Sources of Pesticide Residues in Food: Toxicity, Exposure, and Risk Associated with Use at the Farm Level

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1   Introduction

The contribution of pesticides towards substantial increases in global crop yields during the twentieth century is well understood and has been well documented (see for example, [10]). The so-called Green Revolution of the 1940s–1960s was fuelled by the development of high-yielding crop varieties, the expansion of updated irrigation technologies and the more widespread use of agrochemicals, including synthetic products, for the control of pests and diseases. This sea change in food production methodology is credited with saving the lives of many millions of rural poor in less developed countries and with raising living standards globally. The increasing dependency on, and deployment of, pesticides in crop production that followed the Green Revolution gave birth to an environmental backlash that found voice in Rachel Carson's book Silent Spring (1962). In her book, the author describes a natural environment under threat from the increasing use of agrochemicals; an environment quietened, with bird populations silenced as a result of feeding on insects contaminated by toxic chemicals. Heightened environmental awareness within the general public in developed countries, and increasingly so in less developed countries, has encouraged policy makers to respond with increasingly stringent regulatory management of pesticide deployments. Indeed, in many countries environmental campaigners, through non-governmental organizations (NGOs) have now gained admission to bodies involved in policy development. Furthermore, there is an increasing corpus of internationalized "legislation" with the formulation of a suite of conventions seeking to limit the movement and use of certain pesticides. Nonetheless, problems remain for food producers in developed, especially less developed countries. The issue of risk from pesticide residues fundamentally arises

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from the twin concerns of pesticide toxicity and the hazard it represents, and exposure to these hazards in the environment or in food. Toxicity hazards are related to the intrinsic chemicals (i.e. active ingredients) and so-called inert components of pesticides. Active and other pesticide ingredients have quantifiable toxicities to fish, mammals, bees and humans: they have measurable acute (short term) and chronic (long-term) toxicities. Exposure, *per se*, to a hazardous pesticide is a function of the amount of the chemical in an environment (soil, water or food for example), which is related to that chemical's mobility, persistence and half-life. The food-based residues exposed are related to the intake of specific food items. Of concern to those involved in crop production at the farm level is the exposure route. In other words, it becomes an issue of how the environmental or food load can be minimized using good agricultural practice (GAP). Pesticide loads in the environment or in food are related to the cropping industry's ability to diagnose and quantify a problem and to select an appropriate chemical management solution. The load is also affected by compliance with recommended pesticide dosages and the correct use of appropriate equipment for pesticide application. Load will rise in response to a cavalier approach to the use of personal protective equipment by farm workers, and poor compliance with recommended waiting periods between pesticide application and harvest. Such multifarious elements of the risk quotient are difficult to assess and few attempts have been made to quantify their impact across regions or on downstream sectors of the food industry. In essence, toxicity level and degree of exposure are largely governed by policy; the environmental or food load that leads to exposure is a product of the efficacious implementation of these policies.

2   A Brief History of Pesticides

Although for the public at large the word pesticide is frequently used pejoratively, this is a recent phenomenon. For the vast majority of the history of pesticide use, their character has been seen as benign, positively beneficial. That history is a long one - pesticide use in agriculture goes back several thousand years. Elemental sulphur was used as a dust in Mesopotamia around 2500 BC. In the fifteenth century compounds of mercury, lead and arsenic were being used on crops to fight infestations of insect pests. Indeed, arsenic and mercury containing pesticides remained widely used well into the twentieth century. The nineteenth century saw the emergence of copper containing compounds for the management of fungal diseases. Bordeaux mixture was invented in 1885 as a mixture of copper sulphate and lime. It was as an effective management option for the control of the increasingly damaging vine downy mildew problem and the application of elemental sulphur to the plant surface was difficult to control [28]. Bordeaux mixture and elemental sulphur are still widely used in modern agriculture.

The emergence of chlorine-containing compounds as pesticides was heralded by the synthesis of DDT in 1874 and the subsequent recognition, by Paul Müller in 1939, of its insecticidal properties (for which Müller received a Nobel Prize).

After World War II the use of DDT use in agriculture increased dramatically and an age of organochlorine dominance was established that lasted until the 1970s. After that organophosphate and carbamate insecticides began to replace the chlorine compounds, which was identified for the increasingly serious environmental damage Rachel Carson railed against in Silent Spring.

In Silent Spring [8], Carson critically examines the use of pesticides in controlling insects and the effects of organochlorine and organophosphate pesticides on the broad spectrum of life, including wildlife and indeed, humans. Carson emphasized that the public has a right to know the effects of these chemicals to human health and the environment before their exposure. In the concluding paragraph, Carson says "control of nature is a phrase conceived in arrogance, born of the Neanderthal age of biology and philosophy, when it was supposed that nature exists for the convenience of man. The concepts and practices of applied entomology for the most part date from that Stone Age of science. It is our alarming misfortune that so primitive a science has armed itself with the most modern and terrible weapons, and that in turning them against the insects it has also turned them against the earth" [8].

Recent decades have seen the emergence of systemic pesticides, which has the ability to move within plants. Pesticides such as sulphur, copper sulphate and organo-metal compounds owe their activity to the ability to adhere to the surface of plants to provide a protective coat that repels, through toxicity as it were, the attacking insect or fungus. Systemic pesticides in contrast, are absorbed by the plant and carried through the vascular system. Most systemic pesticides are carried through the xylem, or water conducting vessels of the plant; relatively fewer are phloem transported.

The modes of action of pesticides are as varied as their chemistries. Early organochlorine and organophosphate insecticides were neurotoxins with either very long persistence (some organochlorines) or with extreme toxicity (some organophosphates) [34]. Later developed insecticides also include those with neurotoxicological modes of action (pyrethroids), those that block the enzyme acetylcholinesterase (carbamates), those that act as agonists to acetylcholine (neonicotinoids) and those that mimic the action of insect hormones [34, 51]. Fungicides, like insecticides have a diversity of modes of action. Many act through a disruption of fungal membrane function such as sterol or glycerophospholipid biosynthesis inhibitors, others have effects on cell wall function, inhibit protein synthesis, inhibit respiration or inhibit calcium (Ca^{2+}) signalling [28].

In the years that have followed the publication of Silent Spring, there is no doubt that emphasis at national and international levels has been increased on the reduction of risks associated with pesticide use. Greater efforts have been placed both on the reduction of the toxicological hazards (i.e. limiting exposure via environment and dietary intake) of the active ingredients, which are available in agricultural use. Since 1991 the EU, for example, has withdrawn the registration status of several 100 pesticide active ingredients (http://eur-lex.europa.eu), although as we'll see, the actual number of active, active ingredients withdrawn is a point for debate. Many countries routinely review the safety data relating to pesticides and periodically proscribe additional active ingredients. The Sultanate of Oman, for example, on the grounds of environmental and human safety, recently enacted legislation to prohibit

the use of 131 pesticide active ingredients and restrict the use of a further 30 [3]. In addition to national legislation (or lack thereof) most nations are signatories to international conventions. The Stockholm Convention prohibits the production and use of certain persistent organic pollutants (POPs), including pesticides (Table 1). Similarly, the Rotterdam Convention imposes limitations to the transboundary shipment of certain pesticide active ingredients without prior informed consent (Table 2).

Semantics are important in order to avoid confusion. Because those contributing to the scientific literature relating to pesticides are prone to the use of loose, or poorly defined terminology and the overlapping use of words with similar meanings, it is worthwhile here to introduce some definitions of terms that will be used throughout the rest of the chapter. So, a toxin is a poison; a chemical that is poisonous is a chemical that has toxicity and is capable of causing damage to living things or to the environment. To be exposed is to be open to danger; exposure therefore is the state of having no protection from a danger (or hazard). Finally, a risk is the possibility (or here, mathematical probability) of something (usually unpleasant) happening. Other terms will also crop up here, especially a key component of a novel concept in pesticide risk assessment. So, a hazard is a danger; a hazardous chemical is a chemical that represents a danger, perhaps because of its toxicity. An impact is a marked effect (i.e. degree of damage) or influence.

3   Pesticide Toxicity and Hazard

Pesticides are chemicals (or usually cocktails of different chemicals packaged together for sale). Therefore, each of the ingredients of a pesticide has specific properties - molecular weight, solubility, boiling point, and so on. Chemical pesticides usually consist of two types of ingredients: an active ingredient (sometimes more than one "*ai*" or just "active") that has specific properties making them effective in (usually) killing a target, such as an insect, fungus or weed. The active ingredient of a pesticide may make up less than 50% of the formulated product; sometimes much less than 50%. The remaining contents are usually composed of a mixture of ingredients including perhaps solvents, chemicals that help the *ai* to stick to the plant surface, or chemicals that protect the *ai* from photo-degradation, etc. These non-*ai* ingredients are referred to "inert ingredients" or sometimes simply "inerts", although as we shall see, these so-called inert ingredients are frequently far from inert. All chemical ingredients in a pesticide also have a taxonomy and are classified accordingly; each one has a unique identification code such as the CAS (Chemical Abstract Service) identifier number (www.cas.org). The widely used insecticide active ingredient Avermectin (Abamectin), for example, has the CAS numbers 65195-55-3 and 65195-56-4 for the B1A, B1B forms (different from each other as shown by R in Fig. 1) and 71751-41-2 for the mixture of the B1A and B1B forms. Avermectin, a naturally occurring product from the fermentation of the actinomycete *Streptomyces avermitilis*, is placed within the group of chemicals known as macrocyclic lactones, referring to the basic structure of the molecule:

Table 1 Pesticides covered by the Stockholm Convention on Persistent Organic Pollutants (POPs)

Pesticide included in the original Convention document, coming into force in 2004	CAS number	Chemical group and target	Additional POP pesticides added in 2009 or under consideration for future inclusion	CAS number	Chemical group and target
Aldrin	309-00-2	Organochlorine herbicide	Alpha hexachlorocyclohexane	319-84-6	Organochlorine insecticide
Chlordane	57-74-9	Organochlorine insecticide	Beta hexachlorocyclohexane	319-85-7	Organochlorine insecticide
DDT	50-29-3	Organochlorine insecticide	Chlordecone	143-50-0	Organochlorine insecticide and fungicide
Dieldrin	60-57-1	Organochlorine insecticide	Hexachlorobutadiene	87-68-3	Organochlorine herbicide
Heptachlor	76-44-8	Organochlorine insecticide	Lindane	58-89-9	Organochlorine insecticide and acaricide
Hexachlorobenzene	118-74-1	Organochlorine fungicide	Pentachlorobenzene	608-93-5	Organochlorine fungicide
Mirex	2385-85-5	Organochlorine insecticide	Endosulfan[a]	115-29-7	Organochlorine insecticide and acaricide
Toxaphene	8001-35-2	Organochlorine insecticide	Dicofol[b]	115-32-2	Organochlorine acaricide

Adapted from: www.chm.pops.int; Stockholm Convention [48]
[a]Endosulfan is included but with specific exemptions of use
[b]Dicofol is currently under consideration for inclusion

Table 2 Pesticides subject to the Rotterdam Convention on the Prior Informed Content for the transboundary movement of hazardous chemicals and pesticides in international trade

| Pesticide	CAS number	Chemical group and target	Pesticide	CAS number	Chemical group and target
2,4,5-T and its salts and ester	93-76-5	Synthetic auxin fungicide and herbicide	Ethylene oxide	75-21-8	Cyclic ether fumigant
Alachlor	15972-60-8	Chloroacetamide herbicide	Fluoroacetamide	640-19-7	Acetamide rodenticide and insecticide
Aldicarb	116-06-3	Carbamate insecticide, acaricide and nematicide	HCH (mixed isomers)	608-73-1	Organochlorine insecticide
Aldrin[a]	309-00-2	Organochlorine herbicide	Heptachlor[a]	76-44-8	Organochlorine insecticide
Azinphos-methyl	86-50-0	Organophosphate insecticide, acaricide and molluscicide	Hexachlorobenzene[a]	118-74-1	Organochlorine fungicide
Binapacryl	485-31-4	Dinitrophenol fungicide, insecticide and acaricide	Lindane (gamma-HCH)[a]	58-89-9	Organochlorine insecticide and acaricide
Captafol	2425-06-1	Phthalimide fungicide	Mercury compounds, including inorganic mercury compounds, alkyl mercury compounds and alkyloxyalkyl and aryl mercury compounds	Various	Fungicide and insecticide
Chlordane[a]	57-74-9	Organochlorine insecticide	Methamidophos	10265-92-6	Organophosphate insecticide and acaricide
Chlordimeform	6164-98-3	Formamidine acaricide and insecticide	Monocrotophos	6923-22-4	Organophosphate insecticide and acaricide
Chlorobenzilate	510-15-6	Organochlorine acaricide and insecticide	Parathion	56-38-2	Organophosphate insecticide and acaricide
DDT[a]	50-29-3	Organochlorine insecticide	Pentachlorophenol and its salts and esters	87-86-5 (*)	Organochlorine insecticide, herbicide, fungicide, molluscicide, plant growth regulator and wood preservative

Dinitro-ortho-cresol (DNOC) and its salts (such as ammonium salt, potassium salt and sodium salt)	534-52-1	Dinitrophenol herbicide, insecticide, acaricide and fungicide	Tributyl tin compounds	1461-22-9, 1983-10-4, 2155-70-6, 24124-25-2, 4342-36-3, 56-35-9, 85409-17-2	Organometal fungicide and molluscicide
Dinoseb and its salts and esters	88-85-7 (*)	Dinitrophenol herbicide	Dustable powder formulations containing a combination of benomyl at or above 7%, carbofuran at or above 10% and thiram at or above 15%	137-26-8, 1563-66-2, 17804-35-2	Benomyl – Benzimidazole fungicide and acaricide; Carbofuran – Carbamate insecticide, acaricide and nematicide; Thiram – Carbamate fungicide
EDB (1,2-dibromoethane)	106-93-4	Organobromine fumigant and insecticide	Methyl-parathion (Emulsifiable concentrates (EC) at or above 19.5% active ingredient and dusts at or above 1.5% active ingredient)	298-00-0	Organophosphate insecticide and acaricide
Endosulfan[a]	115-29-7	Organochlorine insecticide and acaricide	Phosphamidon (Soluble liquid formulations of the substance that exceed 1000 g active ingredient/l)	13171-21-6	Organophosphate insecticide and acaricide
Ethylene dichloride	107-06-2	Chlorinated hydrocarbon insecticide			

Chemical groups according to *PPDB* Pesticide Properties DataBase (sitem.herts.ac.uk/aeru/ppdb/en/index.htm)
Adapted from: www.pic.int; Rotterdam Convention [46]
[a]Pesticides also included in the Stockholm Convention, see Table 1

Fig. 1 Chemical structure of Avermectin

Avermectin B$_{1a}$
R = CH$_2$CH$_3$

Avermectin B$_{1b}$
R = CH$_3$
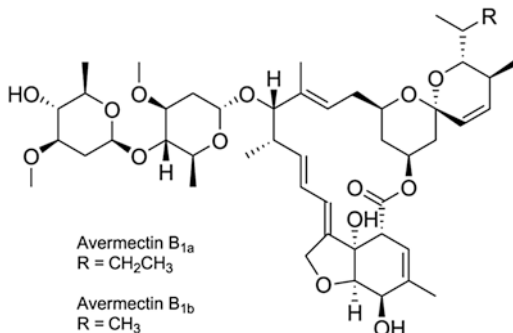
General information about the hazardous nature of a specific chemical pesticide and the risks associated with its use are included in the Material Safety Data Sheet (MSDS). In many countries, the information on the MSDS (and the product label) are approved by the relevant national regulatory body, such as the US Environmental Protection Agency (EPA), and the MSDS thus becomes the legal mechanism of approved rates and uses is given [50]. A typical MSDS also provides information about the toxicology of the pesticide. In the case of Avermectin, this information includes details about oral and dermal toxicities (usually reported as an LD$_{50}$ value), inhalation toxicity (as LC$_{50}$) and skin and eye irritation potential (Table 3). All data is collected from laboratory-based experiments involving small animals.

The MSDS also contains information about the chronic toxicity of pesticides where this is available. This will include any known carcinogenicity reports as well as details of specific target organ effects (eyes, skin, liver, kidneys, central nervous system, and respiratory system), effects on reproduction and development (endocrine effects) and any known genotoxicities. Ecological information is provided in the form of LD$_{50}$ or LC$_{50}$ concentrations used on key indicator species of fish, birds and invertebrates including bees. Environmental fate is usually reported as chemical half-life in soil and in water (Table 3).

Many attempts have been made to bring together the available data on the hazards posed by a specific pesticide. Amongst the most widely referenced is that produced by the World Health Organization [60]. In 2009, WHO revised their criteria for the classification of pesticides based on Acute Toxicity Hazard Categories from experimental data to determine the rat LD$_{50}$ (mg/kg) via the oral and dermal routes (Table 4).

The WHO classification of pesticides, naturally, places the toxicological emphasis on the potential impact of a chemical pesticide on mammalian health. Of course, broader concerns also need to be addressed, including the potential environmental hazard. The Pesticide Action Network (PAN, www.pesticideinfo.org), an international coalition of non-governmental organizations (NGOs) and others that campaigns against the excessive use of pesticides, maintains a database of pesticide active ingredients and their hazards. The PAN database provides toxicology summary information, gleaned from a variety of sources, and summarized as five indicators of hazardousness: acute toxicity, carcinogenicity, cholinesterase inhibition,

Table 3 Toxicological and environmental hazard data for the insecticide Avermectin as provided by the Material Safety Data Sheet (MSDS)[a]

Test	Subject[b]	Result
Oral	Rabbit LD_{50}	300 mg/kg
Dermal	Rat LD_{50}	>5000 mg/kg
Inhalation	Rat 4-h LC_{50}	>2.09 mg/L
Eye irritation	Rabbit	Moderately irritating
Skin irritation	Rabbit	Slightly irritating
Skin sensitization	Not a contact sensitizer in guinea pigs following repeated skin exposure	
Ecotoxicity	Bluegill 96-h LC_{50}	9.6 ppb
	Rainbow trout 96-h LC_{50}	3.6 ppb
	Daphnia 48-h EC_{50}	0.34 ppb
	Honey bee 48-h contact LD_{50}	0.022 µg/bee
	Bobwhite quail oral LD_{50}	>2000 mg/kg
	Bobwhite quail 8-day dietary LC_{50}	3102 ppm
	Mallard duck 5-day dietary LC_{50}	383 ppm
Environmental fate	Average half-life in soil	5–10 h
	Average half-life in water	18 h

[a]Nufarm Abamectin 0.15 EC Insecticide MSDS, issued October 1, 2010
[b]LD_{50}: The median lethal dose is the average amount of a chemical substance capable of killing 50% of the test animals exposed under specific experimental conditions; usually expressed in mg/kg body weight by oral intake or skin exposure; LC_{50}: The median lethal concentration is the average concentration of a chemical as gas, vapour, mist, fume or dust capable of killing 50% of the test animals exposed by inhalation under specific experimental conditions; often expressed as mg/L over a given time of exposure; EC_{50}: The half maximal effective concentration (EC_{50}) is the concentration of a pesticide which induces a response halfway between the baseline and maximum after a specified exposure time.

Table 4 World Health Organization Acute Toxicity Hazard Categories for the classification of pesticide active ingredients

WHO Class		LD_{50} for the rat (mg/kg body weight)		Example active ingredients
		Oral	Dermal	
Ia	Extremely hazardous	< 5	< 50	Captafol
Ib	Highly hazardous	5–50	50–200	Beta-cyfluthrin
II	Moderately hazardous	50–2000	200–2000	Lambda cyhalothrin Endosulfan
III	Slightly hazardous	Over 2000	Over 2000	Hexaconazole
U	Unlikely to present acute hazard	5000 or higher		Mancozeb

reproductive or developmental toxicity, endocrine disruption and potential of the active ingredient to contaminate groundwater (Table 5). In addition, the PAN database labels active ingredients as "Bad Actors" if they have been shown to represent a known toxicological hazard in any one category.

The PAN classification of some widely used pesticide active ingredients is shown in Table 6. The list represent those pesticide active ingredients most extensively

Table 5 Classification system for pesticide active ingredients adopted by the Pesticide Action Network and used to categorize the toxicities of pesticides

	Acute toxicity	Carcinogen	Cholinesterase (ChE) inhibitor	Groundwater contaminant	Development or reproductive toxin	Endocrine disruptor	PAN Bad actor chemical
PAN categories	Extremely toxic	Known	Yes	Known	Yes	Suspected	Yes
	Highly toxic	Known (EPA/P65)[a]	No	Potential	No	Insufficient data	No
	Moderately toxic	Probable		Insufficient data			
	Slightly toxic	Possible					
	Not acutely toxic	Unclassifiable					
		Unlikely					
Other ranking systems with equivalences or sources of information	WHO, US EPA, US National Toxicity Program, MSDS data, US EPA's Toxic Releases Inventory	US EPA, International Agency for Research on Cancer (IARC), US National Institute for Health, State of California Proposition 65 Carcinogen List (P65)	MSDS, California Department of Pesticide Regulation's list of ChE-inhibiting pesticides	**Potential** groundwater contaminants are those that meet the California Department of Pesticide Regulation's (DPR's) criteria. **Known** groundwater contaminants either meet DPR's criteria or have been found repeatedly in groundwater in California (and elsewhere), but are not regulated as groundwater contaminants in California.	US EPA's Toxic Releases Inventory, State of California Proposition 65 List	PAN uses a combination of data sources including the Ilinois EPA List, Danish EPA List of Endocrine Disrupting Auxiliaries, the European Union Prioritization List, the Colborn List, the Keith List and the Benbrook List. See pesticideinfo.org for more details	Based on known toxicities in any one of the other categories

[a]Pesticide active ingredients listed as a carcinogen by US EPA and/or P65 but not by the other organizations

Table 6 Most extensively used (ha treated) active substances on vegetable crops in 2013 in the United Kingdom (excluding seed treatments) along with the PAN classifications and WHO hazard class for these active compounds

Active substance	Use type	Acute toxicity	Carcinogen	Cholinesterase inhibitor	Groundwater contaminant	Development or reproductive toxin	Endocrine disruptor	PAN Bad actor Chemical	WHO
Lambda-cyhalothrin	Insecticide	Moderate	Not likely	No	No data available	No data available	Suspected	Not listed	II
Pendimethalin	Herbicide	Slight	Possible	No	No data available	No data available	Suspected	Not listed	II
Pirimicarb	Insecticide	Moderate	Known (P65)	Yes	No data available	No data available	No data available	Yes	II
Azoxystrobin	Fungicide	Not acutely toxic	Not likely	No	Potential	No data available	No data available	Not listed	U
Mancozeb	Fungicide	Not acutely toxic	Known	No	Potential	Yes	Suspected	Yes	U
Deltamethrin	Insecticide	Moderate	Unclassifiable	No	No data available	No data available	No data available	Not listed	II
Linuron	Herbicide	Slight	Possible	No	Potential	Yes	Suspected	Yes	III
Clomazone	Herbicide	Moderate	Not likely	No	Potential	No data available	No data available	Not listed	II
Prothioconazole	Fungicide	Not acutely toxic	Not likely	No	No data available	No data available	No data available	Not listed	U
Ioxynil	Herbicide	Moderate	No data available	No	No data available	No data available	Suspected	Not listed	II

Source: Garthwaite et al. ([22], [23])

used by vegetable growers in the UK, the data is taken from the most recent series of regular surveys [23]. Although six of the ten active ingredients listed are within Class II of the WHO hazard classification, only three are listed as PAN bad actor chemicals. Herein lies an important issue in the discussion of pesticide toxicity hazard data: although the science behind the estimation of active ingredient toxicities may be precise, the interpretation of this information becomes profoundly less precise if quantitative toxicological data is first transformed into one of several qualitative layers (high, medium, and low, for example) and multiple criteria so transformed are amalgamated into complex quasi-quantitative indices or quotients of environmental or human impact. It is little wonder then that Maud et al. [36] noted a poor correlation between the rankings of pesticides, when the ranks themselves were based on toxicological data.

Problems with impact quotients will be discussed further below. An examination of similar data collected for the same crop types in the UK less than 15 years earlier, in 1999 [26], shows nine of the ten most widely used active ingredients are classed as Moderately Hazardous (Class II) and five are listed as PAN "Bad Actor" chemicals (Table 7). In part, the reduction in Class II pesticides in the top ten list is a result of the withdrawn approval, by EU regulations, of Cyanazine and Propachlor (both herbicides) in 2002 and 2008 respectively. Limitations of quotient systems notwithstanding, clearly there has been an apparent decrease in the hazard level of the most frequently used pesticides over time.

Other reports of time-wise decreases in the overall toxicity hazards represented by the suite of pesticide active ingredients available and/or used in agriculture similarly show a decrease in toxicity over time. Of the ten pesticides most widely (per hectare) used in grassland and fodder crop production in UK in 1997, nine were in WHO toxicity class Ib or II [25]. In 2013, amongst the most widely used on a hectare basis [22] only four products were in Class II with no Class Ib products.

Table 7 Most extensively used (ha treated) active substances on vegetable crops in 1999 in the United Kingdom (excluding seed treatments) along with the PAN classifications and WHO hazard class for these active compounds

Active ingredient	Use type	PAN Bad actor chemical	WHO Classification
Lambda-cyhalothrin	Insecticide	Not listed	II
Pirimicarb	Insecticide	Yes	II
Chlorothalonil	Fungicide	Yes	U
Dimethoate	Insecticide	Yes	II
Metalaxyl	Fungicide	Not listed	II
Ioxynil	Herbicide	Not listed	II
Deltamethrin	Insecticide	Not listed	II
Cypermethrin	Insecticide	Not listed	II
Cyanazine[a]	Herbicide	Yes	II
Propachlor[b]	Herbicide	Yes	II

Source: Garthwaite et al. [26]
[a]Withdrawn from EU approval through regulation 2002/2076
[b]Withdrawn from EU approval through regulation 2008/742

Interestingly in this case the Class Ib active, Methiocarb is currently still permitted under EU regulations, whilst the Class III pesticide Atrazine was withdrawn under EU regulation 2004/248. Although the toxicity range of products used in arable crop production in UK showed little change between 1998 and 2014 with five active ingredients in WHO Class II in 1998 and 2014 [21, 24], Cross and Edwards-Jones [12] reported that, for UK arable crop production between 1992 and 2002, the Environmental Impact Quotient (EIQ, see below) profile of pesticides used fell by 14%. Similarly, the pesticide load (EIQ/amount used) decreased by 15% and the pesticide load per hectare fell by 7%. Although many have questioned the utility of the EIQ system (also see below), the trend of decreasing toxicities of the pesticides used by farmers over time is likely to be correct. Across Europe, the decrease in toxicities of products used in commercial farming has undoubtedly been a result of the loss of approved status of active ingredients following the adoption of EU directives, regulations and amendments to directive 91/414/EC "Placing of Plant Protection Products on the Market Directive" (subsequently replaced by EU Regulation 1107/2009) (http://eur-lex.europa.eu) [29]. The number of actives withdrawn has been significant with Karabelas et al. [29] quoting the loss of 704 ingredients. However, many of the active ingredients withdrawn are within the higher WHO toxicity classes (Table 8). Furthermore, the high number of withdrawals is, to some extent, a reflection of good housekeeping. Many ingredients were never approved for their use in the EU and these are expunged from the system (Table 9). Indeed, obsolete active ingredients make up over 25% of the products listed by the EU for withdrawal of approved status.

   Table 9 also shows that the list of active ingredients with approved status withdrawn is dominated by organophosphates. Organophosphates are powerfully insecticidal, they breakdown rapidly, but are amongst the most toxic of pesticides to vertebrates, including mammals [51]. Elsewhere, Al Zadjali et al. [3] reported a temporal decrease in the overall toxicity levels of pesticides being used in Oman, between 1999 and 2012. Again, this was in response to specific legislation enacted to withdraw from the market specific active ingredients with high toxicities or with other potentially detrimental effects to the environment. Not unexpectedly, the

Table 8 Breakdown by percentage of those pesticide active ingredients with approved status withdrawn following Directive EU/1107/2009

WHO Toxicity Class	Percentage of active ingredients with EU approval withdrawn[a]
Class Ia	4.9
Class Ib	10.9
Class II	27.5
Class III	12.3
Class U	16.9
Obsolete	27.5

[a]Percentages are derived from active ingredients appearing both on the EU list of approved products (ec.europa.eu/food/plant/pesticides/eu-pesticides-database, accessed 7 November 2015) and WHO [60]

Table 9 Chemical group and principal target of pesticide active ingredients with EU approved status withdrawn

WHO pesticide classification	Chemical family	Principal target[a]							
Obsolete pesticides		AC	FU	HB	IN	NE	RO	ST	Total
	Anilide			1					1
	Aryloxyphenoxy-propionate			2					2
	Benzimidazole		1						1
	Bridged diphenyl	3			1				4
	Coumarin						1		1
	Dinitroaniline			2					2
	Organochlorine	3			2			1	6
	Organophosphate		1		22	2			25
	Oxazole		1						1
	Phenylurea			2					2
	Thiocarbamate		1	3					4
	Triazine			1					1
Toxicity class Ia									
	Coumarin						2		2
	Organophosphate				10				10
Toxicity class Ib									
	Coumarin						2		2
	Dinitrophenol			1	1				2
	Organochlorine			1					1
	Organophosphate	1			17				18
	Pyrethroid				2				2
Toxicity class II									
	Anilide			1					1
	Aryloxyphenoxy-propionate			2					2
	Chloroacetamide			3					3
	Dinitroaniline			1					1
	Dinitrophenol	1	1						2
	Organochlorine	1		1	2				4
	Organometal	2	2	1					5
	Organophosphate	1	1	1	16				19
	Oxazole			1					1
	Pyrethroid				7				7
	Thiocarbamate			5	1				6
	Triazine			1					1
Toxicity class III									
	Benzoylurea				1				1
	Chloroacetamide			3					3

(continued)

Table 9 (continued)

WHO pesticide classification	Chemical family	Principal target[a]							
	Chlorophenyl		1						1
	Dinitroaniline			1					1
	Organometal	1							1
	Organophosphate			1	2				3
	Pyrethroid				1				1
	Sulfonylurea			1					1
	Thiocarbamate			3					3
Toxicity class U									
	Anilide			1					1
	Benzimidazole		2						2
	Benzoylurea	1			3				4
	Bridged diphenyl	1							1
	Chloroacetamide			1					1
	Chlorophenyl		2						2
	Dinitroaniline			2					2
	Organochlorine			1	1				2
	Oxazole		1						1
	Phenylurea			1					1
	Pyrethroid				3				3
	Sulfonylurea			3					3
	Thiocarbamate			1					1
	Triazine			2					2

[a]*AC* acaricide, *FU* fungicide, *HB* herbicide, *IN* insecticide, *NE* nematicide, *RO* rodenticide, *ST* sterilant

overall level of the toxicities of pesticides used by farmers has also been reported to change in response to factors such as education and farmer extension programmes [47] and membership of a farmer cooperative [3].

In order to summarize the combined human and environmental hazard of pesticide active ingredients, several attempts have been made to create composite indices of pesticide impact. Amongst the first attempts at summarizing the environmental and human hazards posed by individual chemical pesticides into a single value was the Environmental Impact Quotient (EIQ) developed at Cornell in the 1990s [31]. The EIQ of a pesticide is calculated as the average of three components that assess the farm worker, consumer, and ecological hazard components. The formula used includes measures of dermal and chronic toxicity, active ingredient systemicity, fish, bee, bird and beneficial arthropod toxicity, leaching and plant surface life potential, and soil and plant surface half-life. Even though many alternative and in most cases, more complex and realistic evaluation models have been developed since the EIQ, it remains the most widely used. This is arguably because of its simplicity and because an updated database is available that holds the EIQ scores of

many pesticides. This makes it a simple and tempting tool that provides a single value for the "impact" of a pesticide active ingredient. Many published reports have incorporated an evaluation of pesticide use based on EIQ changes or differences between seasons [37], over time [47], across crop types [20], when transgenic and conventional crops are compared [7, 30], and between farmers [5].

There have been many powerful critiques of the EIQ methodology, especially since its later refinement to include data on field application rates for pesticides. Essentially, the problem lies with the fact that the EIQ system and similar schemes use qualitative labels to estimate risks to the worker, consumer and environment. The EIQ equation incorporates arbitrary qualitative ratings (1, 3 and 5 for low medium and high risk/impact/toxicity/persistence) into a mathematical function as absolute certainty values without reference to probability of occurrence [43]. By way of providing an example of the discrepancies thrown up when uncertainty (probability associated with risk) is explicitly excluded, Peterson and Schleier III [43] cite the examples of cypermethrin and acetamiprid (both insecticides) with EIQ ratings of 36.4 and 28.7 respectively (ie potentially large differences environmental impact). When uncertainty is incorporated the adjusted EIQ values for the two insecticides overlap with each other for more than 90% of their ranges. Peterson and Schleier III [43] argue that instead of qualitative schemes there is a need for alternatives that quantitatively estimate risk through the integration of toxicity and exposure information. Increasingly so, this probabilistic approach is becoming more widely adopted by regulatory agencies and academics. Other concerns about the use of EIQ arise from the difficulty in coping with the increasingly frequent use of pesticide mixtures. The multiplication of an EIQ value by a number of pesticide applications (thereby multiplying the error) [47] and the frequent use of surrogate EIQ scores where the Cornell database does not include an EIQ rating for a specific active ingredient. Such surrogates are frequently calculated from averages of other pesticides within the same class of actives [12, 13, 32]. Alternatives to the EIQ method, using probabilistic analyses, to assess risk as a function of toxicity and exposure are further discussed below.

In any discussion of toxicology, hazard and exposure, the emerging concern surrounding the so-called inert ingredients within pesticide formulations needs to be mentioned. By definition, all pesticide formulations contain at least one (frequently two, occasionally more than two) active ingredients; this (these) may make up less than 50% of the contents of the pesticide container. Inert ingredients may be solvents, food substances (edible oils, spices) or other natural materials such as cellulose. Inert ingredients can play a crucial role in pesticide effectiveness (Table 10). However, "inert" is not synonymous with "non-toxic" and many countries require regulatory approval and a review of safety information of inert ingredients before products containing them can enter the market. Nonetheless, the precise formulation of inert ingredients is frequently a trade secret and argument has raged over whether full public disclosure of inert ingredients should be required [59].

Research suggests that inert ingredients within pesticide formulations can increase the ability of pesticide formulations to alter toxicological outcomes

Table 10 Possible functions of inert ingredients within pesticide formulations

Sl. No.	Function
1	Act as a solvent to help the active ingredient penetrate a plant's leaf surface
2	Improve the ease of application by preventing caking or foaming
3	Extend the product's shelf-life
4	Improve safety for the applicator
5	Protect the pesticide from degradation due to exposure to sunlight

Source: www2.epa.gov/ingredients-used-pesticide-products

Table 11 Comparison of groundwater ubiquity scores for four active ingredients and some of the inert ingredients with which they may be formulated

Name	Koc[a]	Soil half-life (days)	GUS[a] score	GUS designation[b]
Glyphosate	**24,000**	**30**	**-0.56**	**Nonleacher**
1,2-benzisothiazolin-3-one	104	30	2.93	Leacher
POEA	2500–9600	42	0.98	Nonleacher
Imazapyr	**100**	**90**	**3.91**	**Leacher**
Isopropylamine	33	20–200	4.96	Leacher
2,4-D	**53**	**7**	**2.18**	**Transitional**
Butoxyethanol	67	7–28	2.49	Transitional
Alachlor	**161**	**14**	**2.06**	**Transitional**
Chlorobenzene	126	35	2.93	Leacher

Source: Surgan et al. [49]
Active ingredients designated in bold type
[a]*Koc* carbon adsorptivity, *GUS* groundwater ubiquity score
[b]"Leacher" (GUS > 2.8), "Transitional" (GUS 1.8–2.8), and "Nonleacher" (GUS < 1.8) are used as defined by Gustafson [27]

(developmental neurotoxicity, genotoxicity, and hormone function). They can also increase exposure to pesticide active ingredients by increasing dermal absorption, decreasing the efficacy of protective clothing and increasing environmental mobility and persistence. Inert ingredients may also increase the phytotoxicity of pesticide formulations as well as toxicity to fish, amphibians, and microorganisms [6, 11]. In some cases, the inert ingredients have a greater propensity to contaminate groundwater than the actives with which they are co-formulated as indicated by higher GUS (Groundwater Ubiquity) scores ([49], Table 11). The GUS scores are a function of carbon adsorptivity (KOC) and soil half-life (DT50) of the chemicals assessed [27].

As if to emphasise the point that so-called inert ingredients can actually be anything but inert, the US EPA recently proposed the removal of 72 inert compounds from the list of approved chemicals (Table 12). Although none of these chemicals appears in US traded pesticide formulations, they have been recorded in pesticide products in other countries such as Oman (Said Al Zadjali, personal communication).

Table 12 Pesticide inert ingredients with their approved status in doubt as the US EPA proposes their withdrawal

	CAS Reg. No	Chemical Name		CAS Reg. No	Chemical Name
1	109-89-7	Diethylamine	37	16919-19-0	Ammonium fluosilicate
2	78-93-3	Methyl ethyl ketone	38	1762-95-4	Ammonium thiocyanate
3	109-99-9	Tetrahydrofuran	39	25013-15-4	Vinyl toluene
4	123-92-2	1-Butanol, 3-methyl-, acetate	40	25154-52-3	Nonylphenol
5	80-62-6	Methyl methacrylate	41	2761-24-2	Amyl triethoxysilane
6	100-02-7	p-Nitrophenol	42	28300-74-5	Antimony potassium tartrate
7	10024–97-2	Nitrous oxide (N2O)	43	50-00-0	Formaldehyde
8	100-37-8	2-(Diethylamino)ethanol	44	533-74-4	Dazomet
9	101-68-8	4,4-Methylenedi(phenyl isocyanate)	45	552-30-7	Trimellitic acid andydride
10	106-88-7	1,2-Butylene oxide	46	618-45-1	o-m-p-Isopropylphenols
11	107-18-6	Allyl alcohol	47	71-55-6	1,1,1-Trichloroethane
12	107-19-7	Propargyl alcohol	48	7440-37-1	Argon
13	108-46-3	Resorcinol	49	74-84-0	Ethane
14	110-19-0	Isobutyl acetate	50	75-43-4	Dichloromonofluoromethane
15	110-80-5	Ethylene glycol monoethyl ether	51	75-45-6	Chlorodifluoromethane
16	112-55-0	Dodecyl mercaptan	52	75-68-3	1-Chloro-1,1-difluoroethane
17	117-81-7	1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester	53	75-69-4	Trichlorofluoromethane
18	117-84-0	Dioctyl phthalate	54	75-71-8	Dichlorodifluoromethane
19	119-61-9	Benzophenone	55	76-13-1	1,1,2-Trichloro-1,2,2-trifluoroethane
20	121-54-0	Benzenemethanaminium, N,N-dimethyl-N-(2-(2-(4-(1,1,3,3-tetramethylbutyl) phenoxy)ethoxy)ethyl)-, chloride	56	7758-01-2 x	Potassium bromate
21	123-38-6	Propionaldehyde	57	78-88-6	2,3-Dichloropropene
22	124-16-3	Butoxyethoxypropanol	58	79-11-8	Monochloroacetic acid
23	1303-86-2	Boron oxide (B2O3)	59	79-24-3	Nitroethane
24	1309-64-4	Antimony trioxide	60	79-34-5	1,1,2,2-Tetrachloroethane
25	131-11-3	Dimethyl phthalate	61	8006-64-2	Turpentine, oil
26	131-17-9	Diallyl phthalate	62	83-79-4	Rotenone
27	1317-95-9	Tripoli	63	85-44-9	Phthalic anhydride
28	1319-77-3	Cresol	64	88-12-0	N-Vinyl-2-pyrrolidone
29	1321-94-4	Methyl naphthalene	65	88-69-7	2-Isopropylphenol
30	1338-24-5	Naphthenic acid	66	88-89-1	2,4,6-Trinitrophenol
31	139-13-9	Aminotriethanoic acid	67	94-36-0	Benzoyl peroxide
32	141-32-2	Butyl acrylate	68	95-48-7	o-Cresol

Table 12 (continued)

	CAS Reg. No	Chemical Name		CAS Reg. No	Chemical Name
33	142-71-2	Copper acetate	69	97-63-2	2-Propenoic acid, 2-methyl-, ethyl ester
34	149-30-4	2-Mercaptobenzothiazole	70	97-88-1	Butyl methacrylate
35	150-76-5	p-Methoxyphenol	71	98-54-4	p-tert-Butylphenol
36	150-78-7	1,4-Dimethoxybenzene	72	99-89-8	o-m-p-Isopropylphenols

Source: www.federalregister.gov/articles/2014/10/22/2014-24586

Table 13 Most frequently produced generic pesticide active ingredients as of 2006

Rank	Active ingredient	Activity	Number of manufacturers
1	Glyphosate	Herbicide	39
2	Chlorpyrifos	Insecticide	33
3	Cypermethrin	Insecticide	31
4	Carbendazim	Fungicide	23
5	2,4-D	Herbicide	23
6	Imidacloprid	Insecticide	22
7	Acephate	Insecticide	20
8	Mancozeb	Fungicide	20
9	Endosulfan	Insecticide	17
10	Fenvalerate	Insecticide	17

Source: PAN-UK [40]

Finally, it should be mentioned that increasing frequency with which so-called "Me-too" or generic pesticide formulations are entering the crop protection market. The increasing trend in market share occupied by off-patent pesticides has been recognised for some time [54] and is set to increase dramatically with an estimated $4 billion worth of pesticides set to come off-patent by 2020 (news.agropages.com accessed 28 November 2015). The most frequently produced generic pesticides (Table 13) are gaining an increasing market share not only in less developed countries [3] but also in Europe, North America and elsewhere [40]. Between them China and India have over 50% of the manufacturing companies producing generic pesticides [40].

With the increasing market penetration by generic pesticide products comes a concern for ensuring product quality. Research on generic abamectin-containing products from Turkey has shown significant differences in efficacy of active ingredients against specific insect targets, and variations in active ingredient content away from the label specification, by as much as 69% [17]. The risk here is that farmers, in response to reduced efficacy, are tempted to increase dose rates and/or frequency of application with a concomitant enhancement of risk through human and environmental exposure.

4 Worker, Environment and Consumer Exposure and Risk Assessment

Earlier the discussion touched on the inappropriateness of the EIQ and similar systems to provide a reliable indicator of the risk of pesticide use due to the method by which its mathematical equation was constructed using essentially qualitative labels. Exposure is the actual (rather than surrogate qualitative label) environmental or dietary concentration of a pesticide active ingredient [41]. Discussion of exposure must also, therefore, encompass the routes by which exposure loads are generated. Such a discussion thus includes farm practices in relation to pest and disease management: farmer decision-making, especially problem diagnosis and the appropriateness of the response.

Minimizing downstream pesticide exposure relies on maximizing the efficacy of decision-making at the farmer level. Briefly, the decision chain followed during effective pest and disease management begins with correct diagnosis and quantification of the problem, followed (in the current context) by the selection of an appropriate chemical. The chain then relies on accurate mixing of the correct dose and its application at the proper rate using appropriate technology and under conditions conducive to effective delivery to the plant. Finally, the process requires that the crop should not be harvested prior to the implementation of the pre-harvest interval (waiting period) for the specified crop/pesticide combination. At the same time the process of pesticide application to minimize exposure, should require use of personal protective equipment (PPE) and knowledge of appropriate disposal methods for empty containers and unused mixes.

Correct problem diagnosis is a serious problem in many developing countries where extension services may be non-existent, poor or inaccessible. Diagnosis might be based on the type of damage rather than the true causal agent [39] and application of control measures may be more related to the perceived value of the crop rather than the actual need for protection. The ability to make an accurate link between the problem and the most appropriate active ingredient is frequently lacking [44]. Application equipment selection is frequently limited by availability and in many developing countries the knapsack sprayer is routinely used and not infrequently misused [35] even though this may not be the most appropriate tool for some pesticides. Non-observance of the appropriate pre-harvest is commonplace [15, 58]. Consequently, where any one or more of these factors are present, worker and indeed downstream exposure to pesticide active ingredients is likely to be raised.

There is a further set of factors that mitigate against the minimizing exposure to pesticides. These factors involve the attitude towards safety of those responsible for pesticide applications, either through lack of knowledge or wilful neglect of regulations. Many reports exist of poor adherence to the required use of personal protective equipment (PPE) and lax protocols for the disposal of empty containers and unused pesticide mixes (see for example [2, 4]). As Al Zadjali et al. [4] report, a cavalier attitude towards personal safety is unlikely to accompany concern towards

Table 14 US EPA occupational pesticide handler unit exposure surrogate reference table

Exposure scenario (Activity, formulation etc)	Exposure route	Personal protective equipment level	Unit exposure (ug/lb ai)
Mixing/loading wettable powders	Dermal	No gloves	3700
		Gloves	170
		Double layer clothing, gloves	130
		Water soluble packaging	9.8
	Inhalation	No respirator	43.4
		PF5 respirator	8.68
		PF10 respirator	4.34
		Water soluble packaging	0.24
Applicator, open cab groundboom sprayer	Dermal	No gloves	9.9
		Gloves	7.2
		Double layer clothing, gloves	4.2
		Enclosed cab	2
	Inhalation	No respirator	1.2
		PF5 respirator	0.24
		PF10 respirator	0.12
		Enclosed cab	0.22
Applicator, granules by hand	Dermal	No gloves	104,000
		Gloves	71,000
		Double layer clothing, gloves	40,280
	Inhalation	No respirator	470
		PF5 respirator	94
		PF10 respirator	47
Mixer/loader/applicator, backpack crop sprayer, ground/soil directed	Dermal	No gloves	8260
		Gloves	8260
		Double layer clothing, gloves	4120
	Inhalation	No respirator	2.58
		PF5 respirator	0.516
		PF10 respirator	0.258

Extracted from: US EPA [57]

the potential for pesticide residues in food or environment. Models to assess the likely exposure of farm workers to pesticides such as the European EUROPOEM II suggest that, merely through the use of gloves as a single form of PPE, worker exposure is reduced by a factor of 5 [19].

Of course, access to advanced pesticide application machinery is limited in less developed countries. Consequently, the potential exposure to pesticides is likely to be far higher. Table 14 shows an extract of the data compiled by the US EPA (Pesticide Handlers Exposure Database, PHED) to model exposure factors for farm worker operations and the level (if any) of PPE used [57]. The values in Table 14 are surrogates to be used in model development, but are consistent with data obtained experimentally. The data shows that a farm worker in a less developed country who (a) does not use PPE, (b) mixes and loads the pesticide himself and (c) applies that

pesticide using a knapsack sprayer (see for example [2]) has a potential exposure 100 times greater than an applicator using modern tractor driven machinery with an enclosed cab. The PHED database also includes other exposure scenarios and is an invaluable tool in estimating potential risks resulting from pesticide use, including risks to the health of farm workers (see for example [1, 13, 16, 33, 38, 42]). In Europe, the European Food Standards Authority (EFSA) is carrying out similar assessments of exposure under different scenarios that might affect farm workers, by-standers and residents [18].

Ecological exposure hazards arise due to escape, out of the farming environment, of pesticide ingredients. In the USA, the EPA is responsible for conducting ecological hazard assessments to determine what risks are posed by a pesticide and whether changes are necessary to protect the environment. The results of these assessments inform the pesticide registration process. Toxicity data submitted in support of registration is evaluated with respect to potential hazards posed to non-target fish and wildlife species. Assessments are made for direct and indirect (food chain) effects. The EPA and similar authorities elsewhere also assess the hazards posed through the interaction of pesticides with soils, air, sunlight, surface water and ground water. Potentially hazardous exposures are affected by the method and speed by which pesticides degrade and the toxicities of the breakdown products that result. Of critical importance also is the method and route by which pesticides or their breakdown products travel from the application site where they accumulate in the environment. Long term exposures are effected by the active ingredients break down in water, soil, and light; and how easily they evaporate in air; and how quickly they travel through soil. More recent studies have been accumulating on the ease with which pesticides are removed from foliage by direct contact or by weather events. For example, the EUROPOEM II model suggests that the so-called transfer coefficient (TC) of pesticides from the crop surface to harvesting workers can be substantial, presumably the TC to casual bystanders could also be significant. The rate at which pesticides degrade on the plant surface is measured as the foliar half-life (Table 15 for selected active ingredients). The foliar half-life will then have a bearing on the extent to which pesticide active ingredients or their breakdown products will enter the non-agricultural arena. For those seeking more information about the assessment of pesticide exposures in the soil and for terrestrial and aquatic ecosystems and the consequent potential risks might consult the US EPA resource at www.epa. gov/pesticide-science-and-assessing-pesticide-risks.

Pesticide exposure through the dietary route comes about as exposure through consumption of both food and water; active ingredients as residues on food items and active ingredients that have seeped into the groundwater and contaminated the drinking water supply. Maximum residue levels (MRL, or Tolerances in the USA) are established in many countries to set an upper limit to the potential exposure to pesticides in foodstuffs. In the USA, the EPA establishes tolerances for each crop use of a pesticide after developing a risk assessment (see below) that considers:

- The aggregate, non-occupational exposure from the pesticide;
- The cumulative effects from exposure to pesticides that have a common mechanism of toxicity;

Table 15 Foliar half-life (in days) for selected pesticide active ingredients

AI Name	Foliar half-life	AI Name	Foliar half-life
2,4,5-T, triethylamine salt	10	Fluazifop-p-butyl	4
2,4-DB, ester	9	Fosetyl-Al	0.1
Aldrin	2	Glyphosate (ANSI)	3
Arsenic acid	10,000	Imazapyr (ANSI)	30
Atrazine (ANSI)	5	Imazethapyr (ANSI)	30
Azoxystrobin (BSI, ISO)	3	Imidacloprid	3
Benomyl (ANSI)	6	Isofenphos	30
Bifenthrin (ANSI)	7	Lindane	3
Captan (ANSI)	9	Maneb	3
Carbaryl (ANSI)	7	Mecoprop	10
Carbofuran (ANSI)	2	Metalaxyl (ANSI)	30
Chlordane	3	Methidathion (ANSI)	3
Chloroneb (ANSI)	30	Methomyl (ANSI)	1
Clomazone (ANSI)	3	Oxadiazon (ANSI)	20
DDT	4	Parathion (ANSI)	4
Dicamba (ANSI)	9	Permethrin, mixed cis,trans (ANSI)	8
Dicloran	4	Prochloraz (ANSI)	30
Dieldrin	5	Profenofos (ANSI)	3
Dinoseb (ANSI)	10	Propargite (ANSI)	5
Endosulfan (ANSI)	3	Rimsulfuron (ANSI)	3
Endothall (ANSI)	7	Sethoxydim	3
Ethofumesate (ANSI)	10	Terbacil (ANSI)	30
Fenbuconazole (ANSI)	3	Thiabendazole	30
Fensulfothion	3	Thiophanate-methyl (ANSI)	5
Fenthion	2	Thiram	8
Ferbam	3	Triforine (ANSI)	5

Extracted from: EFSA [18]

- Whether there is increased susceptibility to infants and children or other sensitive subpopulations, from exposure to the pesticide and
- Whether the pesticide produces an effect in people similar to an effect produced by a naturally occurring oestrogen or produces other endocrine disruption-effects (www.epa.gov/pesticide-tolerances).

Some risk assessment methods work on the assumption that residues will be present in food at the maximum level permitted by the MRL or Tolerance. Other risk assessments use actual or anticipated residue data. In the USA, the Food and Drug Administration (FDA) enforce tolerances for non-meat foods (see Table 16).

Once pesticide residue data is available (either as MRL/Tolerances, or as actual residues) then this can be linked to consumption data that is frequently accessible through national surveys such as the US National Health and Nutrition Examination Survey/"What We Eat in America" (NHANES/WWEIA) dietary

Table 16 Selected US FDA pesticide residue tolerances for the fungicide azoxystrobin in selected food commodities

Commodity	Parts per million	Commodity	Parts per million
Almond, hulls	4	Pepper/eggplant subgroup 8-10B	3
Artichoke, globe	4	Peppermint, tops	30
Asparagus	0.04	Persimmon	2
Avocado	2	Pistachio	0.5
Barley, grain	3	Rapeseed subgroup 20A	1
Berry, low growing, subgroup 13-07G, except cranberry	10	Rice, grain	5
Brassica, head and stem, subgroup 5A[a]	3	Rice, wild, grain	5
Brassica, leafy greens, subgroup 5B	25	Rye, grain	0.2
Fruit, citrus, group 10–10	15	Star apple	2
Fruit, small vine climbing, except fuzzy kiwifruit, subgroup 13-07F	2	Starfruit	2
Fruit, stone, group 12[b]	1.5	Sugar apple	2
Herb Subgroup 19A, dried leaves	260	Sunflower subgroup 20B	0.5
Herb Subgroup 19A, fresh leaves	50	Tamarind	2
Lychee	2	Tomato subgroup 8-10A	0.2
Nut, tree, group 14	0.02	Vegetable, cucurbit, group 9	0.3
Onion, bulb, subgroup 3-07A	1	Vegetable, foliage of legume, group 7	30
Onion, green, subgroup 3-07B	7.5	Vegetable, leafy, except brassica, group 4	30
Papaya	2	Vegetable, leaves of root and tuber, group 2	50
Passionfruit	2	Vegetable, legume, edible podded, subgroup 6A, except soybean	3
Pawpaw	2	Vegetable, root, subgroup 1A[c]	0.5
Pea and bean, dried shelled, except soybean, subgroup 6C	0.5	Vegetable, tuberous and corm, subgroup 1C	8
Pea and bean, succulent shelled, subgroup 6B	0.5	Watercress	3
Peanut	0.2	Wax jambu	2
Peanut, refined oil	0.6	Wheat, grain	0.2

Extracted from: www.gpo.gov/fdsys/pkg/CFR-2014-title40-vol24/xml/CFR-2014-title40-vol24-part180.xml

[a]USDA reported residues for azoxystrobin in broccoli, peaches and carrot in 2013 were in the range 0.002–0.46 (75/708 positive broccoli samples, EPA tolerance 3.0 ppm), [b]0.002–0.13 (17/285 positive peach samples, EPA tolerance 1.5 ppm) and [c]0.01–0.031 (55/712 positive carrot samples, EPA tolerance 0.5 ppm) [55]

datasets (http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm) or the Dietary Exposure Evaluation Model - Food Commodity Intake Database (DEEM-FCID). Ongoing monitoring of chemical residues in food products of agricultural origin is performed by government bodies in various countries and the information

gathered can be combined with pesticide toxicity datasets to construct probabilistic models that assess risk as a function of both exposure and toxicological information [53].

Systems such as the USDA Continuing Survey of Food Intake by Individuals (CSFII), the Dietary Exposure Evaluation Model–Food Commodity Intake Database (DEEM-FCID/CALENDEX) and Cumulative and Aggregate Risk Evaluation System (CARES) are being used to assess risk from dietary intakes of pesticides and microbes; they use the US EPA as a focus. Similarly, the EU has developed the Pesticide Residue Intake Model (PRIMo) for assessments of pesticide exposure through food intake (http://www.efsa.europa.eu/en/applications/pesticides/tools). The model is based on national food consumption figures and unit weights provided by EU Member States and implements internationally agreed risk assessment methodologies to assess the short-term (acute) and long-term (chronic) exposure of consumers. A third model system, LifeLine™ [52] is a tool for characterizing population-based aggregate and cumulative exposures and risks from pesticide residues in food and tap water as well as in the home following residential uses. LifeLine™ is a probabilistic model of exposures to pesticides applicable to the US and Canadian populations and select sub-populations. A summary of different model systems is shown in Table 17.

Finally, whilst there have been few studies that specifically address the cancer risk from chronic exposures to pesticide residues, Reiss et al. [45] compared the benefits of increased fruit and vegetable consumption with the risk associated with potential exposure to pesticide residues. Using standard risk assessment methods and EPA methodologies to estimate cancer risk for the dietary consumption of pesticide residues on food [56] the authors describe a general formula for estimating the lifetime risk associated with a given commodity–pesticide combination as follows:

$$LR = \overline{C} \times \overline{R} \times Q_1^* / 1000$$

Table 17 A summary of three exposure-risk assessment model systems

Factor	LifeLine	DEEM/Calendex	CARES
Target of evaluation pathway	Food exposure, drinking water, residential exposure		
Food consumption material and population group character	CSFII survey/FCID, National Center for Health Statistics	CSFII survey/ FCID	CSFII survey and population census, CARES (stratified)
Residential pesticide monitoring material	Pesticide data program, total diet study etc		
Assessment result	Exposure rate (personal, aging, exposure pattern and exposure rate) and risk	Exposure rate and risk	Exposure rate and risk
Probabilistic approach	Distribution estimate	Distribution estimate	Distribution estimate

Source: Choi et al. [9]

DEEM dietary exposure evaluation model, *CARES* cumulative and aggregate risk evaluation system, *CSFII* continuing survey of food intake by individuals, *FCID* food commodity intake database

Table 18 Cancer unit risk values for pesticides

Pesticide	Q^*_1 (mg/kg/day)	Pesticide	Q^*_1 (mg/kg/day)
Carbaryl	0.000875	Fluometuron	0.018
Chlordane cis	0.35	Hexachlorobenzene (HCB)	1.6
Carbendazim	0.00239	Imazalil	0.061
DCPA	0.00149	Permethrin cis	0.0096
DDDo,p	0.24	Permethrin Total	0.0096
DDDp,p	0.24	Permethrin trans	0.0096
DDEp,p	0.34	Propargite	0.0033
DDTp,p	0.34	Tetraconazole	0.023
Dieldrin	16	Thiacloprid	0.0406
Diuron	0.0191	Trifluralin	0.0058
Fenbuconazole	0.00359		

Source: Reiss et al. [45]; this reference also provides citations for original source data

where: LR = lifetime cancer risk; $\overline{C}$ = average daily consumption of the commodity across the US population (g/kg bw/day); $\overline{R}$ = average residue level of a pesticide on the commodity (mg/kg of commodity consumed); Q_i^* = cancer unit risk factor (mg/kg/day)$^{-1}$ (Table 18). The factor of 1000 adjusts R to the grams of commodity consumed.

Reiss et al. [45] programmed dietary consumption data from CSFII and USDA pesticide residue data (see for example [55]) into the DEEM–FCID model to provide chronic dietary consumption data for all fruit and vegetable commodities by the general US population. The authors' resulting estimates are that approximately 20,000 cancer cases per year could be prevented by increasing fruit and vegetable consumption, while up to ten cancer cases per year could be caused by the added pesticide consumption. Of course, by the authors' own admission, the estimates have significant uncertainties (not least the reliance on rodent bioassays for cancer risk). Nonetheless "the overwhelming difference between benefit and risk estimates provides confidence that consumers should not be concerned about cancer risks from consuming conventionally-grown fruits and vegetables" [45].

5   Conclusions

The risks associated with pesticide use come about through the combined influences of active ingredient toxicities and the levels to which we are exposed to them in our diet, our employment or in our recreational activities. Over time we have seen a reduction in the toxicities of the pesticides available to farmers and food producers. National governments have become increasingly active in prohibiting the use of the most toxic active ingredients. International ingredients such as the Rotterdam and Stockholm Conventions have helped to raise the awareness of legislators to the dangers posed by certain active ingredients and families of actives. However, we have seen

that within a commercial pesticide formulation, the active ingredient may constitute the minor part of the total content. To understand the potential for harm we need also to consider the role of the so-called inert ingredients. Inert ingredients may have the potential to be anything but inert; some may have toxicities as high as some active ingredients. Our future challenge is to understand the importance of these other ingredients in chemical exposures. We well understand the routes of exposures to pesticides. In the farming arena we can quantify the importance, in terms of reducing exposure, of accurate problem definition, appropriate pesticide selection and sensible application procedures. Our challenge here is to raise standards globally. For most of us, the risks from pesticides come from long-term exposures to small amounts of toxic chemicals. Recent developments in the modelling of the cumulative effects of these exposures helps us to guide legislators in their task of formulating future lists of allowed and prohibited active and inert ingredients. Finally, exposure data and risk models help us to understand the processes by which illnesses, including cancers develop. By understanding the process, we can aim to minimize the occurrence.

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