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Assessing the Ecotoxicity of Pesticide Transformation Products

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Once released to the environment, pesticides may be degraded by abiotic and biotic processes. While parent compounds are assessed in detail in many regulatory schemes, the requirements for the assessment of transformation products are less well developed. This study was therefore performed to explore the relationships between the toxicity of transformation products and their parent compounds and to develop a pragmatic approach for use in the risk assessment of transformation products. Data were obtained on the properties and ecotoxicity of transformation products arising from a wide range of pesticides. Generally, transformation products were less toxic to fish, daphnids, and algae than their parent compound. In instances where a product was more toxic, the increase in toxicity could be explained by either (1) the presence of a pesticide toxicophore; (2) the fact that the product is the active part of a propesticide; (3) the product is accumulated to a greater extent than the parent compound; or (4) the product has a more potent mode of action than the parent. On the basis of the findings, an approach has been proposed to estimate the ecotoxicity of transformation products based on chemical structure and data on the toxicity of the parent compound. The assessments can be performed at an early stage in the risk assessment process to identify those substances that require further testing.

Introduction

When released to the environment, pesticides may be degraded either by microorganisms or chemical processes (*1, 2*). Generally pesticide transformation products will have a lower toxicity to biota than the parent compound (e.g. refs *3*−*5*). However, in some instances a transformation product may be more toxic (e.g. refs *6*−*8*), and consequently these substances may pose a greater risk to the environment than the parent compound. Differences in the environmental behavior of many transformation products compared to the parent, e.g. where a transformation product may have increased mobility compared to the parent (*9*), could also mean that even when a transformation product is less toxic it may still have the potential to have an adverse impact on the environment. Consequently there is a need to consider transformation products during the environmental risk assessment process. In Europe, under EU Directive 91/414/EEC (*10*) and its subsequent amendments, data must be provided for all metabolites, degradation, and reaction products which account for more than 10% of the amount of active substance added. Guidance on assessing the relevance of transformation products has been developed (*11*−*13*).

The effect of a compound on an organism will be dependent on the individual chemical and the interaction between that chemical and the species of interest (*14, 15*). There are a number of possible explanations for a transformation product being more toxic than its parent compound: (1) the active moiety of the parent compound is still present in the transformation product and hence the transformation product has the same toxic mechanism as the parent; (2) the transformation product is the active component of a propesticide, where the applied substance is designed to be absorbed by an organism and once absorbed is metabolized to an active substance that elicits the desired effect (*16*); (3) the bioconcentration factor for the transformation product is greater than the parent and hence more will reach the site of action. This is a key factor affecting the ecotoxicity of compounds which act via a similar mode of action (*17, 18*); and (4) the transformation pathway results in a product with a different and more potent mode of action than the parent compound. Differences in toxicity between pesticides and their transformation products could also be due to the variability inherent in toxicity testing.

If information on the modes of action of parent compounds and transformation products can be obtained and differences in uptake can be determined, it may be possible to identify at a very early stage which transformation products require testing. This study was therefore performed to determine whether the environmental effects of pesticide transformation products can be estimated based on data for the parent compound and information on structure in order to develop a pragmatic approach for their identification and risk assessment. The specific objectives of the study were to (1) collect and collate available data on pesticide transformation products; (2) provide a qualitative means of identifying transformation products which maintain the specific toxic mechanism of their parental pesticides; (3) investigate the relative ecotoxicity to nontarget organisms of pesticide transformation products compared to their associated parent compound; and (4) derive a framework for estimating the effects of transformation products on the environment.

Methods

Data Collation. Initially, an extensive search was undertaken to identify the environmental degradation products of a wide range of pesticides. The majority of the degradation products and pathways were identified using the reviews of Roberts (*1*) and Roberts and Hutson (*2*) and disclosure documents produced for individual active substances by the UK Pesticides Safety Directorate (PSD) (*19*). Only those transformation products that are formed by biological, chemical, and/or physical processes in soil, water, sediment, or air were selected. Transformation products formed solely as a product of metabolism by plants and/or animals were not considered. If a compound was identified to occur as a result of pesticide degradation it was assessed, no matter what amount relative to the parent compound was formed during the transformation process.

Once structures of the transformation products had been identified data were collected on the physicochemical properties (pK_a, log K_{ow}, and log K_{oc}), ecotoxicity and fate and behavior of both pesticides and their transformation products. Data were collected from multiple sources including the open literature, databases such as the USEPA ECOTOX database (*20*), the EU IUCLID database (*21*), the Syracuse

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Research Corporation's EFDB and PHYSPROP databases (*22*, *23*), PSD disclosure documents (*19*), and the report by Belfroid et al. (*24*).

The ecotoxicity data obtained covered a wide range of test species and endpoints. Moreover, multiple values were often available from a number of sources for a particular endpoint. Only a limited amount of information was available on the chronic effects of the transformation products, effects on aquatic macrophytes, and effects on terrestrial organisms. Therefore, for comparative reasons, only data derived from acute tests using fish, daphnids, and algae and following OECD guidelines (*25*−*27*) were selected for further analysis. An algal endpoint (72−96h EC_{50} population), not detailed in the OECD guidelines, was included to increase the number of algal data points.

As many of the data points were obtained from online databases that cite data from the published literature, it was necessary to assess the accuracy of the citations. As a large amount of information was obtained it was impractical to assess all data points by obtaining the original data source that was cited in the database. The original citation was only obtained in the following instances: (1) when a large number of data points were available on a particular substance from a number of sources and where the values for one or more of the data points exhibited a large difference compared to the majority of the data points and (2) when three or fewer data points were reported for a particular substance. If appropriate, the data were revised in light of the results of the quality assessment. All assessed data were then entered into an Accord for Excel Version 5.0 spreadsheet (*28*) which was used for subsequent analyses. Where multiple data points were available for a particular endpoint, the median value was calculated and used in the analyses.

Comparison of Toxicity Values of Parent and Transformation Product. The ecotoxicity data for transformation products and their parent compound were compared to determine whether the products had similar ecotoxicity or were more or less toxic. All of the transformation products were then examined, using the approaches described below, to determine which contained a toxicophore (a chemical moiety that is necessary for a specific toxic mechanism), which were more hydrophobic or less dissociated, and which might have a more potent mode of action than the parent compound.

Identification of Transformation Products Containing Toxicophores. The specific toxic action of a pesticide is due to an interaction between a target site in the organism and the active moiety or toxicophore of the pesticide (*29*). Toxicophores for each of the major classes of pesticide were identified by looking for substructural similarities within a pesticidal class (chemical class obtained from *30*). The Pesticide Manual (*30*) was used as a basis for this work. The structure of each transformation product for which ecotoxicity data were available was then examined to determine whether it contained a pesticide toxicophore.

Identification of Transformation Products that Have an Increased Uptake. Uptake has been shown to relate to hydrophobicity and dissociation of a compound (*31*−*33*). Therefore to determine whether increases in ecotoxicity observed for many of the transformation products could be explained by increases in uptake, the octanol−water partition coefficients (which give a measure of hydrophobicity) and acid dissociation constants (which provide an indication of the degree of dissociation of a substance at neutral pH) for parent compounds and transformation products were compared. Generally experimentally determined values were used. However, in instances where experimental data were not available for log K_{ow} or pK_a, the values were predicted, based on chemical structure, using KOWWIN v 1.6 (*34, 35*) for K_{ow} and SPARC (*36*) for pK_a. Transformation products that had a greater K_{ow} value than their parent or which were less dissociated than the parent were considered likely to bioaccumulate to a greater extent than the parent.

TABLE 1. Summary of the Data Available for Parent Compounds and Their Transformation Products

physicochemical property/taxonomic group	no. of parents	no. of transformation products
log K_{ow}	36	71
pK_a	35	64
log K_{oc}[a]	12	33
fish	30	60
daphnids	27	57
algae	11	16

[a] These data were analyzed independently with a different data set.

Identification of Toxic Modes of Action for the Transformation Products. The structures of each of the transformation products were examined to determine whether they might be expected to have a reactive mode of action (*14*). Three "rule-based" approaches were used (*37*−*39*). Each approach identified structural fragments associated with a range of modes of action; if one of these fragments was contained in the molecule of a transformation product and not in the parent compound, then it was assumed that the product might have the mode of action associated with the fragment and that it might be more toxic than the parent.

Results and Discussion

Using the search strategy, information was obtained on the transformation pathways of 60 active compounds, and based on these pathways the structures of 485 transformation products were identified. The active compounds examined covered a range of chemical classes and included 27 herbicides, 20 insecticides, 12 fungicides, and 1 compound used as a herbicide, fungicide, and insecticide. All the major classes of pesticide were represented by at least one active compound.

The final database (Table 1, Supporting Information) only comprised property and ecotoxicity values for 89 transformation products arising from 37 parent compounds. Twenty-three parent compounds with identified transformation pathways had either no corresponding data or only unsuitable data for their respective transformation products. Log K_{ow} values were available for 71 transformation products, pK_a values were available for 64 transformation products, and K_{oc} values were available for 33 transformation products (Table 1). In terms of the ecotoxicity data, fish 96h LC_{50} values were available for 60 transformation products, daphnid 48h EC_{50} values were available for 57 transformation products, while only 16 transformation products had acute algae toxicity data (Table 1).

A comparison of parent and transformation product ecotoxicity data (Figure 1) demonstrated that the majority (70%) of transformation products have either a similar toxicity to the parent compound or are less toxic. However, a significant proportion (30%; Table 2) are more toxic than their parent compound, and 4.2% of transformation products are more than an order of magnitude more toxic. In terms of ecotoxicity values, in only 20 instances did a transformation product have an acute toxicity value of less than 1 mg L^{-1}, one of the threshold values used in classifying chemicals in the EU, typically separating the classes "very toxic" from "toxic".

Fifty-four toxicophores associated with a wide range of pesticide classes were identified (Figure 2). It was not possible to identify a toxicophore for all the active compounds considered in the study. Some classes contained too few members within their pesticidal class for reasonable toxi-

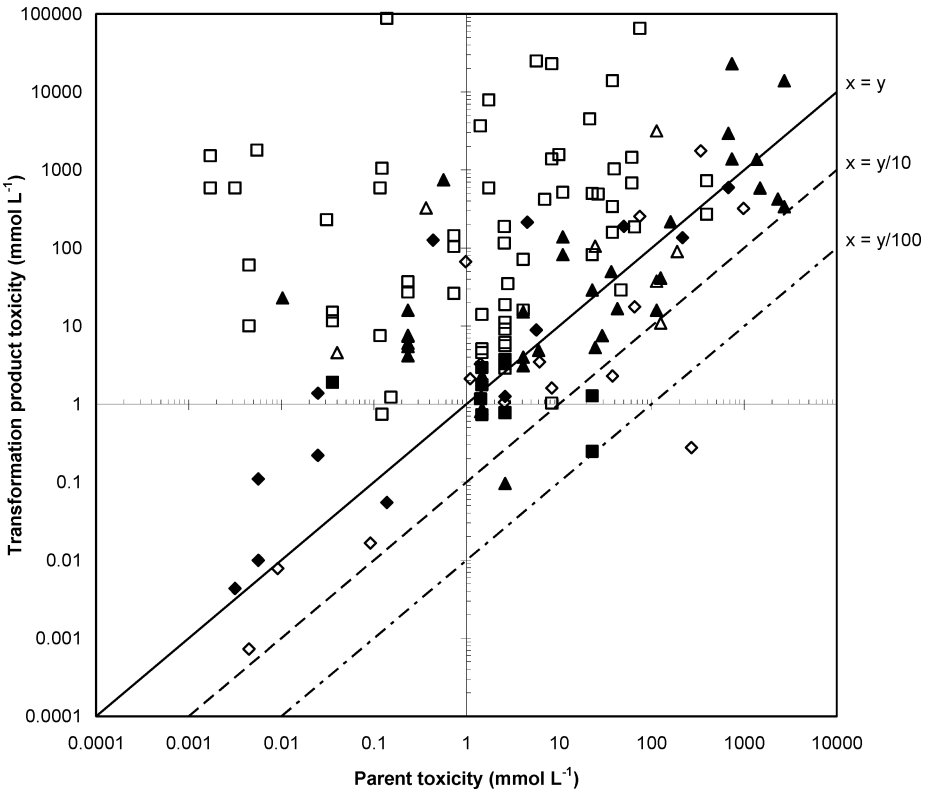

FIGURE 1. Relationship between the ecotoxicity (to fish, daphnids, and algae) of parent compounds and their transformation product that (a) contain a toxicophore (black diamonds), (b) are propesticides (white diamonds), (c) are more hydrophobic than the parent (black triangles), (d) are less dissociated than the parent (white triangles), (e) might be expected to have a more potent mode of action (black squares), or (f) exhibit none of these characteristics (white squares).

cophore identification, while some compounds had an undefined mode of action and/or were not a member of a defined pesticidal class.

When those substances identified as having increased toxicity in relation to their parent compound were evaluated, it was found that over 90% of the observed increases in toxicity could be explained by the presence of a toxicophore, differences in uptake, or differences in mode of action (Table 2; Figure 1). Four substances still contained the parent toxicophore, 5 substances were the active substances resulting from a propesticide, 13 substances were more hydrophobic than their parent compound, and 2 substances would be expected to be less dissociated than their parent compound. Five substances would have a reactive mode of action or act via respiratory uncoupling; these were 5-hydroxy-1,4-naphthoquinone, 1,4-dihydroxybenzene, tetrachloroaniline, 2,3,4,6-tetrachlorophenol, and 2,3,5,6-tetrachlorophenol. 5-Hydroxy-1,4-naphthoquinone and 1,4-dihydroxybenzene are known to be highly reactive (*38*, *39*). The high toxicity of quinones has been attributed to enzymatically based redox cycling resulting in superoxide formation and the regeneration of the quinone (*40*). It has been suggested that the 1,4-dihydroxybenzene can be oxidized to a quinone and thus exhibit the same futile metabolism (*41*). Tetrachloroaniline and tetrachlorophenol are uncouplers of oxidative phosphorylation (*39*). For transformation products that did not have a specific mode of action (i.e. did not contain a toxicophore or are active component of a propesticide), the difference between the toxicity of the parent and the toxicity of the transformation product appeared to depend on the potency of the parent. In situations where a parent compound was highly potent the difference between toxicity values for the parent and transformation product was large, whereas in situations where the parent compound was less potent the difference between the parent and transformation product was small. One possible explanation for this is that most transformation products, after having lost the active moiety, exhibit baseline toxicity, which is considerably lower than the specific toxic effects of the pesticides.

While information on uptake and mode of action explained the increases in toxicity for a significant proportion of the transformation products, a large proportion (30%) of products that were less toxic than the parent compound also had one or more of the characteristics. Many of these observations could however be explained by the following:

(1) The presence of a toxicophore in a transformation product does not necessarily mean that the substance will be more potent than the parent compound. For example, the product may still have pesticide activity but be accumulated to a lesser extent than the parent.

(2) The presence of a toxicophore in a molecule does not always mean that the molecule will have pesticidal activity. For example, interactions with other functional groups in the molecule may mean the toxicophore cannot interact with the site of action.

(3) The mode of action of the toxicophore may not be relevant for certain test species. For example, a substance containing a herbicidal toxicophore would not be expected to exhibit an increase in toxicity to fish and daphnids. Data for the propesticides support this. For insecticidal propesticides increases in toxicity of the transformation products were observed for fish and daphnids, whereas for herbicidal and fungicidal propesticides, the transformation products were less toxic than their parents to fish and daphnids.

(4) A transformation product that is more hydrophobic than its parent compound and does not have pesticidal activity is unlikely to be more toxic than its parent to sensitive species that have a receptor site relevant to the parent mode

TABLE 2. Transformation reactions where the transformation product is more toxic than the parent compound. The taxonomic group where the increase in toxicity was observed is indicated (A = algae, D = dapnids, F = fish) and the possible explanation for the observed increase is given

parent compound	pesticidal class [a]	transformation product	toxicophore present	propesticide	increase in hydrophobicity	decrease in dissociation	change in mode of action	unknown
2,4-D	aryloxyalkanoic acid	2,4-dichlorophenol			F, D			
		4-chlorophenol				F, D, A		
		4-chlorocatechol				F		
acephate	organophosphorus	methamidophos		F, D				
aldicarb	oxime carbamates	aldicarb sulfone	D					
atrazine	1,3,5-triazine	deisopropyldeethyl atrazine	D					
azocyclotin	organotin	cyhexatin		F, D			F	
butylate	thiocarbamate	diisobutylamine						D
carbaryl	carbamates	1,4-dihydroxybenzene					F	
		5-hydroxy-,1,4-naphthoquinone						
dazomet	methyl isothiocyanate precursor	hydrogen sulfide						F
		methyl isothiocyanate		F, D, A				
diuron	urea	3,4-dichloroaniline			D			
fluometuron	urea	3-trifluoromethyl benzenamine			D			
fluridone		m-(trifluoromethyl) benzaldehyde			F			
gamma HCH	organochlorine	1,2,3,5-tetrachlorobenzene			D			
		alpha-HCH			D			
glyphosate		formaldehyde			D			
napropamide	alkanamide	1-naphthol						F
parathion	organophosphorus	paraoxon		F, D				
quinmerac	quinolinecarboxylic acid	BH-518−2	A					
quintozene	aromatic hydrocarbon derivative	2,3,4,6-tetrachlorophenol					D	
		2,3,5,6-tetrachlorophenol					F	
		3,4,5-trichlorophenol						D
		pentachlorophenol			F			
		pentachloroanisole			D			
rimsulfuron	sulfonylurea	IN-70942			D			
tecnazene		2,3,4,5-tetrachloroaniline					F	
		2,3,5,6-tetrachloro-thioanisole			F			
thiodicarb	oxime carbamates	methomyl	D					
triclopyr	arloxyalkanoic acid	3,5,6-trichloro-2-pyridinol			F			
triflusulfuron-methyl	sulfonylurea	IN-D8526−2			F			
zineb	alkylenebis(dithio-carbamates)	ethylenethiourea		A				

[a] From ref *30*.

of action. Examination of the data set supports this and indicates that transformation products which are more hydrophobic than and do not contain the parent toxicophore of an insecticide parent compound are generally less toxic than the parent to fish and daphnids. Similarly, transformation products not containing a toxicophore and which are more hydrophobic than a herbicide parent compound are generally less toxic than the parent to algae.

(5) A transformation product that is less dissociated than its parent may also be much less hydrophobic, the effect on uptake of the decrease in dissociation may therefore be offset by the reduction in hydrophobicity. This may explain why succinic acid is less toxic than 2,4-D even though it is less dissociated; succinic acid has a log K_{ow} of −0.6 compared to a log K_{ow} of 2.81 for 2,4-D.

Therefore, when assessing the potential impacts of a particular transformation product, ideally as much information as possible should be used on the mechanism(s) of action of the parent, the sensitivity of the different taxa to the parent compound, and the properties of both the parent compound and the transformation product.

The availability of data has meant that it has been only possible to investigate the relationships between acute aquatic toxicity endpoints (for fish, daphnids, and algae) for parent compounds and their transformation products. Recent studies using chronic data for aquatic species and data for terrestrial organisms (*42*) indicate that when these endpoints are considered, parents are generally of equal toxicity to or are more toxic than their transformation products. However, as in the current study, there were instances where a transformation product was more toxic than the parent compound. Unfortunately, the studies are based on confidential data so it is not possible to determine whether the factors that explain the increases in acute aquatic ecotoxicity values used in the present study also explain the increases in chronic or terrestrial ecotoxicity.

The findings described above indicate that it is possible to begin to prioritize transformation products based on information on mode of action and uptake. On the basis of the results obtained it is possible to begin to develop a framework that might be used to assess the potential effects of transformation products on aquatic organisms. A three-step process is proposed (Figure 3) which uses information on parent toxicity, transformation product structure, and properties along with assessment factors. The assessment factors were derived from the ecotoxicity data using a cautious systematic approach which ensured that all data points were covered. The assessment factors were generated by creating a series of "bins". These bins were identified using the ecotoxicity comparison data, and, for ease of use, ranges of parent toxicity values and assessment factors were selected to be factors of 10.

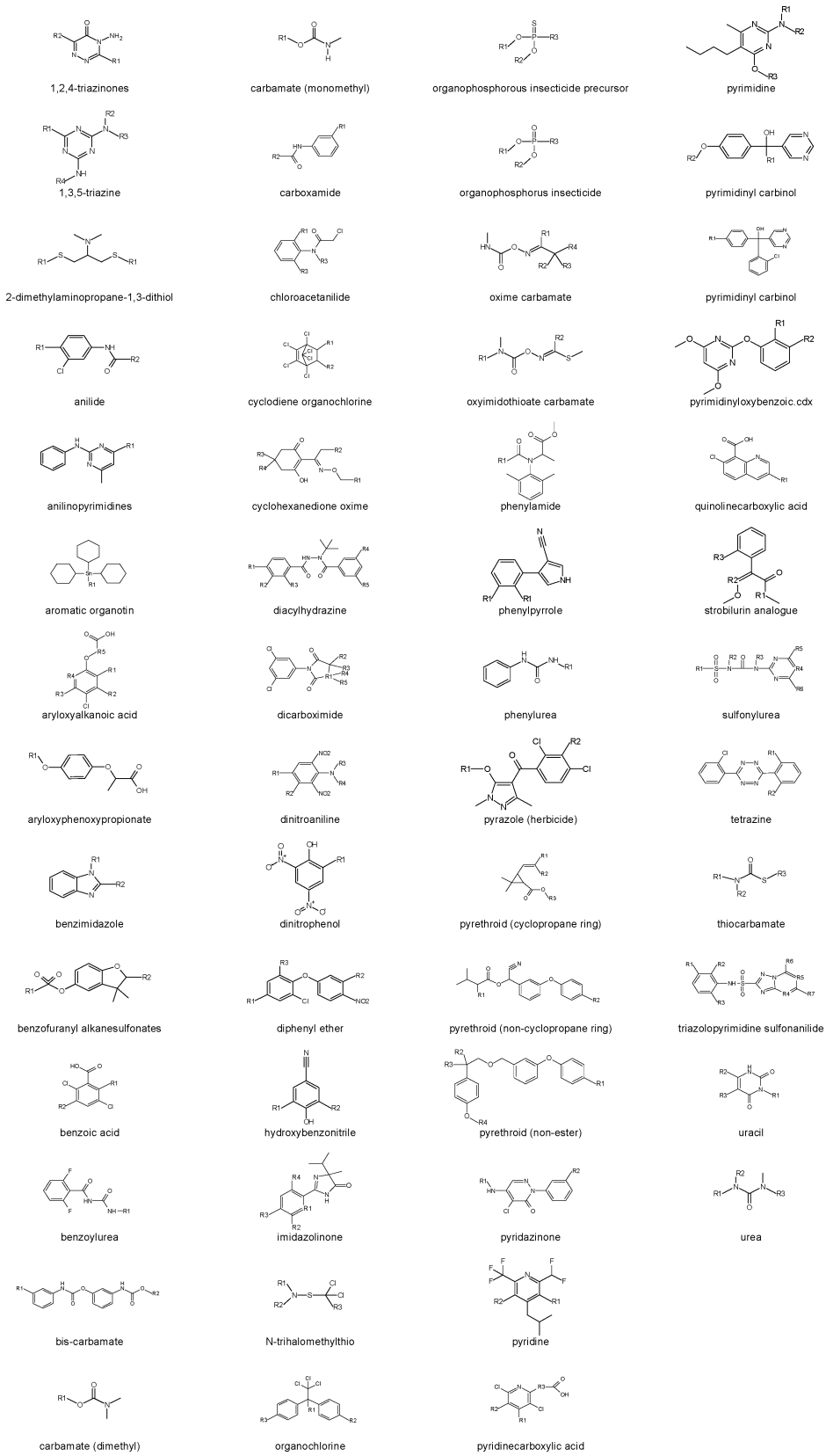

FIGURE 2. Toxicophores identified for major pesticide classes.

Step 1 — Toxicophore Assessment. The structure of the transformation product should be examined to determine whether it contains the parent toxicophore. If the parent toxicophore is present, then the effect of the transformation product can be estimated from ecotoxicity data for the parent compound using eq 1 and an assessment factor (AF) of 0.1 (i.e. transformation products which maintain the toxicophore of the parent can be 10 times more toxic than the pesticide). The AF is derived from the relationship between parent toxicity values and the difference between parent and transformation product toxicity for substances containing the toxicophore (Figure 4a; Table 3). The toxicity endpoint

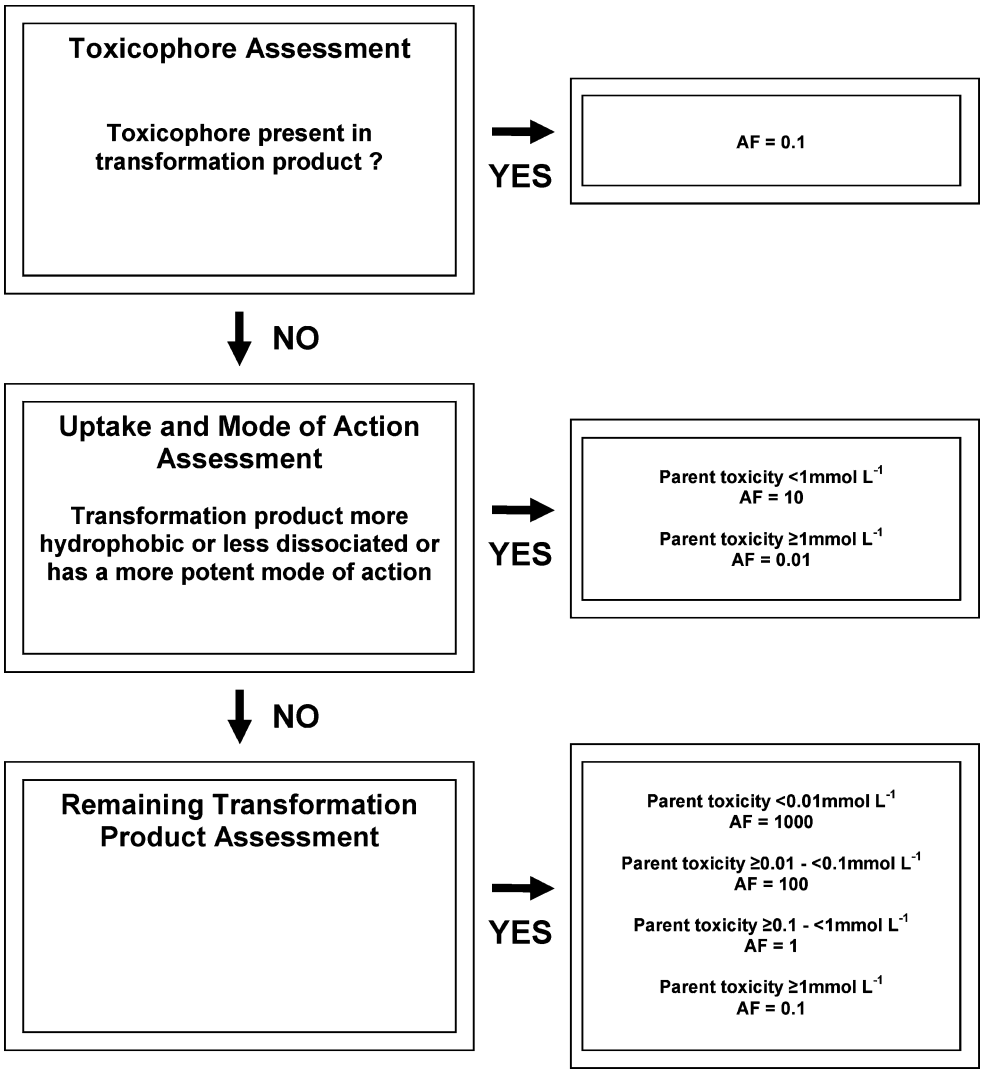

FIGURE 3. Flowchart summarizing proposed transformation product assessment approach.

for the parent ($LC/EC/IC_{50}$) used in eq 1 should be that for the most susceptible species (fish, daphnids, and algae) to the parent pesticide.

$$LC/EC/IC_{50\text{transformation product}} = LC/EC/IC_{50\text{parent}} \times AF \quad (1)$$

Step 2 — Assessment of Uptake and Mode of Action. Those substances that do not contain the parental toxicophore are then assessed to determine whether (1) the product is more hydrophobic than the parent compound; (2) the product is less dissociated than the parent compound; or (3) the product has a different but more potent mode of action than the parent compound. In the absence of experimental data, to determine the hydrophobicity (K_{ow}) of the parent compound and the transformation product it is recommended that SRC's KOWWIN software is used to estimate the octanol–water partition coefficient, while it is recommended that SPARC is used to determine dissociation. The rule based systems of Lipnick (*37*), Verhaar et al. (*38*), and Russom et al. (*39*) should be used to determine whether a transformation product has a reactive mode of action or whether it is a respiratory uncoupler.

For all compounds that are shown to be more hydrophobic, less dissociated, or which have a more potent mode of action than the parent compound, the assessment factors listed in Table 3 should be used along with eq 1. The assessment factors have been derived from the relationship between parent toxicity and the difference between parent and transformation product toxicity for transformation products that are more hydrophobic, less dissociated, or which might be expected to have a more potent mode of action (Figure 4b)—this overcomes the issue of species sensitivity. All compounds that are less hydrophobic than the parent, equally or more greatly dissociated, and which do not have a reactive mode of action or are not respiratory uncouplers should move on to step 3 assessment.

Step 3—Assessment of Remaining Products. The effects of all remaining transformation products should be determined based on the ecotoxicity data for the parent compound using assessment factors and eq 1. The assessment factors (Table 3) have been derived from the relationship between the toxicity of the parent compound and the difference between the toxicity of transformation product and parent for all compounds that do not contain a toxicophore, which would not be expected to accumulate to a greater extent than the parent and which would not be expected to have a more potent mode of action (Figure 4c).

Such an approach is precautionary. As information on the hydrophobicity and dissociation of transformation products can be accurately predicted from chemical structure using quantitative structure–property relationships (QSPR's) (*43*), the only information required to perform the assessments are the structures of the transformation products for

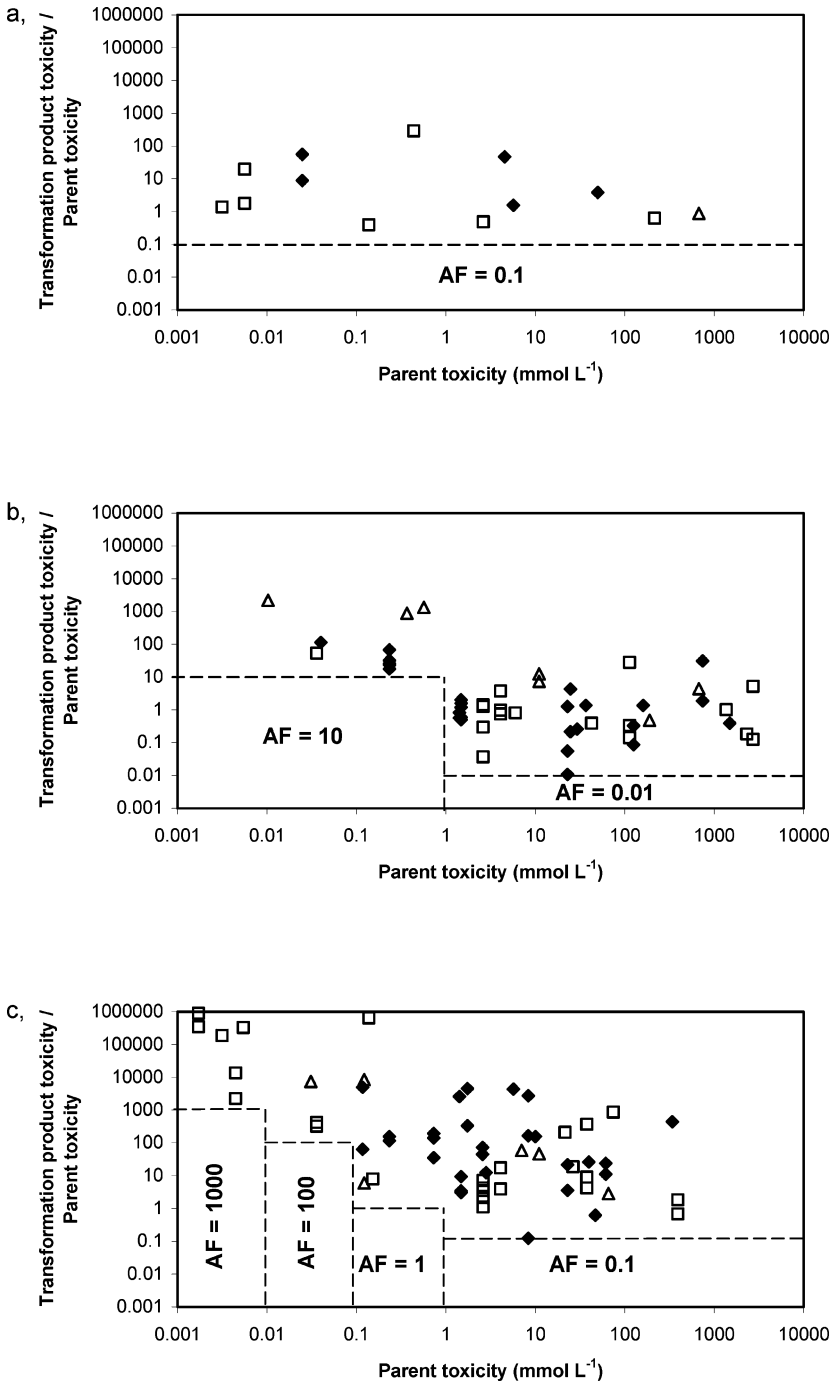

FIGURE 4. Relationship between parent toxicity values (mmol L^{-1}) and the ratio of the toxicity of the transformation product to the parent compound for fish (black diamonds), daphnids (white squares), and algae (white triangles) for (a) transformation products containing a pesticide toxicophore; (b) transformation products that are more hydrophobic, are less dissociated, or have a more potent mode of action than the parent; and (c) the remaining transformation products.

the substance of interest and experimental ecotoxicity values for the parent compound. The methodology could therefore be used at an early stage in the risk assessment process to identify transformation products that might pose a risk to the environment. These compounds could then be taken forward for experimental testing. The application of an approach of this type will result in clear cost and time savings and will minimize the use of laboratory animals.

The scheme and the assessment factors proposed are based on a limited data set and while the data set does cover a range of pesticide classes and modes of action, evaluation and validation against additional data would be beneficial and could allow further refinement of the methodology. This would probably be a requirement if the approach is to be adopted by regulatory authorities. Other studies into the effects of transformation products (e.g. refs *42* and *44*) have had access to unpublished data produced by industry, and these indicate that a large body of data has been generated that could be used for evaluation purposes. These data sets not only include information on acute toxicity to fish, daphnids, and algae but also include data on aquatic plants, sediment dwellers, earthworms, and chronic endpoints.

The assessment process focuses solely on the determination of the potential effects of a particular transformation

TABLE 3. Assessment Factors for Determining Acute Toxicity Values of Transformation Products During the Assessment Scheme

$LC/EC/IC_{50}$ for parent compound (mmol L^{-1})	assessment factor (AF)
Step 1	
any value	0.1
Step 2	
<1	10
≥1	0.01
Step 3	
<0.01	1000
≥0.01 − <0.1	100
≥0.1 − <1	1
≥1	0.1

product. To identify transformation products that might pose a risk to the environment, it will also be necessary to assess exposure. Work has been done assessing the overall persistence and environmental concentrations in different compartments for solvent, surfactant, and herbicidal transformation products (*45*). The development of approaches to assess exposure was beyond the scope of this study. To perform such assessments, information will be required on the persistence and mobility of transformation products. Assessment of currently available QSPRs for determining the sorption of a transformation product in soil or sediment systems indicates that these approaches could be used to assess mobility (*43*). If these data were supplemented with information arising from fate studies (e.g. degradation route studies and lysimeter investigations) and used in exposure models (e.g. ref *46*), it may be possible to derive an estimate of exposure for a transformation product. This could then be used along with the effects estimate to derive a toxicity exposure ratio (TER) (i.e. the ratio of the aquatic ecotoxicity endpoint and the exposure concentration) and hence assess the risk of a particular transformation product.

In conclusion therefore, there is an increasing need for pragmatic approaches to assess the risks posed to the environment by pesticide transformation products. Generally, transformation products have similar toxicity to or are less toxic than their parent compound. However, in instances where a transformation product is more toxic, the increase in toxicity can be explained by a knowledge of pesticide and transformation product mode of action and the relative uptake of the transformation product and parent. Using this information, a pragmatic approach has been developed that can be used to assess transformation products at a very early stage in the risk assessment process to identify those products that do and do not need further testing. The use of such an approach offers a range of benefits including cost and time savings and the reduction in animal testing. The results of the current study are feeding into the EU aquatic ecotoxicology guidance document (*12*). Although the current work focuses on the pesticide registration process in Europe, the approach developed here could be adopted by other geographical areas and used with other biologically active molecules (e.g. biocides, human medicines, and veterinary medicines). The framework has been evaluated for use in the environmental risk assessment of biocides (Sinclair and Boxall, unpublished). Initial results indicate the approach shows promise in this area.

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Supporting Information Available

Ecotoxicity and physicochemical property data for parent compounds and associated transformation products (Table 1). This material is available free of charge via the Internet at http://pubs.acs.org.

Literature Cited

(1) *Metabolic Pathways of Agrochemicals, Part 1: Herbicides and Plant Growth Regulators*; Roberts, T. R., Ed.; The Royal Society of Chemistry: Cambridge, UK, 1998.
(2) *Metabolic Pathways of Agrochemicals, Part 2: Insecticides and Fungicides*; Roberts, T. R., Hutson, D. H., Eds.; The Royal Society of Chemistry: Cambridge, UK, 1999.
(3) Stratton, G. W. The Effects of Selected Pesticides and their Degradation Products on Microorganisms and *Daphnia magna*. Doctoral Thesis, The University of Guelph, Ontario, Canada, 1981.
(4) Day, K. E.; Maguire, R. J. *Environ. Toxicol. Chem.* **1990**, *9*, 1297−1300.
(5) Day, K. E.; Hodge, V. *Water Qual. Res. J. Can.* **1996**, *31*, 197−214.
(6) Stratton, G. W.; Corke, C. T. *Environ. Pollut. A* **1982**, *29*, 71−80.
(7) Osano, O.; Admiraal, W.; Klamer, H. J. C.; Pastor, D.; Bleeker, E. A. J. *Environ. Pollut.* **2002**, *119*, 195−202.
(8) Osano, O.; Admiraal, W.; Otieno, D. *Environ. Toxicol. Chem.* **2002**, *21*, 375−379.
(9) Kolpin, D. W.; Thurman, E. M.; Linhart, S. M. *Environ. Sci. Technol.* **2001**, *35*, 1217−1222.
(10) EU. Council Directive of 15 July 1991 concerning the placing of plant protection products on the market (91/414/EEC). *Official Journal of the European Communities*; 1994.
(11) EU. *Guidance Document of the Assessment of the Relevance of Metabolites in Groundwater of Substances Regulated Under Council Directive 91/414/EEC*; Sanco/221/2000-rev.10; 2003.
(12) EU. *Guidance Document on Aquatic Ecotoxicology*; Sanco/3268/2001-rev.4; 2002.
(13) EU. *Guidance Document on Terrestrial Ecotoxicology under Council Directive 91/414/EEC*; Sanco/10329/2002-rev. 2; 2002.
(14) Bradbury, S. P. *SAR QSAR Environ. Res.* **1994**, *2*, 89−104.
(15) Wroath, A.; Boxall, A. B. A. *Modes of Toxic Action*; R&D Technical Report W52; Environment Agency: UK, 1996.
(16) Drabek, J.; Neumann, R. In *Insecticides: Progress in Pesticide Biochemistry and Toxicology Volume 5*; Hutson, D. H., Roberts, T. R., Eds.; John Wiley & Sons: Chichester, UK, 1985; pp 35−86.
(17) Lipnick, R. L. In *Practical Applications of Quantitative Structure−Activity Relationships (QSAR) in Environmental Chemistry and Toxicology*; Karcher, W., Devillers, J., Eds.; Kluwer Academic Publishers: Dordrecht, Netherlands, 1990; pp 281−293.
(18) Escher, B. I.; Hermens, J. L. M. *Environ. Sci. Technol.* **2002**, *36*, 4201−4217.
(19) PSD. *Advisory Committee on Pesticides: Published Evaluation Document List*; 2003; http://www.pesticides.gov.uk/citizen/Evaluations/evallist.htm.
(20) EPA. *The ECOTOX (ECOTOXicology) database*; 2002; http://www.epa.gov/ecotox/.
(21) EC. *European Chemicals Bureau IUCLID CD-ROM, Public data on high volume chemicals*; Brussels, Belgium, 2000.
(22) SRC. *Environmental Fate Data Base (EFDB)*; 2002; http://esc.syrres.com/efdb.htm.
(23) SRC. *The Physical Properties Database (PHYSPROP)*; 2002; http://esc.syrres.com/interkow/PhysProp.htm.
(24) Belfroid, A. C.; van Drunen, M.; van Gestel, C. A. M.; van Hattum *Relative risks of transformation products of pesticides for aquatic ecosystems*; Report R-96/09; Institute for Environmental Studies: Amsterdam, Netherlands, 1996.
(25) OECD. *Guideline for testing of chemicals 203, Fish acute toxicity test*; Organisation for Economic Co-Operation and Development: Paris, France, 1992.
(26) OECD. *Guideline for testing of chemicals 202, Daphnia sp. acute immobilisation test and reproduction test*; Organisation for Economic Co-Operation and Development: Paris, France, 1984.
(27) OECD. *Guidelines for testing chemicals 201, Alga, Growth inhibition test*; Organisation for Economic Co-Operation and Development: Paris, France, 1984.
(28) Accelrys. *Accord for Microsoft Excel User's Guide*; Cambridge, UK, 2001.

(29) Rand, G. M.; Wells, P. G.; McCarty, L. S. In *Fundamentals of Aquatic Toxicology: Effects, Environmental Fate and Risk Assessment*; Rand, G. M., Ed.; Taylor and Francis: Philadelphia, U.S.A., 1995; pp 3−67.
(30) Tomlin, C. D. S. *The Pesticide Manual*, 11th ed.; British Crop Protection Council: Farnham, UK, 1997.
(31) Hermens, J.; Canton, H.; Janssen, P.; de Jong, R. *Aquat. Toxicol.* **1984**, *5*, 143−154.
(32) Könemann, H. *Toxicology* **1981**, *19*, 209−221.
(33) Esser, H. O.; Moser, P. *Ecotox. Environ. Safe.* **1982**, *6*, 131−148.
(34) Meylan, W. M.; Howard, P. H. *J. Pharm. Sci.* **1995**, *84*, 83−92.
(35) Meylan, W. M.; Howard, P. H. *User's guide for KOWWIN*; Syracuse Research Corporation: Syracuse, U.S.A., 1999.
(36) Karickhoff, S. W.; McDaniel, V. K.; Melton, C.; Vellino, A. N.; Nute, D. E.; Carreira, L. A. *Environ. Toxicol. Chem.* **1991**, *10*, 1405−1416.
(37) Lipnick, R. L. *Sci. Total Environ.* **1991**, *109/110*, 131−153.
(38) Verhaar, H. J. M.; van Leeuwen, C. J.; Hermens, L. M. *Chemosphere* **1992**, *25*, 471−491.
(39) Russom, C. L.; Bradbury, S. P.; Broderius, S. J.; Hammermeister, D. E.; Drummond, R. A. *Environ. Toxicol. Chem.* **1997**, *16*, 948−967.
(40) Mason, R. P. *Environ. Health Persp.* **1990**, *87*, 237−243.
(41) Cronin, M. T. School of Pharmacy and Chemistry, Liverpool John Moores University, UK. Personal communication.
(42) Grasso, P.; Alberio, P.; Redolfi, E.; Azimonti, G.; Giarei, C. *Statistical evaluation of available ecotoxicology data on plant protection products and their metabolites*; Intermediate Report to the European Commission; International Centre for Pesticides and Health Risk Prevention: Milan, Italy, 2002.
(43) Sinclair, C. J.; Boxall, A. B. A. *Assessment of the Environmental Properties and Effects of Pesticide Transformation Products*; Final Report to the Department for Environment, Food and Rural Affairs; Cranfield Centre for EcoChemistry: Derby, UK, 2002.
(44) ECPA. *Comparison of parent and metabolite toxicity for aquatic organisms − preliminary findings*; Report of the ECPA ad hoc Aquatic Ecotoxicology Group; 2002.
(45) Fenner, K. B. Transformation Products in Environmental Risk Assessment: Joint and Secondary Persistence as New Indicators for the Overall Hazard of Chemical Pollutants. Doctoral Thesis, Swiss Federal Institute of Technology, Zurich, Switzerland, 2001.
(46) FOCUS. *FOCUS surface water scenarios in the EU evaluation process under 91/414/EEC*; Report prepared by the FOCUS working group on surface water scenarios; EC Document Sanco/4802/2001-rev-1; 2002.

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