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Report No. 3-32

Developing Risk-based Rankings for Pesticides in Support of Standard Development at Environment Canada: Risk-based Approach for Terrestrial Biota Continued – Incorporating Dermal Exposure in Pesticide Risk Assessments for Birds

Technical Series 2007

Photos:
Bottom Left- clockwise

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DEVELOPING RISK-BASED RANKINGS FOR PESTICIDES IN SUPPORT OF STANDARD DEVELOPMENT AT ENVIRONMENT CANADA: RISK-BASED APPROACH FOR TERRESTRIAL BIOTA CONTINUED – INCORPORATING DERMAL EXPOSURE IN PESTICIDE RISK ASSESSMENTS FOR BIRDS

REPORT NO. 3-32

NOTE TO READERS

The National Agri-Environmental Standards Initiative (NAESI) is a four-year (2004-2008) project between Environment Canada (EC) and Agriculture and Agri-Food Canada (AAFC) and is one of many initiatives under AAFC's Agriculture Policy Framework (APF). The goals of the National Agri-Environmental Standards Initiative include:

- Establishing non-regulatory national environmental performance standards (with regional application) that support common EC and AAFC goals for the environment
- Evaluating standards attainable by environmentally-beneficial agricultural production and management practices; and
- Increasing understanding of relationships between agriculture and the environment.

Under NAESI, agri-environmental performance standards (i.e., outcome-based standards) will be established that identify both desired levels of environmental condition and levels considered achievable based on available technology and practice. These standards will be integrated by AAFC into beneficial agricultural management systems and practices to help reduce environmental risks. Additionally, these will provide benefits to the health and supply of water, health of soils, health of air and the atmosphere; and ensure compatibility between biodiversity and agriculture. Standards are being developed in four thematic areas: Air, Biodiversity, Pesticides, and Water. Outcomes from NAESI will contribute to the APF goals of improved stewardship by agricultural producers of land, water, air and biodiversity and increased Canadian and international confidence that food from the Canadian agriculture and food sector is being produced in a safe and environmentally sound manner.

The development of agri-environmental performance standards involves science-based assessments of relative risk and the determination of desired environmental quality. As such, the National Agri-Environmental Standards Initiative (NAESI) Technical Series is dedicated to the consolidation and dissemination of the scientific knowledge, information, and tools produced through this program that will be used by Environment Canada as the scientific basis for the development and delivery of environmental performance standards. Reports in the Technical Series are available in the language (English or French) in which they were originally prepared and represent theme-specific deliverables. As the intention of this series is to provide an easily navigable and consolidated means of reporting on NAESI's yearly activities and progress, the detailed findings summarized in this series may, in fact, be published elsewhere, for example, as scientific papers in peer-reviewed journals.

This report provides scientific information to partially fulfill deliverables under the Pesticide Theme of NAESI. This report was written by P. Mineau of Environment Canada. The report was edited and formatted by Denise Davy to meet the criteria of the NAESI Technical Series. The information in this document is current as of when the document was originally prepared. For additional information regarding this publication, please contact:

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NOTE À L'INTENTION DES LECTEURS

L'Initiative nationale d'élaboration de normes agroenvironnementales (INENA) est un projet de quatre ans (2004-2008) mené conjointement par Environnement Canada (EC) et Agriculture et Agroalimentaire Canada (AAC) et l'une des nombreuses initiatives qui s'inscrit dans le Cadre stratégique pour l'agriculture (CSA) d'AAC. Elle a notamment comme objectifs :

- d'établir des normes nationales de rendement environnemental non réglementaires (applicables dans les régions) qui soutiennent les objectifs communs d'EC et d'AAC en ce qui concerne l'environnement;
- d'évaluer des normes qui sont réalisables par des pratiques de production et de gestion agricoles avantageuses pour l'environnement;
- de faire mieux comprendre les liens entre l'agriculture et l'environnement.

Dans le cadre de l'INENA, des normes de rendement agroenvironnementales (c.-à-d. des normes axées sur les résultats) seront établies pour déterminer les niveaux de qualité environnementale souhaités et les niveaux considérés comme réalisables au moyen des meilleures technologies et pratiques disponibles. AAC intégrera ces normes dans des systèmes et pratiques de gestion bénéfiques en agriculture afin d'aider à réduire les risques pour l'environnement. De plus, elles amélioreront l'approvisionnement en eau et la qualité de celle-ci, la qualité des sols et celle de l'air et de l'atmosphère, et assureront la compatibilité entre la biodiversité et l'agriculture. Des normes sont en voie d'être élaborées dans quatre domaines thématiques : l'air, la biodiversité, les pesticides et l'eau. Les résultats de l'INENA contribueront aux objectifs du CSA, soit d'améliorer la gérance des terres, de l'eau, de l'air et de la biodiversité par les producteurs agricoles et d'accroître la confiance du Canada et d'autres pays dans le fait que les aliments produits par les agriculteurs et le secteur de l'alimentation du Canada le sont d'une manière sécuritaire et soucieuse de l'environnement.

L'élaboration de normes de rendement agroenvironnementales comporte des évaluations scientifiques des risques relatifs et la détermination de la qualité environnementale souhaitée. Comme telle, la Série technique de l'INENA vise à regrouper et diffuser les connaissances, les informations et les outils scientifiques qui sont produits grâce à ce programme et dont Environnement Canada se servira comme fondement scientifique afin d'élaborer et de transmettre des normes de rendement environnemental. Les rapports compris dans la Série technique sont disponibles dans la langue (français ou anglais) dans laquelle ils ont été rédigés au départ et constituent des réalisations attendues propres à un thème en particulier. Comme cette série a pour objectif de fournir un moyen intégré et facile à consulter de faire rapport sur les activités et les progrès réalisés durant l'année dans le cadre de l'INENA, les conclusions détaillées qui sont résumées dans la série peuvent, en fait, être publiées ailleurs comme sous forme d'articles scientifiques de journaux soumis à l'évaluation par les pairs.

Le présent rapport fournit des données scientifiques afin de produire en partie les réalisations attendues pour le thème des pesticides dans le cadre de l'INENA. Ce rapport a été rédigé par P. Mineau d'Environnement Canada. De plus, il a été révisé et formaté par Denise Davy selon les critères établis pour la Série technique de l'INENA. L'information contenue dans ce document était à jour au moment de sa rédaction. Pour plus de renseignements sur cette publication, veuillez communiquer avec l'organisme suivant :

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1 INTRODUCTION

Environment Canada has been tasked with developing environmental standards for implementation in Agriculture and Agri-Food Canada's Agricultural Policy Framework (AAFC; APF). The Wildlife Toxicology Division of the Wildlife and Landscape Science Directorate of EC's Science and Technology Branch was tasked specifically with developing comparative environmental risk assessment tools for pesticides in support of standard development. As is the case with previous analytical reports we have produced in this series (Mineau et al., 2006; Whiteside et al., 2006; Harding et al., 2006), the data and analyses are presented in detail to allow independent verification of the results and of our interpretations of those results.

Although dermal exposure is currently not considered in routine risk assessment, it is known to be important and, possibly, to exceed other routes of exposure under the right conditions. Quelea control with such avicides as fenthion have demonstrated the importance of dermal exposure in birds (Ward and Pope, 1972; Pope and Ward, 1972). The marketing of fenthion and endrin in toxic perches for nuisance bird control (Rid-a-Bird® products) (Hunt et al., 1991) has shown the importance of absorption through the feet. Fowle (1972) was able to induce severe depression in birds through painting their perches with a concentrated solution of phosphamidon. Birds of prey in nut orchards in California are thought to be exposed primarily through their feet (Fry et al., 1998) and it has been shown that residues in feet can be quite persistent and be released over time (Vyas, 2003; Henderson et al., 1994). Mineau et al. (1990) were able to demonstrate a significant degree of cholinesterase depression in birds exposed to a whole body ULV spray of fenitrothion. However, birds in that experiment were able to preen so that some of their exposure was also oral. Driver et al. (1991) working with methyl parathion in a wind tunnel, were able to more clearly separate the various routes of exposure and showed the overwhelming importance of the

dermal route in their experimental setup. In an analysis that will be repeated and expanded below, Mineau (2002) showed that an understanding of the relative dermal toxicity of insecticides was very important in understanding acute impacts in a large sample of field studies. This analysis formed the basis of the risk-based ranking approach proposed for avian wildlife under NAESI (Mineau et al., 2006). This approach is a clear deviation from currently accepted risk assessment procedures that only consider exposure resulting from the consumption of contaminated foodstuffs.

Unlike current mammalian risk assessment procedures, there is no routine testing of pesticide dermal toxicity in birds. Scant published data exist on the dermal toxicity of pesticides to birds. Schafer and colleagues (1973) studied both the oral and dermal toxicity of several cholinesterase-inhibiting insecticides in the house sparrow (*Passer domesticus*) and red-billed quelea (*Quelea quelea*). Dermal toxicity was measured by placing graded concentrations of pesticides on the sparsely feathered skin overlying the pectoralis muscle of immobilized birds. Hudson and colleagues (1979) compared the acute toxicity of pesticides given orally to ducks to that of a solution of the same pesticide placed on their foot and subsequently covered for a 24 hour period. Hudson and colleagues introduced the concept of a Dermal Toxicity Index (DTI), a ratio of the oral to the dermal toxicity of a pesticide to the same species. A variation on this concept was re-named F_{red} (or route equivalence factor) by the USEPA in their most recent draft of level II probabilistic model for pesticide risk assessments (EPA, 2004). Hudson and colleagues showed that pesticides' DTIs varied greatly suggesting that the relative importance of dermal exposure was likely to vary among pesticides (a finding well known from the mammalian literature). They also proceeded to show that the mallard DTI could be predicted from a simple log-log regression of the more readily available DTIs measured in the shaved rat. Mineau (2002) attempted to draw

a similar direct relationship between avian and rat DTIs but obtained a poor relationship. A model incorporating the rat data but also including several physico-chemical constants, notably Log Kow, molecular weight and molecular volume fared better and this model became the way in which avian DTIs were computed. Determining avian DTIs was shown to be very important because it explained a great deal of the variance in short term avian mortality seen in pesticide field trials.

It has now become necessary to re-visit the concept of dermal exposure and toxicity in birds because of several reasons:

- It has become abundantly clear that this is necessary to an understanding of pesticide risk and that, without this consideration, the current risk paradigm is inefficient and costly in terms of mistakes (the number of false positives and false negatives at review time – Mineau and Whiteside, 2005). The need to consider dermal exposure has been endorsed by every expert group in avian toxicology assembled over the last decade (e.g., OECD, 1996; Hart et al., 2001).
- New dermal toxicity data generated by Schafer and colleagues and hitherto buried in USDA archives were recently published (Schafer and Bowles, 2004) thereby more than doubling the available sample for analysis (by the addition of 51 new oral/dermal comparisons). In order to clarify some of the entries, electronic records were obtained from USDA files and some of the raw data manually checked (John Eisemann, personal communication).
- Some of the experimental organophosphorus compounds from either the published or unpublished USDA records were identified and, from their 'SMILES' notations, some

physico-chemical properties were derived. This added a few more data points also. (The author is grateful for the assistance of profs. Gerrit Schüürmann and Ralf-Uwe Ebert in this matter).

- The DTI models developed by Mineau (2002), although still adequate to help with explaining the field data (i.e., better than nothing), suffered from low r^2 values and relied on correlated variables (i.e., molecular weight and volume). In addition, the models relied on an archaic measure of molecular volume (the Le Bas method). This proved impossible to apply to complicated molecules – e.g., new chemistry pesticides. Also, other QSAR methods of calculating molecular volume met with poor success when substituted in the model estimating DTI.

- The USEPA (2004), in a re-analysis of avian oral and dermal data which included some unpublished data by Schafer (in addition to the two published sources available to Mineau, 2002) were unable to predict DTI with either Log K_{ow}, molecular weight or their measurement of molecular volume. Subsequent analyses of EPA's enhanced dataset (Mineau and Weber unpublished) showed that it was the addition of those new data points which caused problems with the existing models.

1.1 Assembling a new data set

The data used for the new analyses are summarised in the following series of tables.

1.1.1 Pesticide-specific properties

Appendix A gives the basic toxicological and physico-chemical properties of the various pesticides. Because of the increased sample size, I was now able to separate compounds into either direct or indirect toxicants. This determination was made based on the available

toxicological literature and reflects whether the compound needs bioactivation (e.g., conversion to the oxon form in the case of some OPs such as phosphorothioates) to its more toxic form. I surmised that we should obtain the best relationship between DTI and dermal absorption potential for those pesticides not needing any activation, most of which likely takes place in the liver.

Log Kow was determined by means of Syracuse Research Corporation's (SRC) Kow win version 1.67. For comparison, experimentally determined values are also given. Those values chosen by the SRC for their web site are given here unreferenced.

Molar volume values as determined by Mineau (2002) using the Le Bas method are provided for reference. However, as mentioned above, this method was abandoned. Another QSAR package (SPARK at http://ibmlc2.chem.uga.edu/sparc/index.cfm was used to estimate molar volume). This can be done either through entry of the appropriate CAS# or from a SMILES notation. Both methods were used.

Finally, Log vapour pressure, melting point and specific density were obtained mostly from Tomlin (2004). When no value was available, they were estimated with SRC's Mpbpvp software. Note that calculated melting point values especially are suspect because of the apparent discrepancy between empirically derived values and calculated ones. The problem is particularly apparent for pesticides that are liquid at room temperature.

1.1.2 QSAR-based predictors of dermal absorption in mammals

Dermal absorption in mammals (either in vivo or from skin preparations in vitro) has always been measured directly, and a relative toxicity approach as described above (measuring DTI) is simply not encountered in the mammalian literature. Acute toxicity studies are not generally used to estimate skin absorption (WHO, 2006). Oral gavage doses result in very rapid absorption and

peak concentrations in the body whereas dermal doses result in typically more gradual loading. Differences in toxicity between the two routes could therefore reflect a differential 'first pass handling' of the pesticide rather than dermal penetration alone. Yet, because acute exposure measures (including differential handling and toxicity of peak vs. diffuse doses) are highly relevant to our attempts at modeling lethality in field studies, the DTI is kept in this analysis.

Common wisdom is that the stratum corneum, the skin's outer lipid rich layer is the least permeable and rate limiting, and that the movement of chemicals through this layer is subject to a passive, concentration-driven process derived by Fick's first law, namely:

> Steady state flux = Kp (a permeability constant) * C (the concentration of the chemical in the solute)

Kp or the skin permeation coefficient is expressed in cm or μm/hr. This is a simplistic approach which ignores the effect of the solute on permeability (e.g., the nature of pesticide formulations), as well as any interaction of the pesticide with the sub-dermal lipid layer (i.e., storage and long term release). In mammals, the continued release of pesticides from the skin has been demonstrated, both *in vivo* in the rat (Zendzian, 2003) and *in vitro* with human skin in static diffusion cells (Nielsen et al., 2004). The lag time between initial exposure and skin penetration has been demonstrated empirically for a number of pesticides (Nielsen et al., 2004). In birds, it is known that the foot can act as a long term reservoir of dermally-applied pesticides (Vyas, 2003; Henderson et al., 1994) and there is no reason to think that this does not apply to other parts of the body also. The resulting departures from linearity in the relationship between flux and systemic chemical concentration do cast some doubts about whether Kp can be used confidently in risk assessment (Buist et al., 2005). Nevertheless, there has been a great deal of work done in trying

to predict Kp from a number of physicochemical constants – QSPR approaches (quantitative structure permeability relationships) (see Moss et al., 2002 and WHO, 2006 for useful reviews).

QSPR approaches very early zeroed in on two molecular descriptors: the octanol/water partition coefficient (typically Log Kow) as well as a descriptor of molecular size (molecular volume, molecular weight, molecular weight raised to a power or 'corrected' for specific gravity). Log Kow relates to the partitioning of the chemical from an aqueous solution into the stratum corneum while molecular size describes the ease with which the chemical can diffuse across a barrier. This literature was the source of inspiration for the initial avian DTI determinations in Mineau (2002). Both of these molecular descriptors are used often in multiple regression models to explain empirical *in vivo* or *in vitro* results (e.g., Cronin et al., 1999; Fujiwara, 2003). Yet, there is some concern that the effects of these two descriptors on Kp may not be linear or even monotonic (Bunge and Cleek, 1995; Nielsen et al., 2004). Also, some of the analyses, notably that of Cronin et al. (1999) was found to be in error because it mistakenly included QSAR-derived data with empirical data thereby making the resulting models partially circular (WHO, 2006). Other researchers have had some success in using Log Kow only but within several arbitrarily-defined molecular size classes (e.g., Kirchner et al., 1997). It is notable that the EU has applied assumptions of reduced dermal penetration to compounds (10% rather than the worst case 100%) with Kow values of less than -1 and more than 4, or for compounds with MW greater than 500 reflecting the non-linearity of dermal absorption over the wider range of lipophicity and molecular size (WHO, 2006).

A third descriptor, hydrogen-bonding capacity, was found to help in the prediction of Kp (Potts and Guy, 1995; Fu, 2004). Unfortunately, hydrogen-bonding capacity is difficult to determine

and existing QSAR models have not been validated for large complex molecules. I therefore elected to stay away from models requiring hydrogen-bonding capacity. I attempted collecting melting point data because the latter is related to hydrogen bonding capacity (Moss et al., 2002). Unfortunately, this information is seldom available for liquid pesticides and attempts to use QSAR methods revealed very large estimation errors.

Finally, Patel and colleagues (in WHO, 2006) used yet two other QSAR descriptors in addition to Kow and MW: the sum of absolute charges on oxygen and nitrogen atoms as well as the sum of E-state indices for all methyl groups. They claimed an r^2 of 0.9 with these 4 parameters.

Adding more 'lipid to the fire', Magnusson and colleagues (2004) found that maximal chemical flux (Jmax in moles per cm2 per hour), arguably a more important value for risk assessment purposes than Kp, was related to MW only and that Log Kow had but a marginal effect. This plethora of approaches allows us to compute a number of potential predictors of dermal absorption from aqueous solutions in mammals.

Based on my review of the literature, I opted for the following QSPR algorithms for an estimation of Kp:

(a) $\text{Log Kp} = -2.72 + 0.71 \log \text{Kow} - 0.0061 \text{ MW}$ **Equation 1**

(From SRC's DERMwin program version 1.43. This algorithm has the same coefficients but a different intercept than the first such equation derived by Potts and Guy from a compilation of empirical data by Flynn; as cited in Moss et al., 2002)

$\text{Log Kp} = -1.551 + 0.4814 (\log \text{Kow}) - 0.1434 (\text{MW}^{0.5})$ **Equation 2**

(Derived by Wilschut and colleagues (1995) using the original Potts and Guy (1992) algorithm but subsequently modified to use MW raised to the 0.5 rather than the raw MW. These authors investigated 5 different regression-based models which they tested against a dataset of 123 measured permeation coefficients from aqueous solutions (99 different chemicals) for *in vitro* human skin preparations. Of the 5 models examined, I retained this 'modified' Guy and Potts model because it was both one of the simplest and best performing models.)

(b) $\text{Log Kp} = -2.23 + 0.815 (\log \text{Kow}) - 0.011 \text{ MW}$ **Equation 3**

(From Moody and MacPherson (2003). This represents a recent analysis of the available data by Canadian researchers.)

In addition, I computed the following QSPR estimate of Jmax as described by Magnusson et al. (2004):

$\text{Log Jmax} = -4.52 - 0.0141 \text{ MW}$ **Equation 4**

1.1.3 Avian toxicity data

Sources of avian toxicity were mentioned earlier, either the two older sources (Schafer et al., 1973; Hudson et al., 1979) or the new data in Schafer 2004 supplemented by USDA records). The data are summarised in Appendix B. Oral to dermal comparisons were found for several bird species: the budgerigar, mallard duck, red billed quelea, red-winged and tricolored blackbird, European starling, and house sparrow. Carriers and solvents are listed but a certain degree or uncertainty surrounds tests performed by Schafer and colleagues (data sources a and c in Appendix B). Earlier publications by that group make it clear that, although methods were

standardised so that propylene glycol was used preferentially for oral delivery and acetone solutions dried in a stream of air for dermal exposures, methods could occasionally vary and propylene glycol was occasionally replaced by gelatine capsules etc.. A notable difference between the data of Schafer and colleagues, and that of Hudson et al. (source b in Appendix B) is that the latter used corn oil or propylene glycol as a solvent for dermal exposures and wrapped the site of exposure (the mallard foot) with plastic for a 24 hour period, after which the foot was rinsed off. The increased hydration of the skin resulting from occlusion patches is known to affect dermal absorption (WHO, 2006). For dermal tests carried out by Schafer and colleagues (refs. a and c), the site of dermal application was either the sparsely feathered under wing area of the breast or the foot pad. The solvent was usually acetone, evaporated under an air stream. As such, these methods more closely resemble methods used by Gaines and colleagues in the rat (see below). It should be noted that tests carried out by Schafer and colleagues relied on an up and down design with only two birds tested at each dose level. Also, survivors were recycled into the test population after a two week period of rest. Values are therefore approximate.

1.1.4 Mammalian Toxicity data

Because of the paucity of avian dermal toxicity data but the considerable amount of information available for mammals, it has always been tempting to use the mammalian data to make inferences in birds. This was behind Hudson and colleagues' attempts to compare the avian DTI to the rat DTI. The rat is the species most often used for dermal toxicity assessment, followed by the rabbit. I assembled rat oral and dermal data for those pesticides represented in the avian data set. As part of the broader NAESI objectives (Mineau et al., 2006), we are in the process of assembling a database of mammalian acute toxicity data. It became apparent that variations in both oral and dermal toxicity measurements were often considerable, throwing doubts on the

choice of specific values for the determination of a DTI. As a result, I started by revisiting the choice of oral and dermal values used in Mineau (2002) and replacing them to reflect common sources and methodology as much as possible. Data generated by Gaines (1969) were given priority over other sources. Gaines made it clear that his goal had been to generate data under the most standardised and comparable conditions possible. In most cases, he used peanut oil as the carrier for oral dosing and the compounds were dissolved in xylene for dermal application. Dermal applications were made to shaved skin on the back of the animals but there was no occlusion post exposure. This method of exposure best resembles the exposure method of Schafer and colleagues in birds. Because sexes are often tested separately in rats, I opted to calculate separate male and female DTI values when possible and then to use the geometric mean of the two DTI values where both were available. The data reported here represent uncorrected values obtained for the technical grade of the material, a situation analogous to the testing carried out by either Schafer and colleagues or Hudson and colleagues in birds. When data were unavailable from Gaines, I used data from such compendia as RTECS, INCHEM or pesticide manual (Appendix C).

1.1.5 Data gaps

Several data gaps are evident from Appendices 1-3. Any data contributions to fill these gaps would be appreciated.

1.2 Results and analyses

1.2.1 Different species tested with the same pesticide.

The availability of several DTI values for the same pesticide but different species allows us to look at the 'stability' of DTI values. Because of a potentially confounding effect of metabolism, the first analysis is restricted to only direct toxicants tested underwing. The available data consist

of 8 pairs of measured DTIs (Table 1).

Table 1: DTI values for direct toxicants calculated for the same pesticide but different species.

CHEMICAL	SPECIES	AVIAN DTI
Carbofuran	House Sparrow	1.11
Carbofuran	Quelea	0.62
Dicrotophos	House Sparrow	3.37
Dicrotophos	Quelea	3.00
Endrin	Red-wing	2.78
Endrin	Starling	2.94
Ethyl DDVP	Red-wing	2.25
Ethyl DDVP	Starling	1.76
Methamidophos	Red-wing	1.75
Methamidophos	Starling	2.75
Monocrotophos	House Sparrow	1.86
Monocrotophos	Quelea	2.49
Oxydemeton-methyl	Red-wing	2.63
Oxydemeton-methyl	Starling	3.13
Phosphamidon	Red-wing	3.12
Phosphamidon	Starling	3.00

Based on that dataset, a single factor ANOVA with pesticide as independent variable is highly significant ($p=0.004$) despite the random error associated with the repeat measures in different species.

Slightly more data are available for indirect toxicants. Again, only under-wing data are compared (Table 2).

Table 2: DTI values for indirect toxicants calculated for the same pesticide but different species.

CHEMICAL	SPECIES	AVIAN DTI
Bay 50519	House Sparrow	2.88
Bay 50519	Quelea	2.88
Coumaphos	House Sparrow	2.12
Coumaphos	Quelea	2.63
Demeton	House Sparrow	2.63
Demeton	Quelea	2.86
Disulfoton	Red-wing	3.51
Disulfoton	Starling	4.00
Fensulfothion	House Sparrow	2.51
Fensulfothion	Quelea	2.76
Fensulfothion	Red-wing	2.88
Fensulfothion	Starling	2.24
Fenthion	House Sparrow	3.37
Fenthion	Quelea	2.86
Fenthion	Red-wing	2.94
Fenthion	Starling	2.56
Isocarbophos (optunal)	House Sparrow	2.49
Isocarbophos (optunal)	Quelea	2.76
Isofenfos	Red-wing	2.63
Isofenfos	Starling	2.87
Methidathion (supracide)	Red-wing	2.62
Methidathion (supracide)	Starling	2.26
Parathion	House Sparrow	2.86
Parathion	Quelea	3.00
Parathion	Red-wing	3.12
Parathion	Starling	3.52
Prophenofos	Red-wing	2.44
Prophenofos	Starling	1.62

Once again, a one way ANOVA is able to distinguish a clear pesticide effect ($p=0.0025$) despite the error associated with the repeat measures.

In neither case is a species effect significant as judged by a two way main effects ANOVA for chemical and species. This was somewhat unexpected because at least one of the species tested (the European starling) is known to differ markedly in its toxic response to cholinesterase-inhibiting insecticides. There would therefore have been reason to suspect a differential ratio of oral to dermal toxicity with those chemicals needing liver activation because this is a likely source of interspecific variation in pesticide susceptibility.

On an individual compound basis, however, the error can be large as shown by the two methamidophos measurements. Too few foot measurements are available to do the same inter-species comparison.

1.2.2 Different dermal exposure sites and methods for the same species and chemical

Using only those tests where the pesticides were dissolved in acetone before being applied (the work of Schafer and colleagues) we can compare the toxicity of pesticides when applied to two different sites, the foot or underwing area (Table 3).

Table 3: toxicity of pesticides when applied to two different sites on the bird

Species	Chemical	Log Foot LD50	Log Under-wing LD50
RWBB	CPT	1.75	0.73
EUST	CPT	1.40	0.78
RBQU	CPTH	1.62	1.52
EUST	CPTH	1.90	1.55
RWBB	Endrin	0.75	0.60
EUST	Endrin	1.75	0.51
RWBB	Ethyl DDVP	1.62	0.75
EUST	Ethyl DDVP	1.88	0.75
EUST	Fenthion	1.77	1.42

Based on this limited (and heavily pseudo-replicated) data set and subject to the exact methods used by the experimenters, it appears that the under-wing area was more efficient than the foot for dermal absorption although the relationship is not predictable (linear regression N.S.).

In order to more fully evaluate the three methods used by investigators in measuring dermal toxicity in birds, species data were collapsed (species does not seem to be important to the determination of the DTI - see above) and a single (mean) DTI was generated for each pesticide and the three main test conditions: application in acetone to the foot, application in acetone to the under-wing, and application in propylene glycol or corn oil followed by occlusion (the mallard foot only) (Table 4).

Table 4: Mean DTI averaged across bird species for each pesticide and the three main test conditions: application in acetone to the foot, application in acetone to the under-wing, and application in propylene glycol or corn oil to the foot followed by occlusion.

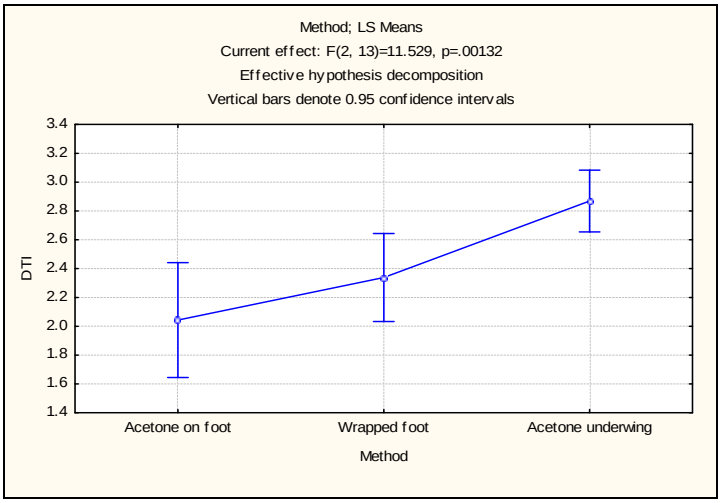
Chemical	Acetone on foot	Acetone on underwing	Propylene glycol (or corn oil) and wrapped foot
CPT	1.69	2.82	
CPTH	2.22	2.65	
Demeton		2.75	2.48
Dichlorvos	2.68	3.50	
Dicrotophos		3.18	2.48
Disulfoton		3.75	2.55
Endrin	2.16	2.86	
Ethyl DDVP	0.63	2.00	
Fenitrothion		2.76	3.37
Fensulfothion		2.60	2.42
Fenthion	2.21	2.93	2.13
Monocrotophos		2.17	2.20
Parathion		3.13	1.92
Phosphamidon		3.06	2.17

The unbalanced design of the matrix prevents us from looking at chemical-method interaction (which is undoubtedly critical) but a main effects ANOVA does indicate that the method of DTI determination is critical. This remains a crude analysis (Table 5; Figure 1) because the data have not been weighted to reflect the fact that some of the values are single data points while others are means with attending variance terms.

Table 5: Results of a main effect two-way ANOVA looking at the effect of chemical and application method on the calculation of avian DTI.

Effect	Univariate Tests of Significance for DTI (Methods comparison.sta) Sigma-restricted parameterization Effective hypothesis decomposition				
	SS	Degr. of Freedom	MS	F	p
Intercept	143.8990	1	143.8990	1043.758	0.000000
Chemical	4.8764	13	0.3751	2.721	0.041299
Method	3.1788	2	1.5894	11.529	0.001319
Error	1.7923	13	0.1379		

Figure 1: Least square mean estimates of the application method for the ANOVA in Table 5.



A Fisher's LSD post hoc test suggests that DTI estimations from the three main test methods should probably not be combined or at least that method should be entered as a variable in any subsequent analysis. The under-wing test with an acetone solution appears to lead to the most absorption. Whether the chemical is applied in acetone and allowed to air dry or as a covered patch in corn oil or propylene glycol appears to be less important than the site of application.

Therefore, if DTI data are to be combined in the same analysis, should be corrected to reflect application method, using the least square mean estimates obtained here (table 6).

Table 6: Least mean square estimates of application method for the available DTI data. AF: application in acetone to the foot; AU: application in acetone to the under-wing; PGF: application in propylene glycol or corn oil to the foot followed by occlusion.

Method	DTI mean	DTI Std. Error	DTI -95%	DTI +95%	N
AF	2.042776	0.184442	1.644313	2.441239	6
PGF	2.338515	0.141135	2.033612	2.643417	9
AU	2.868571	0.099235	2.654187	3.082956	14

By correcting individual data for test method and averaging among species for any given pesticide, it is possible to generate a single standardised DTI value for each pesticide. This is presented in the table below (table 7), bringing all values in line with underwing acetone measurements.

Table 7: Single standardised DTI value for each pesticide adjusted to reflect an underwing acetone measurement.

CHEMICAL	Single standardised DTI per chemical	Direct or indirect toxicant
3-chloro-p-toluidine (CPT)	2.60	
3-chloro-p-toluidine hydrochloride (CPTH; starlicide; DRC-1339))	2.89	
Aldicarb	2.28	D
Azinphos-methyl	2.97	I
Bay 50519	2.88	I
BAY-COE 3664	2.94	
BAY-COE 3675	2.44	
Carbofuran	0.87	D
Coumaphos	2.38	I
Demeton	2.81	I
Dichlorvos	3.63	D
Dicrotophos	3.12	D
Disulfoton	3.45	I
Endosulfan	3.12	D
Endrin	2.96	D
EPN	1.78	I
Ethamphenphion (O-O-Diethyl O-(2-diethylaminomethyl-4-methyylsulphinylphenyl) phosphorothioate)	2.79	I
Ethoprop (ethoprophos)	3.61	I
Ethyl DDVP	1.81	D
Fenamiphos	2.38	D
Fenitrothion	2.96	I
Fensulfothion	2.38	I
Fenthion	2.76	I
Isocarbophos (optunal)	2.63	I
Isofenfos	2.75	I
Methamidophos	2.25	D
Methidathion (supracide)	2.44	I
Methiocarb	1.62	D
Methyl Parathion	3.58	I
Mevinphos	3.15	D
Monocrotophos	2.31	D
Oxydemeton-methyl	2.88	D

Table 7: Single standardised DTI value for each pesticide adjusted to reflect an underwing acetone measurement.

CHEMICAL	Single standardised DTI per chemical	Direct or indirect toxicant
Paraquat Dichloride	3.05	D
Parathion	2.88	I
Phorate Thimet	1.63	I
Phosphamidon	2.97	D
Phosphorothioic acid, O-(3,5-dimethyl-4-(methylthio)phenyl) O,O-dimethylester	3.08	I
Prophenofos	2.03	I
Propoxur (Baygon)	2.15	D
Sulprofos (Bolstar)	2.94	I
TEPP	2.28	D
Thionazin (nemaphos)	2.91	I

1.2.3 Bird-rat comparisons

For the comparison of bird and rat data, average avian DTI values were used provided they were determined by the same method. This means that some of the points in the following regressions are means rather than single values. However, I felt this was preferable to pseudoreplicating those pesticides for which several species were tested. The rat DTI values are either the result of a single test on one sex only or the geometric mean of male and female DTI values where both sexes were tested and reported. The data are shown in table 8.

Table 8: Available comparative data for bird and rat data.

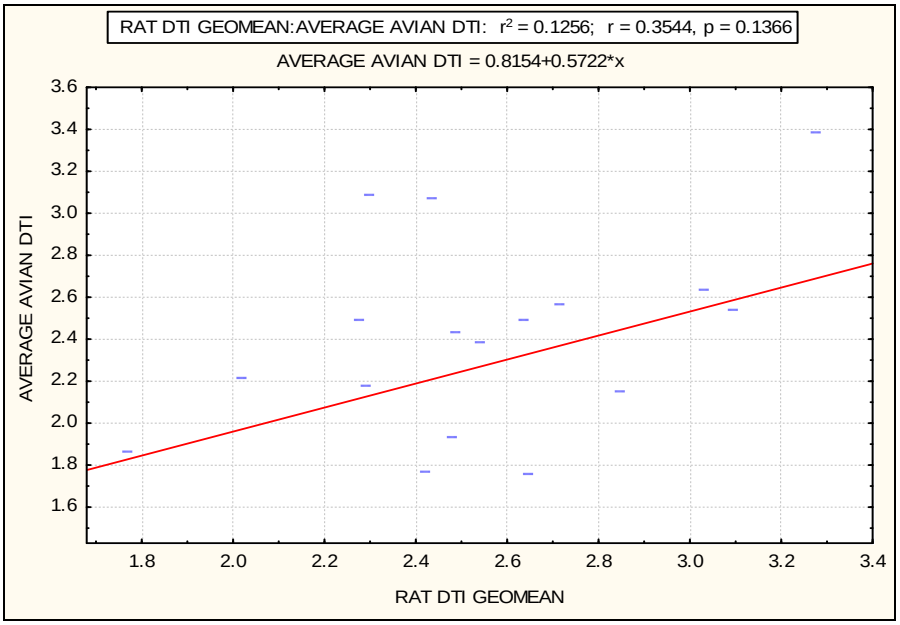
Pesticide	Direct or Indirect toxicant	Site of dermal testing	Solvent	Avian DTI (averaged for all tested species)	Rat DTI (geomean of two sexes)
Aldicarb	D	Foot	Propylene glycol	1.75	2.42
Azinphos-methyl	I	underwing	Acetone	2.97	1.73
Carbofuran	D	underwing	Acetone	0.87	0.64
Coumaphos	I	underwing	Acetone	2.38	1.68
Demeton	I	foot	Corn oil	2.48	2.28
Demeton	I	underwing	Acetone	2.75	2.28
Dichlorvos	D	foot	Acetone	2.68	2.87
Dichlorvos	D	underwing	Acetone	3.50	2.87
Dicrotophos	D	foot	Propylene glycol	2.48	2.63
Dicrotophos	D	underwing	Acetone	3.18	2.63
Disulfoton	I	foot	Corn oil	2.55	2.71
Disulfoton	I	underwing	Acetone	3.75	2.71
Endosulfan	D	underwing	Acetone	3.12	2.45
Endrin	D	foot	Acetone	2.16	2.85
Endrin	D	underwing	Acetone	2.86	2.85
EPN	I	foot	Corn oil	1.25	2.34
Ethoprop (ethoprophos)	I	foot	Corn oil	3.08	2.30
Fenamiphos	D	foot	Corn oil	1.85	1.77
Fenitrothion	I	foot	Corn oil	3.37	3.27
Fenitrothion	I	underwing	Acetone	2.76	3.27
Fensulfothion	I	foot	Propylene glycol	2.42	2.48
Fensulfothion	I	underwing	Acetone	2.60	2.48
Fenthion	I	foot	Acetone	2.21	2.84
Fenthion	I	foot	Corn oil	2.13	2.84
Fenthion	I	underwing	Acetone	2.93	2.84
Isocarbophos (optunal)	I	underwing	Acetone	2.63	1.93
Isofenfos	I	underwing	Acetone	2.75	2.46
Methamidophos	D	underwing	Acetone	2.25	2.32
Methidathion (supracide)	I	underwing	Acetone	2.44	1.94
Methiocarb	D	underwing	Acetone	1.62	1.51

Table 8: Available comparative data for bird and rat data.

Pesticide	Direct or Indirect toxicant	Site of dermal testing	Solvent	Avian DTI (averaged for all tested species)	Rat DTI (geomean of two sexes)
Methyl Parathion	I	foot	Corn oil	3.05	2.43
Mevinphos	D	foot	Propylene glycol	2.62	3.03
Monocrotophos	D	foot	Propylene glycol	2.20	2.01
Monocrotophos	D	underwing	Acetone	2.17	2.01
Oxydemeton-methyl	D	underwing	Acetone	2.88	2.48
Paraquat Dichloride	D	foot	Propylene glycol	2.52	3.09
Parathion	I	foot	Corn oil	1.92	2.48
Parathion	I	underwing	Acetone	3.13	2.48
Phorate Thimet)	I	foot	Corn oil	1.10	2.61
Phosphamidon	D	foot	Propylene glycol	2.17	2.29
Phosphamidon	D	underwing	Acetone	3.06	2.29
Prophenofos	I	underwing	Acetone	2.03	2.35
Propoxur (Baygon)	D	underwing	Acetone	2.15	1.55
Sulprofos (Bolstar)	I	underwing	Acetone	2.94	1.97
TEPP	D	foot	Propylene glycol	1.75	2.64
Thionazin (nemaphos)	I	foot	Corn oil	2.38	2.54

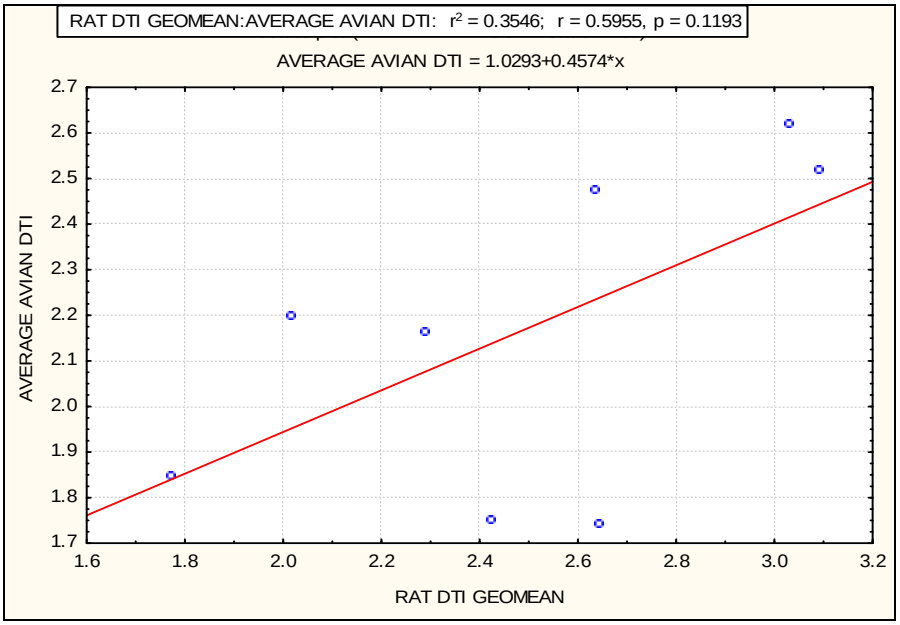
Initially, I attempted to replicate the regression analysis of Hudson and colleagues for their data set on the mallard foot with the pesticide dissolved either in corn oil or propylene glycol on an occluded patch (Figure 2). As in my previous effort (Mineau, 2002), this did not yield a very good regression. It is not clear why the original relationship shown by Hudson and colleagues could not be duplicated. These authors do not provide the mammalian oral and dermal values used although their sources are the same (e.g., primarily Gaines, 1969).

Figure 2: Rat vs. bird DTI for all mallard foot values (an attempt to repeat the analysis of Hudson et al. 1979)



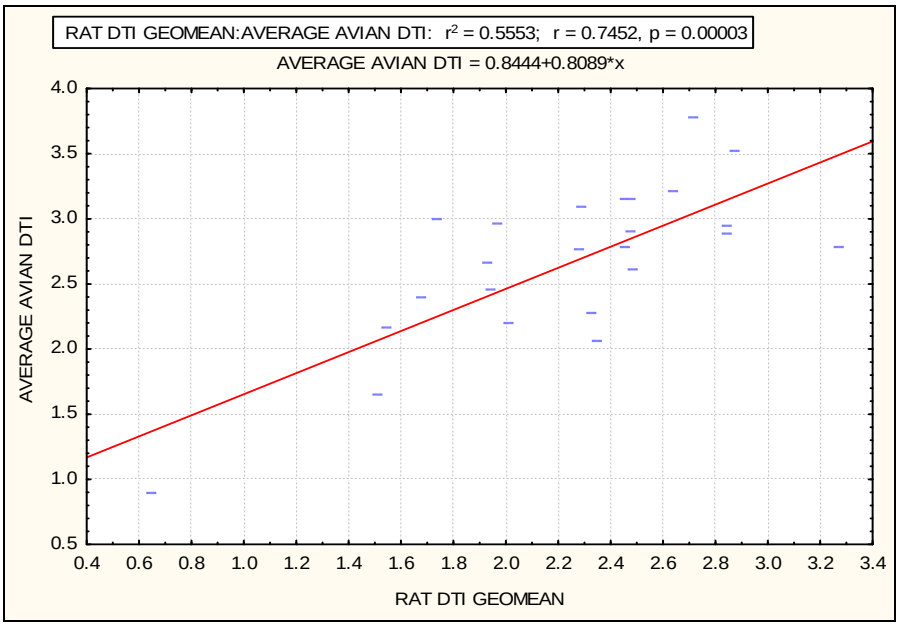
I then plotted only those products that are direct toxicants (Figure 3). The logic here is that given the metabolic differences between birds and rats, the extent to which the dermal toxicity of a pesticide will compare to its oral toxicity is dependent not only on its absorption through the skin but also on how it is handled, activated, metabolised etc.. Restricting the analysis to direct toxicants minimizes the importance of metabolic differences between birds and rats. The overall fit of the relationship is improved minimally but still poor overall.

Figure 3: Rat vs. avian DTI for data on the wrapped mallard foot for directly acting toxicants only.



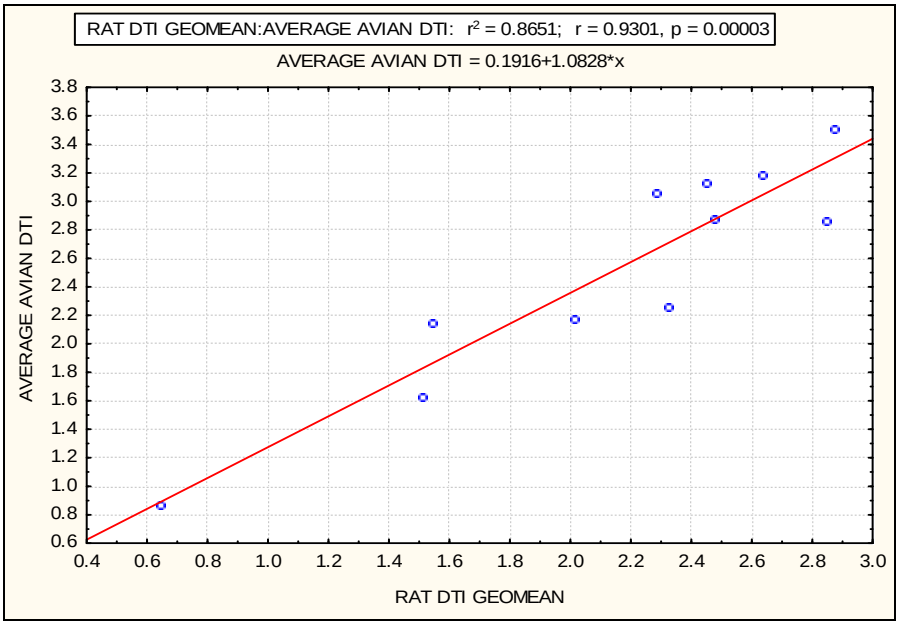
The largest dataset consists of the under-wing data of Schafer and colleagues. Also, in terms of methodology, this is the data most comparable to the rat data of Gaines and others. I compared the under-wing data with the rat data (Figure 4). The overall fit was much improved with an r^2 value of 0.55.

Figure 4: Rat vs. bird DTI for all under-wing test data.



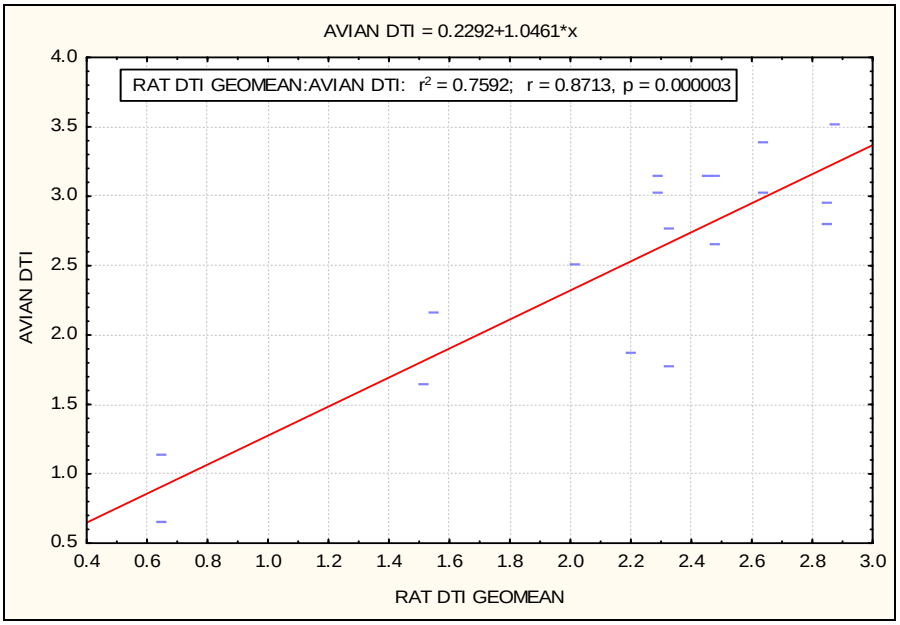
Finally, as predicted above, the best fit of all was obtained when the under-wing data were restricted to the direct toxicants only (Figure 5). Despite the more limited sample of pesticides, the r^2 value reaches 0.86.

Figure 5: Rat vs. bird DTI for under-wing test data with direct-acting pesticides only. Only one average avian DTI value per pesticide only.



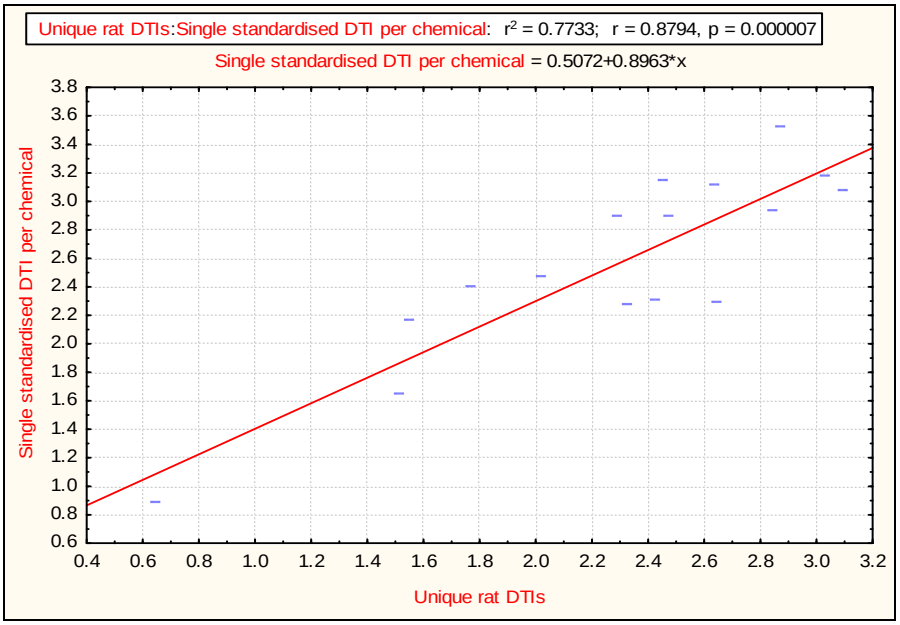
This relationship is still excellent if I relax the rules about pseudo-replication of the rat data and allow all original under-wing avian DTI measurements for direct toxicants into the analysis (Figure 6).

Figure6: Rat vs. bird DTI for under-wing test data with directly-acting pesticides only. All avian DTI values – i.e., >1 species represented for some pesticides.



Finally, the relationship is still excellent when we consider the totality of avian dermal data (for all direct-acting pesticides) adjusted for method as described earlier. This increases the available sample of pesticides to 16 molecules.

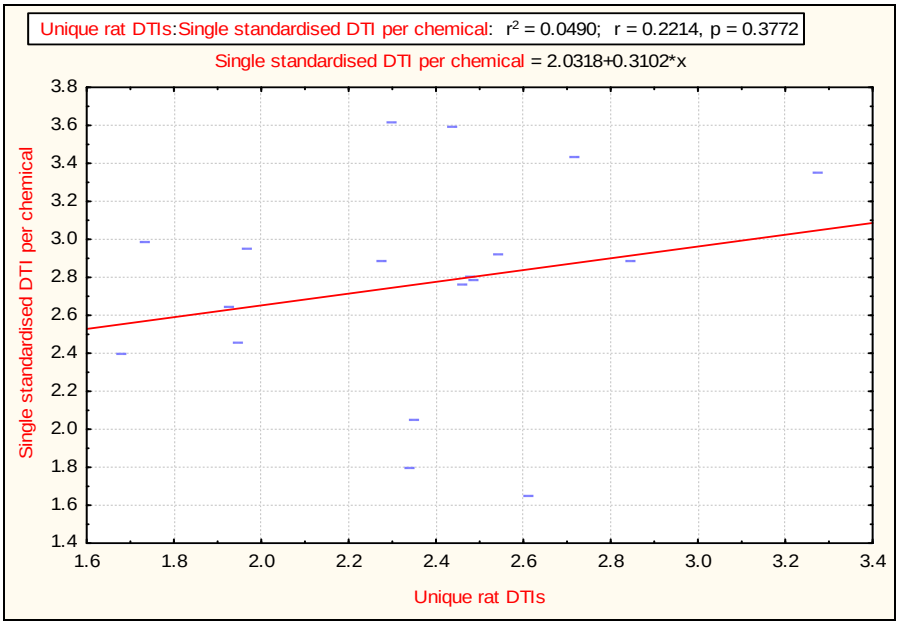
Figure 7: Standardised avian DTI values (as per table 7) against rat DTI values for all direct-acting pesticides.



Not surprisingly, with so much of the variation explained, the relationship between rat and bird DTI with direct toxicants is not significantly improved by consideration of physico-chemical constants. However, as seen below, at least two constants are almost significant and can increase overall model fit beyond the current r^2 of 0.77.

Note that the equivalent plot for indirect toxicants does not offer any relationship between rat and bird.

Figure 8: Standardised avian DTI values (as per table 7) against rat DTI values for all indirect-acting pesticides.



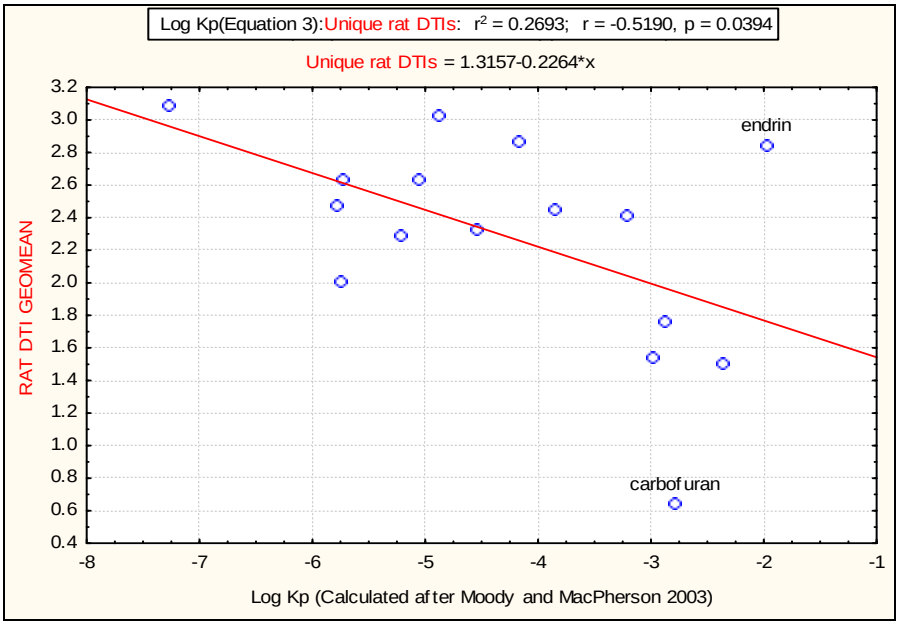
This suggests that, despite notable differences in avian and mammalian skin, both appear to obey the same fundamental properties when it comes to absorption – at least for pesticides in the range of physico-chemical properties studied here and for pesticides initially dissolved in a solvent. This sample includes the methyl carbamates carbofuran, methiocarb and propoxur, the organophosphates dichlorvos, dicrotophos, methamidophos, monocrotophos, oxydemeton methyl and phosphamidon, as well as the organochlorine pesticides endosulfan and endrin – a reasonably broad range of molecular structures and properties.

These results further suggest that it should be possible to use data generated from mammalian skin models (see above) to predict dermal absorption in birds. How the pesticide is handled once it enters avian tissue is undoubtedly much more chemical and species dependant but, at least, we should be able to better estimate how much gets into the bird by using mammalian skin

penetration information.

Disappointingly, none of the algorithms for the measurement of Kp were entirely satisfactory for predicting the rat DTI, even in the case of direct toxicants. Nevertheless, the maximum r^2 was 0.27 ($p = 0.039$) for the Kp estimate calculated from Moody and MacPherson (2003) – equation 3 above. The relationship is plotted in Figure 9. Two pesticides appear to be clear outliers: carbofuran and endrin as indicated in the figure below. The worst fit was with Jmax ($r^2 = 0.04$, $p = 0.41$).

Figure 9: Regression of Kp estimation algorithm (based on Moody and MacPherson, 2003) against rat DTI (geomean of male and female values) for direct toxicants only.

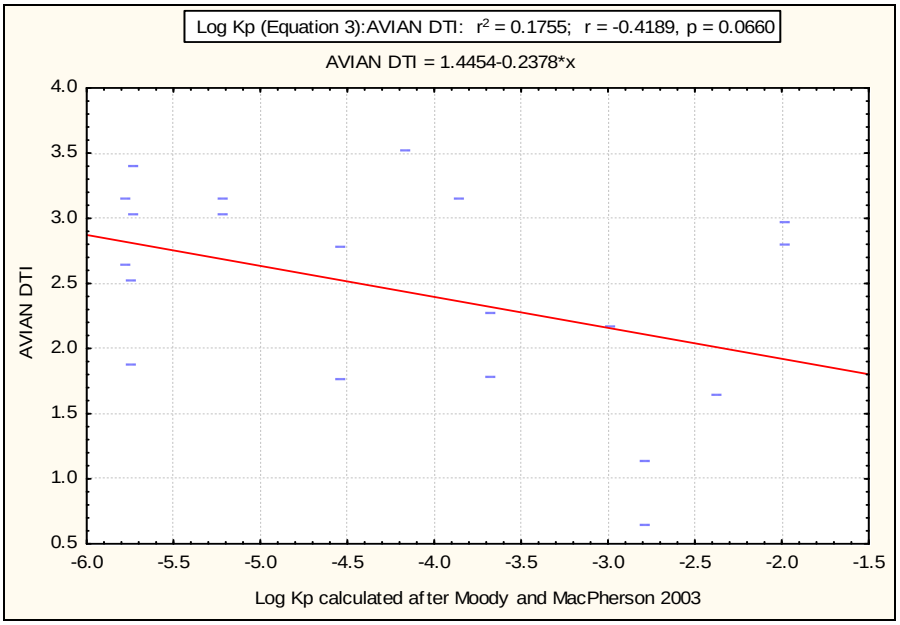


Despite the marginal fit, it is clear that the relationship between estimated Kp and DTI is the inverse of expected. Indeed, a higher Kp (higher dermal penetration) is associated with a lower DTI (reduced dermal toxicity relative to oral toxicity). This will be discussed in greater detail

later.

Not surprisingly, given their mediocre performance at estimating rat DTI values, calculated Kp values are also found wanting for the estimation of avian DTI – even when only direct toxicants and 'underwing acetone' tests are considered, in order to remove as much variability as possible from the dataset (Figure 10). The relationship just misses statistical significance (p= 0.066) but, once again, the relationship between Kp and DTI is counter to the expectation based on mammalian *in vitro* tests.

Figure 10: Regression of estimated from the algorithm of Moody and MacPherson 2003 against all underwing/acetone individual tests for direct toxicants. Note the pseudoreplication because more than 1 species were tested with some of the pesticides represented.



So, we have a situation where relative dermal toxicity (based on avian DTI measures for direct toxicants only so as to minimise pharmacokinetic issues) obtained with a light aromatic solvent

can be reliably predicted from the rat DTI obtained in the same way. However, the predictive power of literature-based QSAR estimators of Kp is much lower. More troubling is the fact that the relationship is counter to expectation for direct toxicants suggesting that smaller lipophilic molecules, despite their higher predicted skin penetration ability are not as acutely toxic as larger water-soluble ones! This apparent contradiction will be discussed in greater detail later.

In light of the poor ability of the 'standard' Kp or Jmax predictors at estimating the relative dermal risk of pesticides (as judged by DTI values), I attempted to derive *de novo* predictors of avian DTIs as was done in Mineau (2002).

2 PREDICTION OF AVIAN DERMAL TOXICITY FROM RAT DATA AND PHYSICO-CHEMICAL PROPERTIES.

2.1 Direct acting toxicants

Because of the limited size of the dataset once direct and indirect toxicants were divided, I used the single standardised DTI value for each chemical, thereby collapsing data across measurement methods.

Possible predictors were various molecular weight (MW & MW^0.5) and volume descriptors, log vapour pressure, and log Kow. Rat DTI values were entered initially but I also tried to define models without rat DTI availability.

The dependant variable (DTI) was found to be roughly normally distributed. In order to guide the choice of variables in further analyses, Aikaike Information Criteria (AIC) were generated for possible competing models (Burnham and Anderson, 2002). Δ AIC values below 2 generally indicate models with a much higher level of empirical support than the rest. Values above 10 suggest that the models have little empirical support relative to the best models. Because the best

model could still explain an insignificant amount of overall variance, the best or chosen models are then put through a normal multiple regression assessment and an r^2 value calculated. For this reason, I chose to not correct AIC values for small sample size in full knowledge that the level of 'penalty' for over fitting a large number of variables is probably insufficient.

Suitable models were restricted *a priori* : either MW, MW^0.5 or MV were accepted in a model but no combination of these in order to avoid model redundancy – one possible weakness of the algorithms in Mineau (2002).

The models with rat data are ranked below (table 9) in decreasing order of plausibility. P values for overall model fit are also provided.

2.1.1 With rat data:

Table 9: Summary of models developed to predict avian DTI values from physico-chemical variables and rat DTI values.

Var. 1	Var. 2	Var. 3	Var. 4	Degr. of	AIC	Delta AIC	L.Ratio	p
MW^0.5	Log_VP	RAT DTI GEOMEAN		3	11.92713	0.00000	26.75121	0.000007
MW	Log_VP	RAT DTI GEOMEAN		3	11.97915	0.05202	26.69919	0.000007
RAT DTI GEOMEAN				1	12.88845	0.96132	21.78988	0.000003
MW^0.5	RAT DTI GEOMEAN			2	13.25806	1.33092	23.42028	0.000008
MW	RAT DTI GEOMEAN			2	13.40313	1.47600	23.27520	0.000009
MV	Log_VP	RAT DTI GEOMEAN		3	13.90220	1.97506	24.77614	0.000017
Log_KOW	MW^0.5	Log_VP	RAT DTI GEOMEAN	4	13.91080	1.98367	26.76753	0.000022
Log_KOW	MW	Log_VP	RAT DTI GEOMEAN	4	13.94799	2.02086	26.73035	0.000023

This analysis reveals the following:

As a descriptor of molecular size M^0.5 as advocated by Wilschut and colleagues (1995) was slightly better than MW although, realistically, the two are so close (Delta AIC of 0.05) as to be indistinguishable. Moody and MacPherson (2003), in their efforts to model an *in vitro* mammalian dataset had found MW to be superior. There does not seem to be any value in computing MV estimates.

Log VP may be an important variable. This is not a variable generally considered in measuring dermal absorption but, we might have predicted that it would be important in predicting the outcome of non-occluded dermal toxicity tests.

With direct-acting toxicants, an estimate of the rat DTI, when available is clearly the most important predictor of avian DTI. Unfortunately, only 16 values are available to model which severely restricts any meaningful model building without the danger of over-fitting the data. As described earlier (see Figure 7), when the best model was entered in a multiple regression (table 10), only the rat DTI was significant at the 0.05 level of significance.

Although, the molecular weight descriptor and log VP both just missed significance, they were left in the final model. However, the coefficients show that they have a much smaller influence overall. Interestingly, log vapour pressure was a better predictor than log Kow.

Table 10. Results of a multiple regression with avian DTI as the dependant variable and rat DTI, MW^0.5 and log VP as independent predictors. (N=16)

	Beta	Std.Err. of Beta	B	Std.Err. Of B	t(12)	p-level
Intercept			-0.711436	0.668503	-1.06422	0.308174
RAT DTI GEOMEAN	0.754190	0.127007	0.792714	0.133495	5.93817	0.000068
MW^0.5	0.281976	0.134580	0.093169	0.044467	2.09522	0.058035
Log_VP	0.259903	0.135414	0.096683	0.050373	1.91932	0.079034

R= .91540781 *R^2= .83797145* *Adjusted R^2= .79746432*

F(3,12)=20.687 *p<.00005* *Std.Error of estimate: .30839*

This provides the following model for direct-acting pesticides for which rat DTI data are available:

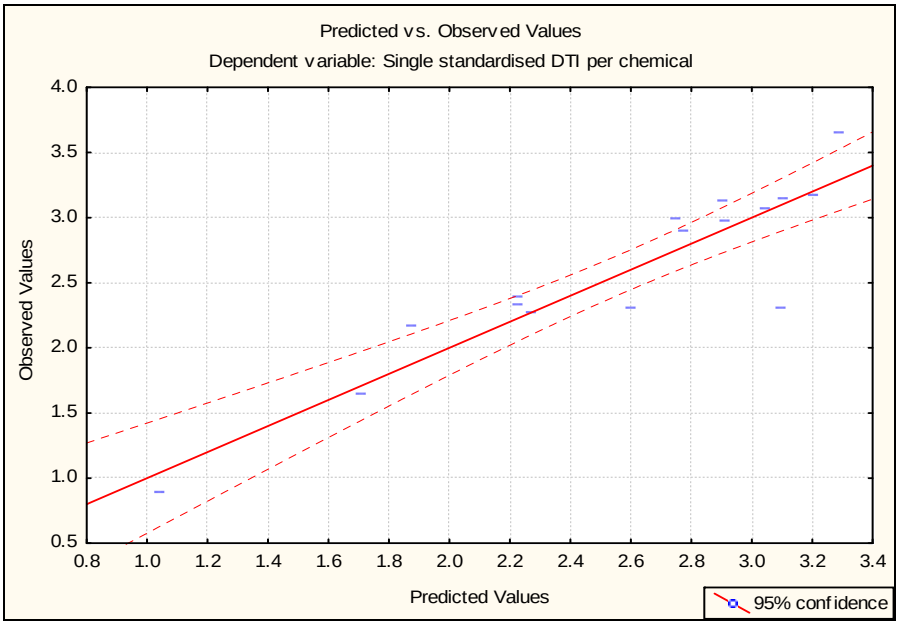
Equation 6

Standardised Avian DTI = -0.711436 + 0.792714 Average rat DTI +0.093169 MW^0.5 + 0.096683 Log Vp*

***** *See above. Standardised to conform to an underwing acetone test.*

The observed to predicted fit for the regression equation is shown below.

Figure 11: Observed vs. predicted values for the multiple regression model predicting avian DTI from the three independent predictors: rat DTI, MW^0.5 and log VP. (N=16)



2.1.2 Without rat data:

In order to build a model without rat data, I initially restricted the data to those physico-chemical Vp values that were known rather than estimated. It was found that Vp dropped out of the best model choices when estimated values were included, suggesting that the problem lay with the estimation of that parameter from the SRC software. Because of the impossibility of obtaining Vp data at a consistent temperature (e.g., 20^{o}C), a certain degree of variability is included in this measure. At this point, values were not corrected but this should be considered as a future improvement should Vp prove critical.

Table 11: Summary of models developed to predict avian DTI values from physico-chemical variables alone.

Var. 1	Var. 2	Var. 3	Degr. of	AIC	Delta AIC	L.Ratio	p
MW	Log_VP		2	27.08027	0.00000	9.59807	0.008238
MW^0.5	Log_VP		2	27.54752	0.46725	9.13082	0.010406
Log_KOW	MW	Log_VP	3	28.01894	0.93867	10.65940	0.013718
Log_KOW	MW^0.5	Log_VP	3	28.70768	1.62741	9.97065	0.018817
MV	Log_VP		2	29.56223	2.48196	7.11611	0.028494

Based on this exploratory analysis, MW, log VP and log Kow were entered in a multiple regression model. Only MW was significant although the other two variables just missed significance ($0.05<p<0.1$). Again, sample size was 16 only. All three variables were kept for the final model (table 12).

Table 12: Results of a multiple regression with avian DTI as the dependant variable and MW, log Kow and log VP as independent predictors. (N=16)

	Beta	Std.Err. Of Beta	B	Std.Err. Of B	t(12)	p-level
Intercept			0.735708	0.619740	1.18712	0.258147
MW	0.772805	0.248280	0.007791	0.002503	3.11263	0.008977
Log_KOW	-0.474738	0.254472	-0.149492	0.080131	-1.86558	0.086726
Log_VP	0.424328	0.231923	0.157848	0.086274	1.82961	0.092250

R= .71471177 *R^2= .51081292* *Adjusted R^2= .38851615*

F(3,12)=4.1768 *p<.03059* *Std.Error of estimate: .53585*

Based on our limited sample of 16 compounds, the regression equation for compounds for which rat oral and dermal data are not available is therefore:

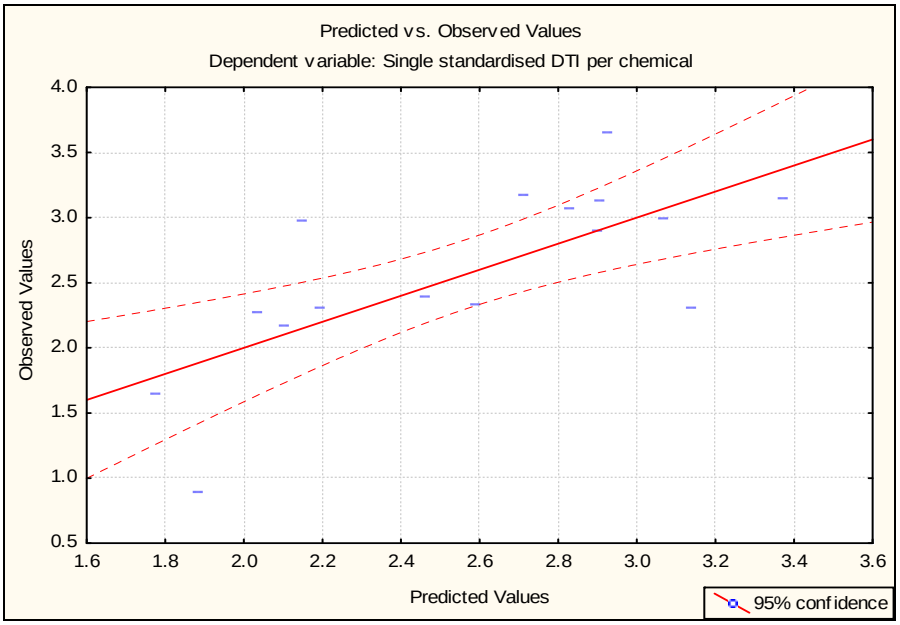
Equation 7

Avian DTI geomean (standardised for underwing acetone tests) = 0.735708 + 0.007791 MW - 0.149492 Log Kow + 0.157848 Log Vp

Model fit is shown in the plot below. Of course, all these plot of observed to predicted are for the training sets only. Data availability is such that model validation is not currently possible except through a 'leave one out cross validation' approach (which has not been done here). In this current analysis, validation of sorts will be through consideration of the field study record, assessing which of the dermal toxicity/penetration measure provides the best fit to the field results.

The form of the final model is consistent with my attempt to relate Kp to relative dermal toxicity (DTI). Compounds which are relatively more hazardous via the dermal than the oral route (i.e., having a higher DTI) tend to be larger and have a lower log Kow. Again, this goes against our initial expectation and will be discussed below.

Figure 12: Observed vs. predicted values for the multiple regression model predicting avian DTI from the three independent predictors: MW, log Kow and log VP. (N=16)



2.2 Indirect-acting toxicants

With indirect-acting pesticides, (N=21 compounds), the rat DTI variable did not make it into the best models (table 13) – as predicted from figure 8 above. The p levels indicate that a model is much more precarious for these compounds.

Table 13: Summary of models developed to predict avian DTI values from physico-chemical variables and rat DTI for indirect-acting compounds. (N=21)

Var.	Var.	Var.	d.f.	AIC	Delta AIC	L.Ratio	p
MW^0.5	Log_VP		2	28.11009	0.00000	6.50064	0.038762
MW	Log_VP		2	28.31833	0.20824	6.29241	0.043015
MW^0.5			1	28.33358	0.22349	4.27715	0.038628
MW			1	28.35300	0.24291	4.25773	0.039072
Log_KOW	MW^0.5	Log_VP	3	29.55008	1.43999	7.06065	0.069990
Log_KOW	MW	Log_VP	3	29.78022	1.67013	6.83051	0.077501

Table 13: Summary of models developed to predict avian DTI values from physico-chemical variables and rat DTI for indirect-acting compounds. (N=21)

Var.	Var.	Var.	d.f.	AIC	Delta AIC	L.Ratio	p
MW^0.5	Log_VP	RAT DTI GEOMEAN	3	29.96405	1.85396	6.64668	0.084054
MW^0.5	RAT DTI GEOMEAN		2	30.12999	2.01990	4.48074	0.106419

On that basis, standard multiple regression was attempted with MW^0.5 and log VP as predictors (table 14). The molecular size factor was significant, Log VP just missed significance. The overall model just missed significance and only 20% of the variance was explained overall.

Table 14: Results of a multiple regression with avian DTI values for indirect-acting pesticides as the dependant variable and MW^0.5 and log VP as independent predictors. (N=21)

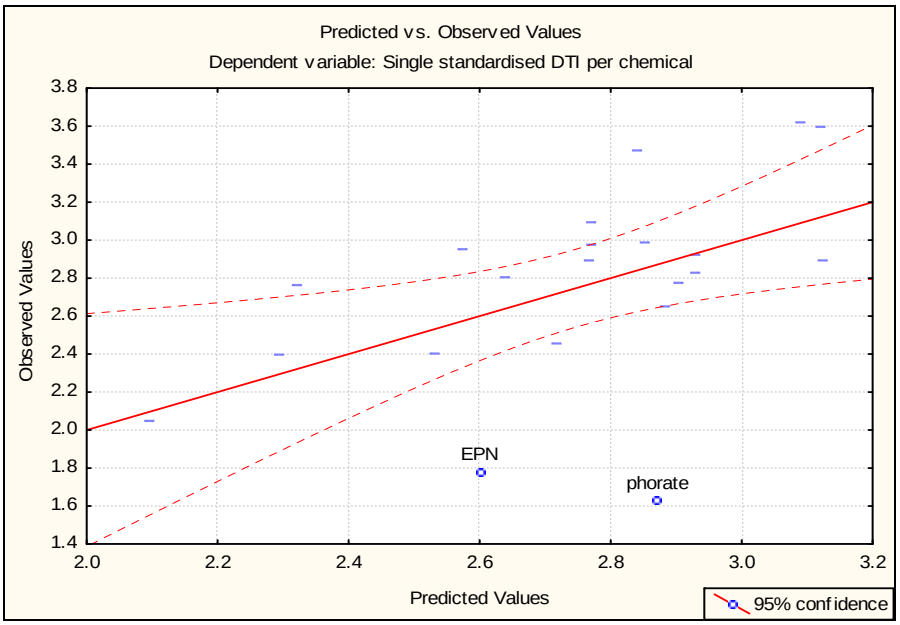
	Beta	Std.Err. of Beta	B	Std.Err. Of B	t(18)	p-level
Intercept			8.514711	2.201671	3.86739	0.001129
MW^0.5	-0.797633	0.304032	-0.337085	0.128486	-2.62352	0.017225
Log_VP	-0.591611	0.304032	-0.105831	0.054387	-1.94588	0.067454

R= .52598182 *R^2= .27665687* *Adjusted R^2= .19628542*

F(2,18)=3.4422 *p<.05421* *Std.Error of estimate: .46193*

The plot of predicted to observed points to two principal outliers: phorate and EPN (figure 13).

Figure 13: Observed vs. predicted values for the multiple regression model predicting avian DTI for indirect-acting pesticides from the independent predictors: MW^0.5 and log VP. (N=21)



If we were to accept this model has better than no predictor, the resulting equation would be:

Equation 8

Avian DTI geomean (standardised for underwing acetone tests) = 8.514711 -0.337085 MW^0.5 - 0.105831 Log Vp

3 CONCLUSION

A comparison between equations 7 and 8 immediately suggests a major difference between direct and indirect-acting compounds as defined here. In the case of the latter, the molecular weight descriptor suggests that smaller molecules present a higher relative risk of dermal intoxication. The different way in which direct and indirect toxicant data sets were fit to the predictive models explains why difficulties were encountered when a few additional data were added to the original

set of Mineau (2002) (see introduction). The success of the original predictive models based solely on physicochemical properties was likely dependant on the exact mix of pesticides in the sample (e.g., the relative proportion of direct and indirect toxicants). The current results for the direct-acting pesticides, however, are consistent with those of Mineau (2002) in that log Kow loaded negatively and molecular size loaded positively in the estimation of DTI.

The best way to assess the relevance of these different observations is compare the relative performance of the DTI concept with that of Kp and Jmax (the more common metrics in the mammalian dermal risk assessment world) in explaining the field data. This we can do with the entire data set assembled in my earlier publication (Mineau, 2002). However, in keeping with the new findings highlighted in this report, it appears advisable to separate results obtained with direct and indirect toxicants in the field also.

4 REVISITING THE ANALYSIS OF FIELD STUDIES OF MINEAU (2002)

My previous analysis can be summarized as follows: As a first step, a measure of acute pesticide toxicity for birds ranging from 20 to 1,000 grams (a weight range that covers most bird species found dead in farm fields) was obtained by applying species sensitivity distribution techniques to the available acute toxicity data for each pesticide (Mineau et al., 2001). A value called the HD_5 ('Hazardous Dose at the 5% tail of the species distribution') was derived. The HD_5 is the amount of pesticide in mg of chemical per kg of body weight estimated to lead to 50% mortality in a species more sensitive than 95% of all bird species, calculated with a 50 percent probability of over- or underestimation. The HD_5 can be calculated mathematically where several toxicity values exist, or extrapolation factors can be applied to single (or, better still, multiple combinations of species-specific toxicity values – see Table 1 in Mineau et al., 2001).

A probability of kill was then derived from a model that used logistic multiple regression with the finding of bird carcasses in fields as the endpoint of interest. Note that this index does not incorporate other toxic effects on birds, or indirect effects. The first and most important variable to be entered was termed 'Toxic Potential' (TP). This was simply the log of the number of HD5 equivalents per kg of body weight per m^2 of field. The second predictor variable was the estimate of avian DTI which, as described earlier, was derived from physicochemical constants such as octanol-water partition coefficient, molecular weight (and molecular volume in the original publication) as well as the ratio of rat oral to dermal data (rat DTI), where available. The third significant descriptor variable was the unitless estimated Henry's law constant for the chemical. Validation of the original (Mineau, 2002) model for the sample of studies in field crops, using a 'leave one out cross validation' approach, indicated that better than 81% of studies were correctly classified – as to whether a given pesticide treatment gave rise to mortality or not (Mineau and Whiteside, 2006).

4.1 All pesticides

In order to compare the various 'dermal factors', whether the original DTI estimate from Mineau (2002), the new one determined from physicochemical properties (preferably with but also without rat DTI when this value is not available) and calculated differently for direct and indirect-acting toxicants, Log Kp or Jmax estimates estimated from prediction equations based on *in vitro* mammalian skin tests, all were entered with TP, the combination of the products' oral toxicity and application rate (Log_HD5/m.sq.). Only one Kp estimate was entered initially (the SRC estimate), all Log Kp values being closely correlated. All field study types (field crop, orchard and forest) were used in this analysis but, these were identified by a categorical variable. The best models (with ΔAICs over 10) and a few select others are summarised in Table 15 below.

The full dataset is reproduced in Appendix F in order to allow independent verification of these results.

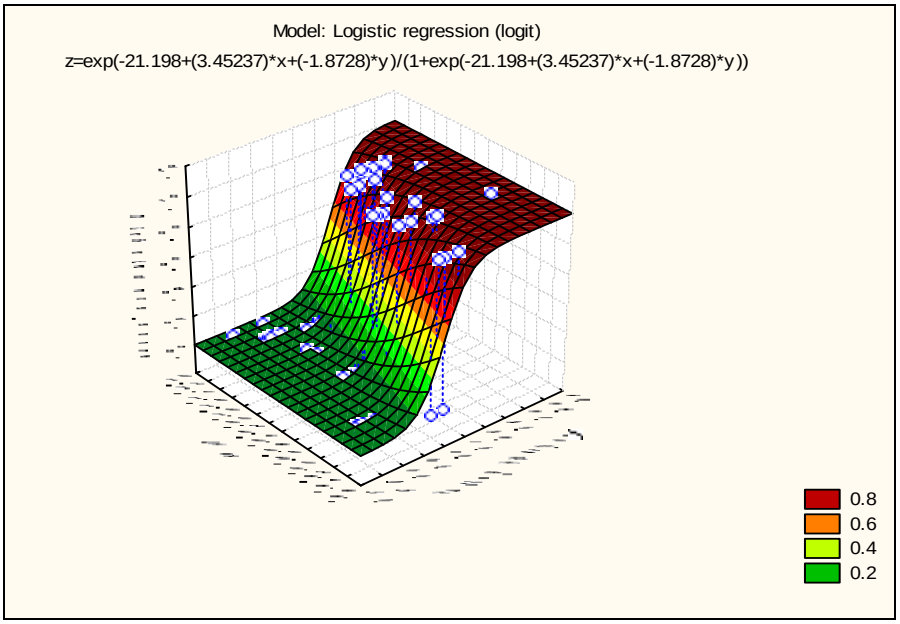
Table 15: Best models developed for field data on all pesticides.

Var.	Var,	Var.	Df	AIC	ΔAICs	L.Ratio	p
TP (Log_HD5/m.sq.)	Original avian DTI (Mineau 2002)	Site_group	4	113.9019	0.0000	92.0538	0.000000
TP (Log_HD5/m.sq.)	Jmax	Site_group	4	120.4932	6.5913	85.4624	0.000000
TP (Log_HD5/m.sq.)	Original avian DTI (Mineau 2002)		2	123.1680	9.2661	78.7877	0.000000
TP (Log_HD5/m.sq.)	New DTI for all toxicants	Site_group	4	130.8159	16.9140	75.1398	0.000000
TP (Log_HD5/m.sq.)	Site_group		3	136.8573	22.9554	67.0983	0.000000
TP (Log_HD5/m.sq.)	Kp(a) SRC	Site_group	4	137.0204	23.1186	68.9352	0.000000
TP (Log_HD5/m.sq.)	Jmax		2	139.8597	25.9578	62.0960	0.000000

Based on this 'global' analysis of the data, it is clear that Log HD5/sq.m. is still the strongest predictor of a field effect (short term lethality) but that alone (with site as categorical), it is vastly inferior to any number of models which include some form of dermal to oral toxicity ratio, some measure of dermal penetration or correlated molecular descriptor. This reinforces conclusions reached by Mineau (2002) that a predictor of either dermal toxicity or at least dermal penetration potential must be considered in avian impact assessments. The importance of site as a categorical variable confirms that the risk is different in fields, forests or orchards for applications of equivalent toxicity. As for choosing the ideal descriptor of dermal toxicity, it is surprising that the original DTI estimates from Mineau (2002) still come out ahead. Because of the problems with its determination (reviewed in the introduction), it might be preferable to go to the second best model as the best 'compromise'. This one uses Jmax, which is only dependant on molecular

weight. That choice itself is surprising in view of the poor performance of Jmax in predicting the available avian DTI data. Clearly, molecular size is related to field level impacts but, how and why is not clear at this point.

Figure 14: Plot of 2-variable logistic model fit with TP and Jmax for all pesticides and use sites combined.



A forward step-wise analysis confirms the utility of all three variables (Table 16).

Table 16: Forward stepwise regression with predictors from the most parsimonious model identified in table 15.

	Effect	Degr. of	Wald stat.	Wald df	Score stat.	Score p	Var. status
Step 1	**TP (Log_HD5/m.sq.)**	1			45.46626	0.000000	Entered
	Jmax	1			6.02916	0.014071	Out
	Site_group	2			0.41531	0.812489	Out
Step 2	**TP (Log_HD5/m.sq.)**	1	33.52461	0.000000			In
	Jmax	1			9.25904	0.002343	Out
	Site_group	2			13.82296	0.000996	Entered

Table 16: Forward stepwise regression with predictors from the most parsimonious model identified in table 15.

	Effect	Degr. of	Wald stat.	Wald df	Score stat.	Score p	Var. status
Step 3	**TP (Log_HD5/m.sq.)**	1	33.53196	0.000000			In
	Site_group	2	12.15834	0.002290			In
	Jmax	1			16.78837	0.000042	Entered
Step 4	**TP (Log_HD5/m.sq.)**	1	29.92104	0.000000			In
	Site_group	2	16.68675	0.000238			In
	Jmax	1	13.76913	0.000207			In

Combining all the field studies into the same model has the advantage of maximizing the use of all available data. However, it forces the critical assumption that the interaction of TP and DTI remains constant across sites and, more importantly, in both direct and indirect-acting pesticides. The overall classification success of studies is as follows (Table 17):

Table 17: Classification success of training dataset with most parsimonious model – all pesticides.

	Predicted 0	Predicted 1
Observed 0	72	14
Observed 1	15	44

… for an overall success of 80% with this training set.

The top model selections for the sample of studies in field crop studies alone (no forest or orchard studies) provide a similar answer, showing the original DTI of Mineau (2002) to be the best predictor, followed by JMax. The final model with TP & JMax correctly classifies 82% of all field studies of the training set (72/88). Addition of the JMax variable represents a highly significant improvement to overall model fit over TP alone (P = 0.000769) but, the further addition of Henry's law constant (marginally significant in Mineau, 2002) is no longer helpful.

Based on the same sample of 88 field crop studies analyzed in Mineau (2002), the model for field crops only now takes the following form:

Equation 9

$$p = \left(\frac{e^{a+b(TP)+c(JMax)}}{1-e^{a+b(TP)+c(JMax)}} \right)$$

where

a = -21.1982

b = 3.000

c = -1.87285

TP = log HD5 equivalents / kg body weight / m2 of treated area

Jmax = -4.52 – 0.0141 MW in moles per cm2 of skin

However, a very large anomaly stands out from this analysis – the fact that JMax is negatively loaded in the model. In other words, with increasing pesticide toxicity, it appears that risk increases faster with compounds having a low estimated dermal flux based on their molecular size alone. This is a situation equivalent to that obtained with the 'contrary to expectation' loading of Log Kow in the assessment of DTI.

However, based on the analyses outlined in earlier sections, it may be counterproductive to try to model both direct and indirect pesticides together. One obvious improvement to the re-analysis of field studies would be to separate the field dataset into direct and indirect toxicants. A disadvantage of this approach is the reduction of the sample of studies available for analysis.

4.2 Field studies with direct toxicants only

I first isolated those studies done in field crops where the insecticide was a direct toxicant (48 field studies representing 12 different pesticides) and repeated the above model selection process with TP as well as both the old or new DTI measure, JMax and one of the Kp measures (SRC). Because of the results obtained with the complete dataset, Henry's law constant was not fitted to the model. As discussed by Mineau (2002), the importance of that variable appeared to originate from studies conducted with a few highly volatile insecticides, especially phoxim which is not a direct acting pesticide anyway.

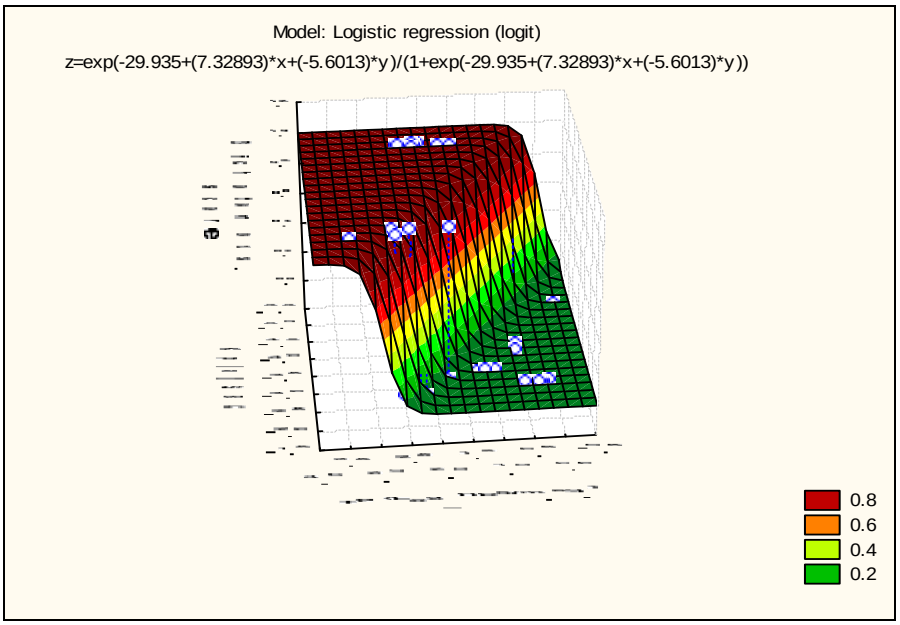
This time, the best model (Table 18) included the Kp measure, just edging the original DTI measure of Mineau (2002). This is obviously quite advantageous because of the ease of computation of this variable.

Table 18: Best predictive models for direct-acting pesticides used in field crops only.

Var. 1	Var. 2	d.f.	AIC	Delta AIC	L.Ratio	p
TP (Log_HD5/m.sq.)	Log Kp(a) SRC	2	17.63600	0.00000	54.15417	0.000000
TP (Log_HD5/m.sq.)	Original avian DTI (Mineau 2002)	2	19.29719	1.66120	52.49297	0.000000
TP (Log_HD5/m.sq.)	New DTI calculation	2	37.17569	19.53969	34.61447	0.000000
TP (Log_HD5/m.sq.)	Jmax	2	37.91724	20.28125	33.87292	0.000000
TP (Log_HD5/m.sq.)		1	38.66243	21.02643	31.12773	0.000000
Jmax		1	51.47588	33.83988	18.31428	0.000019
Log Kp(a) SRC		1	58.69610	41.06010	11.09407	0.000866
Original avian DTI (Mineau 2002)		1	66.84017	49.20418	2.94999	0.085878
New DTI calculation		1	69.57689	51.94089	0.21327	0.644213

All other Kp estimates performed equally well with minor differences only. The striking result here is the degree of model fit provided by these two variables. Fully 95% of cases (46/48) were correctly classified. The risk is shown to increase very rapidly as Log Kp decreases. Again, this is somewhat contrary to expectation because Log Kp is a measure of permeation. A low Log Kp is associated with low Kow compounds of higher molecular weight.

Figure 15: Risk model for fieldcrop studies with direct acting insecticides. The best model is shown here with TP and Kp (based on the SRC algorithm).



Further investigation showed that Log Kow is the key variable affecting field results. Although Log Kp performed slightly better as a predictor, the difference between the two variables was slight.

Because of the danger that the model was affected by the specific combination of the 12 insecticides, I next tested the full dataset of all studies conducted with direct acting pesticides,

regardless of the site of use (field crop, forest or orchard). As in the first analysis above, the site group was identified with a dummy variable. Model selection was repeated with TP as well as both the old or new DTI measure, JMax and the Log Kp measure following the SRC algorithm.

A selection of the best models is given below (Table 19). As usual, models containing two or more of the highly correlated molecular descriptors have been eliminated a priori.

Table 19: Best predictive models for direct-acting pesticides used in field crops, forests or orchards. Use site is entered as a categorical variable.

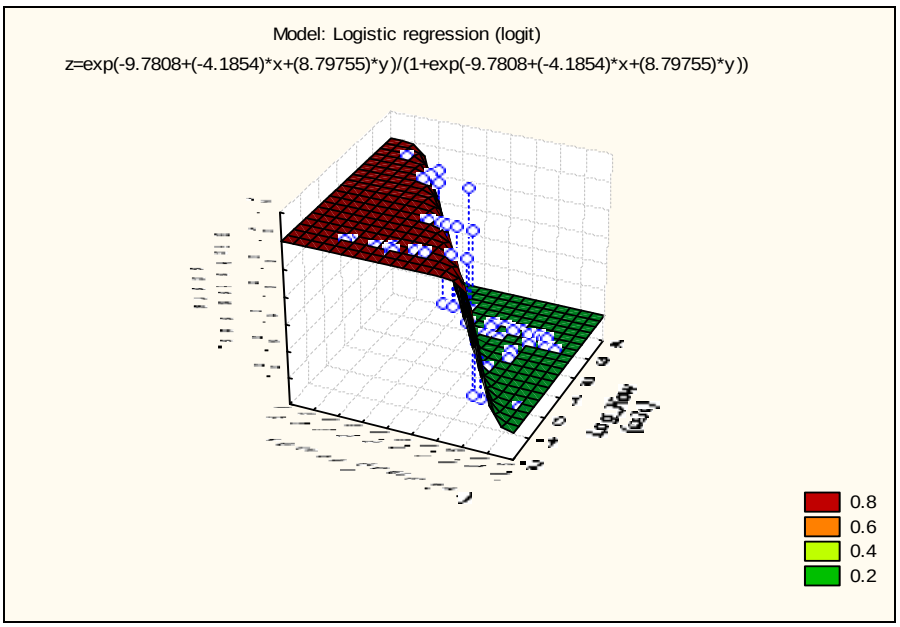
Var. 1	Var. 2	Var. 3	d.f.	AIC	Delta AIC	L.Ratio	p
TP (Log_HD5/m.sq.)	Log Kp(a) SRC		2	23.2047	0.0000	95.3568	0.000000
TP (Log_HD5/m.sq.)	Log Kp(a) SRC	Site_group	4	26.9144	3.7097	95.6471	0.000000
TP (Log_HD5/m.sq.)	Original avian DTI (Mineau, 2002)		2	31.4524	8.2477	87.1091	0.000000
TP (Log_HD5/m.sq.)	Original avian DTI (Mineau, 2002)	Site_group	4	34.7005	11.4958	87.8610	0.000000
TP (Log_HD5/m.sq.)	New DTI measure	Site_group	4	58.2953	35.0906	64.2662	0.000000
TP (Log_HD5/m.sq.)	New DTI measure		2	61.9084	38.7037	56.6531	0.000000
TP (Log_HD5/m.sq.)	Site_group		3	64.4545	41.2498	56.1070	0.000000
TP (Log_HD5/m.sq.)	Jmax	Site_group	4	64.7192	41.5145	57.8423	0.000000
TP (Log_HD5/m.sq.)	Jmax		2	66.7106	43.5059	51.8509	0.000000

Two observations jump out from this analysis. First, Log Kp once again edges all the other molecular descriptors with my original DTI measures (Mineau, 2002) close behind; second, site becomes largely inconsequential for this group of pesticides. Model fit is slightly better (as seen by the slightly higher log likelihood ratio) when sites are kept distinct but the improvement is insufficient to warrant the extra variable, following Akaike's principle of parsimony. Overall

model fit is still spectacular (scary really) with correct classification of 82 out of 84 field studies. The model now includes data for the organophosphorous insecticides: acephate, demeton-S-methyl, dicrotophos, fenamiphos, monocrotophos, phosphamidon, and propoxur; and the carbamates: aminocarb, carbaryl, carbofuran, bendiocarb, pirimicarb, methiocarb, mexacarbate, and oxamyl.

To show the overwhelming influence of Kow in this result, the following plot depicts the still excellent fit (81/84 studies correctly classified) with simply TP and Log Kow. The birds appear to derive a substantial protection with compounds of higher Log Kow.

Figure 16: Two parameter logistic plot for direct-acting pesticides. TP and estimated LogKow are the two predictors.



In summary, the best model for direct-acting pesticides now takes the following form:

Equation 10

$$p = \left(\frac{e^{a+b(TP)+c(\log Kp[SRC])}}{1-e^{a+b(TP)+c(\log Kp[SRC])}} \right)$$

Where …

A = - 39.000

b = 10.000

c = -7.04591

TP = log HD_5 equivalents / kg body weight / m^2 of treated area

and … Log Kp = -2.72 + 0.71 log Kow – 0.0061 MW (from SRC's DERMwin program version 1.43 – equation 1)

4.3 Field studies with indirect-acting pesticides

The situation is very different for those pesticides that are indirect toxicants. For those pesticides, site of application was a significant variable in all the best models (Table 20).

Table 20: Best predictor model with indirect-acting pesticides.

Var. 1	Var. 2	Var. 3	df	AIC	Delta AIC	L.Ratio	p
TP (Log_HD5/m.sq.)	New DTI measure	Site_group	4	60.50434	0.00000	32.72689	0.000001
TP (Log_HD5/m.sq.)	Jmax	Site_group	4	63.94132	3.43698	29.28991	0.000007
TP (Log_HD5/m.sq.)	Kp(a) SRC	Site_group	4	65.86377	5.35943	27.36746	0.000017
TP (Log_HD5/m.sq.)	Site_group		3	68.56404	8.05970	22.66719	0.000047
TP (Log_HD5/m.sq.)	Original avian DTI (Mineau 2002)	Site_group	4	70.41250	9.90816	22.81873	0.000138
TP (Log_HD5/m.sq.)	Kp(a) SRC		2	71.64900	11.14466	17.58223	0.000152
TP (Log_HD5/m.sq.)	New DTI measure		2	71.65756	11.15322	17.57367	0.000153

Log Kow was also entered on its own but found to not be as efficient a predictor as the new DTI algorithm developed specifically for indirect-acting pesticides.

Repeating this analysis with field crop studies only (40 studies; more limited number of pesticides) gives similar results. The new DTI measure is the best predictor after TP, this time followed by JMax.

Returning to the full dataset of indirect-acting pesticides, standard stepwise forward regression confirms the significance of the three predictors chosen on the basis of the most parsimonious model (Table 21).

Table 21. Forward stepwise regression confirming most parsimonious model identified for indirect-acting pesticides.

	Effect	df	Wald stat	Wald p	Score stat	Score p	Var. status
Step 1	**TP (Log_HD5/m.sq.)**	1			10.79793	0.001016	Entered
	Original avian DTI (Mineau, 2002)	1			0.00511	0.943023	Out
	New DTI measure	1			1.00609	0.315841	Out
	Kp(a) SRC	1			7.88651	0.004980	Out
	Jmax	1			0.01598	0.899395	Out
	Site_group	2			0.78002	0.677050	Out
Step 2	**TP (Log_HD5/m.sq.)**	1	8.311624	0.003939			In
	Original avian DTI (Mineau, 2002)	1			0.12247	0.726370	Out
	New DTI measure	1			5.04346	0.024719	Out
	Kp(a) SRC	1			4.54087	0.033095	Out
	Jmax	1			1.04345	0.307021	Out
	Site_group	2			9.02333	0.010980	Entered

Table 21. Forward stepwise regression confirming most parsimonious model identified for indirect-acting pesticides.

	Effect	df	Wald stat	Wald p	Score stat	Score p	Var. status
Step 3	**TP (Log_HD5/m.sq.)**	1	9.762027	0.001782			In
	Site_group	2	7.764149	0.020608			In
	New DTI measure	1			9.23187	0.002378	Entered
	Kp(a) SRC	1			4.21944	0.039963	Out
	Jmax	1			6.13490	0.013254	Out
	Original avian DTI (Mineau, 2002)	1			0.15215	0.696491	Out
Step 4	**TP (Log_HD5/m.sq.)**	1	9.954928	0.001604			In
	Site_group	2	9.320066	0.009466			In
	New DTI measure	1	7.641578	0.005704			In
	Kp(a) SRC	1			0.01768	0.894211	Out
	Jmax	1			0.54054	0.462209	Out
	Original avian DTI (Mineau, 2002)	1			0.08324	0.772947	Out

Overall model fit was not as good as with the direct-acting pesticides with correct classification of 48 of 61 studies or roughly 79%. Addition of Henry's law constant did increase the model fit very slightly but not enough to be considered the most parsimonious solution.

The main form of the equation for the most parsimonious model is therefore:

Equation 11

$$p = \left(\frac{e^{a+b(TP)+c(DTI)}}{1-e^{a+b(TP)+c(DTI)}} \right)$$

Where:

a = 4.056710 (field); 6.986740 (forest); and 3.85394 (orchard)

(… incidentally indicating that the field and orchard field studies give more similar results than forestry studies)

b = 4.41475

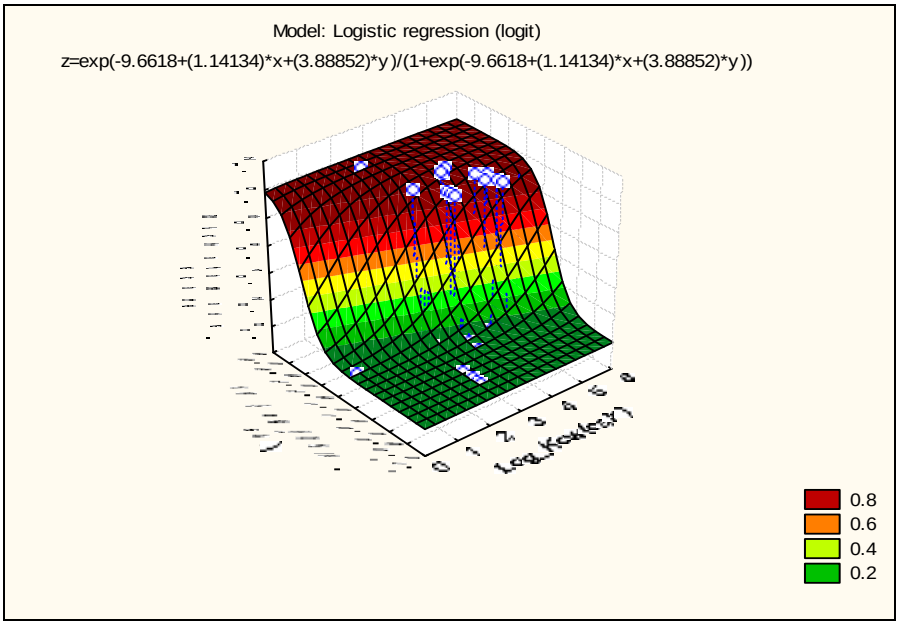
c = - 3.76727

TP = log HD_5 equivalents / kg body weight / m^2 of treated area

Avian DTI = 8.514711 -0.337085 MW^0.5 - 0.105831 Log Vp (*from equation 8*)

As outlined earlier, Log Kow was not as good a predictor for indirect-acting compounds as was the DTI estimate based on molecular size and vapour pressure alone. However, when forced into a model with TP, Log Kow is still a significant variable and this is shown below to highlight the apparent fundamental difference between direct and indirect-acting pesticides. Only field crop studies are included – which still gives a sample size of 40 field studies.

Figure 17: Two parameter plot of logistic model for indirect-acting pesticides and field crops only. The two predictors are TP and Log kow.



What is most interesting is that, unlike the situation with direct-acting pesticides, risk appears to increase faster with higher Log Kow.

5 DISCUSSION AND RECOMMENDATION FOR MODELING

Clearly, DTI (the relative lethal toxicity of a pesticide delivered through the dermal route) is a very different measure than measures of dermal absorption from a liquid medium (Log Kp, Jmax etc.). The best functional explanation for the inverse relationship between DTI and the latter is illustrated by the dermal absorption model of Guy and colleagues (1995). Pesticide absorption from the skin is described as a four compartment model: the skin surface, the stratum corneum, the viable epidermis and then blood and urine, the ultimate media in which absorbed pesticides are often measured. Pesticide absorption is modeled through 4 different rate constants. One of those rate constants (K_3) runs counter to the other three and is needed to model the extent to

which pesticide movement into the body is slowed down by the physicochemical interactions between the chemical and the stratum corneum. This rate constant is estimated for 9 different chemicals of varying characteristics dissolved in acetone and applied directly to live rats. Most interesting for the interpretation of our results, K_3 was found to be directly proportional to Log Kow (although there is a discrepancy in the paper between the tabulated data and the regression shown). In other words, whereas it is true that more lipophilic chemicals may partition more readily into the skin from an aqueous solution, this higher lipophicity will also ensure that release from the lipid-rich stratum corneum (and sub-cutaneous fat depots) into the underlying aqueous vascularised tissue is delayed – or follows a bi-phasic pattern (Riviere and Chang, 1992). Unless a compound is a cumulative toxin (in which case the rate of entry matters less than the total 'area under the curve'), a slower systemic release of the toxicant from the outer skin layers should reduce the likelihood of acute intoxication. Any delay in systemic release following dermal exposure will allow for gradual metabolism and depuration and/or physiological adjustment to the cholinesterase inhibition (tolerance). In addition, such a delay will ensure that exposure from the oral and dermal routes are not synchronised, thereby reducing the possibility of a critical threshold dose being achieved. This interpretation is consistent with the field study data we have for direct-acting OPs and carbamate pesticides and also explains why laboratory-derived DTI values are actually lower with compounds predicted to have a high Kp.

It becomes more complicated to hypothesise why the effect of pesticide lipophicity appears to be the reverse in the case of pesticides needing activation to their more toxic form although the relationship to Kow was variable for this group of compounds. If the interpretation above is correct, a greater field risk from some of the more lipophilic indirect-acting compounds suggests that toxicity may be potentiated as a result of the delayed release into the bloodstream. Given that

all the indirect toxicants in this sample of studies are phosphorothioates needing conversion to the oxon, this suggests that sufficient oxon conversion may take place in the skin and that toxicity (and attending risk of mortality) is increased by having the oxon released directly into the bloodstream upstream from the liver. P-450 mediated conversion of 'thions' has been documented in perfused porcine skin (Riviere and Chang, 1992). Alternatively, the high binding affinity of lipophilic pesticides to plasma constituents may facilitate the compounds' passage through the liver and into the brain where oxon formation critical to the compound's toxicity appears to take place (Chambers, 1992; Nakatsugawa, 1992).

Possibly complicating the whole issue is the fact that pesticides are not applied as technical active ingredients. With the plethora of solvents, emulsifiers, stickers, anti-foaming agents and other constituents of pesticide formulations, vehicle effects are bound to be important in the real world. Guy and colleagues (1985) do mention that acetone or such solvents might facilitate initial movement of a chemical into the stratum corneum and that their kinetic model described above does not take vehicle effects into consideration.

From a risk assessment point of view, this raises a question about the best approach for pesticides where the mode of action is not known or poorly characterised. I believe that, in the absence of data to the contrary, the model for direct-acting substances should be used preferentially. Because the model appears to be so accurate and is based on physico-chemical constants and partitioning, there should not be any *a priori* reason not to extend it to other classes of pesticides (beyond the OPs and carbamates modeled here). More important than the specific anticholinesterase mode of action of these pesticides is whether a pesticide of interest is of the 'C_{max}' type (where attainment of a lethal threshold is the key) or is an 'area under the curve' type

(compounds with the potential for cumulative toxicity). Clearly, OPs and carbamates fall into the first group. The model developed for the phosphorothioates may represent a special case if the key to the field toxicity of this group of pesticides is extra-hepatic oxon formation as hypothesised here.

There are grounds to be careful, however, with very large molecules often typical of new chemistry pesticides. The available sample of field studies with direct toxicants only encompassed a limited range of molecular size. The relationship between Log Kp (or DTI or Log Kow) and MW may not be monotonic and MW may indeed begin to seriously impede movement across the epidermis beyond a certain value. Knowing that avian DTI predictions are not fundamentally different from rat DTI predictions, it would be productive to attempt deriving models for rat DTI for different size classes of more modern insecticides.

Finally, adoption of the new equations for avian risk based on direct acting toxicants means that Henry's law constant (the stand-in for inhalation toxicity in the original model of Mineau, 2002) has dropped out of the model. Nevertheless, the slight improvement (as judged by log likelihood ratio) suggests that this may need to be revisited with highly volatile chemicals.

5.1 Comparison of new model outputs with the original Mineau (2002) predictions

One highlight of the models presented in Mineau (2002) is that the answers provided were reasonable for the better-known pesticides. When application rate was plotted against the probability of kill for different products, model results appeared very much in line with the available evidence. This may seem to be a bit of a circular argument given that the field studies on which our knowledge depends were used in the models but it is important to recall that the

models were built with a much larger sample of studies representing several dozen active ingredients. Examples are given below.

5.1.2 Monocrotophos

Extensive experience with this insecticide used for grasshopper control in Argentina and elsewhere indicates that kills of Swainson's hawks were reported by growers at rates as low as 120 g ai/ha and massive kills recorded at 400g ai/ha (Canavelli and Zaccagnini, 1996). Based on this and other field evidence, it was estimated (Mineau, unpublished) that 80-100 g ai/ha was close to the 'safe' threshold for birds. Model predictions from 2002 were in good agreement (Figure 16). The new model elaborated here for direct inhibitors (of which monocrotophos is one) gives a very different prediction with a much higher apparent risk at very low application levels (Fig 17).

Figure 18: Probability of a kill against application rate for monocrotophos according to field model in Mineau (2002).

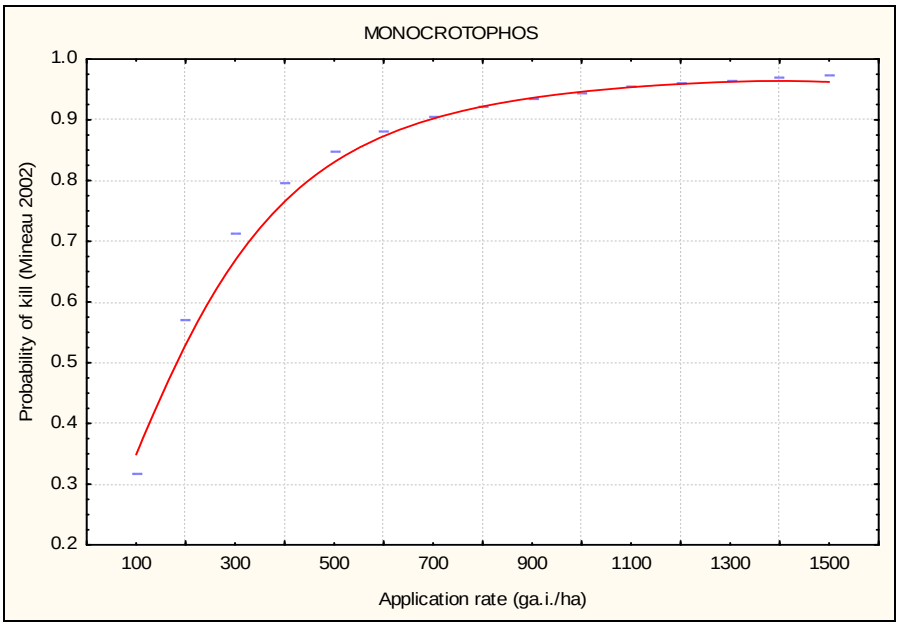
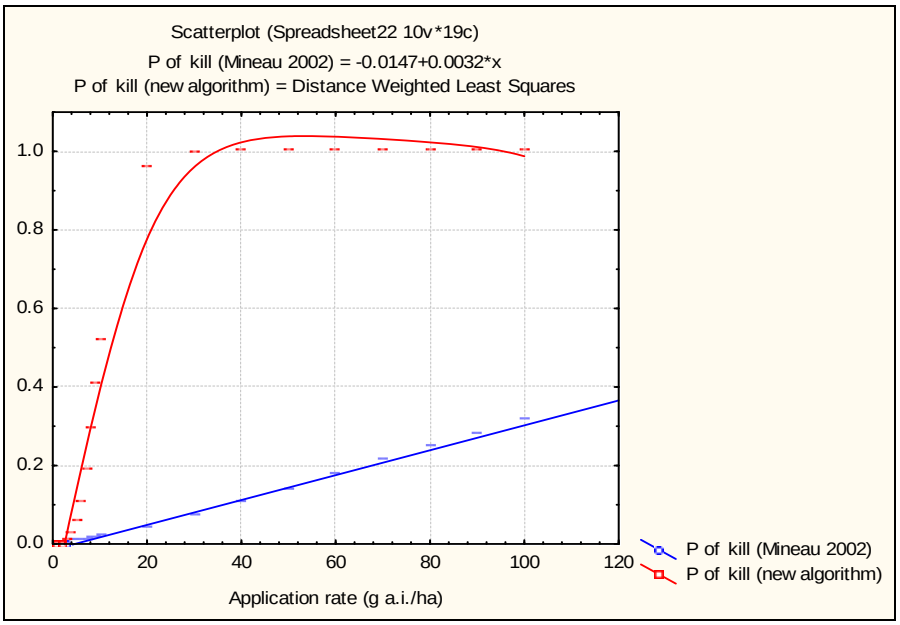


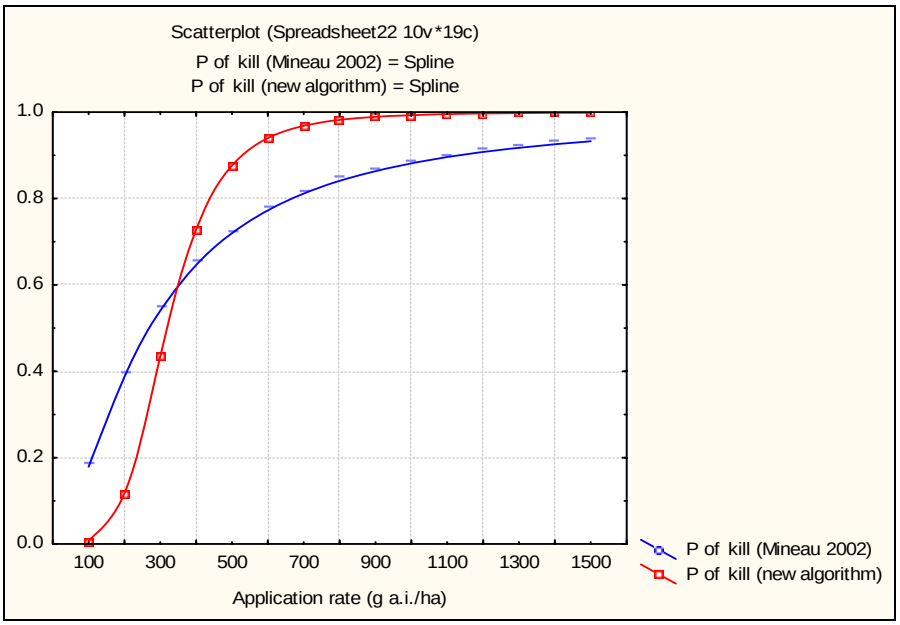
Figure 19: Probability of a kill against application rate for monocrotophos according to new model considering only direct-acting insecticides (equation 10) compared to prediction from Mineau (2002).



5.1.2 Carbofuran

Carbofuran, being a carbamate, is also one of the products included in the group of direct toxicants. The old and new models do not differ very much in their predictions (Figure 18) – both appear reasonable in light of documented problems at 140 g ai/ha in some species but not in others and well documented and largely inevitable kills (based on available field studies) at the U.S. registered rate in corn of 1100 g ai/ha.

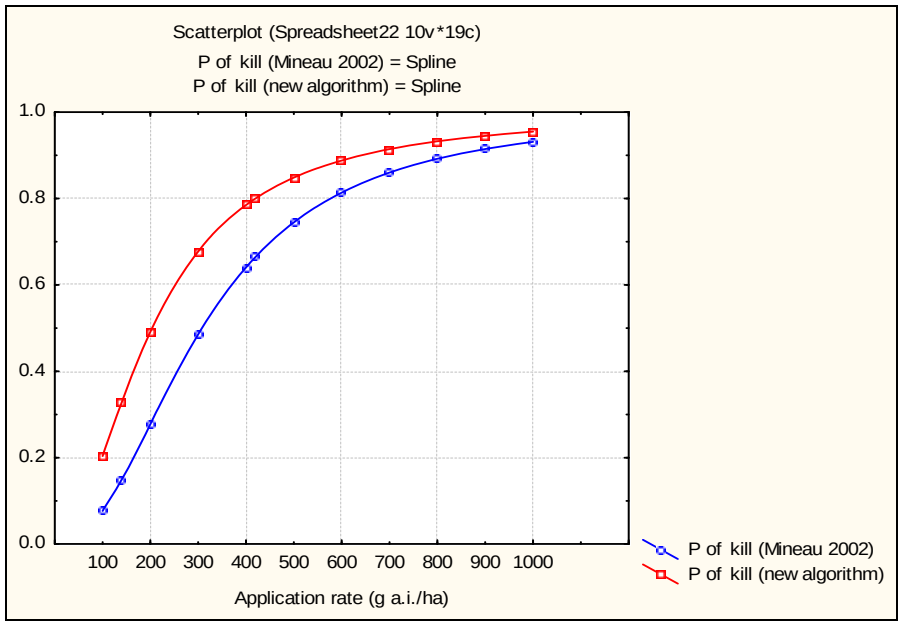
Figure 20: Probability of a kill against application rate for carbofuran according to new model considering only direct-acting insecticides (equation 10) compared to prediction from Mineau (2002).



5.1.3 Fenitrothion

Fenitrothion, of course, needs to be converted to its toxic oxon form and is therefore one of the pesticides that was modeled separately from monocrotophos or carbofuran. I compared results for a forest application between the new and older algorithm. There is one instance of kills having been recorded at 140 g a.i/ha; they were occasionally seen at the more commonly used 210 g a.i./ha and impacts on nesting White-throated sparrows were catastrophic at 420 g a.i./ha. Either curve is a possible good fit to the evidence but the new algorithm may overestimate risk slightly.

Figure 21: Probability of a kill against application rate for fenitrothion according to new model considering only indirect-acting insecticides (equation 11) compared to prediction from Mineau (2002).

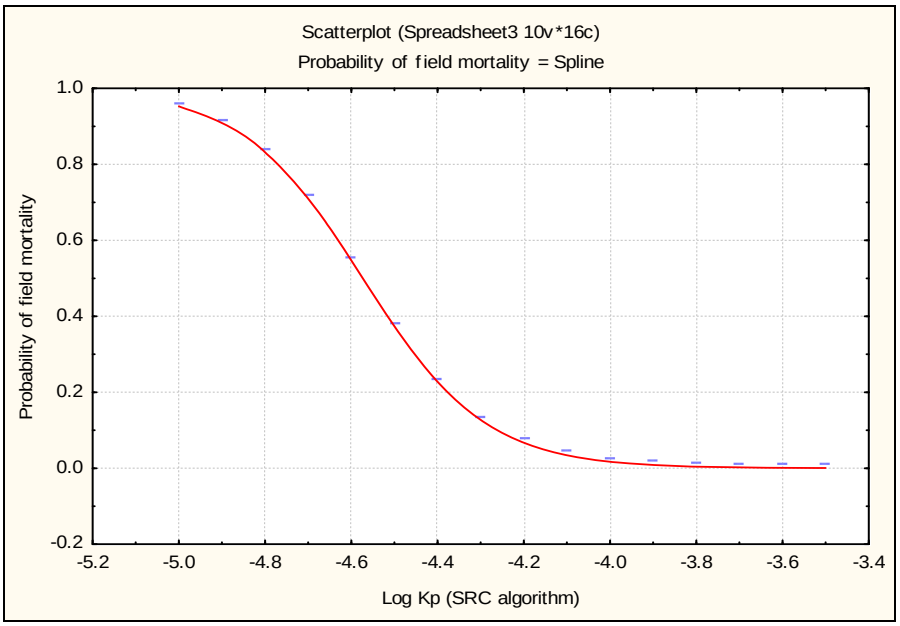


5.2 Discussion of overall 'credibility' of new models

The difficulty is explaining the apparent overestimation of risk for monocrotophos. It is difficult to believe the product could readily kill birds at rates as low as 20 g a.i./ha although there is no experience with this products at these low rates at which it no longer is efficacious against the pest. Yet, the overall model fit for monocrotophos-like compounds (direct-acting pesticides) is almost perfect. The importance of the 'dermal' factor (Log Kp in this case) is so large in that model and the increase in the resulting lethal risk so sharply demarcated (a veritable knife edge in the plot) that the extreme value of Log Kp for monocrotophos (-5.01, the lowest value of all field-tested pesticides) makes it an extreme case – with extreme predictions. In comparison, my original model (a compromise likely dependant on the mix of direct and indirect-acting pesticides) gave what appeared to be more reasonable predictions – <u>despite a poorer fit overall</u>.

To look at the effect of Log Kp on model results, I plotted monocrotophos results, holding application rate at 20 g a.i/ha and increasing Log Kp from its current -5.01.

Figure 22: Simulation (based on equation 10) of the effect of changing Log Kp on the probability of field mortality using a 20 g ai/ha application of a pesticide of the toxicity of monocrotophos.



This shows the overriding importance of physico-chemical structure (Log Kow and MW) in the model developed for direct-acting pesticides. Log Kp values, in the sample of pesticides for which field data are available go as high as – 0.68. If these models become adopted for risk assessment, there will need to be a closer scrutiny of the Kow measurements given that this factor appears to be almost as important as toxicity in defining the field acute impacts of pesticides. Kow values are known to vary with the measurement method – capillary, shake flask etc.. In the models generated here, monocrotophos was given a log Kow of -1.31 based on the QSAR estimate when one measured value cited in the SRC program is -0.20 – clearly less extreme.

On the basis of a curve such as the one above, it would be simple to generate relative risk indices and convert those into F_{red} (or route equivalence factors) as proposed by the USEPA in their most recent draft of level II probabilistic model for pesticide risk assessments (USEPA, 2004). By means of a probit slope, the increased risk from inclusion of the 'dermal factor' (whether Log Kp of DTI) could readily be back-transformed into an equivalent oral dose, alleviating the need to empirically measure dermal absorption.

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7 APPENDICES

APPENDIX A: Toxicological and physico-chemical characteristics of pesticides for which we now have dermal and oral toxicity data.

CHEMICAL	CAS #	Direct or indirect toxicant	Log Kow (KOWwin v.1.67)	Experimental KOW	MW	LeBas MV Mineau (2002)	SPARC MV (cm3/mol)	Specific density (20-25°C)*	Log vapour pressure (mPa at circa. 20°C)*
3-chloro-p-toluidine (CPT)	95-74-9		2.27		141.60		119.66	*1.184*	*-3.3034*
3-chloro-p-toluidine hydrochloride (CPTH; starlicide; DRC-1339))	7745-89-3		2.27		141.60		119.66	*1.184*	*-3.3034*
Aldicarb	116-06-3	D	1.36	1.13 (a)	190.30	227.0	175.18	1.195	1.114
Azinphos-methyl	86-50-0	I	2.53	2.75 (a)	317.32		225.64	1.518	-3.244
Bay 50519	50335-09-6	I	5.41		356.25		294.83	1.208	*-9.1841*
BAY-COE 3664	39457-24-4								
BAY-COE 3675	39457-25-5								
Carbofuran	1563-66-2	D	2.30	2.32 (a)	221.26	240.8	188.14	1.18	-1.509
Coumaphos	56-72-4	I	4.47	4.13 (b)	362.77	324.7	275.94	1.474	-1.886
Demeton	298-03-3	I	3.21		258.33	252.0	227.54	1.12	1.580
Dichlorvos	62-73-7	D	0.60	1.47 (c)	221.00		160.08	1.425	3.506
Dicrotophos	141-66-2	D	-1.10	-0.49 (a)	237.19	255.2	206.31	1.216	0.968
Disulfoton	298-04-4	I	3.86	4.02 (a)	274.39	282.1	234.57	1.144	0.857
Endosulfan	115-29-7	D	3.50	3.83 (a)	406.92		261.95	1.8	-0.081

CHEMICAL	CAS #	Direct or indirect toxicant	Log Kow (KOWwin v.1.67)	Experimental KOW	MW	LeBas MV Mineau (2002)	SPARC MV (cm3/mol)	Specific density (20-25°C)*	Log vapour pressure (mPa at circa. 20°C)*
Endrin	72-20-8	D	5.45	5.20 (d)	380.91		301.94	1.64	-4.699
EPN	2104-64-5	I	4.47	4.78 (e)	323.31	315.2	243.67	1.27	-1.387
Ethamphenphion (O-O-Diethyl O-(2-diethylaminomethyl-4-methyylsulphinylphenyl) phosphorothioate)		I	3.09		393.51		325.90	1.207	*-7.6501*
Ethoprop (ethoprophos)	13194-48-4	I	3.14	3.59 (b)	242.33	185.7	218.30	1.094	1.667
Ethyl DDVP	72-00-4	D	1.59		249.03		191.30	1.302	*3.7751*
Fenamiphos	22224-92-6	D	3.29	3.23 (a)	303.36	315.8	279.19	1.191	-0.921
Fenitrothion	122-14-5	I	3.30	3.30 (a)	277.23	229.7	213.37	1.328	1.255
Fensulfothion	115-90-2	I	2.35	2.23 (a)	308.35	292.5	234.68	1.2	0.602
Fenthion	55-38-9	I	4.08	4.09 (a)	278.32	264.6	227.62	1.25	-0.131
Isocarbophos (optunal)	24353-61-5	I	2.71	2.70 (f)	289.29	262.1	237.84	*1.216*	*-0.9572*
Isofenfos	25311-71-1	I	4.65	4.12 (a)	345.40	367.6	302.87	1.131	-0.658
Methamidophos	10265-92-6	D	-0.93	-0.8 (b)	141.13	140.2	115.89	1.27	0.362
Methidathion (supracide)	950-37-8	I	1.58	2.2 (a)	302.30		202.63	1.51	-0.602
Methiocarb	2032-65-7	D	2.87	2.92 (a)	225.31	261.4	188.05	1.236	-1.824
Methyl Parathion	298-00-0	I	2.75	2.86 (a)	263.21	207.5	198.19	1.21	-0.699
Mevinphos	26718-65-0	D	-0.24	0.13 (b)	224.15	221.1	187.00	1.24	1.230

CHEMICAL	CAS #	Direct or indirect toxicant	Log Kow (KOWwin v.1.67)	Experimental KOW	MW	LeBas MV Mineau (2002)	SPARC MV (cm3/mol)	Specific density (20-25°C)*	Log vapour pressure (mPa at circa. 20°C)*
Monocrotophos	919-44-8	D	-1.31	-0.2 (a)	223.17	233.0	183.56	1.22	-0.538
Oxydemeton-methyl	301-12-2	D	-1.03	-0.75 (b)	246.28		194.09	1.289	0.580
Paraquat Dichloride	1910-42-5	D	-2.71		257.20			1.25	-2.000
Parathion (ethyl)	56-38-2	I	3.73	3.83 (a)	291.26	264.0	230.08	1.2694	-0.051
Phorate Thimet)	298-02-2	I	3.37	3.56 (a)	260.37	259.1	216.31	1.167	1.929
Phosfolan (cyolane)	947-02-4	D	1.17		255.29		189.67	*1.35*	-1.509
Phosphamidon	297-99-4	D	0.38	0.79 (b)	299.69	283.5	247.90	1.21	0.342
Phosphonamidothioic acid, P-ethyl-, O-3-methyl-4-(methylthio)phenyl ester	35335-60-5	I	3.62		261.34		218.68	1.195	*-0.1571*
Phosphorothioic acid, O-(3,5-dimethyl-4-(methylthio)phenyl) O,O-dimethylester	55-37-8	I	4.63		292.35		242.48	1.2057	*-0.1729*
Prophenofos	41198-08-7	I	4.82	4.68 (a)	373.63		267.51	1.455	-0.907
Propoxur (Baygon)	114-26-1	D	1.90	1.52 (a)	209.20		184.95	1.17	0.114
Sulprofos (Bolstar)	35400-43-2	I	5.65	5.48 (b)	322.44	325.5	267.95	1.2	-1.076
TEPP	107-49-3	D	0.45		290.19	246.2	246.00	1.185	1.322
Thionazin (nemaphos)	297-97-2	I	1.86		248.24	231.5	204.19	1.207	2.602

** Most values from the Pesticide manual (2003) values in italics were estimated by SRC's software rather than empirically derived.*

APPENDIX B: Avian oral and dermal toxicity data available for analysis

Chemical	CAS #	Species	Log oral LD_{50}	Carrier for oral dosing	Log dermal LD_{50}	Site of dermal appln.	Solvent for dermal appln.	AVIAN DTI	Data source
3-chloro-p-toluidine (CPT)	95-74-9	Budgerigar	1.51	propylene glycol	1.51	underwing	acetone	3.00	c
3-chloro-p-toluidine (CPT)	95-74-9	Mallard	1.62	propylene glycol	1.88	underwing	acetone	2.75	c
3-chloro-p-toluidine (CPT)	95-74-9	Quelea	1.51	propylene glycol	1.62	underwing	acetone	2.88	c
3-chloro-p-toluidine (CPT)	95-74-9	Red-wing	0.19	propylene glycol	1.75	foot	acetone	1.44	c
3-chloro-p-toluidine (CPT)	95-74-9	Red-wing	0.19	propylene glycol	0.73	underwing	acetone	2.46	c
3-chloro-p-toluidine (CPT)	95-74-9	Starling	0.34	propylene glycol	1.40	foot	acetone	1.94	c
3-chloro-p-toluidine (CPT)	95-74-9	Starling	0.34	propylene glycol	-0.11	underwing	acetone	3.45	c
3-chloro-p-toluidine (CPT)	95-74-9	Tricolor BB	0.38	propylene glycol	1.00	underwing	acetone	2.38	c
3-chloro-p-toluidine hydrochloride (CPTH; starlicide; DRC-1339))	7745-89-3	Quelea	1.51	propylene glycol	1.62	foot	acetone	2.88	c
3-chloro-p-toluidine hydrochloride (CPTH; starlicide; DRC-1339))	7745-89-3	Quelea	1.51	propylene glycol	1.52	underwing	acetone	2.99	c
3-chloro-p-toluidine hydrochloride (CPTH; starlicide; DRC-1339))	7745-89-3	Starling	0.45	propylene glycol	1.90	foot	acetone	1.55	c
3-chloro-p-toluidine hydrochloride (CPTH; starlicide; DRC-1339))	7745-89-3	Starling	0.45	propylene glycol	1.15	underwing	acetone	2.31	c

Chemical	CAS #	Species	Log oral LD_{50}	Carrier for oral dosing	Log dermal LD_{50}	Site of dermal appln.	Solvent for dermal appln.	AVIAN DTI	Data source
Aldicarb	116-06-3	Mallard	0.53	none; gelatin capsule	1.78	foot	propylene glycol	1.75	b
Azinphos-methyl	86-50-0	Red-wing	0.90	propylene glycol	0.93	underwing	acetone	2.97	a
Bay 50519	50335-09-6	House Sparrow	0.38	propylene glycol	0.51	underwing	acetone	2.88	a
Bay 50519	50335-09-6	Quelea	0.62	propylene glycol	0.75	underwing	acetone	2.88	a
BAY-COE 3664	39457-24-4	House Sparrow	0.75	propylene glycol	0.88	underwing	acetone	2.87	a
BAY-COE 3664	39457-24-4	Quelea	0.38	propylene glycol	0.38	underwing	acetone	3.00	a
BAY-COE 3675	39457-25-5	House Sparrow	0.26	propylene glycol	0.88	underwing	acetone	2.38	a
BAY-COE 3675	39457-25-5	Quelea	-0.12	propylene glycol	0.38	underwing	acetone	2.49	a
Carbofuran	1563-66-2	House Sparrow	0.11	propylene glycol	2.00	underwing	acetone	1.11	a
Carbofuran	1563-66-2	Quelea	-0.38	propylene glycol	2.00	underwing	acetone	0.62	a
Coumaphos	56-72-4	House Sparrow	1.00	propylene glycol	1.88	underwing	acetone	2.12	a
Coumaphos	56-72-4	Quelea	0.51	propylene glycol	0.88	underwing	acetone	2.63	a
Demeton	298-03-3	House Sparrow	0.75	propylene glycol	1.11	underwing	acetone	2.63	a
Demeton	298-03-3	Mallard	0.86	none; gelatin capsule	1.38	foot	corn oil	2.48	b
Demeton	298-03-3	Quelea	0.11	propylene glycol	0.26	underwing	acetone	2.86	a
Dichlorvos	62-73-7	Red-wing	1.18	propylene glycol	1.51	foot	acetone	2.68	c
Dichlorvos	62-73-7	Starling	1.25	propylene glycol	0.75	underwing	acetone	3.50	c
Dicrotophos	141-66-2	House Sparrow	0.62	propylene glycol	0.26	underwing	acetone	3.37	a
Dicrotophos	141-66-2	Mallard	0.63	none; gelatin capsule	1.15	foot	propylene glycol	2.48	b

Chemical	CAS #	Species	Log oral LD_{50}	Carrier for oral dosing	Log dermal LD_{50}	Site of dermal appln.	Solvent for dermal appln.	AVIAN DTI	Data source
Dicrotophos	141-66-2	Quelea	0.11	propylene glycol	0.11	underwing	acetone	3.00	a
Disulfoton	298-04-4	Mallard	0.82	none; gelatin capsule	2.28	foot	corn oil	1.53	b
Disulfoton	298-04-4	Red-wing	0.51	propylene glycol	0.00	underwing	acetone	3.51	c
Disulfoton	298-04-4	Starling	2.12	propylene glycol	1.12	underwing	acetone	4.00	c
Endosulfan	115-29-7	Red-wing	1.38	propylene glycol	1.26	underwing	acetone	3.12	c
Endrin	72-20-8	Red-wing	0.38	propylene glycol	0.75	foot	acetone	2.63	c
Endrin	72-20-8	Red-wing	0.38	propylene glycol	0.60	underwing	acetone	2.78	c
Endrin	72-20-8	Starling	0.44	propylene glycol	1.75	foot	acetone	1.69	c
Endrin	72-20-8	Starling	0.44	propylene glycol	0.51	underwing	acetone	2.94	c
EPN	2104-64-5	Mallard	0.85	none; gelatin capsule	2.60	foot	corn oil	1.25	b
Ethamphenphion (O-O-Diethyl O-(2-diethylaminomethyl-4-methyylsulphinylphenyl) phosphorothioate)		Mallard	1.02	none; gelatin capsule	1.75	foot	corn oil	2.26	b
Ethoprop (ethoprophos)	13194-48-4	Mallard	1.10	none; gelatin capsule	1.03	foot	corn oil	3.08	b
Ethyl DDVP	72-00-4	Red-wing	0.00	propylene glycol	1.62	foot	acetone	1.38	c
Ethyl DDVP	72-00-4	Red-wing	0.00	propylene glycol	0.75	underwing	acetone	2.25	c
Ethyl DDVP	72-00-4	Starling	-0.49	propylene glycol	1.88	foot	acetone	0.63	c
Ethyl DDVP	72-00-4	Starling	-0.49	propylene glycol	0.75	underwing	acetone	1.76	c
Fenamiphos	22224-92-6	Mallard	0.23	none; gelatin capsule	1.38	foot	corn oil	1.85	b
Fenitrothion	122-14-5	Mallard	3.08	none; stomach tube	2.70	foot	corn oil	3.37	b
Fenitrothion	122-14-5	Starling	1.04	propylene glycol	1.28	underwing	acetone	2.76	c
Fensulfothion	115-90-2	House Sparrow	-0.49	propylene glycol	0.00	underwing	acetone	2.51	a

Chemical	CAS #	Species	Log oral LD_{50}	Carrier for oral dosing	Log dermal LD_{50}	Site of dermal appln.	Solvent for dermal appln.	AVIAN DTI	Data source
Fensulfothion	115-90-2	Mallard	-0.13	none; gelatin capsule	0.46	foot	propylene glycol	2.42	b
Fensulfothion	115-90-2	Quelea	-0.62	propylene glycol	-0.38	underwing	acetone	2.76	a
Fensulfothion	115-90-2	Red-wing	-0.62	propylene glycol	-0.49	underwing	acetone	2.88	c
Fensulfothion	115-90-2	Starling	-0.25	propylene glycol	0.51	underwing	acetone	2.24	c
Fenthion	55-38-9	House Sparrow	0.75	propylene glycol	0.38	underwing	acetone	3.37	a
Fenthion	55-38-9	Mallard	0.77	none; gelatin capsule	1.64	foot	corn oil	2.13	b
Fenthion	55-38-9	Quelea	0.11	propylene glycol	0.26	underwing	acetone	2.86	a
Fenthion	55-38-9	Red-wing	0.41	propylene glycol	0.48	underwing	acetone	2.94	c
Fenthion	55-38-9	Starling	0.98	propylene glycol	1.77	foot	acetone	2.21	c
Fenthion	55-38-9	Starling	0.98	propylene glycol	1.42	underwing	acetone	2.56	c
Isocarbophos (optunal)	24353-61-5	House Sparrow	0.00	propylene glycol	0.51	underwing	acetone	2.49	a
Isocarbophos (optunal)	24353-61-5	Quelea	-0.12	propylene glycol	0.11	underwing	acetone	2.76	a
Isofenfos	25311-71-1	Red-wing	0.00	propylene glycol	0.37	underwing	acetone	2.63	c
Isofenfos	25311-71-1	Starling	1.12	propylene glycol	1.25	underwing	acetone	2.87	c
Methamidophos	10265-92-6	Red-wing	0.25	propylene glycol	1.50	underwing	acetone	1.75	c
Methamidophos	10265-92-6	Starling	1.00	propylene glycol	1.25	underwing	acetone	2.75	c
Methidathion (supracide)	950-37-8	Red-wing	0.88	propylene glycol	1.26	underwing	acetone	2.62	c
Methidathion (supracide)	950-37-8	Starling	1.26	propylene glycol	2.00	underwing	acetone	2.26	c
Methiocarb	2032-65-7	Quelea	0.62	propylene glycol	2.00	underwing	acetone	1.62	a
Methyl Parathion	298-00-0	Mallard	1.78	none; gelatin capsule	1.73	foot	corn oil	3.05	b
Mevinphos	26718-65-0	Mallard	0.67	none; gelatin capsule	1.05	foot	propylene glycol	2.62	b
Monocrotophos	919-44-8	House Sparrow	0.11	propylene glycol	1.26	underwing	acetone	1.86	a

Chemical	CAS #	Species	Log oral LD_{50}	Carrier for oral dosing	Log dermal LD_{50}	Site of dermal appln.	Solvent for dermal appln.	AVIAN DTI	Data source
Monocrotophos	919-44-8	Mallard	0.68	none; gelatin capsule	1.48	foot	propylene glycol	2.20	b
Monocrotophos	919-44-8	Quelea	0.11	propylene glycol	0.62	underwing	acetone	2.49	a
Oxydemeton-methyl	301-12-2	Red-wing	1.25	propylene glycol	1.63	underwing	acetone	2.63	c
Oxydemeton-methyl	301-12-2	Starling	2.25	propylene glycol	2.12	underwing	acetone	3.13	c
Paraquat Dichloride	1910-42-5	Mallard	2.30	none; stomach tube	2.78	foot	propylene glycol	2.52	b
Parathion	56-38-2	House Sparrow	0.11	propylene glycol	0.26	underwing	acetone	2.86	a
Parathion	56-38-2	Mallard	0.37	none; gelatin capsule	1.45	foot	corn oil	1.92	b
Parathion	56-38-2	Quelea	0.26	propylene glycol	0.26	underwing	acetone	3.00	a
Parathion	56-38-2	Red-wing	0.38	propylene glycol	0.26	underwing	acetone	3.12	c
Parathion	56-38-2	Starling	0.75	propylene glycol	0.23	underwing	acetone	3.52	c
Phorate Thimet)	298-02-2	Mallard	0.41	none; gelatin capsule	2.31	foot	corn oil	1.10	b
Phosfolan (cyolane)	947-02-4	House Sparrow	0.38	propylene glycol	1.26	unknown	acetone	2.12	c
Phosfolan (cyolane)	947-02-4	Quelea	0.26	propylene glycol	1.00	unknown	acetone	2.26	c
Phosphamidon	297-99-4	Mallard	0.58	water	1.41	foot	propylene glycol	2.17	b
Phosphamidon	297-99-4	Red-wing	0.38	propylene glycol	0.26	underwing	acetone	3.12	c
Phosphamidon	297-99-4	Starling	0.75	propylene glycol	0.75	underwing	acetone	3.00	c
Phosphonamidothioic acid, P-ethyl-, O-3-methyl-4-(methylthio)phenyl ester	35335-60-5	Quelea	0.75	propylene glycol	1.88	unknown	acetone	1.87	c
Phosphorothioic acid, O-(3,5-dimethyl-4-(methylthio)phenyl) O,O-dimethylester	55-37-8	Red-wing	0.88	propylene glycol	0.80	underwing	acetone	3.08	c
Prophenofos	41198-08-7	Red-wing	0.26	propylene glycol	0.81	underwing	acetone	2.44	c

Chemical	CAS #	Species	Log oral LD_{50}	Carrier for oral dosing	Log dermal LD_{50}	Site of dermal appln.	Solvent for dermal appln.	AVIAN DTI	Data source
Prophenofos	41198-08-7	Starling	0.88	propylene glycol	2.25	underwing	acetone	1.62	c
Propoxur (Baygon)	114-26-1	House Sparrow	1.15	propylene glycol	2.00	underwing	acetone	2.15	c
Sulprofos (Bolstar)	35400-43-2	Red-wing	1.25	propylene glycol	1.31	underwing	acetone	2.94	c
TEPP	107-49-3	Mallard	0.55	none; gelatin capsule	1.81	foot	propylene glycol	1.75	b
Thionazin (nemaphos)	297-97-2	Mallard	0.23	ethanol; gelatin capsule	0.85	foot	corn oil	2.38	b

APPENDIX C: Rat oral and dermal toxicity data for those pesticides represented in the avian toxicity dataset.

CHEMICAL	CAS #	Log oral LD_{50} (male)	Log dermal LD_{50} (male)	RAT_DTI MALE	Log oral LD_{50} (female)	Log dermal LD_{50} (female)	RAT_DTI FEMALE	FINAL RAT DTI	RAT DATA SOURCE
3-chloro-p-toluidine (CPT)	95-74-9	3.18							RTECS
3-chloro-p-toluidine hydrochloride (CPTH; starlicide; DRC-1339))	7745-89-3	2.82							RTECS
Aldicarb	116-06-3	-0.10	0.48	2.43	-0.19	0.40	2.41	2.42	Gaines et al., 1969
Azinphos-methyl	86-50-0	1.04	2.34	1.70	1.11	2.34	1.77	1.73	Gaines et al., 1969
Bay 50519	50335-09-6								
BAY-COE 3664	39457-24-4								
BAY-COE 3675	39457-25-5								
Carbofuran	1563-66-2	0.94	3.30	0.64	0.94	3.30	0.64	0.64	INCHEM
Coumaphos	56-72-4	1.61	2.93	1.68				1.68	Master
Demeton	298-03-3	0.79	1.15	2.65	0.40	0.91	2.48	2.56	INCHEM
Dichlorvos	62-73-7	1.90	2.03	2.87	1.75	1.88	2.87	2.87	INCHEM
Dicrotophos	141-66-2	1.32	1.63	2.69	1.20	1.62	2.58	2.63	Gaines et al., 1969
Disulfoton	298-04-4	0.94	1.30	2.65	0.45	0.67	2.78	2.71	INCHEM
Endosulfan	115-29-7	1.63	2.11	2.52	1.26	1.87	2.39	2.45	Gaines et al., 1969
Endrin	72-20-8	1.26	1.26	3.00	0.88	1.18	2.70	2.85	Gaines et al., 1969
EPN	2104-64-5	1.56	2.36	2.19	0.89	1.40	2.49	2.34	Gaines et al., 1969

CHEMICAL	CAS #	Log oral LD_{50} (male)	Log dermal LD_{50} (male)	RAT_DTI MALE	Log oral LD_{50} (female)	Log dermal LD_{50} (female)	RAT_DTI FEMALE	FINAL RAT DTI	RAT DATA SOURCE
Ethamphenphion (O-O-Diethyl O-(2-diethylaminomethyl-4-methyylsulphinylphenyl) phosphorothioate)									
Ethoprop (ethoprophos)	13194-48-4	1.79	2.35	2.44	1.52	2.35	2.16	2.30	INCHEM
Ethyl DDVP	72-00-4	0.40							RTECS
Fenamiphos	22224-92-6				0.83	2.06	1.77	1.77	INCHEM
Fenitrothion	122-14-5	2.87	2.54	3.33	2.76	2.54	3.22	3.27	Gaines et al., 1969
Fensulfothion	115-90-2	0.61	1.28	2.33	0.26	0.61	2.64	2.48	Gaines et al., 1969
Fenthion	55-38-9	2.33	2.52	2.81	2.39	2.52	2.87	2.84	Gaines et al., 1969
Isocarbophos (optunal)	24353-61-5	1.58	2.65	1.93				1.93	Master
Isofenfos	25311-71-1	1.30	1.85	2.46				2.46	Pesticide Manual 2000
Methamidophos	10265-92-6	1.19	1.87	2.32				2.32	Bayer, AGRITOX
Methidathion (supracide)	950-37-8	1.41	2.47	1.94				1.94	Ciba, AGRITOX
Methiocarb	2032-65-7	1.78	3.30	1.48	1.85	3.30	1.54	1.51	Gaines et al., 1969
Methyl Parathion	298-00-0	1.15	1.83	2.32	1.38	1.83	2.55	2.43	Gaines et al., 1969
Mevinphos	26718-65-0	0.79	0.67	3.11	0.57	0.62	2.94	3.03	Gaines et al., 1969
Monocrotophos	919-44-8	1.26	2.10	2.15	1.30	2.05	2.25	2.20	Gaines et al., 1969
Oxydemeton-methyl	301-12-2	1.67	2.24	2.43	1.72	2.20	2.52	2.48	Gaines et al., 1969
Paraquat Dichloride	1910-42-5	2.00	1.90	3.10	2.04	1.95	3.09	3.09	INCHEM
Parathion	56-38-2	0.56	1.11	2.44	0.83	1.32	2.51	2.48	INCHEM
Phorate Thimet)	298-02-2	0.36	0.79	2.57	0.04	0.40	2.64	2.61	Gaines et al., 1969
Phosfolan (cyolane)	947-02-4	0.95	2.00	1.95				1.95	RTECS

CHEMICAL	CAS #	Log oral LD_{50} (male)	Log dermal LD_{50} (male)	RAT_DTI MALE	Log oral LD_{50} (female)	Log dermal LD_{50} (female)	RAT_DTI FEMALE	FINAL RAT DTI	RAT DATA SOURCE
Phosphamidon	297-99-4	1.38	2.16	2.22	1.38	2.03	2.35	2.29	Gaines et al., 1969
Phosphonamidothioic acid, P-ethyl-, O-3-methyl-4-(methylthio)phenyl ester	35335-60-5								
Phosphorothioic acid, O-(3,5-dimethyl-4-(methylthio)phenyl) O,O-dimethylester	55-37-8	3.00							
Prophenofos	41198-08-7	2.55	3.21	2.35				2.35	Master
Propoxur (Baygon)	114-26-1	1.92	3.38	1.54	1.93	3.38	1.55	1.55	Gaines et al., 1969
Sulprofos (Bolstar)	35400-43-2	2.48	3.74	1.74	2.25	3.03	2.22	1.97	Pesticide Manual, 2000
TEPP	107-49-3	0.02	0.38	2.64				2.64	Gaines et al., 1969
Thionazin (nemaphos)	297-97-2	0.81	1.23	2.58	0.54	1.04	2.50	2.54	Gaines et al., 1969

APPENDIX D: Dataset of average DTI values for all pesticide-test method combinations.

CHEMICAL	CAS #	Direct or indirect toxicant	Log Kow	MW	MW^0.5	MV (SPARK)	Log VP	Test Method**	AVIAN DTI	RAT DTI
3-chloro-p-toluidine (CPT)	95-74-9		2.27	141.60	11.90	119.66		FA	1.69	
3-chloro-p-toluidine (CPT)	95-74-9		2.27	141.60	11.90	119.66		UA	2.82	
3-chloro-p-toluidine hydrochloride (CPTH; starlicide; DRC-1339))	7745-89-3		2.27	141.60	11.90	119.66		FA	2.22	
3-chloro-p-toluidine hydrochloride (CPTH; starlicide; DRC-1339))	7745-89-3		2.27	141.60	11.90	119.66		UA	2.65	
Aldicarb	116-06-3	D	1.36	190.30	13.79	175.18	1.11	FPG&O	1.75	2.42
Azinphos-methyl	86-50-0	I	2.53	317.32	17.81	225.64	-3.24	UA	2.97	1.73
Bay 50519	50335-09-6	I	5.41	356.25	18.87	294.83	-9.18	UA	2.88	
BAY-COE 3664	39457-24-4							UA	2.94	
BAY-COE 3675	39457-25-5							UA	2.44	
Carbofuran	1563-66-2	D	2.30	221.26	14.87	188.14	-1.51	UA	0.87	0.64
Coumaphos	56-72-4	I	4.47	362.77	19.05	275.94	-1.89	UA	2.38	1.68
Demeton	298-03-3	I	3.21	258.33	16.07	227.54	1.58	FPG&O	2.48	2.28
Demeton	298-03-3	I	3.21	258.33	16.07	227.54	1.58	UA	2.75	2.28
Dichlorvos	62-73-7	D	0.60	221.00	14.87	160.08	3.51	FA	2.68	2.87
Dichlorvos	62-73-7	D	0.60	221.00	14.87	160.08	3.51	UA	3.50	2.87

CHEMICAL	CAS #	Direct or indirect toxicant	Log Kow	MW	MW^0.5	MV (SPARK)	Log VP	Test Method**	AVIAN DTI	RAT DTI
Dicrotophos	141-66-2	D	-1.10	237.19	15.40	206.31	0.97	FPG&O	2.48	2.63
Dicrotophos	141-66-2	D	-1.10	237.19	15.40	206.31	0.97	UA	3.18	2.63
Disulfoton	298-04-4	I	3.86	274.39	16.56	234.57	0.86	FPG&O	2.55	2.71
Disulfoton	298-04-4	I	3.86	274.39	16.56	234.57	0.86	UA	3.75	2.71
Endosulfan	115-29-7	D	3.50	406.92	20.17	261.95	-0.08	UA	3.12	2.45
Endrin	72-20-8	D	5.45	380.91	19.52	301.94	-4.70	FA	2.16	2.85
Endrin	72-20-8	D	5.45	380.91	19.52	301.94	-4.70	UA	2.86	2.85
EPN	2104-64-5	I	4.47	323.31	17.98	243.67	-1.39	FPG&O	1.25	2.34
Ethamphenphion (O-O-Diethyl O-(2-diethylaminomethyl-4-methyylsulphinylphenyl) phosphorothioate)		I	3.09	393.51	19.84	325.90	-7.65	FPG&O	2.26	
Ethoprop (ethoprophos)	13194-48-4	I	3.14	242.33	15.57	218.30	1.67	FPG&O	3.08	2.30
Ethyl DDVP	72-00-4	D	1.59	249.03	15.78	191.30	3.78	FA	0.63	
Ethyl DDVP	72-00-4	D	1.59	249.03	15.78	237.84	3.78	UA	2.00	
Fenamiphos	22224-92-6	D	3.29	303.36	17.42	279.19	-0.92	FPG&O	1.85	1.77
Fenitrothion	122-14-5	I	3.30	277.23	16.65	213.37	1.26	FPG&O	3.37	3.27
Fenitrothion	122-14-5	I	3.30	277.23	16.65	213.37	1.26	UA	2.76	3.27
Fensulfothion	115-90-2	I	2.35	308.35	17.56	234.68	0.60	FPG&O	2.42	2.48
Fensulfothion	115-90-2	I	2.35	308.35	17.56	234.68	0.60	UA	2.60	2.48

CHEMICAL	CAS #	Direct or indirect toxicant	Log Kow	MW	MW^0.5	MV (SPARK)	Log VP	Test Method**	AVIAN DTI	RAT DTI
Fenthion	55-38-9	I	4.08	278.32	16.68	227.62	-0.13	FA	2.21	2.84
Fenthion	55-38-9	I	4.08	278.32	16.68	227.62	-0.13	FPG&O	2.13	2.84
Fenthion	55-38-9	I	4.08	278.32	16.68	227.62	-0.13	UA	2.93	2.84
Isocarbophos (optunal)	24353-61-5	I	2.71	289.29	17.01	237.84	-0.96	UA	2.63	1.93
Isofenfos	25311-71-1	I	4.65	345.40	18.58	302.87	-0.66	UA	2.75	2.46
Methamidophos	10265-92-6	D	-0.93	141.13	11.88	115.89	0.36	UA	2.25	2.32
Methidathion (supracide)	950-37-8	I	1.58	302.30	17.39	202.63	-0.60	UA	2.44	1.94
Methiocarb	2032-65-7	D	2.87	225.31	15.01	188.05	-1.82	UA	1.62	1.51
Methyl Parathion	298-00-0	I	2.75	263.21	16.22	198.19	-0.70	FPG&O	3.05	2.43
Mevinphos	26718-65-0	D	-0.24	224.15	14.97	187.00	1.23	FPG&O	2.62	3.03
Monocrotophos	919-44-8	D	-1.31	223.17	14.94	183.56	-0.54	FPG&O	2.20	2.01
Monocrotophos	919-44-8	D	-1.31	223.17	14.94	183.56	-0.54	UA	2.17	2.01
Oxydemeton-methyl	301-12-2	D	-1.03	246.28	15.69	194.09	0.58	UA	2.88	2.48
Paraquat Dichloride	1910-42-5	D	-2.71	257.20	16.04		-2.00	FPG&O	2.52	3.09
Parathion	56-38-2	I	3.73	291.26	17.07	230.08	-0.05	FPG&O	1.92	2.48
Parathion	56-38-2	I	3.73	291.26	17.07	230.08	-0.05	UA	3.13	2.48
Phorate Thimet)	298-02-2	I	3.37	260.37	16.14	216.31	1.93	FPG&O	1.10	2.61
Phosfolan (cyolane)	947-02-4	D	1.17	255.29	15.98	189.67	-1.51		2.19	1.95
Phosphamidon	297-99-4	D	0.38	299.69	17.31	247.90	0.34	FPG&O	2.17	2.29

CHEMICAL	CAS #	Direct or indirect toxicant	Log Kow	MW	MW^0.5	MV (SPARK)	Log VP	Test Method**	AVIAN DTI	RAT DTI
Phosphamidon	297-99-4	D	0.38	299.69	17.31	247.90	0.34	UA	3.06	2.29
Phosphonamidothioic acid, P-ethyl-, O-3-methyl-4-(methylthio)phenyl ester	35335-60-5	I	3.62	261.34	16.17	218.68	-0.16		1.87	
Phosphorothioic acid, O-(3,5-dimethyl-4-(methylthio)phenyl) O,O-dimethylester	55-37-8	I	4.63	292.35	17.10	242.48	-0.17	UA	3.08	
Prophenofos	41198-08-7	I	4.82	373.63	19.33	267.51	-0.91	UA	2.03	2.35
Propoxur (Baygon)	114-26-1	D	1.90	209.20	14.46	184.95	0.11	UA	2.15	1.55
Sulprofos (Bolstar)	35400-43-2	I	5.65	322.44	17.96	267.95	-1.08	UA	2.94	1.97
TEPP	107-49-3	D	0.45	290.19	17.03	246.00	1.32	FPG&O	1.75	2.64
Thionazin (nemaphos)	297-97-2	I	1.86	248.24	15.76	204.19	2.60	FPG&O	2.38	2.54

*** UA= underwing with acetone; FA= foot application in acetone; FPG&O= foot application in propylene glycol or oil with subsequent covering.*

APPENDIX E: Rat toxicity data for those pesticides represented in the field dataset of Mineau (2002). Because of the large variation encountered among different sources, precedence was given to data obtained from the same source; e.g., Gaines, 1969 or data reviewed by a regulatory body, e.g., data reported by INCHEM. Also greater attention was paid to identifying limit values in the dataset (see 'qualifier' column).

CHEMICAL	CAS #	Log oral LD_{50} (male)*	Log dermal LD_{50} (male)*	RAT_DTI MALE	Log oral LD_{50} (female)	Log dermal LD_{50} (female)	RAT_DTI FEMALE	Qualifier#	FINAL RAT DTI	RAT DATA SOURCE
Acephate	30560-19-1	2.98	3.30	2.67				<<	2.67	WHO, AGRITOX
Aminocarb	2032-59-9	1.60	2.45	2.15	1.58	2.51	2.07		2.11	Gaines, 1969
Azinphos-methyl	86-50-0	1.04	2.34	1.7	1.11	2.34	1.77		1.73	Gaines, 1969
Bendiocarb	22781-23-3	1.90	2.83	2.07					2.07	Pesticide Manual, 2000
Carbaryl	63-25-2	2.93	3.60	2.33	2.70	3.60	2.10	<<	2.21	Gaines, 1969
Carbofuran	1563-66-2	0.94	3.3	0.64	0.94	3.3	0.64		0.64	INCHEM
Chlorpyrifos	2921-88-2	2.19	2.31	2.88	1.91				2.88	Gaines, 1969
Cyanophos	2636-26-2	2.85	3.30	2.55				<<	2.55	Pesticide Manual, 2000
Demeton-S-methyl	919-86-8	1.73	1.85	2.88					2.88	INCHEM
Diazinon	333-41-5	2.03	2.30	2.73	1.88				2.73	Gaines, 1969
Dicrotophos	141-66-2	1.32	1.63	2.69	1.2	1.62	2.58		2.63	Gaines, 1969
Dimethoate	60-51-5	2.18	2.55	2.63					2.63	INCHEM
Disulfoton	298-04-4	0.94	1.3	2.65	0.45	0.67	2.78		2.71	INCHEM
Fenamiphos	22224-92-6				0.83	2.06	1.77		1.77	INCHEM
Fenitrothion	122-14-5	2.87	2.54	3.33	2.76	2.54	3.22		3.27	Gaines, 1969

CHEMICAL	CAS #	Log oral LD_{50} (male)*	Log dermal LD_{50} (male)*	RAT_DTI MALE	Log oral LD_{50} (female)	Log dermal LD_{50} (female)	RAT_DTI FEMALE	Qualifier[#]	FINAL RAT DTI	RAT DATA SOURCE
Fenthion	55-38-9	2.33	2.52	2.81	2.39	2.52	2.87		2.84	Gaines, 1969
Isofenfos	25311-71-1	1.3	1.85	2.46					2.46	Pesticide Manual, 2000
Malathion	121-75-5	3.14	3.65	2.49	3.00	3.65	2.35		2.42	Gaines, 1969
Methamidophos	10265-92-6	1.19	1.87	2.32					2.32	Bayer, AGRITOX
Methiocarb	2032-65-7	1.78	3.3	1.48	1.85	3.3	1.54		1.51	Gaines, 1969
Methomyl	16752-77-5	1.23	3.00	1.23	1.37	3.00	1.37	<	1.3	INCHEM
Methyl Parathion	298-00-0	1.15	1.83	2.32	1.38	1.83	2.55		2.43	Gaines, 1969
Mevinphos	26718-65-0	0.79	0.67	3.11	0.57	0.62	2.94		3.03	Gaines, 1969
Mexacarbate	315-18-4	1.57	3.29	1.28	1.40	3.29	1.11		1.19	Gaines, 1969
Monocrotophos	919-44-8	1.26	2.1	2.15	1.3	2.05	2.25		2.2	Gaines, 1969
Oxamyl	23135-22-0	0.73	3.35	0.38	0.45	3.35	0.09		0.23	Dupont, AGRITOX
Parathion	56-38-2	0.56	1.11	2.44	0.83	1.32	2.51		2.48	INCHEM
Phosalone	2310-17-0				2.08	3.18	1.90		1.9	Rhone Poulenc, AGRITOX
Phosphamidon	297-99-4	1.38	2.16	2.22	1.38	2.03	2.35		2.29	Gaines et al., 1969
Phoxim	14816-18-3	3.34	3.00	3.34	3.30	3.00	3.30	<<	3.32	INCHEM
Pirimicarb	23103-98-2				2.15	3.30	1.85	<	1.85	Pesticide Manual, 2000
Propoxur (Baygon)	114-26-1	1.92	3.38	1.54	1.93	3.38	1.55		1.55	Gaines, 1969
Sulprofos (Bolstar)	35400-43-2	2.48	3.74	1.74	2.25	3.03	2.22		1.97	Pesticide Manual, 2000
Triazophos	24017-47-8	1.76	3.30	1.46				<	1.46	Pesticide Manual, 2000

CHEMICAL	CAS #	Log oral LD_{50} (male)*	Log dermal LD_{50} (male)*	RAT_DTI MALE	Log oral LD_{50} (female)	Log dermal LD_{50} (female)	RAT_DTI FEMALE	Qualifier[#]	FINAL RAT DTI	RAT DATA SOURCE
Trichlorfon	52-68-6	2.80	3.30	2.50	2.75	3.30	2.45	<<	2.47	Gaines et al., 1969

** includes data where sex not specified*

[#] *< indicates that the dermal toxicity value was a limit value and that the true DTI is lower than the stated value; << indicates that the true DTI is likely very much lower than the stated value*

APPENDIX F: Full dataset of pesticide data used.

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
acephate	D	1.15E-10	-0.6459	-0.9025	13.53	field	-0.25	3.33	2.20	-4.48	-3.926	-4.91	-4.98	-7.10	1	0	McEwen and DeWeese, 1981
acephate	D	1.15E-10	-0.6459	-0.9025	13.53	field	-0.24	3.33	2.20	-4.48	-3.926	-4.91	-4.98	-7.10	1	0	Peterson et al., 1981
acephate	D	1.15E-10	-0.6459	-0.9025	13.53	field	0.48	3.33	2.20	-4.48	-3.926	-4.91	-4.98	-7.10	2	0	McEwen et al., 1980
acephate	D	1.15E-10	-0.6459	-0.9025	13.53	forest	0.48	3.33	2.20	-4.48	-3.926	-4.91	-4.98	-7.10	1	0	Bart et al., 1975; Bart, 1979
acephate	D	1.15E-10	-0.6459	-0.9025	13.53	forest	0.49	3.33	2.20	-4.48	-3.926	-4.91	-4.98	-7.10	2	0	Zinkl, 1977; Zinkl et al., 1980
acephate	D	1.15E-10	-0.6459	-0.9025	13.53	forest	0.62	3.33	2.20	-4.48	-3.926	-4.91	-4.98	-7.10	1	0	Bart et al., 1975; Bart, 1979
acephate	D	1.15E-10	-0.6459	-0.9025	13.53	forest	0.66	3.33	2.20	-4.48	-3.926	-4.91	-4.98	-7.10	2	0	Zinkl et al.,1984
acephate	D	1.15E-10	-0.6459	-0.9025	13.53	forest	0.78	3.33	2.20	-4.48	-3.926	-4.91	-4.98	-7.10	3	1	Richmond et al., 1979
acephate	D	1.15E-10	-0.6459	-0.9025	13.53	forest	1.08	3.33	2.20	-4.48	-3.926	-4.91	-4.98	-7.10	3	1	Richmond et al., 1979
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	field	0.17	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	Fair et al., 1995
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	field	0.19	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	McEwen and Knittle, 1968
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	field	0.26	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	McEwen et al., 1966a

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	field	0.27	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	Fair et al., 1995
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	field	0.30	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	Fox et al., 1989
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	field	0.35	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	McEwen et al., 1969
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	field	0.56	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	McEwen et al., 1965
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	field	0.56	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	McEwen et al., 1963
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	forest	1.34	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	Bart, 1979
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	forest	0.87	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	Richmond et al., 1979 and Zinkl et al., 1979
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	forest	0.57	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	DeWeese et al., 1979; Zinkl et al., 1977; 1979
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	forest	0.57	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	Doane and Schaefer, 1971 and Studholme, 1972 reviewed in Peakall and Bart, 1983
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	forest	0.57	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	Bednarek and Davidson, 1967
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	forest	0.56	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	Bart, 1979

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
carbaryl	D	1.28E-07	-1.3872	2.3484	14.19	forest	0.27	1.60	1.73	-2.28	-2.455	-2.59	-2.53	-7.36	1	0	Gramlich, 1979
pirimicarb	D	1.07E-07	-0.3979	1.3994	15.44	field	0.62	1.88	2.32	-3.18	-3.091	-3.70	-3.71	-7.88	1	0	Edwards, 1972
demeton-S-methyl	D	1.05E-07	1.6021	1.1104	15.17	field	0.57	2.50	3.14	-3.34	-3.193	-3.84	-3.86	-7.77	2	0	Hart et al. 1992; Thompson et al., 1992
Dicroto-phos	D	4.89E-11	0.9680	-1.0957	15.40	field	1.52	2.45	2.90	-4.94	-4.287	-5.62	-5.73	-7.86	3	1	McEwen et al., 1967
Dicroto-phos	D	4.89E-11	0.9680	-1.0957	15.40	field	1.72	2.45	2.90	-4.94	-4.287	-5.62	-5.73	-7.86	3	1	Palmer et al., 1987
Dicroto-phos	D	4.89E-11	0.9680	-1.0957	15.40	field	2.12	2.45	2.90	-4.94	-4.287	-5.62	-5.73	-7.86	3	1	Sheeley et al., 1987
Phos-phamidon	D	6.20E-11	0.3420	0.3788	17.31	forest	2.02	2.51	2.75	-4.28	-3.851	-5.12	-5.22	-8.75	3	1	Finley, 1965
Phos-phamidon	D	6.20E-11	0.3420	0.3788	17.31	forest	1.97	2.51	2.75	-4.28	-3.851	-5.12	-5.22	-8.75	4	1	Schneider, 1966
Phos-phamidon	D	6.20E-11	0.3420	0.3788	17.31	forest	1.97	2.51	2.75	-4.28	-3.851	-5.12	-5.22	-8.75	3	1	Ciba Agro-chemical division, 1967 in Smith, 1987
Phos-phamidon	D	6.20E-11	0.3420	0.3788	17.31	forest	1.71	2.51	2.75	-4.28	-3.851	-5.12	-5.22	-8.75	4	1	Fowle, 1971; 1965
Phos-phamidon	D	6.20E-11	0.3420	0.3788	17.31	forest	1.59	2.51	2.75	-4.28	-3.851	-5.12	-5.22	-8.75	4	1	Pearce, 1968; Fowle, 1971; 1965
Phos-phamidon	D	6.20E-11	0.3420	0.3788	17.31	forest	1.41	2.51	2.75	-4.28	-3.851	-5.12	-5.22	-8.75	3	1	Pearce, 1968, Fowle, 1965; 1971

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
Phos-phamidon	D	6.20E-11	0.3420	0.3788	17.31	forest	1.11	2.51	2.75	-4.28	-3.851	-5.12	-5.22	-8.75	3	1	Pearce, 1968
Phos-phamidon	D	6.20E-11	0.3420	0.3788	17.31	forest	0.81	2.51	2.75	-4.28	-3.851	-5.12	-5.22	-8.75	1	0	Peakall and Bart, 1983
aminocarb	D	2.30E-08	0.3617	1.8973	14.43	forest	-0.10	1.43	2.34	-2.64	-2.707	-3.01	-2.97	-7.46	1	0	Peakall and Bart, 1983
aminocarb	D	2.30E-08	0.3617	1.8973	14.43	forest	0.03	1.43	2.34	-2.64	-2.707	-3.01	-2.97	-7.46	1	0	Busby et al., 1982; 1983
aminocarb	D	2.30E-08	0.3617	1.8973	14.43	forest	0.11	1.43	2.34	-2.64	-2.707	-3.01	-2.97	-7.46	1	0	Peakall and Bart, 1983
aminocarb	D	2.30E-08	0.3617	1.8973	14.43	forest	0.41	1.43	2.34	-2.64	-2.707	-3.01	-2.97	-7.46	1	0	Peterson, 1976 and Brown, 1978 in Peakall and Bart, 1983
bendiocarb	D	2.69E-09	0.6628	2.5515	14.94	field	2.67	1.76	2.39	-2.27	-2.465	-2.66	-2.61	-7.67	3	1	
bendiocarb	D	2.69E-09	0.6628	2.5515	14.94	field	2.67	1.76	2.39	-2.27	-2.465	-2.66	-2.61	-7.67	3	1	
mono-crotophos	D	2.23E-11	-0.5380	-1.3069	14.94	field	2.43	2.33	2.27	-5.01	-4.322	-5.64	-5.75	-7.67	4	1	Dingledine, 1986
mono-crotophos	D	2.23E-11	-0.5380	-1.3069	14.94	field	2.43	2.33	2.27	-5.01	-4.322	-5.64	-5.75	-7.67	4	1	Pease and O'Brien, 1987
mono-crotophos	D	2.23E-11	-0.5380	-1.3069	14.94	field	2.43	2.33	2.27	-5.01	-4.322	-5.64	-5.75	-7.67	4	1	Canavelli and Zaccagnini, 1996
mono-crotophos	D	2.23E-11	-0.5380	-1.3069	14.94	field	2.38	2.33	2.27	-5.01	-4.322	-5.64	-5.75	-7.67	4	1	Ali-Dervish, 1970

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
mono-crotophos	D	2.23E-11	-0.5380	-1.3069	14.94	field	2.15	2.33	2.27	-5.01	-4.322	-5.64	-5.75	-7.67	3	1	Plant Protection and Agro-chemistry Centre of Hungary, 1980
mono-crotophos	D	2.23E-11	-0.5380	-1.3069	14.94	field	2.09	2.33	2.27	-5.01	-4.322	-5.64	-5.75	-7.67	3	1	Plant Protection and Agro-chemistry Centre of Hungary, 1980
mono-crotophos	D	2.23E-11	-0.5380	-1.3069	14.94	field	2.06	2.33	2.27	-5.01	-4.322	-5.64	-5.75	-7.67	4	1	Benson and Baker, 1971
mono-crotophos	D	2.23E-11	-0.5380	-1.3069	14.94	orchard	2.90	2.33	2.27	-5.01	-4.322	-5.64	-5.75	-7.67	3	1	Hughes et al., 1971
mono-crotophos	D	2.23E-11	-0.5380	-1.3069	14.94	orchard	3.00	2.33	2.27	-5.01	-4.322	-5.64	-5.75	-7.67	4	1	Hughes et al., 1970
fenamiphos	D	3.95E-09	-0.9210	3.2932	17.42	field	3.42	1.73	2.23	-2.23	-2.463	-2.91	-2.88	-8.80	3	1	Whitmore et al., 1991
propoxur	D	1.37E-07	0.1140	1.9034	14.47	field	1.33	1.39	1.88	-2.65	-2.709	-3.02	-2.98	-7.47	1	0	McEwen et al., 1966a
propoxur	D	1.37E-07	0.1140	1.9034	14.47	field	1.33	1.39	1.88	-2.65	-2.709	-3.02	-2.98	-7.47	1	0	McEwen et al., 1969
propoxur	D	1.37E-07	0.1140	1.9034	14.47	field	1.18	1.39	1.88	-2.65	-2.709	-3.02	-2.98	-7.47	1	0	McEwen et al., 1969
propoxur	D	1.37E-07	0.1140	1.9034	14.47	field	1.18	1.39	1.88	-2.65	-2.709	-3.02	-2.98	-7.47	1	0	McEwen et al., 1970
propoxur	D	1.37E-07	0.1140	1.9034	14.47	field	1.03	1.39	1.88	-2.65	-2.709	-3.02	-2.98	-7.47	1	0	McEwen et al., 1969

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
propoxur	D	1.37E-07	0.1140	1.9034	14.47	field	1.03	1.39	1.88	-2.65	-2.709	-3.02	-2.98	-7.47	1	0	McEwen et al., 1970
methiocarb	D	4.66E-08	-1.8240	2.8678	15.01	field	2.55	1.27	1.71	-2.06	-2.323	-2.44	-2.37	-7.70	1	0	DeHaven et al., 1976 in Dolbeer et al., 1994
methiocarb	D	4.66E-08	-1.8240	2.8678	15.01	field	2.32	1.27	1.71	-2.06	-2.323	-2.44	-2.37	-7.70	2	0	Hothem et al., 1981 in Dolbeer et al., 1994
methiocarb	D	4.66E-08	-1.8240	2.8678	15.01	field	2.32	1.27	1.71	-2.06	-2.323	-2.44	-2.37	-7.70	2	0	Pearce and Garrity, 1974 in Dolbeer et al., 1994
methiocarb	D	4.66E-08	-1.8240	2.8678	15.01	field	2.30	1.27	1.71	-2.06	-2.323	-2.44	-2.37	-7.70	1	0	Dolbeer et al., 1994
methiocarb	D	4.66E-08	-1.8240	2.8678	15.01	field	2.21	1.27	1.71	-2.06	-2.323	-2.44	-2.37	-7.70	1	0	Stickley, 1976 and Woronecki et al., 1981 in Dolbeer et al., 1994
methiocarb	D	4.66E-08	-1.8240	2.8678	15.01	orchard	1.88	1.27	1.71	-2.06	-2.323	-2.44	-2.37	-7.70	1	0	Tobin and Dolbeer, 1989 in Dolbeer et al., 1994
methiocarb	D	4.66E-08	-1.8240	2.8678	15.01	orchard	2.32	1.27	1.71	-2.06	-2.323	-2.44	-2.37	-7.70	1	0	DeHaven et al., 1979 in Dolbeer et al., 1994

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
methiocarb	D	4.66E-08	-1.8240	2.8678	15.01	orchard	2.32	1.27	1.71	-2.06	-2.323	-2.44	-2.37	-7.70	2	0	Rogers and Ingram, 1976 in Dolbeer et al., 1994
methiocarb	D	4.66E-08	-1.8240	2.8678	15.01	orchard	2.61	1.27	1.71	-2.06	-2.323	-2.44	-2.37	-7.70	3	1	Hardy et al., 1993
mexa-carbate	D	2.54E-08	4.1239	2.4446	14.91	forest	0.70	1.51	2.02	-2.34	-2.512	-2.73	-2.68	-7.65	1	0	Pearce and Rick, 1969
mexa-carbate	D	2.54E-08	4.1239	2.4446	14.91	forest	1.00	1.51	2.02	-2.34	-2.512	-2.73	-2.68	-7.65	1	0	Busby et al., 1987; Fleming et al., 1992
mexa-carbate	D	2.54E-08	4.1239	2.4446	14.91	forest	1.09	1.51	2.02	-2.34	-2.512	-2.73	-2.68	-7.65	1	0	Pillmore et al., 1971; Flickinger et al., 1965, 1966; Peterson, 1967
mexa-carbate	D	2.54E-08	4.1239	2.4446	14.91	forest	1.33	1.51	2.02	-2.34	-2.512	-2.73	-2.68	-7.65	1	0	Garrity, 1985
mexa-carbate	D	2.54E-08	4.1239	2.4446	14.91	forest	0.70	1.51	2.02	-2.34	-2.512	-2.73	-2.68	-7.65	1	0	Busby et al., 1987; Fleming et al., 1992; Busby and Blacquiere, 1986
carbofuran	D	6.66E-08	-1.5090	2.3007	14.87	field	1.80	1.54	1.04	-2.44	-2.576	-2.83	-2.79	-7.64	2	0	Johnson et al., 1996, Martin, 1991
carbofuran	D	6.66E-08	-1.5090	2.3007	14.87	field	1.80	1.54	1.04	-2.44	-2.576	-2.83	-2.79	-7.64	2	0	Somers et al., 1988

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
carbofuran	D	6.66E-08	-1.5090	2.3007	14.87	field	1.80	1.54	1.04	-2.44	-2.576	-2.83	-2.79	-7.64	3	1	Fox et al., 1989
carbofuran	D	6.66E-08	-1.5090	2.3007	14.87	field	1.82	1.54	1.04	-2.44	-2.576	-2.83	-2.79	-7.64	2	0	Irvine (1987, 1990) and Forsyth et al., (1989)
carbofuran	D	6.66E-08	-1.5090	2.3007	14.87	field	2.43	1.54	1.04	-2.44	-2.576	-2.83	-2.79	-7.64	3	1	Booth et al., 1989
carbofuran	D	6.66E-08	-1.5090	2.3007	14.87	field	2.43	1.54	1.04	-2.44	-2.576	-2.83	-2.79	-7.64	3	1	Booth et al., 1989
carbofuran	D	6.66E-08	-1.5090	2.3007	14.87	field	2.73	1.54	1.04	-2.44	-2.576	-2.83	-2.79	-7.64	3	1	Jorgensen et al., 1989
carbofuran	D	6.66E-08	-1.5090	2.3007	14.87	field	2.73	1.54	1.04	-2.44	-2.576	-2.83	-2.79	-7.64	3	1	Jorgensen et al., 1989
carbofuran	D	6.66E-08	-1.5090	2.3007	14.87	field	2.73	1.54	1.04	-2.44	-2.576	-2.83	-2.79	-7.64	3	1	Booth et al., 1989
carbofuran	D	6.66E-08	-1.5090	2.3007	14.87	field	2.73	1.54	1.04	-2.44	-2.576	-2.83	-2.79	-7.64	3	1	Booth et al., 1989
oxamyl	D	1.44E-09	-1.2924	-1.1991	14.81	field	2.16	2.16	0.73	-4.91	-4.252	-5.51	-5.62	-7.61	3	1	Frey et al., 1992
cyanophos	I	1.68E-05	2.0212	2.48	15.60	field	3.08	2.71	3.04	-2.44	-2.594	-2.92	-2.88	-7.95	4	1	Mullié et al., 1999
phoxim	I	3.02E-03	-0.7447	4.39	17.27	field	1.58	1.86	2.77	-1.42	-1.914	-2.01	-1.93	-8.73	3	1	McEwen et al., 1972
phoxim	I	3.02E-03	-0.7447	4.39	17.27	field	1.27	1.86	2.77	-1.42	-1.914	-2.01	-1.93	-8.73	3	1	McEwen et al., 1972
phoxim	I	3.02E-03	-0.7447	4.39	17.27	field	1.01	1.86	2.77	-1.42	-1.914	-2.01	-1.93	-8.73	1	0	McEwen et al., 1972

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
trichlorfon	I	1.08E-10	-0.6778	-0.277	16.04	forest	0.92	3.52	3.18	-4.49	-3.985	-5.20	-5.29	-8.15	1	0	DeWeese et al., 1979; Peakall and Bart, 1983
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	field	1.39	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	3	1	Mullie and Keith, 1993
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	field	1.25	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	3	1	McEwen et al., 1969
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	field	1.16	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	3	1	Mullie and Keith, 1993
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	field	0.95	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	1	0	McEwen et al., 1969
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	field	0.90	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	2	0	McEwen et al., 1970
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	field	0.73	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	2	0	McEwen et al., 1970
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	field	0.43	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	1	0	McEwen et al., 1970
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	forest	0.62	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	3	1	Peterson, 1971 and others in Busby et al., 1989
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	forest	0.72	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	3	1	Busby et al., 1989
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	forest	0.79	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	3	1	Pearce, 1974; Fudge and Associates, 1989; Busby et al., 1989

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	forest	0.92	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	2	0	Millikin and Smith, 1990
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	forest	0.92	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	3	1	Pearce, 1968
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	forest	0.95	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	1	0	Spray et al., 1987
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	forest	0.95	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	2	0	Hamilton et al., 1981
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	forest	1.10	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	3	1	Pearce, 1967; Busby et al., 1989; Busby et al., 1990
fenitro-thion	I	7.59E-06	1.2552	3.296	16.65	forest	1.22	2.76	2.77	-2.07	-2.352	-2.64	-2.59	-8.43	3	1	Pearce 1967; 1968
chlor-pyrifos	I	1.03E-04	0.4314	4.6582	18.72	field	0.86	2.77	2.16	-1.55	-1.994	-2.34	-2.29	-9.46	2	0	Mullie and Keith, 1993
chlor-pyrifos	I	1.03E-04	0.4314	4.6582	18.72	field	1.01	2.77	2.16	-1.55	-1.994	-2.34	-2.29	-9.46	3	1	Mullie and Keith , 1993
chlor-pyrifos	I	1.03E-04	0.4314	4.6582	18.72	field	1.17	2.77	2.16	-1.55	-1.994	-2.34	-2.29	-9.46	2	0	McEwen et al., 1986
chlor-pyrifos	I	1.03E-04	0.4314	4.6582	18.72	field	1.17	2.77	2.16	-1.55	-1.994	-2.34	-2.29	-9.46	3	1	Booth et al., 1989
chlor-pyrifos	I	1.03E-04	0.4314	4.6582	18.72	field	1.17	2.77	2.16	-1.55	-1.994	-2.34	-2.29	-9.46	3	1	Booth et al., 1989
chlor-pyrifos	I	1.03E-04	0.4314	4.6582	18.72	field	1.47	2.77	2.16	-1.55	-1.994	-2.34	-2.29	-9.46	3	1	Booth et al., 1989
chlor-pyrifos	I	1.03E-04	0.4314	4.6582	18.72	field	1.47	2.77	2.16	-1.55	-1.994	-2.34	-2.29	-9.46	3	1	Booth et al., 1989

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
fenthion	I	5.60E-05	-0.1308	4.0791	16.68	field	2.14	2.28	2.90	-1.52	-1.980	-2.05	-1.97	-8.44	4	1	Bruggers et al., 1989; Keith et al., 1994; Keith and Bruggers, 1998; Mullié et al., 1999
fenthion	I	5.60E-05	-0.1308	4.0791	16.68	field	0.78	2.28	2.90	-1.52	-1.980	-2.05	-1.97	-8.44	2	0	Powell, 1984
diazinon	I	3.57E-06	1.0792	3.8637	17.45	field	1.97	1.83	2.52	-1.83	-2.193	-2.48	-2.43	-8.81	3	1	McEwen et al., 1967
diazinon	I	3.57E-06	1.0792	3.8637	17.45	field	2.06	1.83	2.52	-1.83	-2.193	-2.48	-2.43	-8.81	3	1	McEwen et al., 1966b
diazinon	I	3.57E-06	1.0792	3.8637	17.45	orchard	2.01	1.83	2.52	-1.83	-2.193	-2.48	-2.43	-8.81	2	0	Rondeau and Desgranges, 1995
diazinon	I	3.57E-06	1.0792	3.8637	17.45	orchard	2.76	1.83	2.52	-1.83	-2.193	-2.48	-2.43	-8.81	3	1	Kendall, 1990
diazinon	I	3.57E-06	1.0792	3.8637	17.45	orchard	2.76	1.83	2.52	-1.83	-2.193	-2.48	-2.43	-8.81	3	1	Kendall, 1990
disulfoton	I	8.57E-05	0.8573	3.8578	16.56	orchard	2.06	1.95	2.84	-1.65	-2.069	-2.18	-2.10	-8.39	2	0	White and Seginak, 1990
dimethoate	I	8.63E-10	-0.6021	0.2781	15.14	field	1.18	2.75	3.47	-3.92	-3.588	-4.48	-4.53	-7.75	1	0	Riedel and Riedel, 1992
dimethoate	I	8.63E-10	-0.6021	0.2781	15.14	orchard	1.02	2.75	3.47	-3.92	-3.588	-4.48	-4.53	-7.75	1	0	Rondeau and Desgranges, 1995
ethyl parathion	I	1.21E-05	-0.0506	3.7309	17.07	field	1.44	2.88	2.77	-1.85	-2.202	-2.45	-2.39	-8.63	1	0	Custer et al., 1985
ethyl parathion	I	1.21E-05	-0.0506	3.7309	17.07	field	1.44	2.88	2.77	-1.85	-2.202	-2.45	-2.39	-8.63	1	0	Custer et al., 1985

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
ethyl parathion	I	1.21E-05	-0.0506	3.7309	17.07	orchard	3.32	2.88	2.77	-1.85	-2.202	-2.45	-2.39	-8.63	4	1	Buttiker, 1961 in Pimentel, 1971
methyl parathion	I	6.87E-06	-0.6990	2.7487	16.22	field	1.82	2.77	3.12	-2.37	-2.554	-2.92	-2.89	-8.23	3	1	Brewer et al., 1988
methyl parathion	I	6.87E-06	-0.6990	2.7487	16.22	field	1.82	2.77	3.12	-2.37	-2.554	-2.92	-2.89	-8.23	3	1	Robinson et al., 1988
methyl parathion	I	6.87E-06	-0.6990	2.7487	16.22	field	1.71	2.77	3.12	-2.37	-2.554	-2.92	-2.89	-8.23	1	0	Smithson, 1978
methyl parathion	I	6.87E-06	-0.6990	2.7487	16.22	field	1.60	2.77	3.12	-2.37	-2.554	-2.92	-2.89	-8.23	1	0	Custer et al., 1985
methyl parathion	I	6.87E-06	-0.6990	2.7487	16.22	field	1.50	2.77	3.12	-2.37	-2.554	-2.92	-2.89	-8.23	2	0	Niethammer and Baskett, 1983
methyl parathion	I	6.87E-06	-0.6990	2.7487	16.22	field	1.42	2.77	3.12	-2.37	-2.554	-2.92	-2.89	-8.23	1	0	Kilbride et al., 1992
methyl parathion	I	6.87E-06	-0.6990	2.7487	16.22	field	1.42	2.77	3.12	-2.37	-2.554	-2.92	-2.89	-8.23	2	0	Edwards and Graber, 1968
malathion	I	3.43E-08	0.7243	2.2878	18.18	field	-0.01	2.18	2.31	-3.11	-3.056	-3.97	-4.00	-9.18	1	0	Parsons and Davis, 1971
malathion	I	3.43E-08	0.7243	2.2878	18.18	field	-0.27	2.18	2.31	-3.11	-3.056	-3.97	-4.00	-9.18	1	0	Keith et al., 1995
malathion	I	3.43E-08	0.7243	2.2878	18.18	field	-0.40	2.18	2.31	-3.11	-3.056	-3.97	-4.00	-9.18	1	0	Ells et al., 1969; 1970
malathion	I	3.43E-08	0.7243	2.2878	18.18	field	-0.40	2.18	2.31	-3.11	-3.056	-3.97	-4.00	-9.18	1	0	McEwen et al., 1964
malathion	I	3.43E-08	0.7243	2.2878	18.18	field	-0.47	2.18	2.31	-3.11	-3.056	-3.97	-4.00	-9.18	1	0	McEwen et al., 1968

Chemical	Mode of action (Direct or Indirect)	Henry's_unitless (calc)	Log Vp (mPa at circa 20 C)	Log_Kow (calc)	MW ^ 0.5	Site group	TP (Log HD5 / m.sq.)	Original avian DTI (Mineau, 2002)	New DTI calculated separately for direct and indirect pesticides	Kp(a) SRC	Kp(b) (Guy and Potts, revised)	Kp(c) Cronin et al.	Kp(d) Moody and MacPherson	Jmax	Initial rating of study	Dichotomous score	Reference
malathion	I	3.43E-08	0.7243	2.2878	18.18	forest	-0.08	2.18	2.31	-3.11	-3.056	-3.97	-4.00	-9.18	1	0	Pascual, 1994
sulprofos	I	6.52E-05	-1.0757	5.6483	17.96	field	1.39	1.29	2.58	-0.68	-1.407	-1.29	-1.17	-9.07	2	0	Schrecken-gast et al., 1989
phosalone	I	1.61E-05	-1.2218	4.2924	19.18	orchard	-0.06	2.36	2.18	-1.92	-2.235	-2.80	-2.78	-9.71	1	0	White and Seginak, 1990
azinphos-methyl	I	1.17E-08	-3.3010	2.5315	17.81	field	1.09	2.70	2.86	-2.86	-2.887	-3.64	-3.66	-8.99	1	0	McEwen and et al., 1968
azinphos-methyl	I	1.17E-08	-3.3010	2.5315	17.81	field	1.34	2.70	2.86	-2.86	-2.887	-3.64	-3.66	-8.99	1	0	Graham and Desgranges, 1993
azinphos-methyl	I	1.17E-08	-3.3010	2.5315	17.81	orchard	1.87	2.70	2.86	-2.86	-2.887	-3.64	-3.66	-8.99	3	1	Johnson et al., 1988
azinphos-methyl	I	1.17E-08	-3.3010	2.5315	17.81	orchard	1.87	2.70	2.86	-2.86	-2.887	-3.64	-3.66	-8.99	2	0	Sheeley et al., 1988
azinphos-methyl	I	1.17E-08	-3.3010	2.5315	17.81	orchard	1.89	2.70	2.86	-2.86	-2.887	-3.64	-3.66	-8.99	1	0	Graham and Desgranges, 1993