globally 10,000s tonnes of CWA have dumped at sea in the years following 1945 [2–4], e.g. more than 30,000 tonnes in the Baltic Sea alone [2]. In 1999, 126 countries ratified the Chemical Weapons Convention (CWC) [5,6] mandating that all CWAs should be disposed of by April 2007. Until recently disposing of CWAs was achieved in part by dumping at sea without sound knowledge of the environmental consequences, however, nowadays most of the disposing is done by incineration or by conversion to peaceful purposes/products by the chemical industry [3,7].

There is evidence of both accidental human exposure, primarily fishermen [8], as well as environmental exposures due to releases from corroding and leaking containers at sea [2,4]. These documented releases have renewed concerns over the human and environmental risks associated with CWAs dumped at sea. There are very few baseline environmental toxicity and physio-chemical property data available in the open literature [1,9] to help guide site specific risk assessments and prioritize remediation initiatives, and provide scientific support in prevention of munition dumping at sea. The relative datagap with regard to CWAs compared to many other compounds in the open literature is expected due to the elevated individual and societal security precautions needed to perform laboratory work on CWAs. In this added security context application of predictive tools such as Quantitative Structure–Activity Relationships ((Q)SARs) for screening level assessment of environmental properties is prudent [10].

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The European Technical Guidance Document (EU TGD) in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No. 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market, includes a chapter on marine risk assessment, which states that using (Q)SARs and freshwater species toxicity data *in lieu* of absent specific marine data on chemicals persistence, bioconcentration, toxicity (PBT) properties may be required [11].

In light of the imminent potential environmental hazards posed by CWAs, the lack of comprehensive environmental property and toxicity data for CWAs as well as their hydrolysis products. Hence, the aim of this paper is to; provide a compilation of predicted environmental toxicity data of parent and hydrolysis products of CWAs; evaluated the conservatism of (Q)SAR predictions with regards to CWAs acute aquatic toxicity; and finally, briefly touch upon their persistence and bioconcentration potential. In other words, to present the predicted environmental PBT profile of CWAs according to EU TGD approaches.

2. Materials and methods

2.1. Compounds

The majority of CWAs mentioned in the CWC and their known major degradation products [1], primarily hydrolysis products [12], are covered in the analysis, in total 49 compounds, see Table 1.

2.2. Models

The Estimation Program Interface modules (EPI Suite v. 3.12) used in this assessment is developed by the Syracuse Research Corporation on behalf of the United States Environmental Protection Agency (USEPA) and comprises a suite of regression based (Q)SAR models with Log Kow as one of the most significant descriptors. ECOSAR is based on approximately 150 (Q)SARs for 50 different compound structure/classes (e.g. neutral organics, aliphatic amines, esters, etc.) (http://www.epa.gov/oppt/exposure/docs/episuitedl.htm). The models are widely used and accepted for screening chemicals from a broad spectrum of the chemical universe [13]. Carlsen [14,15] have previously applied the EPI Suite models to nerve agents, and Munro et al. [1] reported data generated by EPI Suite for nitrogen mustard gas, and Tørnes et al. [2] used the models on organoarsenic CWAs and nerve gases. Finally, the models have been widely used by the US National Institute of Health (NIH) in assessing the physio-chemical and fate properties of CWAs [10]. In this study, we applied the BIOWIN v.2.15 model to assess the biodegradation, PCKOCWIN v.1.66 for Koc values, BCFWIN v.4.02 for bioconcentration factor values, and ECOSAR for the environmental toxicity predictions. The EPI Suite program and associated information regarding the models may be downloaded of the USEPA website: http://www.epa.gov/oppt/exposure/docs/episuitedl.htm.

3. Results

3.1. Persistence

The EU TGD [11] recommends using the BIOWIN model from the EPI Suite for assessment of persistence. It is recommended to use BIOWIN models 2, 3 and 5, with the following default benchmark values (non-linear model (<0.5 biodegradation probability = persistent)); or MITI non-linear model (<0.5) and ultimate biodegradation ≥ months, respectively). If the compound fulfils these requirements an "open-ended" categorization as being potentially persistent (P) can serve as an indicator for the need for further experimental evaluation. Based on this approach the following CWAs are potentially persistent compounds: Adamsite; Lewisite; the three Nitrogen mustards; Sulphur mustard, Yperite; HT; VX; VG; VM; Cyclosarin; Soman; Chloropicrin (PS) and Diphosgene (DP).

In relation to marine risk assessments under the EU TDG [11], it is moreover noted that one needs to conservatively consider site specific parameters such as: temperature; frequent anaerobic conditions below the top 5 mm of the sediment; salinity; alkalinity; the less favourable conditions for microbial communities to degrade xenobiotics (less exposure and adaptation, e.g. due to increased drift and flux) and general physio-chemical conditions governing the persistence of chemicals in marine environments. Generic site specific parameters in the EU TGD [11], suggests that degradation in estuaries are approximately four times lower than in freshwater environments and even lower further away from land. For the predicted persistent CWAs it would be recommended to use default marine mineralization half-lives of >150 days [11], see Table 1.

3.2. Bioconcentration

None of the agents are predicted to bioconcentrate significantly (BCF < 2000). Clark I and Adamsite have the highest BCF = 600 (Log Kow = 4.52) and 262 (Log Kow = 4.05), respectively. The remaining CWAs had BCFs < 70. The geometric mean BCF value for the parent compounds = 8.1. For the hydrolysis products the BCF were, as expected, lower with a geometric mean of 3.9, with the VX hydrolysis product (MPA) CAS# 2387-23-7, as the outlier at BCF = 206. It should also be noted that the solubility of a contaminant is normally reduced in saline waters, typically by a factor of 1.36 [11]. The resulting biomagnification factor (BMF) for all the CWAs covered in this assessment is thus predicted to be insignificant (=1) according to EU TGD [11], see Table 1.

3.3. Acute aquatic toxicity

Table 1 summarizes the predicted LC50 values (mg l^{-1}) for the parent compound and know major hydrolysis products. The relative predicted species sensitivity frequency rank based in their geometric mean LC50 for the parent compounds is thus; algae 4.6 > daphnid 16.8 > fish 24.1 (mg l^{-1}). For the hydrolysis products the rank is; algae 43.4 > daphind 101 > fish 426 (mg l^{-1}). All the parent compounds were more toxic than the

Table 1
Screening level PBT assessment of CWAs and hydrolysis products

	CAS#	Log Kow	BCF	Koc	Biodeg	LC50 Fish (mg/l)	LC50 Daphnid (mg/l)	LC50 Algae (mg/l)	ECOSAR class	Measured LC50 (mg/l)
Compound										
Chloropicrin (PS)	76-06-2	1.32	8.1	36	Pers	61.3	20.3	22	Neutral organics	NA
Phosgene	75-44-5	−0.71	3.1	2.2	Not pers	989	NA	NA	Acid Chloride/halides	NA
Diphosgene (DP)	503-38-8	1.49	2.8	17.4	Pers	88.7	NA	NA	Acid Chloride/halides	NA
CAP (CN)	532-27-4	1.93	0.8	89	Not pers	17	7	8.5	Neutral organics	NA
Lewisite	541-25-3	2.56	18.6	125	Pers	1.8	33.6	15.6	Vinyl/allyl halides	2 (F), 50 (A) [1]
N mustard I	538-07-8	2.02	7.17	365	Pers	45.5	3.3	1.4	Aliphatic amines	25 (F) [1]
N mustard II	51-75-2	1.53	3.1	188	Pers	86	6	1.9	Aliphatic amines	10 (F), 1.1 (D) [9]
N mustard III	555-77-1	2.27	11.2	672	Pers	38	2.8	1.4	Aliphatic amines	8 (F) [1]
Adamsite	578-94-9	4.05	262	5000	Pers	0.44	0.38	0.7	Neutral organics	NA
Yperite	505-60-2	2.41	14.3	275	Pers	6.7	3.3	4.4	Neutral organics	25 (F) [1]
Clark I	712-48-1	4.52	600	19000	Not pers	0.162	0.165	0.33	Neutral organics	NA
Clark II	23525-22-6	3.29	68	6980	Not pers	1.8	1.2	1.9	Neutral organics	NA
Zyklon B	74-90-8	−0.69	3.16	2.7	Not pers	422	95	68	Neutral organics	NA
VX	50782-69-9	2.09	8.1	640	Pers	13.8	5	2.3	Aliphatic amines	1 (F, D, A) [1]
VG	78-53-5	1.7	4.1	942	Pers	27.8	8.2	2.9	Aliphatic amines	NA
VM	21770-86-5	1.23	1.7	257	Pers	47	13.7	5.5	Aliphatic amines	NA
HT	63918-89-8	2.71	24.5	588	Pers	6.06	3.3	4.6	Neutral organics	NA
Sarin	107-44-8	0.3	3.1	5.5	Not pers	89.6	4446	10.3	Esters	0.002 (F) [1]
Cyclosarin	329-99-7	1.6	3.4	42.2	Pers	22.5	330	2.7	Esters	NA
Soman	96-64-0	1.82	4.68	24.3	Pers	23	334	2.7	Esters	NA
Tabun	77-81-6	0.29	3.16	22.5	Not pers	97.7	4634	11.3	Esters	1.3 (F) [1]
CK	506-77-4	−0.38	3.1	4.5	Not pers	570	129	98	Neutral organics	0.15 (F) [1]
Major Hydrolysis Products										
S-mustard, Yperite	693-30-1	0.69	3.1	8.3	Not pers	185	50.3	47.3	Neutral organics	NA
	111-48-8	−0.62	3.1	1	Not pers	1696	383	278	Neutral organics	1000 (F) [1]
	64036-79-9	0.09	3.1	316	Not pers	1400	321	268	Neutral organics	NA
N mustard I–III	139-87-7	−1.01	3.1	1	Not pers	3096	155	11.5	Neutral organics	160 (F) [1]
	111-42-2	−1.71	3.1	1	Not pers	6857	314	15.5	Neutral organics	1664 (F), 55 (D), 75 (A) [1]
	637-39-8	−5.24	3.1	10	Not pers	60000	12500	4000	Neutral organics	62 (F), 1360 (D), 5000 (A) [1]
	63867-58-3	1.27	3.1	1273	Not pers	100	33	35	Neutral organics	NA
	63905-05-5	−0.19	3.1	5.7	Not pers	955	53	6.4	Neutral organics	NA
	54060-15-0	−4.27	3.1	1	Not pers	98000	20000	73000	Neutral organics	NA
	63978-53-0	0.56	3.1	20.3	Not pers	427	26	4.8	Neutral organics	NA
	63978-75-6	−0.83	3.1	10	Not pers	2989	153	12.5	Neutral organics	NA
Lewisite	3088-37-7	1.94	6.2	80.8	Not pers	3.5	140	34	Neutral organics	NA
Tabun	63917-41-9	−0.26	3.1	6.15	Not pers	1016	231	180	Neutral organics	NA
	124-40-3	−0.17	3.1	13.4	Not pers	303	17	2	Neutral organics	120 (F), 50 (D) [1]
	7664-38-2	−0.77	3.1	1	Not pers	1751	395	278	Neutral organics	NA
Sarin	1832-54-8	0.27	3.1	5.52	Not pers	422	99	85	Neutral organics	NA
	993-13-5	−0.7	3.1	1	Not pers	15000	3400	2450	Neutral organics	NA
Soman	616-52-4	1.63	3.6	24.3	Not pers	36	13.5	15.4	Neutral organics	NA
	993-13-5	−0.7	3.1	1	Not pers	15000	3438	2455	Neutral organics	NA
	464-07-3	1.64	2.7	4.67	Not pers	20	7.5	8.5	Neutral organics	NA
VX	1832-53-7	−0.15	3.1	3.57	Not pers	781	178	142	Neutral organics	10.6 (F); 3.3 (D); 17800 (A) [1]
	5842-07-9	2.55	18.2	1033	Not pers	1.4	0.074	1.1	Neutral organics	NA
	73207-98-4	1.52	2.9	175	Not pers	133	9.2	2.9	Neutral organics	NA
	18005-40-8	0	3.1	3.57	Not pers	119	7354	13.7	Neutral organics	NA
	96-80-0	0.88	3.1	14.9	Not pers	208	13	2.9	Neutral organics	NA
	4128-37-4	1.19	1.6	71.8	Not pers	69.8	22.5	23.3	Neutral organics	NA
	2387-23-7	3.92	206	169	Not pers	0.458	0.379	0.676	Neutral organics	NA

A, Algae; D, Daphnids and F, Fish.

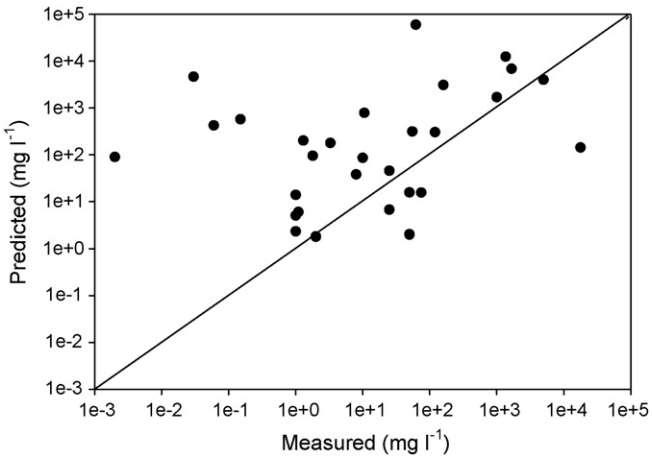

Fig. 1. Measured vs. predicted LC50 values—species specific (mg l^{-1}).

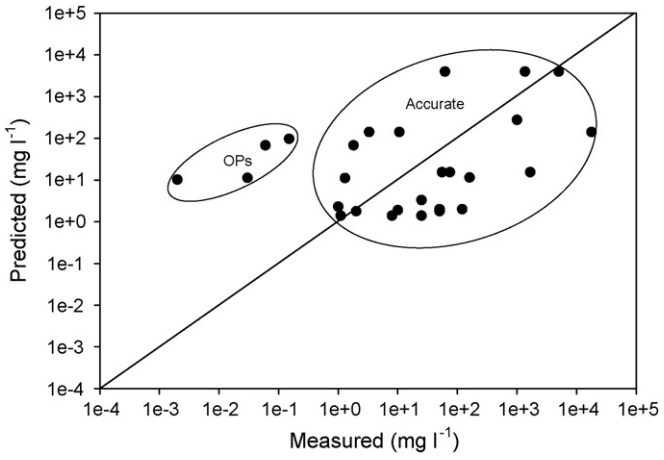

Fig. 2. Measured vs. predicted LC50—not species specific (lowest predicted) (mg l^{-1}).

hydrolysis products, except for two hydrolysis products of VX (CAS# 2387-23-7 and 5842-07-9), which are predicted to be 10 and 30 times more toxic towards aquatic species than the parent compound, respectively.

The predicted no observed effect concentration ($PNEC_{pelagic\ marine}$) can be derived by dividing the predicted EC50 by a default assessment factor of 10,000 [11]. The $PNEC_{sediment\ marine}$ can be derived by applying thermo-dynamic partitioning modelling based on DiToro et al. [16]. Elevated sediment toxicity based on Log Kow and Koc values of the compounds may be predicted for the organoarsenic CWAs Adamsite (Log Kow > 4 and Koc > 5000); Clark I and II (Log Kow > 4 and Koc > 19,000; Log Kow > 3 and Koc > 6000). For the remaining compounds sediment toxicity are not expected to be significantly different from the pelagic risk assessment PEC/PNEC ratio (less than a factor of 10), due to the relatively low Koc and Log Kow values and thus expected low sorption affinity [11].

3.3.1. Model evaluation

Whenever using predictive tools such as (Q)SARs it is recommended to compare available experimental data to the predicted data to evaluate the conservatism of the predictions. Fig. 1 illustrates such an evaluation by comparing measured to predicted acute aquatic toxicity values (LC50) for the same trophic level organism for all parent and major hydrolysis products with measured data. For 27% of the compounds, toxicity is overestimated by the model (are below the line) and 76% of the predictions are within one order of magnitude (±) of the measured value. The geometric mean of the standard error of the predictions (SEP = modelled/measured/2.7 [17]) in Fig. 1 equals 4.5, more than 83% of the predictions have SEPs >1.

If instead we consistently use the lowest predicted toxicity value regardless of species as a measure of conservatism, we find that 73% of the predictions are overestimating the toxicity relative to the measured effect concentration (below the line), and that 85% of the predictions are within one order of magnitude (±) of the measured value. The geometric mean SEP in Fig. 2 =0.6, and 46% of the predictions had SEPs <1. The organophosphorous CWAs nerve gases (OPs) have a specific toxic mode of action (acetylcholinesterase (AChE) inhibition) and is generally underestimated by the model, as illustrated by Fig. 2.

This suggests that the models are applicable and conservative enough to be applied to CWAs at a screening level.

There were no available measured persistence and bioconcentration data in the open literature to evaluate the predictions against hence, these relatively broad parameters are assumed to have comparable reliability as the toxicity predictions.

4. Discussion

Significantly higher incidents of histological lesions recorded in fish species from a CWA dump site in the Mediterranean [4] indicates a chronic state of illness presumably from exposure to blistering agents (Lewisite and Yperite), suggesting a continuous release and/or persistence of these materials. Furthermore, Tørnes et al. [2] note that organoarsenic CWAs are stable in aquatic environments (sediments) and may persist for years. These findings support the predictions for certain potentially persistent CWAs in this paper, denoted in Table 1.

With regards to the generally low predicted BCFs, the apparent lack of traditional lipid based bioconcentration potential is confirmed by Noort et al. [18] who, however, documented that significant amounts of, e.g. sulphur mustard CWA persist in blood for weeks to months in humans after 50–90% have been urinary excreted. Amato et al. [4] determined relative low fish tissue concentrations of organoarsenic CWAs (mainly Lewisite) due to rapid entry into blood circulation as a result of their high affinity with proteins. Organophosphorous CWAs nerve gases can however accumulate in bivale molluscs resistant to acetylcholinesterase (AChE) inhibition [19].

The various CWAs have different specific toxic modes of action (MOAs), which is not necessarily captured in the predicted effect concentrations. Amato et al. [4] found significantly higher EROD activities in contaminated sites than in comparable reference sites, suggesting the P450 system is involved in metabolizing the organoarsenic CWAs in fish. The blistering agents, e.g. Lewisite, toxicity is *inter alia* caused by disruption of the pyruvate dehydrogenase complex in mammals [18] and likely

also disrupted in fishes liver. Moser and Leier [20] demonstrated the apoptosis followed by necrosis in cells caused by alkylating toxicants like Yperite. Henriksson et al. [21] also found that organoarsenic CWAs is significantly more toxic with respect to cell proliferation than positive As_2O_5 controls, suggesting that the organoarsenic CWAs toxicity only to a minor part can be explained by their arsenic content. Organophosphorous CWAs, such as nerve gas agents, inhibit acetylcholinesterase (AChE) thus potentially affecting a wide range of non-target organisms from insects to mammals [18,22]. This specific MOA will significantly elevate the toxicity relative to the predicted values, and is evident for the organophosphorous CWAs Sarin and VX as well as for the halogenated cyanide CK with EC50 values of; 0.002; 0.15 and 1 mg l^{-1}, respectively [1]. AChE appears not to have relevance to microbial survival, *Pseudodomonas melophthora* and *testoteroni* are capable of degrading such organophosphorous compounds, and *Psedimonas putida* utilizes the resulting metabolites as a phosphorus source [12]. As evident from Fig. 2 for the majority of the remaining compounds the predictions are within one order of magnitude of the measured values, suggesting non-specific acute aquatic toxic mode of action.

The reported effect concentrations in Table 1 are related to acute survival, however, potential chronic toxicity as a consequence of persistent or pseudo-persistent (e.g. continual releases from leaking containers) can elicit non-lethal impairment or de-selection mechanisms in exposed organisms as palpable by behavioural changes, which indirectly may affect the function of an ecosystem (e.g. via species avoidance) over time. Green et al. [23] found rapid (from minutes to a less than 6 h) significant changes in nine different sub-lethal behavioural endpoints in *Daphnia magna* exposed to organophosphorous CWAs. They registered effect concentrations at: Soman < 0.006; Sarin < 0.01; Tabun < 0.03 and Cyclosarin < 0.06 (mg l^{-1}) [23], suggesting species potential avoidance of contaminated sites, thereby disrupting the species diversity and thus function of the local contaminated ecotone.

5. Conclusion

Conservative use of EPI Suite can generate reliable and conservative estimations of CWAs acute aquatic toxicity. However, the toxicity of organophosphorous CWAs may be underestimated and would need further experimental investigation. All of the CWA compounds have relatively low BCF and Koc values suggesting relatively low bioconcentration potential and low sediment specific toxicity, according to EU TGD [11]. The parent compounds are generally more toxic, persistent, and have higher Log Kows suggesting an elevated, yet low, potential for biomagnificantion [19] relative to the hydrolysis products, except for two hydrolysis products of VX (CAS# 2387-23-7 and 5842-07-9). Adamsite; Lewisite; the three Nitrogen mustards; Sulphur mustard, Yperite; HT; VX; VG; VM; Cyclosarin; Soman; Chloropicrin (PS) and Diphosgene (DP), would be characterized as persistent according to EU TGD [11].

From an environmental PBT screening point of view the organoarsenic CWAs Clark I and Adamsite represent the highest hazards among the screened CWAs based on overall PBT properties warranting further investigation of these compounds if found in relation to a site specific environmental risk assessment. The mustard gas agents (sulphur and nitrogen) and the organophosphorous CWAs (in particular Sarin and Soman) are a secondary category of concern based upon their acute aquatic toxicity (T) alone. The remaining compounds are of relatively less acute environmental concern based on a screening level PBT assessment, however the chronic aquatic toxicity (presumably a factor 10 lower than the acute toxicity for most CWAs except organophosphorous CWAs [24]) needs more attention for hazard and risk assessment.

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