GENERIC RISK ASSESSMENT MODEL FOR INSECTICIDES USED FOR LARVICIDING AND MOLLUSCICIDING

SECOND EDITION

World Health Organization

Generic risk assessment model for insecticides used for larviciding and mollusciciding

2nd Edition

World Health Organization
Communicable Diseases cluster
Department of Control of Neglected Tropical Diseases
Vector Ecology and Management
&
Climate and Other Determinants of Health cluster
Department of Public Health, Environmental and Social Determinants of Health
International Programme on Chemical Safety
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The Secretariat revised the document based on these comments; advice was then sought on open questions during an expert consultation from Health Canada of the Government of Canada, the British Health and Safety Executive, the Finnish Institute of Occupational Health and the Dutch National Institute for Public Health and the Environment (RIVM). The document was then finalized by the Secretariat as the second edition. Comments received during peer review and the views of experts consulted during the expert consultation were advisory in nature, and the contents of the document are the responsibility of the Secretariat.

Terminology, abbreviations and acronyms

ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
AUC	area under curve
BCF	bioconcentration factor
BMD	benchmark dose
CICAD	Concise International Chemical Assessment Document
C_{max}	peak plasma concentration
DDD	daily dietary dose
DFI	daily food intake
EC	European Commission
EC_{50}	concentration having a 50% effect on test populations against a specific end-point
EFSA	European Food Safety Authority
EPPO	European and Mediterranean Plant Protection Organization
ETR	exposure–toxicity ratio
EU	European Union
EUROPOEM	European Predictive Operator Exposure Model
GHS	Globally Harmonized System of Classification and Labelling of Chemicals (United Nations, 2015)
GLP	good laboratory practice
guideline scenario	exposure scenario which assumes that the product is used according to the instructions given on the product label and in WHO guideline information
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety
JMPM	Joint Meeting on Pesticide Management
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint Meeting on Pesticide Residues
lax standard scenario	exposure scenario in which no personal protective equipment other than light clothing covering the trunk is assumed
LC_{50}	concentration killing 50% of the test organisms
LOAEL	lowest-observed-adverse-effect-level
LOEC	lowest-observed-effect concentration
NOAEL	no-observed-adverse-effect-level
NOEC	no-observed effect concentration
NOED	no-observed effect dose (terminology used in environmental risk assessment (EPPO, 2003)
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure level
PEC	predicted environmental concentration
PNEC	predicted no-observed-effect concentration
PPE	personal protective equipment
RfC	reference concentration
RfD	reference dose
RPE	respiratory protective equipment
TSD	tolerable systemic dose
TSD_{AC}	tolerable systemic dose, acute exposure
TWA	time-weighted average
TWAC	time-weighted average concentration
UF	uncertainty factor
UKPOEM	UK Predictive Operator Exposure Model
USEPA	United States Environmental Protection Agency
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme
WP	wettable powder formulation, diluted in water before use

1. Introduction

This generic risk assessment model can be applied for both larviciding and molluscicide products. The terms “insecticide” or “pesticide” are used in this document as generic terms and should be understood to refer also to chemical products used to control larvae, snails and relevant life-cycle stages as appropriate. A risk assessment model for vector traps which use larvicides or adulticides is annexed to this document.

Immature stages of vectors living in permanent or semipermanent water bodies can be controlled by applying a larvicide. This is usually done in urban and other densely populated areas, including refugee camps, but may also take place in extensively irrigated farms or other wetlands close to residential areas. Larviciding is a part of larval source management and should be applied within an integrated vector management approach involving use of other vector control methods and approaches. It can be applied to control vectors of malaria, dengue and other mosquito-borne diseases, as well as nuisance mosquitoes, but is most effective in ecological situations where mosquito breeding habits are few, fixed and findable (WHO, 2005b; WHO, 2006).

A number of products can be used in larviciding.[1] These are chemical insecticides, including insect growth regulators and juvenile hormone mimics; biological/microbial formulations (e.g. bacterial larvicides); petroleum and other types of oils; and monomolecular surface films. The WHO-recommended larvicide classes are: bacterial larvicides; benzoylureas; juvenile hormone mimics; organophosphates; and spinosyns. The end-use larvicide products include liquid formulations (emulsifiable concentrates and suspension concentrates) as well as solid formulations (tablets for direct application; granules; matrix release formulations; water-dispersible granules; and wettable powders). The solid formulations are designed either for immediate release of their active ingredients into water, or their solid matrix provides a slow and prolonged release of the active ingredients giving a prolonged residual action of weeks or months, and applied in certain habitats, e.g. water-storage containers.

Larvicide products may be applied to water used for irrigation of food crops, or to treat drinking-water supplies. Pyrethroids are not recommended by WHO for larviciding since they are considered to have too wide an impact spectrum on non-target aquatic species.

Schistosomiasis is an acute and chronic neglected tropical disease caused by infection with the larval forms of parasitic worms. Fresh-water snails are an intermediate host of the causative agent, the trematode worms of the genus *Schistosoma*. Molluscicide, i.e. decreasing the populations of the host snails by application of molluscicides, is a component of many campaigns against schistosomiasis. WHO currently recommends use of an emulsifiable concentrate and a wettable powder formulation of a molluscicide active ingredient (niclosamide).

The active ingredients used in larviciding and molluscicide are different and have different toxicity profiles. The formulated products and use patterns are not the same. However, the ways in which these products are applied are such that the exposures are likely to be similar. Therefore, a common generic risk assessment model can be applied for both larviciding and molluscicide products.

The equipment used to apply the liquid formulations of mosquito larvicides and molluscicides are typically compression-sprayers and lever-operated back-pack (knapsack) sprayers fitted with either a fan or a cone nozzle. Solid formulations are dispersed by the use of an applicator (e.g. for granules) and manually by gloved hands. WHO has published specifications for the equipment used in such applications (WHO, 2018a). The

[1] http://www.who.int/neglected_diseases/resources/WHOPES/en/; http://www.who.int/pq-vector-control/prequalified-lists/en/

requirements, procedures and criteria for testing and evaluation of mosquito larvicides are available in WHO guidelines (WHO, 2005b). Watering cans, hand-operated compression sprayers and motorized sprayers can be used to apply molluscicide to moist soil or still water. WHO has also published an operational guideline on field use of molluscicides (WHO, 2017a).

2. Purpose

The purpose of this document is to provide a generic model that can be used for risk assessment of larviciding and molluscicidingl; it aims to harmonize the risk assessment of such pesticides for public health use. The assessment considers both adults and children (all age groups) as well as people in the following specific categories:

– those handling products and preparing/loading the spray liquid in application equipment;
– those applying the spray or other formulations; and
– residents who may come into contact with treated waters during washing, bathing, fishing or any other activity, or use the treated waters.

Assessments of human health risk should consider the use of larvicides and molluscicides in potable water. Aspects of ecological risk must also be assessed because of the direct application of the products into the aquatic environments – and in this case, risk assessment should also characterize the risk to populations of non-target organisms.

The structure of this document follows that of *A generic risk assessment model for insecticide-treated nets* (WHO, 2018b). Because risk assessment is a constantly evolving process, guidance is also subject to change. Readers are therefore advised to consider any newer guidance published by WHO and other authoritative sources.

3. Background

It is recommended that risk assessments proposed for larviciding and molluscicidingl products are not conducted de novo; rather, risk assessments that have already been generated for pesticides in the regulatory context of crop protection can be used as a starting point where applicable and available. Preference should be for international assessments, followed by peer-reviewed regional or national assessments; risk assessments published in reputable journals would be a third possible source.

For each component of the risk assessment, the additional information – or modification of the existing assessment – likely to be needed will be identified and discussed. It is assumed that the generic guidance given here will be followed in parallel with one of the published regulatory schemes. These regulatory schemes are intended for guidance and none is wholly prescriptive; all state specifically that expert judgement is required. Similarly, expert judgment will be needed to determine the modifications needed to make published risk assessments from regulation of pesticides suitable for the specific task of risk assessment of larviciding and molluscicidingl products.

3.1 Probabilistic vs. deterministic risk assessment models

Historically, exposure models have been based on point estimates. This deterministic approach has the advantages of simplicity and consistency. Risk characterization is relatively straightforward: the exposure estimate is compared with a health-based guidance value, which is also a point estimate. For the screening – or first-tier assessment – of products, the deterministic assessment is completely appropriate. However, it has an important drawback in that it incorporates no information about the variability of exposure.

The probabilistic technique offers a complementary modelling approach that incorporates variability of exposure between individuals and at different points in time and allows an assessment of the uncertainty of the assessment outcome (uncertainty of data, such as limited availability of empirical information, as well as limitations in the measurements,

models or techniques used to develop representations of complex physical, chemical and biological processes) (WHO, 2008). Probabilistic modelling uses distributions of values rather than single values. The advantage of the technique is that it provides the probability of occurrence and/or amount of exposure, which offers a realistic and informative way of characterizing risk. Just as for deterministic models, however, the validity of the exposure estimate depends on the quality and extent of the input data and the reliability of the estimation algorithm.

Probabilistic methods have been used widely in North America in dietary exposure estimations (for example by the United States Environmental Protection Agency, USEPA). During the past few years, regulatory bodies and industry have also moved towards the use of probabilistic techniques in refining exposure estimates in occupational exposures (for example, in estimates produced by the United Kingdom's Chemicals Regulation Division). The European Commission and the OECD (Organisation for Economic Co-operation and Development) Working Group on Pesticides have prepared reports on the use of probabilistic methods for assessing operator exposure to plant protection products. In addition, use of probabilistic methods has been proposed for effects assessment (both for hazard identification and for assessment factors).

Problems in using probabilistic techniques lie principally in the following areas:
– the difficulty of using the models;
– algorithm development;
– collection of good-quality input distributions;
– criteria for decision-making (what is an acceptable risk and what is not); and
– communicating the results to stakeholders.

Models that are easier to understand and more "user-friendly" are under development and should be available in the near future. Nevertheless, despite this apparent simplicity, it is critical that risk assessors and regulators remain fully aware of the pitfalls of modelling. They must have comprehensive knowledge of the principles of exposure assessment and the techniques used to describe the exposure and risk – and thus be able to ask the right questions. Probabilistic modelling has proved to be a very useful technique in more complex situations or when deterministic assessments have identified exposures of concern (second- and higher-tier assessments) (Nordic Council of Ministers, 2007).

WHO encourages anyone using the models published here to consider the probabilistic approach as an alternative, especially when higher-tier assessments are needed. Sophisticated probabilistic models are also being developed for hazard characterization and may provide alternative ways of setting acceptable exposure levels in the future (WHO, 2009a).

3.2 Essential elements of a health risk assessment model

Comprehensive presentations on the principles of risk assessment are available elsewhere in the scientific literature (e.g. WHO, 1999; WHO, 2009b); only a summary is given here.

Hazard is defined as the inherent capacity of a chemical substance to cause adverse effects in humans and animals and to the environment.

Risk is defined as the probability that a particular adverse effect will be observed under certain specified conditions of *exposure* or use.

Risk characterization is the process of combining hazard and exposure information to describe the likelihood of occurrence and the severity of adverse effects associated with a particular exposure in a given population.

Risk assessment refers to the entire process of hazard assessment, exposure estimation and risk characterization. Consideration of any *uncertainties* in the hazard assessment,

exposure assessment and risk characterization is an essential part of a valid, good-quality risk assessment.

Risk management is the subsequent process that considers the risk assessment in parallel with any potential benefits, socioeconomic and political factors, and the possibilities for risk reduction, as well as other issues of relevance in making operational decisions on the acceptability of a particular level of risk.

Risk assessments involve three steps:

1. *Hazard assessment*. Hazard assessment comprises hazard identification and hazard characterization, i.e. identification of the possible toxic effects of a substance, the dose/exposure levels at which those effects occur, and the dose/exposure levels below which no adverse effects are observed.
2. *Exposure assessment*. Exposure assessment may concern operators (applicators), residents of treated areas, bystanders, domestic animals, wildlife and the environment. Exposure should be assessed in a "**guideline scenario**", which assumes that the product is used according to the instructions given on the product label and in WHO guideline information (WHO, 2006; WHO, 2017a). A "**lax standard scenario**", however, takes into account the reality that these instructions are not necessarily followed completely. Conservative, high end-point estimates of the default distributions are used as defaults. No account is taken of intentional misuse. All relevant routes of exposure are covered.
3. *Risk characterization*. Risk characterization compares estimates of exposure with acceptable exposure levels previously defined in hazard assessment in all relevant exposure situations.

The various sections of this document deal with specific information demands, data sources, uncertainties, discussion on vulnerable or sensitive subgroups, selection of default values and the underlying assumptions.

4. The health risk assessment model

4.1 Hazard assessment

The purpose of a human health hazard assessment is to identify:

– whether an agent may pose a hazard to human health; and
– the circumstances in which the hazard may be expressed (WHO, 1999).

It involves the assessment of all available data on toxicity and on mode of action, and the establishment of dose–response curves and the threshold dose below which the toxic effects are no longer observed. The principles of human health hazard assessment are discussed in greater detail elsewhere (e.g. WHO, 1999; WHO 2009b); they are generally applicable to all chemical classes and patterns of use, although there may be some differences, e.g. in data requirements.

4.1.1 Sources of data

Hazard identification is based on collecting and analysing relevant data on the possible effects of the larvicide or molluscicide on humans. These data may include both toxicological (in vivo and in vitro) data as well as human data. It is recommended that, when available, risk assessments that have already been generated for the substance, e.g. in the regulatory context of crop protection, be used as a starting point. These risk assessments usually contain all the relevant health hazard data available for the substance in question and are therefore important sources of data. Preference should be for international assessments, followed by peer-reviewed regional or national assessments; evaluations published in reputable, peer-reviewed journals are also possible sources.

Examples of this type of authoritative evaluation are given in Table 1. Many can be accessed on the Internet, for example via OECD's eChemPortal (http://www.echemportal.org).

When existing evaluations are used as a starting point, the original study reports should also be consulted if they are identified as critical to the risk assessment. Literature searches should be conducted for any new published data, and any relevant unpublished studies should be evaluated and considered.

4.1.2 Types of health hazard data

Human data

If larvicides or molluscicides have been in use for many years, human data on their hazardous properties may be available. These data include:

– case reports of accidental and deliberate exposures and poisonings;
– epidemiological studies, including occupational studies on those manufacturing or using the product formulations in question, or general population studies; and
– ethically approved volunteer studies examining mild, temporary effects of acute exposure or toxicokinetics of the substance in a limited number of subjects.

Evaluation of the relevance of these studies to risk assessment and their advantages and limitations are discussed in greater detail elsewhere (e.g. WHO, 1999). In general, however, existing reliable human data on particular aspects of toxicity should take precedence over animal data in the risk assessment. Hazard information data are most often available only for active ingredients, but all available data on the formulation should be noted. The so-called non-active ingredients also present in product formulations should be recognized and taken into account whenever possible. Exposure assessment, however, always considers formulations.

Table 1. Examples of authoritative evaluations that may be used as starting points for the risk assessment of larvicides and molluscicides

Joint Meeting on Pesticide Residues (JMPR) – Monographs and Evaluations	http://www.inchem.org/pages/jmpr.html
International Programme on Chemical Safety (IPCS):	
Concise International Chemical Assessment Documents	http://www.inchem.org/pages/cicads.html
Environmental Health Criteria Monographs	http://www.inchem.org/pages/ehc.html
International Agency for Research on Cancer (IARC) – Monographs on the Evaluation of Carcinogenic Risks to Humans	http://monographs.iarc.fr/
United States Environmental Protection Agency (USEPA) – Pesticide evaluations	https://iaspub.epa.gov/apex/pesticides/f?p=chemicalsearch:1
European Food Safety Authority (EFSA) – Pesticide Risk Assessments	http://www.efsa.europa.eu/en/pesticides/pesticidesscdocs.htm
European Chemicals Agency – Information on Chemicals search page	https://echa.europa.eu/information-on-chemicals

Experimental toxicity data

For many substances, the human database is very limited. In these cases, hazard assessment relies on information from experimental animals and on in-vitro studies. For substances recently registered or reregistered for use by regulatory authorities, it is expected that comprehensive toxicology studies will have been conducted according to modern standards and good laboratory practice (GLP), using internationally accepted protocols for toxicological testing such as those published by OECD (2011) or USEPA (2010). For older substances, animal toxicity data may be limited and may not encompass modern requirements (unless they have been recently evaluated in regulatory programmes intended to review older regulated substances).

Like all substances, chemicals used in larviciding or mollusciciding have the potential to cause a wide range of toxic effects. To identify the critical effects of the substance in question, a range of toxicity studies is usually needed. Although test requirements may vary to some extent with the country or region or with the precise use of the product, the range of toxicity tests normally needed for health risk assessment, for example in regulatory approval of pesticides and biocides in OECD countries, is very similar (see Table 2).

It should be noted that toxicity test data are usually available only for technical materials of the active ingredients or solvents used in product formulations rather than for the product formulations themselves. Sometimes, however, some acute toxicity tests may also be performed with a formulation.

4.1.3 Range of toxicity tests normally required for pesticide approval

In addition to the general requirements outlined in the previous section, information on dermal absorption is valuable in assessing the health risks of substances used in larviciding or molluscicide because of the possible repeated dermal exposure of inhabitants of treated areas. Inhalation toxicity studies may also be of value in the assessment of risks to operators who are subject to potential acute and repeated inhalation exposure.

Table 2. Range of toxicity tests normally required for pesticide approval
Note: Studies marked with an asterisk (*) may provide useful dose–response data.

- **Toxicokinetic studies**, usually in the rat, using single and repeat oral dosing, to provide information on absorption, metabolism, distribution and excretion of the parent compound and its metabolites.
- **Acute toxicity studies**, to define the approximate lethal doses by oral, percutaneous, and sometimes inhalation routes, and the effects on body weight, clinical signs and gross pathology produced at lower dose levels following single- dose administration.
  - **Skin irritation studies**
  - **Eye irritation studies**
  - **Skin sensitization studies**
- **Repeat-dose oral toxicity studies***, normally for a minimum of 90 days in both rat and dog, to identify effects on organs, tissues, blood cells, and blood and urine chemical analytes.
- **Repeat-dose dermal and inhalation studies*,** of 28 or 90 days, may sometimes be required.
- **Genetic toxicity studies**, in vitro for gene mutation and chromosomal damage. If any in-vitro tests indicate positive results, in-vivo genetic toxicity studies should also be carried out.
- **Chronic oral toxicity and carcinogenicity studies***, in the rat and mouse, to assess long-term toxicity and tumour incidence.
- **Reproductive toxicity studies***, including a multigeneration study in the rat and developmental toxicity studies in the rat and rabbit, to assess effects on male and female reproductive capacity and effects on embryonic/fetal development.
- **Delayed neurotoxicity studies** are required for insecticides with structures related to those known to cause delayed neurotoxicity, such as organophosphates.
- Studies on developmental neurotoxicity, dermal penetration, immunotoxicology and other specialized studies* may also have been performed. There may be occasions where in vitro tests may replace the need for the whole animal tests described above.

Absorption of the larvicide or molluscicide by inhalation, ingestion or through the skin should be estimated in the hazard assessment. If no chemical-specific data exist, default values of 100% for inhalation and ingestion are used. If the assessor is aware that specific dermal absorption data exist for a substance, those data should be used in preference to a default value. For dermal absorption of larvicides or molluscicides with molecular mass > 500 and octanol/water partition coefficient (log P_{OW}) < –1 or > 4, 10% is used as the default. For other substances, where no data are available, the inverse relationship between concentration and dermal absorption is applied: for product formulations with the active ingredient (a.i.) content > 5%, a default dermal absorption value of 25% is used, whereas for mixtures with a concentration ≤ 5%, the default used is 75% (EFSA, 2012). It should be noted that operators may be exposed to the undiluted formulation during mixing and loading, and also to the product as sprayed, i.e. a diluted solution. Thus, for mixing and loading, the absorption rate of the non-diluted formulation is to be used, whereas for other dermal exposure, that of the diluted spray is more appropriate (EFSA, 2012).

4.1.4 Evaluation of the toxicity information

An experienced toxicologist should evaluate the range and quality of the human and animal toxicity information available. Although all the toxicity tests described in the previous section are useful for assessment of the hazard potential of a substance used for

larviciding or molluscicide, it must be recognized that not all such tests may have been performed, that not all the studies performed were of good quality, and that data are therefore valid for use in risk assessment only with restrictions. However, although good-quality studies may be missing for some toxic end-points, potential health hazards can often be characterized by weight-of-evidence analysis. It is especially important to recognize possible critical data gaps that may make the assessment uncertain. If the database is poor, information on chemically-related compounds may be useful in the assessment.

- The following points are of particular importance in evaluating the relevance of toxicological studies to hazard identification and risk assessment:
- Experimental design and quality of the critical study or studies. This includes, for example, purity of the active ingredient tested, physicochemical properties (stability, etc.), size of the study (number of exposure groups, group sizes, sex, etc.), suitability of the exposure levels used, duration of exposure, extent of toxicological and statistical evaluation, relevancy of the route of exposure to humans, and whether the study adhered to established guidelines and GLP (WHO, 1999).
- Nature of the effects seen, their severity and sites, and whether they would be reversible on cessation of exposure.
- Is it possible to identify dose–response relationship, no-observed-adverse-effect-level (NOAEL) and lowest-observed-adverse-effect-level (LOAEL)?

4.1.5 Substances not recommended for use in larviciding or molluscicide

Compounds meeting the criteria of carcinogenicity, mutagenicity or reproductive toxicity categories 1A and 1B of the *Globally harmonized system of classification and labelling of chemicals* or GHS (UN, 2015) can be regarded as highly hazardous pesticides (JMPM, 2008). The Joint Meeting on Pesticide Management (JMPM) has issued a general recommendation that pesticides meeting the criteria for highly hazardous pesticides should not be registered for use unless:

– a clear need is demonstrated;
– there are no relevant alternatives based on risk–benefit analysis; and
– control measures, as well as good marketing practices, are sufficient to ensure that the product can be handled with acceptable risk to human health and the environment.

The International Code of Conduct on Pesticide Management (FAO/WHO, 2014) also states that prohibition of the importation, distribution, sale and purchase of highly hazardous pesticides may be considered if, based on risk assessment, risk mitigation measures or good marketing practices are insufficient to ensure that the product can be handled without unacceptable risk to humans and the environment. It is suggested that this recommendation be followed in the case of larvicides and molluscicides as well. It is generally considered that compounds that are both genotoxic and carcinogenic are particularly likely to exert effects at very low doses: even if studies indicate apparent NOAELs, these should not be used for risk characterization.

4.1.6 Mixtures of pesticides and pesticide active ingredients with other constituents of the formulation

If two or more pesticides are used concurrently, possible interactions between those pesticides should be considered. Pesticides with similar action may produce additive toxic effects (dose/concentration addition); organophosphates, for example, decrease acetylcholinesterase activity. For toxicants with dissimilar (independent) action, the combined effect can be estimated directly from the probability of responses to the individual components (response addition) or the sum of biological effects (effects addition). Other forms of interaction include synergistic (supra-additive) and antagonistic effects, which may be caused by different classes of pesticides, for example because of

metabolic interactions. Synergism is usually only noted at high exposure levels and may be considered unlikely at levels acceptable for the individual components (SCHER, 2011). In this document, the conservative recommendation of the International Programme on Chemical Safety (IPCS) to consider effects of mixtures as dose/concentration additive (Meek et al., 2011) is adopted as the default, except in cases in which a different mode of action has been demonstrated for the two components of the mixture.

Interactions may also occur between the active ingredient and the solvent(s) used in the formulated product. Moreover, impurities, e.g. in organophosphate products, may interact with the product and affect its final toxicity. Specification of technical material is thus of the utmost importance (see http://www.who.int/pq-vector-control/en/).

4.1.7 Dose–response assessment and setting of acceptable exposure levels

Dose–response assessment is an essential part of hazard assessment for deriving health-based guidance values and for the assessment of risks. Different methods are available (WHO, 2009a). The standard NOAEL approach can be regarded as a simplified form of dose–response analysis, identifying a single dose assumed to be without appreciable adverse effects (WHO, 2009a). An important alternative approach is the benchmark dose method, based on the calculation of benchmark doses at which a particular level of response would occur (WHO, 2009a). Use of these approaches in the setting of acceptable exposure levels requires knowledge of the assumed shape of the dose–response curve. For endocrine-mediated toxicity, however, the shape of the dose–response curve may not be well defined, which poses problems for the risk assessment of substances with such activity.

NOAEL approach

For most end-points it is generally recognized that there is a dose or concentration below which adverse effects do not occur; for these, an NOAEL and/or LOAEL can be identified. For genotoxicity and carcinogenicity mediated by genotoxic mechanisms, dose-response is considered linear, meaning that risk cannot be excluded at any exposure level. For non-genotoxic carcinogenicity mechanisms, the critical cancer events may be threshold phenomena.

The NOAEL and LOAEL values are study-specific dose levels at which no adverse effects or minimal adverse effects, respectively, have been observed in toxicity studies (or, in some cases, in humans). The study design and the sensitivity of the test system can have a significant influence on NOAELs and LOAELs, which therefore represent only surrogates for the real no-effect and lowest- effect levels. Dose-response data and NOAELs/LOAELs can be obtained from repeated-dose toxicity studies, chronic toxicity/carcinogenicity studies, reproductive toxicity studies and some specialized toxicity studies. Human epidemiological studies, e.g. on occupationally exposed workers, may also provide useful dose-response data.

Different NOAELs/LOAELs are usually identified for different toxicities/end-points; they can be tabulated for each type of toxicity to help in identification of the critical end-point and the critical study (WHO, 2009a). The lowest relevant NOAEL/LOAEL value should normally be used for risk characterization and the setting of acceptable exposure levels. It should be noted, however, that the critical effects may not always be the same for each exposure scenario. For example, for scenarios involving high-level acute exposure to an acutely toxic insecticide, such as spraying of the insecticide, acute effects and irritation may be identified as critical effects, whereas effects from long-term/chronic studies should be considered in setting of reference values for long-term low-level residual exposure of inhabitants via skin and hand–mouth contact.

The following additional points should be noted when identifying NOAELs/LOAELs for a substance (WHO, 2009a):

- If irreversible toxicity is noted in any organs at higher dose levels than that at which the critical effect occurs, these levels should also be noted in case they may be relevant to the setting of tolerable exposure limits or to prediction of possible additional risks that may be present if certain exposures are exceeded.
- In the case of insecticides such as carbamates and organophosphates, which act on specific and nonspecific cholinesterases, the dose levels that cause measurable effects – even if those effects are not considered "adverse" – should be noted. For example, while inhibition of plasma or brain butyrylcholinesterase serves mainly as an indicator of internal exposure, a statistically significant inhibition ≥ 20% of brain or red blood cell acetylcholinesterase is considered to be of clear toxicological significance (JMPR, 1998).
- There may be studies in which the lowest dose tested is a clear effect level and in which it is not possible to identify either an NOAEL or an LOAEL. In these cases, this lowest dose should be tabulated, noting that LOAEL and NOAEL may be significantly lower. Alternatively, the method for the derivation of benchmark dose can be used (see below).
- If the highest dose tested is without any effect, this dose may be tabulated as the NOAEL noting that the true NOAEL may be significantly higher.

Benchmark dose model

A benchmark dose (BMD) model may be used as an alternative to the NOAEL-based approach in setting acceptable exposure levels where appropriate dose–response data are available (WHO, 2009a). Whereas a NOAEL represents a dose level assumed to be without appreciable effect, a BMD is based on data from the entire dose–response curve of the critical effect (WHO, 2009a). For end-points with an assumed threshold level, a BMD model can be used as a point of departure for setting acceptable exposure levels in the same way as an NOAEL is used by applying similar uncertainty factors. A BMD model may also be helpful in situations where there is a need for low-dose extrapolation, such as occurs in carcinogenicity mediated by a genotoxic mechanism, when it is assumed that the dose–response is linear. Usually, BMD_{10} – representing a level with 10% response – is used as a starting point for low-dose linear extrapolation in these situations (WHO, 2009a).

Setting tolerable systemic doses: the use of uncertainty factors

In the setting of tolerable systemic dose levels (TSDs), critical NOAELs/LOAELs (or BMDs) (corrected for absorption) are divided by uncertainty factors (UFs) to account for variability and uncertainties. Thus, a TSD can be derived from long-term studies on oral toxicity:

$$TSD = Abs_{oral} \times N(L)OAEL/UF$$

A TSD is usually expressed in mg absorbed chemical/kg body weight per day.

Uncertainty factors should take account of uncertainties in the database, including interspecies and interindividual differences. Unless there are chemical-specific data to support the use of chemical-specific UFs (WHO, 2005a), the use of default UFs to account for these uncertainties is a standard approach in the setting of TSDs. If the critical NOAEL/LOAEL is derived from an animal study, a default UF of 10 is usually recommended to account for interspecies differences (WHO, 1994; WHO, 1999). A default UF of 10 is also used to account for interindividual differences in the general population (WHO, 1994; WHO, 1999). Contributors to the overall UF are normally multiplied because they are considered to be independent factors; the most commonly used default UF for the setting of TSDs in the general population is therefore 10 x 10 = 100 (WHO 1994; WHO, 1999). However, this default approach can be modified if appropriate chemical-specific toxicokinetic or toxicodynamic data exist that justify smaller or larger UFs for interspecies or interindividual differences. Moreover, if chemical-specific toxicokinetic or toxicodynamic data suggest higher interspecies or interindividual differences, UFs should be modified accordingly. Further details on chemical-specific uncertainty factors may be found elsewhere (WHO, 2005a; Bhat et al., 2017).

The default setting of a TSD is based on cumulative effect upon repeated/continuous exposure. Thus, the systemic dose is averaged over a year, and years are thought be similar *vis a vis* exposure. Furthermore, the effect is considered to be linked to the total absorbed dose, which is reflected in the plasma area under curve (AUC) – from which the kinetic variability factors $10^{0.6}$ = 4 (for interspecies uncertainty) and $10^{0.5}$ = 3.16 (for human interindividual variability) are derived. However, this is not necessarily true for all substances. For example, some carbamates are rapidly excreted, and they exert their toxic effect through transient, reversible inhibition of cholinesterase enzyme. The rapid reactivation of carbamate-inhibited enzyme means that the toxic effect mainly depends on the peak plasma concentration (C_{max}) and is not cumulative. Since the C_{max} varies less than that of the area under the plasma concentration curve (AUC), the kinetic component of interspecies extrapolation and the kinetic component of the interindividual human differences may both be lowered 50% [2 and 1.58, respectively], and the overall variability factor thus be lowered from the traditional 100 (4×2.5×3.16×3.16) to 25 (2×2.5×1.58×3.16) (JMPR, 2008). When the effect is not cumulative over time as is the case for come carbamates, as substantiated by data on bendiocarb (JMPR, 1982, 1984), the dose averaging over time is not appropriate; rather, the maximal daily dose is compared with the ADI.

In some cases, the use of additional UFs is justified (Dorne & Renwick, 2005; Dourson, Knauf & Swartout, 1992; Herrman & Younes, 1999; Vermeire et al., 1999; WHO, 1999; WHO, 2005a). Situations in which additional UFs should be considered include the following:

- When LOAEL is used instead of NOAEL, an additional UF (e.g. 3 or 10) is usually incorporated.
- When an NOAEL from a sub-chronic study (in the absence of a chronic study) is used to derive a TSD for long-term exposure, an additional UF (e.g. 3–10) is usually incorporated to take account of the attendant uncertainties.
- If the critical NOAEL relates to serious, irreversible toxicity, such as developmental abnormalities or cancer induced by a non-genotoxic mechanism, especially if the dose–response is shallow (WHO, 1999).
- When there are exposed subgroups, which may be extra-sensitive to the effects of the compound (e.g. neonates because of the incompletely developed metabolism).
- If the database is limited.

Smaller UFs may be considered in certain situations, including the following:

- If the NOAEL/LOAEL is derived from human data, the UF for interspecies differences need not be taken into account.
- If chemical-specific data on the toxicokinetics or toxicodynamics of the insecticide in either animals or humans are available, the default UF of 100 may be modified to reflect these data (see WHO, 2005a)
- The effect is not cumulative and is related to peak plasma concentration, not AUC (see above).

Types of tolerable exposure limits needed for the risk assessment of larviciding and mollusciciding

Different reference doses/TSDs may be needed according to the type of substance; a TSD based on repeated or long-term exposure is usually the most relevant. For substances with marked acute toxicity, however, it is also important to verify that the maximal daily exposure is acceptable; for this purpose, the tolerable systemic dose for acute exposure, TSD_{AC} (based on, for example, the acute reference dose, ARfD) is used (Solecki et al., 2005).

Repeated exposure

The long-term TSD is usually based on systemic effects observed in long- term studies and is expressed as mg per kg body weight per day (mg $kg_{bw}^{-1}d^{-1}$). For most substances used as larvicides or molluscicides, guidance values for long-term TSDs have already been set by international or national bodies; these include acceptable daily intakes (ADIs) set by JMPR or by the European Union, and reference doses or concentrations (RfDs, RfCs) set by the USEPA. While preference in the risk assessment for larviciding or molluscicide should be the ADIs set by WHO, guidance values set by other authoritative bodies can be used, especially in the absence of WHO guidelines or when WHO guidelines no longer represent current knowledge.

Long-term TSDs are set on the basis of oral studies: chronic studies most commonly use the oral route and many values, such as the ADIs set by JMPR, are intended primarily to control pesticide residue intake through the diet. However, operators and residents of treated areas are also exposed via skin contact. All exposure routes must therefore be taken into account in estimating the total systemic exposure. Specifically, it should be noted that the Joint FAO/WHO Expert Committee on Food Additives (JECFA) ADIs usually presume 100% gastrointestinal absorption; if actual data are available, the TSD (representing absorbed dose) should be derived from the ADI by considering the gastrointestinal absorption. However, it is important that TSDs also protect against possible local effects, for example on the respiratory tract.

In route-to-route extrapolation, one further issue worthy of note is the possibility of first-pass effect in oral exposure situations (EC, 2006). Parent compounds absorbed into the circulation of the gut are rapidly transported to the liver and may be extensively metabolized before reaching the systemic circulation (and possible target organs). Thus, systemic concentrations of parent compounds may be higher following dermal or inhalation exposure than following oral exposure.

Since operators may potentially be at risk of inhalation exposure, it is critical to ensure that the substance used has no significant local respiratory effects and that TSDs for long-term systemic exposure are also protective against possible respiratory effects. However, when larvicides or molluscicides are applied as sprays, the droplet size is relatively large (to allow droplets to fall into the water). Even when efforts are made to project the spray over a wide swath, droplets are normally larger than is the case for other vector control methods such as space spraying or indoor residual spraying (IRS), and respiratory effects should be negligible.

Regional and national occupational exposure levels (OELs) may be available for pesticides used for public health protection. However, it should be noted that these values do not take into account absorption via the skin which, for exposure to larvicides and molluscicides, which may be more significant than that via inhalation (Hayes, 1975). In the case of larviciding and molluscicide, inhalation exposure can even be assumed to be insignificant. In addition, OELs are usually set on the assumption that the insecticide is used by adult, healthy workers exposed only for the duration of the working day or for shorter periods of time, and may thus reflect only the need to protect against local effects such as irritation. The UFs applied in setting acceptable exposure levels for space spraying thus usually need to be significantly larger than those applied in setting OELs.

It is recommended that the same systemic TSD be applied for operators as for the general population.

Acute exposure

Guidance values for acute (24-hour) dietary exposure to agricultural plant protection products have been set by JMPR for insecticides with significant acute toxicity such as acutely neurotoxic insecticides, including those with anticholinesterase activity

(organophosphates and carbamates); these values are called acute reference doses (ARfDs).

The ARfD is defined as the amount of a chemical, expressed on a body weight basis, that can be ingested over a short period of time, such as one day, without appreciable risk to health (JMPR, 1998; Solecki et al., 2005). It is derived similarly to the long-term ADI, using relevant human or animal studies of acute dosing. The critical NOAEL from such studies is used to derive the ARfD by application of a UF. If the data are based on animal data, an overall UF of 100 is commonly used unless chemical-specific information is available that supports the use of a different UF (see above).

For organophosphates and carbamates, inhibition of acetylcholinesterase in either red blood cells or brain, measured minutes to hours after dosing, (and compared with a value before exposure), is an appropriate parameter on which to base the guidance value for acute exposure. For example, the ARfD for chlorpyrifos is based on a study in human volunteers, in which an NOAEL of 1 mg kg_{bw}^{-1} was identified for the inhibition of erythrocyte acetylcholinesterase activity (JMPR, 1999). As the study was carried out in humans, no interspecies extrapolation was needed and an ARfD of 0.1 mg kg_{bw}^{-1} was set using a UF of 10.

For larviciding and molluscicidingg, a tolerable systemic dose for acute exposure, TSD_{AC}, derived from e.g. the ARfD, may be used in the risk assessment, notably for products with significant acute toxicity, to take into account the acute risks related to application and exposure to treated water.

For some of the substances used for larviciding or molluscicidingg, an ARfD from JMPR is available for the derivation of the TSD_{AC}, or JMPR has concluded that because of lack of significant acute toxicity, no ARfD is needed (JMPR, 2012). JMPR has also laid down principles for the derivation of ARfDs for agricultural pesticides (Solecki et al., 2005); these can be adjusted for substances used for larviciding or molluscicidingg when no authoritative acute reference dose is available.

4.2 Exposure assessment

The second step in performing a risk assessment is to estimate exposure to the larvicide or molluscicide in the various groups of people potentially at risk. Exposure must take account of various parameters, including the route of exposure, the actual amounts of material involved, the duration of exposure in terms of both daily and annual exposure and seasonality, and the periodicity of exposure (intermittent or continuous). The following groups of people may be exposed to chemical substances through larviciding or molluscicidingg:

- operators applying the products; and
- residents (meaning residents of communities where larviciding or molluscicidingg are undertaken who may come into contact with treated water)
  - adults
  - children (including breastfed infants).

Exposure algorithms, default values and unit exposures, which describe the relationship between operational conditions and exposure, are taken from *Standard operating procedures for residential pesticide exposure assessments* (USEPA, 2012),and *Exposure factors handbook: 2011 edition* (USEPA, 2011); different agricultural field-study databases and modelling approaches (European Predictive Operator Exposure Model (EUROPOEM II, 2003); UK Predictive Operator Exposure Model (PSD, 2007)). The default values should be modified by the user of the models on a case-by-case basis and replaced with appropriate measured or otherwise improved point estimates or distributions, when applicable. Similarly, application of anthropometric and physiological datasets derived from the true target population, when available, is likely to yield more accurate exposure predictions.

The ability of a chemical to cause adverse health effects depends on the route of exposure (ingestion, inhalation, dermal contact), the frequency and duration of the exposure, the toxicity of the substance and the inherent sensitivity of the exposed person. Exposure is also strongly related to the actual amount of product or active ingredient handled and applied. Exposure assessment of larviciding and molluscicide therefore consists of several different scenarios for different target groups.

For the risk characterization, a total systemic dose estimate must be calculated by summing up all relevant exposure routes and pathways.

The exposure assessment described in this document should be considered as a first-tier approach. Whenever needed, higher-tier assessments with more complex methods should be used. For example, probabilistic risk assessment with quantification of uncertainties can be used to estimate risks in more detail. Guidance on exposure models and communicating uncertainties has been published by WHO (WHO, 2005c; WHO, 2008).

Among the residents of the treated areas or users of treated water, unborn and newborn babies as well as children are of special concern because of their pattern of exposure and possibly greater sensitivity to toxic chemical action. This document provides a rough means of assessing the risks to these sensitive groups, but additional, chemical-specific information is likely to greatly improve the accuracy of the risk assessments, especially in the case of unborn and newborn babies.

Another important area of uncertainty is the risk assessment of bioaccumulative active ingredients, such as DDT; chemical-specific information on the metabolism and toxicokinetics is crucial for accurate risk assessment.

Assuming that properly calibrated and well-functioning equipment is used for application and that instructions - including safety precautions - are strictly followed, the exposure in larviciding and molluscicide should generally be low. However, optimum conditions do not always prevail during the spraying operations, and risk assessments that assume appropriate equipment and strict compliance with instructions may lead to an underestimation of the level of exposure. Unintentional misuse, however, is very difficult to take into account in models, and similar problems arise in trying to include the effect of contaminated clothing, perspiration on the skin, use of contaminated rags or towels to wipe the skin, etc. in the risk assessments. In most cases, these parameters are impossible to quantify. Situations related to misuse or accidents are mostly not covered by this document. Reusing product containers is, however, mentioned but this exposure is not routinely modelled. This scenario may be taken into account in specific cases and can be more reliably quantified than most misuse situations. Moreover, the model does not take account of concurrent use of the same products for agricultural purposes. If the user of the models has any knowledge that suggests usage of risky equipment or work patterns, he or she is strongly recommended to use that more case-dependent information as the source of default parameters.

It is the aim of this document to provide an estimate of the risks to operators and residents in:

- optimal conditions, i.e. the guideline scenario; and
- a lax standard scenario, which allows for some common deviations from the instructions.

Excessively high exposures from malfunctioning equipment and clear misuses are not covered in this risk assessment. Similarly, use of empty product packages to store food items or drinking-water is not covered in this risk assessment.

4.2.1 General parameters for exposure assessment

The parameters provided below are common in both operator and residential exposure assessments. It should be emphasized that more chemical-specific or case-specific data should always be sought and used when possible.

- Risks for residents are estimated for adults, children (aged 6–11 years), toddlers (aged 12–24 months) and infants (aged < 12 months), as recommended by the European Human Exposure Expert Group (HEEG, 2013a). Exposure via mother's milk is estimated for infants (up to 12 months) and newborns (birth to 1 month).
- Anthropometric and physiological input parameters (weight, skin surface area and ventilation rate) have an effect on the risk estimates. Ideally, data from the target population should be used. However, it is also important that the database is internally consistent: all needed parameters for all age groups are available and are derived from the same population. The database produced by the USEPA (2011) is extensive and up-to-date, covering all age groups and all relevant anthropometric and physiological data-points. It is also recommended for use by the European Human Exposure Expert Group (HEEG, 2013a), and was therefore used in this document (Table 3). For body weight, the 25th percentiles are applied; for respiration rate, the HEEG recommendations are used. For the estimation of drinking water consumption, the USEPA (2011) 95th percentile values are applied, as the use of these products is in practice limited to tropical countries. When appropriate anthropometric data are available for the population for which the risk assessment is made, these should be used.
- Adult operators and residents are assumed to weigh 60 kg. Risks are also estimated for children aged 6–11 years (assumed to weigh 23.9 kg), toddlers aged 12–24 months (10 kg) and infants from birth to 12 months of age (8 kg). Exposure via mother's milk is assessed also for newborns (birth to 1 month, weight 4.2 kg (USEPA, 2011; HEEG 2013a)).
- The film thickness of a non-viscous liquid likely to be in contact with unprotected, immersed skin is assumed to be 0.01 cm after run-off; thus 8.2 mL is the maximum amount of liquid on the hands of an adult (total surface area of hands 820 cm^2 – see Table 3) (USEPA, 2011; HEEG, 2013a).
- In most instances, exposure assessment consists of multiplication of several estimated parameters with an inherent variability. If for each such parameter a high percentile of the distribution, say 95th percentile is used, this leads to an exposure estimate that is unrealistically conservative. Therefore, when available, a lower percentile is applied, usually the 75th percentile.

Table 3. Anthropometric and physiological characteristics used in the model (USEPA, 2011; HEEG, 2013a)

	Adult	Child 6–11 yr	Toddler 12–24 mo	Infant ≤ 12 mo
Weight[a] (kg)	60	23.9	10	8
Body surface[a] (m^2)				
total	1.6600	0.9200	0.4800	0.4100
hands	0.0820	0.0428	0.0230	0.0197
arms	0.2270	0.1270	0.0619	0.0582
forearms	0.1129	0.0497	0.0269	0.0230
legs	0.5330	0.2742	0.1219	0.1041
lower legs	0.230[c]	0.1070[d]	0.054[e]	0.046[e]
feet	0.1130	0.0605	0.0288	0.0246
head	0.1110	0.0529	0.0403	0.0344
trunk	0.5710	0.3376	0.1795	0.1533
Respiration rate[b]				
short-term m^3/h	1.25	1.32	1.26	0.84
long-term m^3/24 h	16	12	8	5.4
Water consumption litres/day[f]	2.0	1.0	1.0	

[a] Weight and body surface are 25th percentiles based on females (aged 30–40 years) (USEPA, 2011; HEEG, 2013a).
[b] These values represent mean values under moderate physical work load (USEPA, 2011; HEEG, 2013a).
[c] Source: USEPA, 2011.
[d] 11.6% of the total skin surface (USEPA, 2011).
[e] 11.2% of the total skin surface of a 2-year old (USEPA, 2011).
[f] Water consumption defaults are those used in the development of guideline values for chemicals in the WHO guidelines for drinking-water quality (WHO, 2017b).

Parameters for exposure assessment – operator exposure

The procedures for mosquito larviciding (WHO, 2005b; WHO, 2006) and for mollusciciding (WHO, 2017a) are detailed elsewhere. Typically, the equipment used for application of the liquid formulations consists of compression sprayers and lever-operated knapsack (back-pack) sprayers fitted with either a fan or a cone nozzle (WHO, 2018a). Solid formulations are dispersed by the use of an applicator (e.g. for granules) or manually by gloved hand. Watering cans, hand-operated compression sprayers and motorized sprayers can be used to apply molluscicide to moist soil or still water. Treatment of large areas by spraying from aircraft is not considered in this model, nor are automatic dispensing or drip-feed systems.

Operator exposure is expected to be highest from spraying, and spraying is modelled as representing the worst-case situation. Operator exposure from other methods of application such as dispersing solid products, pumping products into water bodies via hose systems or using watering cans is assumed to result in lower operator exposures, and these are not modelled.

In the guideline scenario exposure assessment, it is assumed that WHO recommendations and product label instructions are being followed.

In the lax standard scenario, no personal protective equipment other than light clothing covering the trunk is assumed.

Specific exposure scenarios are described below. The tasks that are considered to cause exposure to the operators are:

– mixing and loading; and
– application of the product by spraying, and washing and maintenance of the equipment.

The pesticide formulations commonly used in larviciding and molluscicide are emulsifiable concentrates and wettable powders, as well as granules and other solid formulations. Some formulations (e.g. tablets) are used only in certain applications, e.g. for water-storage containers.

For the assessment of operator exposure to larvicides and molluscicides applied as liquid sprays, it is assumed that the inhalation exposure of the spray operator is negligible: spraying takes place outdoors and uses a coarse spray, directed downwards. Dermal exposure during spraying, and washing and maintenance of spray equipment, is assumed to be limited to hands. When granules or tablets are dispersed, hand exposure is considered to be negligible.

Mosquito larviciding includes the treatment of artificial habitats, e.g. rice fields, ditches, roadside and other gutters or drainage channels, and water-storage containers, as well as natural habitats such as ponds and temporary pools and marshlands. It is limited to small breeding sites or to specific locations within larger aquatic habitats and where the presence of larvae has been observed, and is more commonly used in urban settings.

Larviciding is commonly used in dengue and malaria control programmes and is limited to periods when conditions are suitable for mosquito breeding (generally associated with periods of rain).

Molluscicide includes the treatment of natural habitats of snails (shallow water with slow or moderate current and strong solar illumination) and opportunistic habitats in the fringes of the above, as well as artificial habitats such as irrigation ditches, tanks and furrows with low current gradient, which are continuations of streams, lakes or reservoirs used for pisciculture, horticulture or agriculture (de Souza, 1995).

For exposure assessment of spray operators, it is assumed that the spray operator works six days a week. For larviciding, it is assumed that the duration of a treatment round will be 6 weeks and that two treatment rounds take place within a 6-month season. For molluscicide, a one-week treatment round taking place each month is assumed as a conservative default, although the frequency will vary depending on epidemiological and transmission scenarios. These defaults should be replaced if specific treatment scenarios are being assessed.

It is assumed that correct maintenance procedures of the spray equipment are followed to ensure that no leakages occur during the spray operations. For example, that no leakages occur on the hands from the trigger valve.

It is assumed that a single spray operator could apply a maximum of 12 tank-loads during a day. Each tank-load is assumed to be 10 litres, and the area is treated with a product-specific amount per unit area. The number of tank-loads will need to be adjusted in line with local situations. The urban situation is considered to be a worst-case scenario because the need for multiple treatments will increase the number of tank-loads. Inhalation exposure is considered negligible during mixing and loading. Contamination of the hands during filling of the tank is assumed to depend on the size of the product container and the diameter of the container opening. In the worst case, 0.5 mL of the product per tank-load is assumed to contaminate unprotected (no gloves) hands (UKPOEM data: PSD, 2007; see Table 4). For solid formulations, USEPA data on standard operating procedures are used. Unit dermal exposure for wettable powders (WP) during mixing and loading according to USEPA standard operating procedures is 9.7 mg a.i./kg a.i., that for

water dispersible granules (WG) is 0.07 mg a.i./kg a.i and that for product packaged in water soluble bags is 0.04 mg a.i./kg a.i (USEPA, 2012).

The concentration of the spray liquid is to be checked from product labels or material safety data sheets.

Table 4. Default values for potential hand contamination (mL/operation) during mixing and loading of a liquid pesticide formulation (no gloves used)[a]

Size of container and diameter of opening	Contamination of hands (mL/operation)
1 litre, any closure	0.01
2 litres, any closure	0.01
5 litres, narrow closure	0.2
5 litres, 45 mm or 63 mm closure	0.01
10 litres, narrow closure	0.5
10 litres, 45 mm closure	0.1
10 litres, 63 mm closure	0.05
20 litres, narrow closure	0.5
20 litres, 63 mm closure	0.05

[a] Source: PSD, 2007.

Inhalation exposure to chemicals used in vector control is often low due to the low volatility of the chemicals used (WHO, 2018b; USEPA, 2012; HEEG, 2013b). For spraying during larviciding and molluscicidingg, inhalation exposure is further reduced because spraying takes place outdoors and uses a coarse spray, directed downwards.

In the guideline case scenario, it is assumed that operators wear appropriate personal protective equipment (PPE), e.g. gloves, other protective clothing such as overalls, respirators etc., according to the label instructions and the relevant WHO manual – both when mixing and loading and when spraying. In the lax standard scenario, however, it is assumed that no PPE is used, which may be quite common in view of the likely climatic conditions in which larviciding or molluscicidingg are carried out. When full PPE (respirator, protective gloves, long-sleeved protective clothes) is used, an overall reduction coefficient of 0.1 (10%) is applied (EUROPOEM II, 2003).

Washing and maintenance of spray equipment may cause exposure to operators' hands. In the guideline case scenario, gloves are used, providing 90% protection. In the lax standard scenario, it is assumed that no PPE is used.

Malfunctioning equipment (leaks, variable and intermittently high spray pressure, equipment with the outer surface contaminated by the product) may lead to very high exposure both by inhalation and by the dermal (larger areas of skin exposed) routes. Such misuses are not covered in this risk assessment.

Parameters for exposure assessment – residents

Larviciding of a target site is assumed to be performed at 7-day intervals during treatment rounds within a 6-month season (not every week but in 6-week treatment rounds). The frequency of molluscicidingg differs in different epidemiological and transmission scenarios (WHO, 1992). In this document, a frequency of once per month throughout the year is used as a conservative default.

Exposure of adults and children of all ages, through ingestion of treated water, or through bathing with or swimming in treated water, is similar. No inhalation exposure is assumed in any circumstances. For products that are toxic and extensively excreted in mother's milk, breast milk may be an important source of exposure to newborns.

It has been stated that larviciding and molluscicide should not, if avoidable, treat water that could be used as drinking-water by humans or domestic animals; for some active ingredients, however, maximum dosages have been estimated that are not considered harmful. Ingestion exposure depends on water consumption (2 litres/day for adults and 1 litre/day for children and toddlers (Table 3)).

For dermal exposure due to bathing, body surface areas are assumed to be 1.66 m^2 for adults, 0.92 m^2 for children, 0.48 m^2 for toddlers and 0.41 for infants (Table 3). It is assumed that one full bathing is undertaken per week, plus daily body washing which is equivalent to one weekly full bathing – a total of 2 x 52 = 104 bathing (or swimming) events per year (USAID, 2006). During a 6-month larviciding season, 52 events of whole body dermal exposure are thus assumed. For molluscicide, 104 events are assumed as a worst-case for intense treatment of transmission hot spots (all year).

Improper disposal of pesticide containers may contaminate soil, groundwater and surface water, which can result in exposure via the dermal or ingestion route when drinking, or bathing or swimming in, contaminated water. While it is also possible that this contaminated water is used for irrigation of edible crops, that scenario is considered to be negligible compared with exposure by contact with deliberately treated water. Contamination of groundwater as a result of pesticides getting into subsurface waters or of improper disposal of used packages containing pesticide residues can be estimated when relevant; that is, when the active ingredient is liable to access groundwater. When the larviciding method by definition includes spreading chemicals into water sources, it is important to assess this accessibility carefully and not use substances that are dangerous to groundwater. Chemical-specific data should be available from registration data for estimating the concentration of contaminants in the groundwater.

4.2.2 Algorithms used to estimate exposure and absorbed dose caused by larviciding and molluscicide

Operator exposure

Mixing and loading pesticide formulations

In mixing and loading, inhalation exposure is not considered significant.

The formulations used in larviciding or molluscicide include emulsifiable concentrate, which is a liquid formulation. Solid formulations such as granules or tablets are used directly and do not need to be mixed. Default dermal exposure (hand contamination) from handling liquid products during each mixing and loading session is given in Table 4, and exposure may be calculated as shown in Box 1a.

For solid products such as wettable powders, default dermal exposure values derived from USEPA standard operating procedures can be applied (USEPA, 2012), and exposure may be calculated as shown in Box 1b.

Box 1a. Mixing and loading, dermal exposure; liquid formulations

$SysD_{TWA}$ = $UE_{LIQ} \times PPE \times CF \times NOD \times ABS_D \times EF / (BW \times AT)$
$SysD_{MAX}$ = $UE_{LIQ} \times PPE \times CF \times NOD \times ABS_D / BW$
where:

$SysD_{TWA}$	=	TWA systemic dose mg/kg bw/day
$SysD_{MAX}$ =		Maximal daily systemic dose mg/kg bw
UE_{LIQ}	=	Unit exposure for a liquid formulation mL/operation (see Table 4)
PPE	=	PPE efficacy 0.1 (90% protection) in guideline scenario; 1.0 (no protection) in lax standard scenario
CF	=	Concentration of formulation mg/mL (product label)
NOD	=	Number of mixing operations per day (default, 12)
ABS_D	=	Dermal absorption for the concentrated formulation (see section 4.1.3)
EF	=	Exposure frequency (larviciding 6 days/week, 6 weeks per treatment round, 2 rounds/year = 72 days/year; molluscicide 6d/week, 1 week per month through the year = 72 days/year)
BW	=	Body weight (60 kg; see Table 3)
AT	=	Averaging time (365 days)

Box 1b. Mixing and loading, dermal exposure; solid formulations (e.g. WP)

$SysD_{TWA}$ = $UE_{SOL} \times PPE \times ML \times ABS_D \times EF / (BW \times AT)$
$SysD_{MAX}$ = $UE_{SOL} \times PPE \times ML \times ABS_D / BW,$
where:

$SysD_{TWA}$	=	TWA systemic dose mg/kg bw per day
$SysD_{MAX}$	=	Maximal daily systemic dose mg/kg bw
UE_{SOL}	=	Unit exposure for a solid formulation, mg/kg a.i. handled (9.7 for wettable powders, 0.07 for water-dispersible granules, 0.04 for product in water-soluble bags)
PPE	=	PPE efficacy 0.1 (90% protection) in guideline scenario; 1.0 (no protection) in lax standard scenario
ML	=	Amount of chemical (a.i.) handled per day; default 12 loads per day, 10 L tank, concentration of the a.i. in the spray from the product label and dilution for spraying
ABS_D	=	Dermal absorption for the concentrated formulation (see section 4.1.3)
EF	=	Exposure frequency (larviciding 6 days/week, 6 weeks per treatment round, 2 rounds/year = 72 days/year; molluscicide 6 days/week, 1 week per month throughout the year = 72 day/year)
BW	=	Body weight (60 kg; see Table 3)
AT	=	Averaging time (365 days)

Application of pesticide formulation with a compression sprayer, and washing and maintenance of the spray equipment

Inhalation exposure

Inhalation exposure can be assumed to be negligible. The large droplet size (coarse spray), downward spraying direction and the fact that spraying takes place only outdoors justify the assumption of low inhalation exposure.

Dermal exposure

In a **lax standard scenario**, hands are exposed to the spray liquid during application and during washing and maintenance of the equipment.

In the **guideline scenario**, the sprayer is fully leak-proof, and protective clothing (including, for example, overalls, face mask and goggles as well as boots) and

appropriate gloves are used during both spraying and washing or maintenance of the equipment. Protective clothing and gloves are assumed to provide 90% protection.

The dermal exposure during application, washing and maintenance may be calculated as shown in Box 2.

Box 2. Application, washing and maintenance, dermal exposure

$SysD_{TWA} = VS_{dermal} \times C_{spray} \times PPE \times EF \times Abs_D / (BW \times AT)$

$SysD_{MAX} = VS_{dermal} \times C_{spray} \times PPE \times Abs_D / BW$

$SysD_{TWA}$	=	TWA systemic dose mg/kg bw per day
$SysD_{MAX}$	=	Maximal daily systemic dose mg/kg bw
VS_{dermal}	=	Volume of spray on hands = 8.2 mL (see section 4.2.1)
C_{spray}	=	Concentration of the active ingredient in the spray in mg/mL, derived from the concentration of the active ingredient in the formulation and its dilution for spraying
PPE	=	Protection provided by the protective equipment, 0.1 for the guideline scenario, 1.0 for the lax standard scenario
EF	=	Exposure frequency (larviciding 6 days/week, 6 weeks per treatment round, 2 rounds/year = 72 days/year; molluscicide 6 days/week, 1 week per month throughout the year = 72 days/year)
ABS_D	=	Dermal absorption of the spray (see section 4.1.3)
BW	=	Body weight (60 kg)
AT	=	Averaging time, 1 year (365 days)

Residential exposures

Residential exposure is assumed to result from using treated water as drinking-water or of swimming and bathing in treated water. For biopersistent fat-soluble products, mother's milk may be an important source of exposure of newborns; such active ingredients are not usually recommended for larviciding or molluscicide.

Because larviciding is relatively frequent, usually every 7–10 days, larvicides that have a long dissipation half-time may accumulate in the water body; this becomes an important determinant of residential exposure. As the frequency of molluscicide is much lower (seldom as frequent as once/month), accumulation of the molluscicide in the water body need not normally be considered. To accommodate molluscicide in both stagnant and flowing water, the concentration of the molluscicide in water is assumed to stay unchanged for **five** days after the treatment. This is very much a worst-case assumption as products recommended for molluscicide will not normally persist at a significant concentration in water for longer than 24 hours; however, some types of formulation and some environments where these products are used may cause the active ingredient to persist for longer.

For some products, a restriction on the use of treated water in the post-application period is recommended, but this restriction may not be maintained in all cases.

The exposure of residents from ingestion of treated water may be calculated as shown in Box 3.

Box 3. Ingestion exposure, drinking contaminated water

$SySD_{TWA}$	=	*CDW × WIR ×AbsO ×EF / (BW ×AT), where*
$SySD_{MAX}$	=	*CDW × WIR ×AbsO / BW*
		where:
$SySD_{TWA}$	=	TWA systemic daily dose mg/kg bw per day
$SySD_{MAX}$	=	Maximal systemic daily dose mg/kg bw
CDW	=	Concentration in drinking water, mg active ingredient/Litre. For products with a dissipation half-time, T½ ≤ 5 days, the first-tier CDW is the estimated target concentration = spraying rate in g/ha $\times 10^{-4}$ divided by the depth of the waterbed (metres); the default value is 0.5. For products with a dissipation T½ >5 days, CDW is calculated from target concentration × T½ /ln(2). If a second-tier estimation is needed for a product with a dissipation T½ ≤ 5 days, actual dissipation data are used.
WIR	=	Water ingestion rate (2 litres/day for adults, 2 litres/day for children and toddlers; 0.75 litres/day would be used if an assessment is undertaken for bottle-fed infants)
Abs_O	=	Default, 100%
EF	=	Exposure frequency. For larviciding, daily during a 6-month spraying season= 183 days. For molluscicide, EF = 12 occasions in the year x 5 days exposure from each occasion = 60 days/year
BW	=	Body weight (60 kg for adults, 23.9 kg for children, 10 kg for toddlers)
AT	=	Averaging time, 1 year (365 days)

The exposure of residents from dermal contact with treated water (bathing, swimming, use of treated water for washing clothes, etc.) may be calculated as shown in Box 4.

Box 4. Dermal exposure, bathing/swimming in contaminated water

$SysD_{TWA}$	=	*CW × WS_{dermal} × AbsD ×EF / (BW ×AT) CW × WS_{dermal} ×AbsD × EF / (BW × AT)*
$SysD_{MAX}$	=	*CW × WS_{dermal} ×AbsD / BW*
		Where:
$SysD_{TWA}$	=	TWA systemic daily dose mg/kg bw per day
$SysD_{MAX}$	=	Maximal systemic daily dose mg/kg bw
CW	=	Concentration in water, mg active ingredient/Litre. For products with a dissipation half-time, *T½* ≤ 5 days, the first-tier *CDW* is the estimated target concentration = spraying rate in g/ha $\times 10^{-4}$ divided by the depth of the waterbed (metres); the default value is 0.5. For products with a dissipation *T½* > 5 days, *CDW* is calculated from target concentration × *T½* / ln(2). If a second-tier estimation is needed for a product with a dissipation *T½* ≤ 5 days, actual dissipation data are used.
WS_{dermal}	=	Volume of water on skin, 0.01 cm (0.0001 m) film on skin after run-off (default volume for adults is 1.66 m^2 x 0.0001 m = 166 mL, for children 92 mL, for toddlers 48 mL, for infants 41 mL, using the total body surface values in Table 3)
Abs_O	=	Dermal absorption (see section 4.1.3).
EF	=	Exposure frequency, assuming 1 bath or swim per week and daily body washing for 1 year (7 daily body washings equals 1 bathing event; thus, total events in a year is 2 x 52 = 104 events). The treatment season for larviciding is assumed to be 6 months; 104/2 = 52 events/year. For larviciding, EF is therefore 52. For molluscicide with 60 days of contaminated water per year, the proportion of exposed events per year will be 60/365 x 104 = 17 exposed events. For molluscicide, EF is therefore 17
BW	=	Body weight (60 kg for adults, 23.9 kg for children, 10 kg for toddlers, 8 kg for infants)
AT	=	Averaging time, 1 year (365 days)

Although infants do not swim, they might be washed more frequently than older age groups: the same exposure frequencies are therefore used for infants.

Use of emptied pesticide packages as water containers may lead to exposures that cause acute intoxications and is a practice that should be effectively prohibited. Since larviciding and molluscicide are major undertakings, carried out by government or other authorized bodies, this should be a fully avoidable exposure; it is not covered in this document.

Exposure via breast milk

When information is available on the fraction of the mother's dose excreted in her milk, this can be used to estimate the dose of the breast-fed infant. When extrapolating from animal data, the IPCS default variability factor for kinetics, $10^{0.6} = 3.98$, is applied (WHO, 1999) (Box 5).

Box 5. Exposure via breast milk estimated from fraction of dose excreted in milk

$SysD_{TWA} = 3.98 \times Fr_{milk} \times Abs_O \times Dose_M / BW$

where:

$SysD_{TWA}$	=	TWA systemic dose of the breast-fed infant due to the excretion of the pesticide in mother's milk mg/kg body weight per day
Fr_{milk}	=	Fraction of the dose excreted in milk in an experimental animal
Abs_O	=	Oral absorption rate (default, 100%)
$Dose_M$	=	Dose the mother has received, mg [estimated dose mg/kg bw x body weight of the mother, kg (default, 60 kg)]
BW	=	Body weight (newborn, 4.2 kg; infant, 8 kg) (see Table 3)

When data on actual excretion in milk are not available, an upper bound of the exposure from mother's milk can be roughly estimated from the physicochemical characteristics, and kinetics of the pesticide as follows (Box 6).

Concentration of the pesticide in breast milk is estimated from the exposure of the mother at steady state. Body burden = daily dose mg/kg bw × T½ (days)/ln(2) (JECFA, 2002). For water-soluble pesticides, the body burden is assumed to be concentrated in the water compartment of the body, and the concentration in breast milk equals this concentration; that is, the concentration in breast milk (mg/L) is 1.4 × body burden = 1.4 × daily dose mg/kg bw × T½ (days)/ln(2) (SolC = 2.02 in Box 6). For lipid-soluble compounds (pKow ≥ 2), the chemical is concentrated in the adipose tissue, and the concentration in adipose tissue is (20% fat content of the body) 5 × body burden mg/kg. The average fat content of breast milk is assumed to be 50 g/L. Thus, the concentration in mother's milk for a fat-soluble chemical is 5 × mother's daily dose ×0.05/ln(2) = 0.361 × dose of the mother (SolC =0.361 in Box 6).

Box 6. Exposure via breast milk estimated from kinetic properties

$SysD_{TWA} = SolC \times Dose_{Mbw} \times T½ \times IR \times Abs_O / BW$

where:

$SysD_{TWA}$	=	TWA systemic daily dose mg/kg bw per day
SolC	=	Solubility constant; 2.02 for water-soluble and 0.361 for lipid-soluble pesticides
$Dose_{Mbw}$	=	Daily dose to the mother (mg/kg bw)
T½	=	First-order kinetics half-time in the body of the pesticide, days. Chemical-specific data to be used, as no meaningful default can be given
IR	=	Ingestion rate of milk, kg/day; 660 mL/day (average of mean values for the first 12 months; 510 mL for the first month (USEPA, 2011)
Abs_O	=	Fraction absorbed (default is 100%)
BW		Body weight (infant, 8 kg; newborn 4.2 kg; USEPA, 2011; HEEG, 2013a)

4.2.3 Total exposure assessment

Total systemic dose is calculated by summing the contributions via different routes. Any valid, chemical-specific data that are available should be used.

Exposure and risk should be calculated for operators and for residents (adults and children of different age groups) of communities where larviciding or molluscicide are undertaken and who may therefore come into contact with treated water.

4.2.4 Uncertainties in exposure-determining factors and risk calculations

Default values for anthropometric measurements used in the risk assessment model are obtained from sources representing North American populations. Characteristics of African and Asian populations, for example, may be different. Generic datasets applicable to all populations, however, are not available. When available, values specific to the target population should be used.

Some defaults vary widely with the source of data. For example, estimates from agricultural exposure databases seem to be higher than those from databases concerning residential exposure. For tasks such as mixing and loading, the agricultural databases are more suitable since the task is similar in agricultural and public health settings. For application tasks, however, the agricultural databases may not be the best possible source of data.

4.3 Risk characterization

The aim of the risk characterization is to evaluate the probability of adverse effects occurring under defined exposure conditions. In its simplest form, risk characterization consists of the comparison of estimates of time-weighted average (TWA) exposure with tolerable systemic doses (TSDs) defined in hazard assessment in all relevant exposure situations.

$$Ratio = \frac{Estimated\ TWA\ systemic\ dose}{TSD}$$

When the pesticide has significant acute toxicity (e.g. an ARfD has been set by JMPR or another organization), the risk is also estimated for acute exposure:

$$Ratio = \frac{Estimated\ maximal\ daily\ systemic\ dose}{TSD_{AC}}$$

When these ratios are <1, the health risk is considered to be acceptable. When either one is >1, there are possible health risks, and the planned use for larviciding or molluscicide may be unacceptable. Application of chemical-specific data instead of model defaults may be sought to refine the risk assessment. In the case of operators, it may be possible to reduce the risk – for example by changing recommended operational conditions or the amount of active ingredient in the technical product. A risk–benefit analysis, in which the risks of potential toxicity are compared with potential health benefits (disease prevention), may be needed in some cases.

5. The environmental risk assessment model

Environmental risk assessment is complex and multifaceted. Regional and national guidelines have been published yet there is no globally established system for environmental risk assessment. The published guidelines are all based on very similar premises although they differ considerably in detail; all are extensive, running to several hundred pages. This document does not cover the detail of such a scheme or propose a single scheme for international harmonization: any of the established schemes could form the starting point for environmental risk assessment associated with the public health use of pesticides. It does, however, cover the components of pesticide risk assessment schemes and the specific information likely to be needed for assessing aquatic larvicide/molluscicide use for public health purposes.

This generic model has much in common with the generic model for space spraying, in that there is commonality in the organisms likely to be exposed, although the primary application habitat (aquatic and terrestrial) and the method of application differ. Larvicides and molluscicides applied aerially over water will drift to expose soil organisms; insecticides applied over land in space spraying will drift to expose adjacent aquatic organisms. In summary, hazard is the same, exposure is different.

As in human health risk assessment, environmental risk assessment compares hazard, identified through hazard assessment, with exposure, calculated through exposure assessment, to provide risk characterization. However, environmental risk assessment seeks to characterize the risk to populations of organisms rather than to individual humans. In general, the mortality of individual organisms in the environment is naturally very high. To maintain stable populations over time, parents need to generate only two individuals over their lifetime which survive to reproduce. The very large numbers of offspring produced by many organisms in the wild reflect the considerable losses to predation, starvation and chance. The additional mortality caused acutely by pesticides would then be offset by density-dependent ecological factors; the reduced population following pesticide application would be less likely to be predated and less likely to starve. However, effects at the population level are complex to estimate and are often inferred from short-term testing.

For convenience, the components of pesticide environmental risk assessment in the European and Mediterranean Plant Protection Organization (EPPO) scheme (EPPO, 2003) are followed here, but this does not imply endorsement of one scheme over others. It is assumed throughout that good practice, as outlined by WHO (WHO, 2006), will be followed during the application of pesticides for aquatic larviciding or molluscicide.

The first stage for general pesticide regulatory risk assessment is to determine which components of the overall scheme are particularly relevant to the specific use(s) of the pesticide. This allows a logical progression through the series of components because output from one area is required as input to others. This progression can be similarly defined for public health use of larvicides/molluscicides:

- Pesticides applied as granules to surface waters will not become airborne. Pesticides applied with hand-held spray equipment to shallow surface water will not drift significantly. Following application, pesticides may become airborne by volatilization from water or soil. Possible exposure via deposition from the air is required as input to all other compartments, so this should be the starting point for risk assessment.
- Aerial spray applied to surface waters will drift and may contaminate adjacent soil and vegetation. The ultimate fate of the pesticide in aquatic systems (partitioned primarily to the water body or to sediment) determines which are the most appropriate organisms to include in the risk assessment.
- Once the initial likely concentrations of pesticides in these different environmental compartments have been defined, persistence of the active ingredient in these compartments, together with information on repeat usage, allows longer-term estimates of likely concentrations to be derived.

- Concentrations of pesticides, their distribution in different environmental compartments and the time course of their disappearance determine both the types of organism that should be included in the comparison between exposure and effect and the type of effects information (acute or chronic) that is relevant to the particular exposure pattern for both soil and surface water.
- Risk to organisms exposed through their food requires estimation of residues in food. Information on the potential for bioaccumulation in food chains is also needed.

  For all of the above, simple equations are available for estimating concentrations in environmental compartments, and standard test organisms are used to determine effect. In all cases, however, these focus on temperate conditions; the further information required to extrapolate exposure and effect estimates to tropical conditions is unlikely to be available for most pesticides.

  The final stages of risk assessment for regulation of plant protection products would be refinement of the assessment and determination of appropriate risk management. The latter would require actual measurements of residue levels in the environment and/or field studies to confirm the level of effects. Neither of these is likely to be routinely available for the conditions pertinent to public health use of pesticides.

  Environmental risk assessment of larvicides/molluscicides can be used to address four issues:

  – the absolute risk to non-target organisms for each type of pesticide used;
  – the relative risk of different pesticides;
  – the number of repeat applications likely to lead to risk to organisms in the environment; and
  – current best practice for the application of pesticides to minimize risk.

5.1 Environmental exposure assessment

5.1.1 Air

Pesticides may become airborne during the spraying process and, following application, by volatilization from soil, water and vegetation surfaces. The degree of spray drift is dependent on the physical characteristics of the spray application – the equipment used, the droplet size and the height above ground at which the spray is applied. Surface-water applications by hand-held sprays for larviciding or mollusciciding will lead to insignificant drift; spray drift can therefore be ignored in the calculations.

The guidance on application of insecticides for vector control (WHO, 2003) specifies a maximum wind speed of 15 km/hour for application, equivalent to the maximum wind speed assumed in regulatory schemes. WHO guidance refers to the need to avoid overspraying of crops (although it is recognized that overspraying of rice paddies is required to kill mosquito larvae) and other direct sources of human contamination, which implies a maximum wind speed (WHO, 2003). It is therefore assumed that spraying would conform to plant protection product guidance in this respect.

Aerial application over rice paddies will give wider drift, which will settle out onto the wider environment over a large area; at recommended wind speeds, the dose would fall to 1% within 100 metres (Hewitt et al., 2002; Teske et al., 2002) in the case of agricultural application but would be much higher in vector control, with significant drift occurring over hundreds or thousands of metres.

The AGDRIFT (Hewitt et al., 2001) or AGDISP (Bilanin et al., 1989) aerial application models, developed by industry and government in the USA, should be used to determine the fraction of spray drift likely at the distance of the nearest significant surface water body

to the application area. Temperature, humidity, etc. relevant to the geographical area of use should be input into the model.

Guidance values for spray drift are generally expressed as a percentage of the applied dose. They are tabulated for use in risk assessment according to crop type, crop growth stage of the crop and equipment types typical for the region. Values cannot, therefore, be directly transferred to public health applications. In general, the degree of spray drift increases with the energy applied by the equipment (hand-held back-pack spraying causes less drift than tractor-powered application) and with the height of the vegetation, or other surface, being sprayed.

Suggested values for percentage spray drift are given in Table 4.

Redistribution of deposited pesticide to the air after application can be considerable. Most studies in this area have concerned volatilization from soil surfaces; few studies have concerned plant surfaces, and volatilization from water bodies has not been studied. The basic, worst-case assumptions for environmental risk assessment classify pesticides as being of high, medium or low relative volatility based on vapour pressure and Henry's Law constant (a measure of the partition between air and water). Measured or estimated vapour pressure and Henry's Law constant are requirements for pesticide registration and should be readily available in published regulatory assessments.

Table 4. Default values for spray drift following direction application to surface waters[a]

Distance (metres)	Spray drift (%)
1	4
5	0.6
10	0.4
30	0.1

[a] Source: Ganzelmeier et al., 1995.

Henry's Law constant (*H*) can be calculated from vapour pressure, water solubility, molecular weight and temperature:

$$H = \frac{\text{vapour pressure (Pa)} \times \text{molecular weight (kg mol}^{-1}\text{)}}{\text{water solubility (kg m}^{-3}\text{)} \times R \times \text{temperature (K)}}$$

where *R* is the gas constant (in Pa m^3 mol^{-1} K^{-1}).

Correction can therefore be made for local temperature. Vapour pressure is expressed at 20 °C and adjustments for temperature are not possible without further data, which are unlikely to be available. Vapour pressure values are therefore likely to underestimate volatilization at ambient temperatures above 20 °C. However, this is not considered a major factor in the risk assessment.

Table 5 gives the classification criteria suggested for pesticides in the EPPO (2003) guidelines. Suggested maximum daily loss by volatilization as a percentage of the applied dose in the first 24 hours after application.

For surface waters, classification should be based on Henry's Law constant. However, there are no estimates of maximum daily loss from surface waters since field studies are not available for this route. Soil losses by volatilization from thin films of water at the soil surface; overall percentage loss would reflect the partitioning of the pesticide between this surface film and adsorption to the soil matrix. Loss from surface water might be comparable

to soil loss while the pesticide remained in the surface film, which is common immediately after application for pesticides applied in oil formulations. However, as the pesticide transfers to the water body or the bottom/suspended sediment (if that is its ultimate fate), availability for volatilization will fall. No values can be put on such losses and it is suggested that the classification of relative volatility as high, medium or low be used simply as a flag for pesticides applied to water.

Table 5. Default values for loss of applied active ingredient by volatilization in the first 24 hours[a]

Relative volatility (class)	Henry's Law constant at 20 °C	Vapour pressure (Pa) at 20 °C		Maximum daily loss (% of applied dose) in first 24 h	
		For soil	For plants	For soil	For plants
High	$> 10^{-3}$	$> 10^{-1}$	$> 10^{-3}$	50	50
Medium	$10^{-6} – 10^{-3}$	$10^{-3} – 10^{-1}$	$10^{-5} – 10^{-3}$	10	25
Low	$< 10^{-6}$	$< 10^{-3}$	$< 10^{-5}$	1	10

[a] Source: EPPO, 2003.

In regulatory assessments, this basic assessment of the probability of volatilization and redistribution in the environment would be followed by models/measurements to determine the likely concentration in air and the movement of the active ingredient through the environment. Deposition from the air would also be estimated over time and distance from the applied source to give estimated concentrations in the receiving medium (soil or water). There is no standardization of such models and each has advantages and disadvantages depending on the medium from which volatilization occurs (soil or water) and the conditions of transport.

It is suggested that the worst-case calculations described above are adequate for general generic risk assessment for vector control for public health. Model calculations in registration risk assessment should be consulted during the risk assessment process to provide an estimate of the magnitude of the likely impact on the overall risk assessment, on a case-by-case basis. Specific expert judgement would be required in their use.

5.1.2 Soil

Applicability

Soil may be affected by spray drift from surface water application of larvicide or by redeposition after volatilization.

The worst-case calculation of initial soil concentration assumes instantaneous uniform distribution in a stated depth of soil following application. Allowance is made for pesticide that does not reach the soil surface because it is intercepted by vegetation. (Vegetation is another source of exposure of organisms and is treated separately.) The next section outlines the basic calculation (EPPO, 2003) and suggests defaults.

Estimation of initial concentration in soil (worst case)

$C_i = A \times (1 – f_i) \times 10^6 / (I \times 10^4 \times d)$

where:

C_i = initial concentration in soil (mg/kg soil)

A = application rate (kg/ha)

f_i = fraction intercepted by vegetation

I = thickness of soil layer (metres); suggested default 0.1 m

d = bulk density of soil (kg/m^3); suggested default 1500 kg/m^3

The application rate (A) would be the proportion expected from spray drift where no direct spraying of soil occurs.

Percentage interception equates, roughly, to percentage ground cover of the vegetation. A default value of 0.5 (50%) is suggested (Becker et al., 1999).

Risk for *short-term* exposures of soil organisms would use this value. It is likely that input to soil from application as an aquatic larvicide or molluscicide would be very low from both spray drift and volatilization. If the estimate of initial soil concentration is very low, further assessment, as follows, would be unnecessary; see section 5.1.3.

For calculation of longer-term exposure risk, the half-life of the insecticide in soil must be known. This is a standard requirement for regulatory risk assessment and should be readily available. These standard biodegredation tests should have followed guidelines to determine the appropriate kinetics for the substance in the test soils. Aerobic degradation is the usual route relevant to risk assessment for soils (unless waterlogged soil is the norm in the area sprayed). Degradation is temperature-dependent and most test results will be reported for 20 °C. Adjustments can be made for other temperatures: in the European Union, a factor of 2.58 is used for 10 °C changes (normally applied for lower temperatures in Europe but can be used for higher temperatures in the tropics) (EFSA, 2007).

Risk assessment for chronic exposure of soil organisms requires calculation of the concentration in soil (as a time-weighted average) over the same time period as used for exposure of standard organisms in chronic toxicity tests.

Calculation of time-weighted average concentration (TWAC) in soil (worst case)

TWAC (mg/kg soil) = $C_i \times (DT_{50}/(t \times \ln(2))) \times [1 - \exp(-t \times \ln(2)/DT_{50})]$

where:

C_i = initial concentration in soil (mg/kg soil) (from earlier calculations)

DT_{50} = half-life (days) from laboratory degradation tests (adjusted for local temperature)

t = time period of choice (days)

Risk calculations for *chronic* exposure of soil organisms would use this value.

For environmental risk assessment for soils it is important to determine whether the pattern of use of the insecticide leads to build-up of residues of the active ingredient. From any single application of insecticide, the concentration in soil at any specific time interval after application can be calculated from the equation in the following section.

Calculation of concentration at time *t* after application

C_t (mg/kg soil) = $C_i \times \exp -(\ln(2)/DT_{50} \times t)$

where:

C_i = initial concentration in soil (mg/kg soil), from earlier calculations

DT_{50} = half-life (days) from laboratory degradation tests (adjusted for local temperature)

t = time period of choice (days)

For repeat applications, concentrations in soil can be calculated over time, taking into account the overlap of residues remaining from previous applications with further spraying. The straightforward calculations assume a constant application rate and constant intervals between applications; in these circumstances, a steady state will be achieved over time. For irregular application intervals, each application would need to be calculated separately and the results added for overlap. The latter is likely to be the situation for vector control.

Calculation of upper and lower plateau concentrations for repeat application at constant rate and constant time intervals

Lower plateau concentration (residue at the end of the *n*th application):

$$R_{low} = \frac{C_i \times X \times (1 - X^n)}{1 - X}$$

$R_{low} = C_i \times X \times (1 - X^n) / 1 - X$

where:

R_{low} = lower plateau concentration at the end of the *n*th application (mg/kg soil)

X = the proportion of the applied dose remaining after the first application

C_i = initial concentration in soil after application of A (kg/ha)

n = the number of applications

Upper plateau concentration:

$$R_{high} = \frac{C_i \times (1 - X^n)}{1 - X}$$

$R_{high} = C_i \times (1 - X^n) / 1 - X$

For irregular application intervals or different application rates, the equation for the calculation of concentration C_t at time t after application should be used and overlapping calculated concentrations summed.

The remaining essential value required for soil is the adsorption coefficient K_d which measures the partition between the soil matrix and the interstitial water. This is an indicator of the likelihood of the pesticide leaching down through the soil to reach groundwater and of lateral movement through the soil. The value is often normalized to the organic matter fraction of the soil, the matrix in which most adsorption generally occurs. This is expressed either as K_{OM} (for organic matter) or K_{OC} (for organic carbon). The normalized value should be taken unless there is indication that the organic material content of the relevant soils differs significantly from the default/measured values used in its calculation.

The above scheme for soil makes worst-case assumptions. In a regulatory context, the estimates of likely soil concentration would be combined with effects information to calculate risk. The risk observed would then be used to determine what further information was required to refine the risk assessment. An unacceptable risk would trigger further testing: in the case of soil, field studies would be required to confirm the concentrations found following expected patterns of use. Ideally, this should be the same for vector control – if the risk were unacceptable on a worst-case, precautionary basis, field measurements would be conducted. Field studies can be expensive and time-consuming, particularly since the locations for vector control are likely to be much more varied than agricultural fields.

If local field studies are not available, the likely case, extrapolating to probable reality, could be based on the refinement level of regulatory risk assessment available from temperate countries. The field conditions of these refinement-level tests may be very different from those of vector control. Expert judgement is thus the only means of applying "correction" factors to the first, precautionary, estimates of risk.

It is beneficial to know both the degree to which environmental damage will occur and the likely time needed for environmental recovery. It is suggested that a calculation be performed to predict the number of repeat applications that would lead to the soil residues of concern at the worst-case and likely realistic assessment levels. Calculations are also suggested to estimate the time taken for soil residues to fall to non-damaging levels after cessation of treatment.

Calculation of number of applications that would lead to soil concentrations of concern

These calculations can be performed by iterations of the equations for upper and lower plateau concentrations presented above (or the results for overlapping irregular applications) until a concentration of concern is reached; this concentration is determined as a no-observed-effect concentration for soil organisms, derived in later stages of the risk assessment. The result is expressed as a value of n (number of applications).

Calculation of time to return to non-damaging concentrations after cessation of spraying

On cessation of spraying, the final estimate of soil concentration (plateau concentration equations using actual value for n) would be used as the starting concentration C_i for the equation for concentration at time t after application. The time period, t, required to reach non-damaging concentrations would then be calculated iteratively.

5.1.3 Surface water and aquatic sediment

Applicability

Sprayed larvicides and molluscicides are applied directly to surface water. For risk assessment, water/sediment concentrations can be determined with spraying as the sole source, since other inputs will be minor in comparison.

For the application of larvicide/molluscicide to surface water, calculation of initial concentration would assume instant even distribution in the water body. This is not normally calculated for registration purposes since few pesticides are applied directly to water.

Estimation of initial concentration in water from larvicide / molluscicide application (worst case)

$C_{iw} = 100 \times A/D$

where:

C_{iw} = initial concentration in water (µg/litre)

A = application rate (kg/ha)

D = depth (metres); suggested default 0.5 m

Risk for *short-term* exposures of organisms living in the open water body would use this value.

Insecticide reaching surface water will partition between the water body and sediment (both bottom sediment and suspended particulates). This partitioning is key to understanding which organisms are likely to be exposed to the residues and therefore which compartment is relevant to the risk assessment.

Concentrations resulting (at equilibrium) from such partitioning are given below.

Estimation of concentrations in water and sediment following partition equilibrium

Partition coefficient:

$K_{s/l} = C_{sed} / C_{water}$

where:

$K_{s/l}$ = sediment/water distribution coefficient (litres/kg)

C_{sed} = concentration in sediment (mg/kg)

C_{water} = concentration in water (mg/litre)

Fractions dissolved and sorbed:

$f_{dissolved} = 1/(1 + K_{s/l})$ and

$f_{sorbed} = K_{s/l}/(1 + K_{s/l})$

Concentration:

Total emissions to the water/sediment compartment are divided by the estimated volume of the compartment.

Residues of insecticide in water will dissipate over time. Concentrations may be affected by any or all of the following factors: biodegradation (aerobic or anaerobic), advection, hydrolysis, photodegradation, sedimentation and resuspension.

As for soil, the biodegradation half-life should be available for the water/sediment compartment since it is a requirement for registration. Separate studies are conducted for this compartment (OECD, 2011) and should generate separate half-lives for the water, the sediment and the whole system.

Advection – transport in fluid – is relevant to the risk assessment if the water body receiving the insecticide is flowing or renewed (water being pumped into or out of the body). However, this is not usually the case for larvicidal application, which commonly involves small, static bodies of water.

Hydrolysis may be included in the value for biodegradation; it is not necessarily measured separately in the test (using sterilized medium). Care must be taken if the pK_a value for the substance is close to (within 1 unit) of the pH of the water; this could lead to significant dissociation of the substance into ionic species, which will affect both hydrolysis and the adsorption characteristics of the substance.

Photodegradation is often considered unlikely in registration assessments based on temperate regions but may be much more important in tropical areas. High turbidity in the receiving water will greatly reduce photodegradation.

Sedimentation is the loss of insecticide residue from the water body to sediment by adsorption to particulates, which then fall to the bottom; sediment particles may also be resuspended following disturbance of bottom sediments by flow or other factors.

These processes can be summed as rate constants, K_x, which can be calculated from half-life DT_{50} according to the general formula:

$$K_x = \ln(2)/DT_{50}$$

Total dissipation may then be estimated from the equation in the following section.

Dissipation from the water body over time (*t*)

$K_{total\_dissipation} = (K_b + K_s - K_r + K_v + K_h + K_p) \times f_{dissolved} + K_a$

where:

$K_{total\_dissipation}$ = total reaction rate constant for all processes together assuming first-order kinetic (days^{-1})

K_b = rate constant for biodegradation (days^{-1})

K_s = rate constant for sedimentation (days^{-1})

K_r = rate constant for resuspension (days^{-1})

K_v = rate constant for volatilization (days^{-1})

K_h = rate constant for hydrolysis (days^{-1})

K_p = rate constant for photodegradation (days^{-1})

$f_{dissolved}$ =fraction of dissolved substance (See partition equilibrium above)

K_a = rate constant for advection (days^{-1})

Then:

$C_t = C_i \times \exp(-K_{total\ dissipation} \times t)$

where:

C_t = concentration at time t (mg/litre)

C_i = initial concentration from all sources (mg/litre)

t = time (days)

Comparison with acute toxicity test results can be made against concentration at time zero; comparison with chronic toxicity test results would be against a time-weighted average concentration over t days calculated as:

$$TWAC = \frac{C_i \times (1 - e^{-k_{total\ dissipation} \times t})}{k_{total\ dissipation} \times t}$$

where t is comparable with the time period of the chronic tests.

Dissipation from the sediment over time (*t*)

A comparable calculation can be made for dissipation from the sediment over time but only biodegradation and, possibly, sedimentation and resuspension would be relevant.

5.2 Effects

5.2.1 Aquatic organisms

Acute tests on a range of aquatic organisms representing three trophic levels in aquatic ecosystems are an absolute requirement for registration of new pesticides and should be available as a minimum for all pesticides. Acute tests on microalgae, daphnids and fish are the common feature of all regulatory systems. For herbicides, an additional test on an aquatic macrophyte would normally be added; these tests, usually on the floating plant *Lemna*, are unlikely to be available for newer insecticides but have often been performed for older insecticides.

Testing should normally be done on the pesticide as the formulation that will be used in the field, but this may not have been the case for older pesticides. Ideally, testing of both the pure active ingredient and the formulation should be available to indicate the toxicity caused by each component. Care should be taken with reported values from toxicity tests in which the concentrations tested substantially exceed the water solubility of the substance.

Small or minimal acute datasets can be handled for risk assessment only by using deterministic approaches. Comparison of the lowest reported LC_{50} (concentration killing 50% of the test organisms – the usual end-point for acute tests on animals) or EC_{50} (concentration having a 50% effect on test populations against a specific end-point – often growth or biomass and the usual end-point for algal tests) with the predicted (or measured) environmental concentration (PEC) gives a ratio, the exposure–toxicity ratio (ETR). The ETR is a measure of the margin between exposure and toxicity, a simple safety margin, and is normally expressed as a single ratio for the most sensitive species tested. Risk is thus completely dependent on a single data point, a single toxicity test result. Further tests will not affect the risk calculation provided that they show lower sensitivity than the existing tests; however, a new test with a lower LC_{50} or EC_{50} will change the outcome.

Commonly, these simple ratios are used in regulatory systems to generate an initial classification of the pesticide and to inform the need for further testing.

Application of an insecticide to surface water with the intent of killing aquatic larvae will, inevitably, pose a risk to species related to the target insect. All, or most, other insects are likely to be killed since a lethal concentration is deliberately applied; other arthropods are also likely to be affected and percentage kill may be the same as for as the target species. Within the standard test species, the daphnids would be most likely to be affected by an insecticide. An overall ETR would be of little value for risk assessment of larvicidal application of insecticide.

It is suggested that ETRs be calculated for all three types of organism likely to be represented in the dataset – algae, fish and daphnids – plus other invertebrates if test results are available. Classification against unrelated organisms might then distinguish between different insecticides. Larvicidal application is always likely to classify insecticides as high risk because of their direct application to water.

Exposure–toxicity ratios for short-term exposure (EPPO, 2003)

The ETR is derived by dividing the initial concentration in surface water (C_{iw}) by the lowest reported LC_{50} or EC_{50} for algae, invertebrates and fish, plus any other group of organisms for which acute toxicity test results are available. Results are tabulated.

For pesticides that dissipate rapidly from water, the TWAC would be more appropriate than initial concentration for deriving ETR.

- If the ETR is low (< 0.1, equivalent to a safety margin of 10), the value is classified as *low acute risk*.
- If the ETR is moderate (0.1–1, equivalent to a safety margin between 10 and 0), the value is classified as *medium risk*.
- If the ETR is high (> 1, equivalent to an exceeded safety margin), the value is classified as *high acute risk*.

  If any ETR is classified as indicating low acute risk, no further consideration is given to it in the risk assessment.

In regulatory systems, additional tests over a longer exposure period would be triggered by persistence of the pesticide in either water or sediment and/or medium to high acute risk classification. For older pesticides, many such tests were conducted outside the regulatory framework and published in scientific journals.

For older pesticides, existing schemes often did not distinguish between the media in which the pesticide was likely to partition; for these older active ingredients, tests will therefore be available on organisms that are unlikely to be exposed and unavailable for those that are likely to be exposed. Methods for extrapolation are available in this case. Modern regulatory systems would tailor requirements for longer-term toxicity tests to the most sensitive species and the appropriate medium (water or sediment) for the ultimate fate of the pesticide.

Chronic tests will thus be available for most pesticides that have been used for some time but may not be ideal for risk assessment or conform to modern guidelines. This does not make them unusable but increases the uncertainty of the resulting risk assessment.

Results of chronic tests would normally establish a no-observed-effect concentration (NOEC) rather than the effect concentrations determined in acute tests. In some cases, no NOEC will have been established and a lowest-observed-effect-concentration (LOEC) will be available instead.

The strict definition of “chronic” would be “over the lifetime of the organism”. Algal tests cover multiple generations of the algae, even for short-term exposure (typically 3–4 days), and are often used in both acute and chronic toxicity assessments. The end-points in algal tests (growth or biomass) are indications of population-level effects and would conform to an alternative definition of chronicity – of relevance to population level. Chronic tests on daphnids are typically run over 28 days and would include two generations, fulfilling both definitions of chronicity. Some daphnid species can achieve the same number of generations in a much shorter time. “Chronic effects” on fish are commonly derived from tests conducted over shorter periods than would meet either definition. The decision on whether a fish test should be regarded as acute or chronic can have significant effects on the outcome of the risk assessment and should be made by an expert. Early life-stage tests, exposing fish from the egg stage through larval development to the juvenile, are often done as chronic tests. Longer-term fish tests that measure only survival are not usually considered as chronic. Tests measuring non-lethal end-points, for example enzyme systems (common for organophosphate insecticides), are not usually included in chronic risk assessment.

Ideally, chronic tests would involve species relevant to the environment local to the application under risk assessment. Most common test species are temperate, and the tests will have been conducted at lower temperatures. Some tropical species are used in non-standard testing and might be available but should not be used in preference in risk assessment for public health application of larvicides/molluscicides; they should be examined for evidence of higher toxicity at higher temperatures. It is unlikely that the dataset will be sufficiently large for confident predictions in this respect.

Classifications for chronic toxicity are then based on a recalculation of ETR, as for short-term exposure.

Exposure–toxicity ratios for chronic exposure

The ETR is derived by dividing the TWAC in surface water over the time period of the chronic test (with starting concentrations those used for acute exposure) by the lowest reported NOEC for algae, invertebrates and fish, plus any other group of organisms for which chronic toxicity test results are available. Results are tabulated.

For pesticides that dissipate rapidly from water, the TWAC would be more appropriate than initial concentration for deriving ETR.

- If the ETR is low (< 0.1, equivalent to a safety margin of 10), the value is classified as *low chronic risk*.
- If the ETR is moderate (0.1–0.2, equivalent to a safety margin between 10 and 5), the value is classified as *medium risk*.
- If the ETR is high (> 0.2, equivalent to a safety margin less than 5), the value is classified as *high chronic risk*.

Note: The risk assessor should be aware of the results of the partitioning calculations. If there is rapid or complete partitioning from water to sediment, the chronic risk assessment should concentrate on the latter medium.

Calculation of ETR would be based on calculated sediment concentration of the insecticide and tests on sediment-dwelling invertebrates. If sediment tests are not available, aquatic test results may be compared with estimated interstitial water concentrations in sediment.

Biodegradation in the sediment should be taken into account in estimating exposure over the time period of the chronic test. Some partitioning out of the water body will also affect the concentration in water over the period of a chronic test on a species living in the water body.

For larger datasets, a probabilistic approach can be taken, using all the available data to derive a predicted no-observed-effect concentration (PNEC) from a fitted distribution curve. This approach has not been widely applied to pesticide risk assessment but scientifically is the more desirable approach. A probabilistic distribution has the advantage that new single tests have little influence on the outcome. The complete dataset increases confidence that a realistic NOEC has been derived that is protective of a wide range of species.

In pesticide regulatory systems, strict criteria are usually applied to the use of the probabilistic approach (number of data points, number of trophic levels/representative groups of organisms, etc.). Only chronic NOECs are used as input for curve-fitting. In the present context, it is suggested that less strict criteria be established because the approach is useful in determining the degree of concern when headline ETRs indicate high risk.

In Australia and New Zealand, guidance on applying probabilistic approaches to risk assessment for water quality guidelines allows the application of factors to acute data to increase the number of chronic points available for curve-fitting. The number of tests required for the approach is also reduced. This less stringent guidance has been followed in the WHO Concise International Chemical Assessment Document (CICAD) series and its use has been the subject of international peer-review in this context.

It is suggested that, if the dataset allows, distribution curves be fitted (log-logistic or comparable) for the full dataset and for the dataset without aquatic invertebrates. This should inform the final decision on risk to target (and related) and non-target organisms in vector control.

Fit a distribution curve to available chronic data (if sufficient are available)

- Derive values for concentration protective of 95% of species with an error of 50% for all species and for non-target species (excluding invertebrates).

  Bioaccumulation influences the perceived risk over longer time frames. Following estimation of chronic risk, account should be taken of indicative bioaccumulation in the test species or trophic level.

Bioaccumulation potential can be estimated from P_{ow}, the octanol/water partition coefficient; this is commonly done for industrial chemicals where the availability of test data is limited. However, it is probable that bioaccumulation tests, at least in fish, will have been conducted for most pesticides. These experimental values should be used in preference in the risk assessment. A more precautionary approach is generally taken with pesticides than with industrial chemicals, and a ratio, at steady state, of 1000 for a BCF (bioconcentration factor: concentration in the test organism expressed as whole-body concentration/concentration in the test medium, usually water) is considered to be of concern.

Establish bioaccumulation potential

- Estimate from P_{ow}: BCF = 0.048 x P_{ow}

  or preferably:

- Obtain BCF from studies at least on fish. Classify as potentially bioaccumulative if BCF > 1000.

The need for specific decisions on the suitability of species, the requirement for chronic testing, the interpretation of test results, and whether or not probabilistic approaches can be applied is emphasized as a requirement for expert ecotoxicological input into the process in all regulatory systems. A need for expert judgement is also suggested here. The additional extrapolation from temperate to tropical conditions would also argue for specific expertise.

The availability of any further tests or field data should be established here. Mesocosm and field studies will indicate whether predicted worst-case ETRs are realistic.

5.2.2 Soil organisms and soil function

Risk assessment for soil organisms is comparable to that for aquatic organisms; comparison is made between a predicted or measured concentration in soil and the results of toxicity tests. In addition to single-species toxicity testing, tests for generalized toxicity to soil microflora may be performed, measuring effects on nitrogen or carbon transformation processes in the soil.

Standard testing of soil organisms involves many fewer species than testing the aquatic environment. Earthworms are the most likely species to have been tested and the tests could be acute (lethality end-point) or chronic (reproductive end-point). Other organisms were seldom tested in the past and standard tests are unlikely to be available for older pesticides; non-standard tests might have been carried out and reported in the scientific literature. Tests that comply with international guidelines are often conducted in artificial soils to reduce variability; results are usually corrected to reflect differences in organic matter content between the artificial and natural soils. A correction factor of 2 is usually applied in Europe. However, this assumes that agricultural soils are neither very sandy nor very peaty; neither assumption can necessarily be made in the environment generally.

A wide range of soil function tests have been conducted in the past. Comparisons between different test methods suggest considerable variability, and interpretation of older tests therefore requires expert input.

Field tests on soil organisms are rare for older pesticides and are unlikely to be relevant to risk assessment in the context of disease vector control.

In general, ETRs are calculated as follows.

Estimation of exposure–toxicity ratios for soil organisms

Acute

- Comparison is made between the initial concentration in soil, C_i, and the acute LD_{50} from an earthworm test corrected for soil organic matter (normally a factor of 2 is used but this should be determined by expert input).
- If the ETR is > 0.2 (equivalent to a safety margin of 5), acute toxicity for earthworms is of concern.

Chronic

- Comparison is made between the TWAC in soil over the time period of the chronic test and the chronic NOEC for reproduction in earthworms.
- A chronic test with measurement of reproductive success should give some indication of likely population effects in the field. The degree of concern for chronic effects on earthworms is based on the likelihood of effects persisting for more than one season or of substantial reduction in reproductive potential within a single season, estimated against toxicity test results and likely exposure over one season.

  Further acute or chronic ETRs may be calculated if toxicity test results are available for other soil organisms.

Bioaccumulation in earthworms is considered of relevance to the risk assessment for soil organisms but is of interest principally in consideration of secondary poisoning in the food chain.

Establish bioaccumulation potential for terrestrial organisms

The bioconcentration factor is estimated from the octanol/water partition coefficient (P_{ow}):

$BCF = (0.84 + 0.01P_{ow})/F_{oc}\,K_{oc}$

where:

P_{ow} = octanol/water partition coefficient

F_{oc} = organic carbon content of the soil (default value is 0.02)

K_{oc} = organic carbon adsorption coefficient

Ideally, however, BCF is obtained from studies on earthworms.

Significant bioaccumulation leads to consideration of risk by secondary poisoning to predators eating worms (see later).

Reasonable cut-off values for results on soil function

These tests should be conducted over an adequate period of time; early tests were often short-term. For valid test results on carbon and nitrogen transformation in soil:

- If deviation from control is < 25% at all time periods, the risk is considered to be *negligible*.
- If deviation from control is < 25% after 28 days, the risk is considered to be *low*.
- If deviation from control is < 25% between 42 and 100 days, the risk is considered to be *medium*.
- If deviation from control is > 25% after 100 days, the risk is considered to be *high*.

Reported field studies on soil organisms would inform the risk assessment process at this stage; these are unlikely to be available in situations relevant to disease vector control.

5.2.3 Non-target terrestrial arthropods including honeybees

Risk assessment for non-target terrestrial arthropods is a standard component of regulatory risk assessment for pesticides. However, it is not considered relevant to risk assessment for aquatic application for public health.

5.2.4 Terrestrial vertebrates

Possible effects of ingestion of insecticide residues by birds and mammals, either directly through their food or indirectly through prey, form a major component of environmental risk assessment. These organisms are highly visible components of the natural environment, have relatively lower reproductive rates than lower organisms and, in the case of predators, represent the top of the food chain and therefore integrate effects at lower trophic levels.

Testing of pesticides, acutely and for longer-term reproductive effects, has been common in regulatory schemes for a considerable time and both testing regimes will probably be represented in the literature for older pesticides. No specific testing is conducted on wild mammals but the dataset on laboratory rodents, from tests performed for human health risk assessment, informs the risk assessment for wild mammals.

Laboratory testing for both birds and mammals usually exposes the organism via food in longer-term tests. In short-term toxicity tests, mammals are dosed via the diet and birds either by gavage or, more usually, through the diet. Short-term risk assessment is based on acute LD_{50}/LC_{50} test results; long-term risk assessment would use NOELs/NOECs from dietary tests. Longer-term studies would normally be aimed at reproductive end-points in birds and at a range of toxic end-points in mammals.

Comparison of effects against dose thus requires calculation or measurement of pesticide residues in food items. For insecticides used as aquatic larvicides, this would involve prey items such as worms and fish. For fish-eating species, whole-body residues will have been calculated from the bioaccumulation studies in the section on aquatic organisms. For birds

that eat earthworms, whole-body residues will have been obtained in the soil organisms section.

The relationship between body weight and food consumption for birds and mammals has been comprehensively studied. When particular local species likely to be exposed through contaminated food are known, their body weights can be estimated and there is a general indication of their diet from which specific calculations can be done for risk if the generalized assessment indicates concern. Daily dietary dose (DDD), as mg/kg body weight per day, can be calculated from the concentration in food items and the amount of food consumed.

Risk assessment is conducted on birds or mammals feeding in the sprayed areas. Possible effects outside the "field" of application are not usually considered, nor is any account taken of the indirect effects on bird or mammal populations of reduction in food as a direct consequence of pesticide application. For insectivorous birds and mammals, therefore, no risk assessment will be conducted on the basis of reduction in insect prey numbers following spraying. This can be a major factor in the risk of pesticide use, but there are no recognized schemes for assessing it; de-novo development of such schemes for disease vector control would be extremely complex and is considered to be outside the remit of the current project.

The exposure estimates calculated above are compared with toxicity information to generate ETRs. The values of ETR from short-term exposure determine whether exposure and ETR calculations are required for the medium term; similarly, medium-term results indicate the need to consider long-term exposure.

Indications of bioaccumulation from either the aquatic organisms section (fish) or the soil section (earthworms) would generate a requirement for risk assessment for fish-eating or worm-eating species; this is done for the medium-term exposure scenario and could be extended to the longer term if a risk were identified. Indications of bioaccumulation would be a log K_{ow} > 3 or BCF > 1000.

Calculation of exposure–toxicity ratios for birds and mammals

Medium-term exposure

The DDD values are divided by lethality in short-term tests. For birds, the lethality end-point (LC_{50}) is taken from a 5-day acute toxicity test; for mammals, the end-point (NOEC) is taken from a 28-day rat study. In both cases, the value is converted from LC_{50} (mg/kg food) into LD_{50} (mg/kg body weight per day).

$LD_{50} = LC_{50} \times DFI/1000$

where DFI = daily food intake (in g x 1000/body weight in g)

Note: Applicability of the short-term dietary toxicity test in birds (5 days) for risk assessment has been called into question (Mineau et al., 1994). Results of the test are often a consequence of starvation because of repellency of the diet and should therefore be used with caution[1].

Long-term exposure

The DDD values are divided by non-lethal NOEC results from medium- to long-term tests (mammalian testing and avian reproductive testing). The NOEC is converted to NOED (mg/kg body weight per day).

Uncertainty is related to the dataset available for mammals and birds. If only small numbers of tests results are available (one or two species, for example), an uncertainty factor – commonly 10 – is applied to the calculated ETR. If larger numbers of tests results

[1] Interpretation of the results of the test is the responsibility of the assessor.

are available, a probabilistic approach can be used to determine the appropriate NOEC, comparable to the approach described for aquatic organisms.

The risk assessment result can be scaled against likely environmental risk only by reference to field studies on the appropriate organisms. The literature should be searched for such studies at this stage of the risk assessment.

5.2.5 Higher terrestrial plants

It is proposed that risk assessment for higher terrestrial plants is not included; such effects are very unlikely from exposure to pesticides used as aquatic larvicides or molluscicides.

6. Conclusions

The models described in this document are intended for first-tier risk assessments. The default values presented should be replaced by case- specific or substance-specific values or distributions whenever available. In the interests of the transparency of the process, it is of utmost importance that the decisions taken are soundly and scientifically justified and accurately recorded.

7. Summary of the human health risk assessment model and a worked example

In this worked example, an emulsifiable concentrate formulation of organophosphate insecticide “X" is used as a model compound.

Generic risk assessment model	Worked example
1. Toxicity data *Aim:* To assess available toxicity data and derive acceptable exposure levels.	**1. Toxicity data** *Aim:* To assess available toxicity data and derive acceptable exposure levels Relevant TSDs for human health include a TCD_{AC} for short-term exposure and a long-term TSD for operators’ exposure.
1.1 Conduct literature search for human, animal and in-vitro toxicity data and any necessary physicochemical data on the insecticide.	1.1 Literature search on insecticide X conducted on MEDLINE, TOXLINE and sources of reviews (WHO/IPCS (EHCs, CICADs), JMPR, USEPA, PSD, IARC, ATSDR, EFSA, etc.).
1.2 Obtain relevant reviews and key original papers.	1.2 Comprehensive reviews available from JMPR and the European Commission Directorate D on food safety. Key studies obtained.
1.3 Tabulate types of study, toxic effects observed, NOAELs and LOAELs.	1.3 All available relevant animal and human studies tabulated.
1.4 Assess whether quality of database is adequate for risk assessment (range of studies, conduct of studies, adequacy of dose–response data, etc.).	1.4 Studies available on all relevant types of toxicity, most via oral route, but also some inhalation and dermal studies. Most conducted to acceptable standards with adequate dose–response data.
1.5 If database is adequate, identify critical toxic effect(s).	1.5 Insecticide X is a moderately toxic organophosphate pesticide (oral LD_{50} rat < 100 mg/kg bw) and its critical effect is reversible neurotoxicity due to cholinesterase inhibition. Data on cholinesterase inhibition available from human and animal studies.
1.6 If the insecticide is genotoxic, carcinogenic or extremely acutely toxic via dermal or oral routes, consider whether it is worth proceeding with risk assessment. Consider this also if it causes clear reproductive toxic effects at dose levels causing no general toxicity.	1.6 The substance is not genotoxic, carcinogenic or a specific reproductive toxicant. It is moderately acutely toxic. Proceed with risk assessment.
1.7 If 1.6 does not apply, identify pivotal study/studies giving dose–response data for critical effect(s).	1.7 Pivotal studies were: • human volunteer single- and repeated-dose oral studies describing oral NOAELs for cholinesterase inhibition; • human volunteer single-dose dermal studies; • rat dermal 21-day studies; • rat oral 13-week studies; and • dog oral 2-year studies.
1.8 Identify critical NOAEL(s) from pivotal studies for short-term exposure and for longer-term (repeat- dose) exposure.	1.8 Critical NOAELs: • acute (single-dose), oral NOAEL, human, based on cholinesterase inhibition, 1 mg/kg; acute dermal NOAEL, human, 5 mg/kg; • repeated-dose oral NOAEL (9 days), human, based on cholinesterase inhibition, 0.1 mg/kg;

Generic risk assessment model	Worked example
	• subchronic oral NOAEL, rat, based on cholinesterase inhibition, 1 mg/kg; • chronic oral NOAEL, dog, based on cholinesterase inhibition, 1 mg/kg; and • dermal NOAEL, rat, 21 days, based on cholinesterase inhibition, 5 mg/kg.
1.9 Assess whether the database allows the setting of TSDs for short- and long-term exposure via oral, dermal and inhalational routes.	1.9 Database is adequate for the setting of TSDs, including both long-term and short-term levels, for the substance.
1.10 Set TSDs by dividing NOAEL for the critical effect from the pivotal study by an uncertainty factor (UF): TSD = NOAEL/UF A default UF of 100 is recommended for NOAELs derived from animal studies. A default UF of 10 is recommended for NOAELs derived from human studies.	1.10 The ADI of 0–0.01 mg/kg bw per day is set by JMPR. This is based on rat/dog studies showing cholinesterase inhibition at 1 mg/kg bw and applying a UF of 100 and on repeated-dose human study with an NOAEL of 0.1 mg/kg and a UF of 10. In addition, JMPR has set an ARfD of 0.1 mg/kg bw based on single-dose human volunteer study describing an NOAEL of 1 mg/kg bw and using a UF of 10. The absorption of X from the gastrointestinal tract is > 90%, and thus the ADI is taken to represent tolerable systemic dose (TSD) (EC, 2006).
1.11 Tabulate TSDs for use in subsequent risk characterization.	1.11 TSDs used in risk characterization: • long-term TSD, 0.01 mg/kg bw per day • short-term guidance value (TSD_{AC}), 0.1 mg/kg bw.
2. Exposure assessment. The active ingredient content of the product is 500 mg/mL; the container size 5L, and closure size of the container 45 mm. The hand contamination (Table 3) is thus 0.01 mL/operation; a maximum number of 12 tank-loads per day is assumed. The operators work in larviciding 6 days/week for 6 months = 156 days/year. The recommended application rate of X for larviciding is 11–25 g/ha, which leads to an initial concentration of X in surface water of ≤ 5 µg/litre. For a product with a dissipation half-time of 2 days, this is also the estimated drinking-water concentration over the period of 6 months. As exposure is likely to be to both suspended and dissolved X, partition is not considered. The water ingestion rate is assumed here to be 2 litres/day for adults, 1 litre/day for children and 1 litre/day for toddlers. Thickness of the liquid film on skin is 0.001 dm, skin surface exposed 166, 92, 48, and 41 dm^2 for adults, children, toddlers and infants. The frequency of swimming/bathing episodes is 52/year. The body weight is 60 kg for adults, 23.9 kg for children, 10 kg for toddlers, 8 kg for infants and 4.2 kg for newborns. In two limited studies in humans, urinary excretion of metabolites of X was 1 and 1.3% of the dermal dose applied; 4% is used in this assessment ($1.3 \times 10^{0.5}$). In goats, ≤ 0.14% of an oral dose was excreted in milk. Thus $0.14 \times 10^{0.6} = 0.6\%$ is used as the estimate for milk excretion in exposed humans.	
2.1 Operator exposure *a) Exposure during mixing and loading* It is assumed that inhalation exposure of the operator during mixing and loading is negligible. *Predicted TWA systemic dose* $SysD_{TWA}$ = $UE_{LIQ} \times PPE \times CF \times NOD \times ABS_D \times EF / (BW \times AT)$ *Predicted maximal daily systemic dose* $SysD_{MAX}$= $UE_{LIQ} \times PPE \times CF \times NOD \times ABS_D / BW$, *where* UE_{LIQ} = 0.01 mL/operation *PPE* = 0.1 for guideline scenario, 1 for lax standard scenario *CF* = 500 mg/mL *NOD* = 12	In the guideline scenario, the predicted TWA systemic dose is 0.01 × 1 × 500 × 12 × 0.04 × 156 / (60 × 365) = **1.7 µg/kg bw per d** And the predicted maximal daily dose is 0.01 × 1 × 500 × 12 × 0.04 / 60 = **4.0 µg/kg bw** In the lax standard scenario, TWA systemic dose is 0.01 × 1 × 500 × 12 × 0.04 × 156 / (60 × 365) = **17.1 µg/kg bw per d** In the lax standard scenario, maximal daily systemic dose is

Generic risk assessment model	Worked example
ABS_D = 0.04 EF = Exposure frequency, 156 *BW* = 60 kg AT = Averaging time, 365 days	0.01 × 1 × 500 × 12 × 0.04 / 60 = **40.0 µg/kg bw**
b) Exposure during application and washing and maintenance of the equipment Inhalation exposure can be assumed to be negligible due to large droplet size, downward spraying direction, and working outdoors Predicted TWA systemic dose $SysD_{TWA}$ = $VS_{dermal} \times C_{spray} \times PPE \times EF \times Abs_D / (BW \times AT)$ *Preicted maximal daily systemic dose* $SysD_{MAX}$ = $VS_{dermal} \times C_{spray} \times PPE \times Abs_D / BW$, *where* VS_{dermal} = volume of spray on hands (8.2 mL) C_{spray} = concentration of a.i. in the spray, 0.5 mg/mL *PPE* = 1 for the lax standard scenario, 0.1 for the guideline scenario *EF* = exposure frequency = 156 d/yr Abs_D = 4% *BW* = 60 kg *AT* = 365 d	In the guideline scenario, the predicted TWA systemic dose is 8.2 × 0.5 ×0.1 ×156 ×0.04 / (60 ×365) **= 0.12 µg/kg bw**. In the guideline scenario, the predicted maximal daily systemic dose is 8.2 × 0.5 ×0.1 × 0.04 / 60 = **0.27 µg/kg bw**. In the lax standard scenario, the predicted TWA systemic dose is 8.2 × 0.5 ×1 ×156 ×0.04 / (60 × 365) = = **1.17 µg/kg bw per day**. In the lax standard scenario, the predicted maximal daily systemic dose is 8.2 × 0.5 × 1 × 0.04 / 60 = = **2.73 µg/kg bw**.
c) Total operator predicted dose, exposures are combined:	In the guideline scenario, TWA systemic dose: 1.7+0.12 = **1.82 µg/kg bw per day** In the lax standard scenario, TWA systemic dose: = 17.11+1.17 **= 18.2 µg/kg bw per day**. The maximal systemic daily dose in the guideline scenario is 4.3 µg/kg bw and 42.7 µg/kg bw in the lax standard scenario.
2.2 Residential exposure *a) Drinking treated water* Predicted TWA systemic dose $SySD_{TWA}$ = *CDW* × *WIR* ×*AbsO* ×*EF / (BW* ×*AT)* *Maximal daily systemic dose,* $SysD_{MAX}$ = *CDW* × *WIR* ×*AbsO / BW, where* *CDW* = concentration in drinking-water 5 µg/L *WIR* = water ingestion rate; adults 2, children and toddlers 1 L/d *AbsO* = oral absorption 100% *EF* = exposure frequency, 183 d *BW* = body weight; 60, 23.9 and 10 kg for adults, children, and toddlers *AT* = averaging time, 365 days	Predicted systemic TWA dose due to drinking treated water, adults: = 5 µg/L × 2 L × 1 × 183 / (60 × 365) **= 0.084 µg/kg bw per day** children: 5 µg/L × 1 L × 1 × 183 / (23.9 × 365) **= 0.105 µg/kg bw per day** toddlers: 5 µg/L × 1 L × 1 × 183 / (10 × 365) **= 0.25 µg /kg bw per day** Predicted maximal daily systemic dose due to drinking treated water, adults = 5 µg/L × 2 L × 1 /60 **= 0.17 µg/kg bw** children = 5 µg/L × 1 L × 1 /23.9 **= 0.21 µg/kg bw** toddlers = 5 µg/L × 1 L × 1 /10 **= 0.50 µg /kg bw**
b) Bathing and swimming in treated water, dermal exposure *TWA systemic dose,* $SySD_{TWA} = CW \times WS_{dermal} \times AbsD \times EF / (BW \times AT)$ *Maximal daily systemic dose,* $SySD_{MAX} = CW \times WS_{dermal} \times AbsD \times EF / BW$, *where* *CW* = concentration in water 5 µg/L WS_{dermal} = volume of water on the skin; 166, 92, 48, 41 and 27 mL for adults, children, toddlers, infants and newborns respectively *AbsD* = dermal absorption, 4% *EF* = exposure frequency, 52	Systemic TWA dose due to contact with treated water is adults =5 × 0.166 × 52 × 0.04 / (60 × 365) = **0.00008 µg/kg bw per day** children= 5 × 0.108× 52 × 0.04 / (23.9 × 365) **= 0.00013 µg/kg bw per day** toddlers =5 × 0.061× 52 × 0.04 / (10 × 365) **= 0.00014 µg/kg bw per day** infants = 5 × 0.041 × 52 × 0.04 / (8 × 365) **= 0.00015 µg/kg bw per day** Newborns = 5 × 0.027 × 52 × 0.04 / (8 × 365) **= 0.00018 µg/kg bw per day** Maximal daily systemic dose is adults = 5 × 0.166 × 0.04/60 = **0.00055 µg/kg bw**

Generic risk assessment model	Worked example
BW = body weight; 60, 23.9, 10, 8 and 4.2 kg for adults, children, toddlers, infants and newborns respectively *AT* = averaging time, 365 days	children = 5 × 0.092× 0.04 / 23.9 **= 0.00077 µg/kg bw** toddlers = 5 × 0.061× 0.04 / 10 **= 0.00096 µg/kg bw** infants = 5 × 0.041 × 0.04 / 8 **= 0.0010 µg/kg bw** newborns = 5 × 0.027 × 52 × 0.04 / 4.2 **= 0.0013 µg/kg bw**
c) Total resident exposure. Exposures from different sources are combined: Adults, children and toddlers: drinking contaminated water and swimming/bathing; Infants: bathing in contaminated water, drinking breast milk (see below)	Predicted TWA systemic dose for adults: 0.084 + 0.00008 = **0.084 µg/kg bw per day** children: 0.105 + 0.0001 = **0.105 µg/kg bw per day** toddlers: 0.25 + 0.0001 = **0.25 µg/kg bw per day** infants **0.00001 µg/kg bw per day** Predicted maximal daily systemic dose is for adults: 0.17 + 0.0005 = **0.17 µg/kg bw** children, 0.21 + 0.008 = **0.218 µg/kg bw** toddlers, 0.50 + 0.001 = **0.50 µg/kg bw** infants **0.001 µg/kg bw per day**
d) Total exposure of resident operators Exposures from different activities are combined	**Predicted total TWA systemic dose** for a resident mother **0.084 µg/kg bw per day** for a resident operator in guideline scenario 0.084 + 1.8 = **1.89 µg/kg bw per day** for a resident operator in lax standard scenario 0.21 + 18.2 = **18.4 µg/kg bw per day** **Predicted total daily maximal systemic dose** for a resident is **0.17 µg/kg bw** for a resident operator in guideline scenario 0.17 + 4.3 = **4.47 µg/kg bw** for a resident operator in lax standard scenario 0.17 + 42.7 = **42.9 µg/kg bw**
e) Ingestion exposure via breast milk Estimated TWA systemic dose $SysD_{MAX}$ = 3.*98* × Fr_{milk} × Abs_O × $Dose_M$ / *BW, where* Fr_{milk} = fraction of the dose excreted in milk in an experimental animal, 0.14% Abs_O = oral absorption, 100% $Dose_M$ = dose of the mother (mg); TWA: resident 0.005 mg, resident operator, guideline scenario, 0.113 mg, resident operator, lax standard operator mother, 1.111 mg Maximal daily exposure resident 0.01 mg, resident operator, guideline scenario, 0.268 mg, resident operator, lax standard operator, 2.57 mg *BW* = body weight newborn 4.2, infant 8 kg	For a mother who is a resident of the treated area, using treated water for household purposes, the predicted dose for the suckling newborn is: 3.98 × 0.0014 × 1 × 0.005 / 4.2 = **0.006 µg/kg bw per day** For the newborn of a mother who also works as a larviciding/molluscicide operator, the predicted TWA doses are: Guideline operator scenario: 3.98 × 0.0014 × 1 × 0.113 / 4.2 **= 0.15 µg/kg bw per day**. Lax standard operator scenario: 3.98 × 0.0014 × 1 × 1.111 / 4.2 **= 1.47 µg/kg bw per day**. The predicted maximal daily systemic doses are 0.013, 0.36 and 3.4 µg/kg bw in newborns of resident mothers, resident operator mothers in guideline scenario and resident operator mothers in lax standard scenario respectively. The estimated doses of the infants (0–12 months) are 52% of those of the newborns.
3. Risk characterization ***3.1 Comparison of exposure estimates with TSDs for operator risk characterization*** For products with appreciable acute toxicity or irritative properties, consideration should be given to ARfDs. If the exposure calculated for a subgroup and exposure route is below the respective limit value,	The irritation capacity of X is low. Thus, local effects are not important aspects in the risk assessment, which is based on comparison with long-term exposure with the long-term TSD as well as comparison of the short-term exposure with the short-term $TSD_{AC.}$ From 1.11, TSD used in subsequent risk characterization is 0.01 mg = 10 µg/kg bw per

Generic risk assessment model	Worked example
in worst-case conditions, it can be assumed that the exposure is acceptable and does not cause unacceptable risk to human health. If the exposure is above the TSD and refining the assessment process, e.g. by use of chemical-specific data, fails to bring the exposure below the TSD, measures to reduce the exposure must be implemented.	day and the TSD_{AC} = 0.1 mg = 100µg/kg bw. Predicted doses to be used in subsequent risk characterization: *Total TWA operator predicted doses:* Guideline scenario =**1.82 µg/kg bw**. Lax standard scenario = **18.2 µg/kg bw** In the guideline scenario, the exposure is considered acceptable. The predicted dose is 18% of the TSD. The TSD is exceeded in the lax standard scenario, due to the high exposure estimate in the mixing and loading task. Use of risk management measures related to use of appropriate PPE is therefore mandatory**.** Maximal daily systemic dose in the guideline scenario, 4.3 µg/kg bw, which is 43% of the TSD_{AC}; in the lax standard scenario the maximal daily dose, 42.7 µg/kg bw, is 43% of the TSD_{AC}.
3.2 Comparison of exposure estimates with TSDs for resident risk characterization	*Total resident predicted TWA doses:* Adults Dose from drinking treated water + dose from bathing in treated water = **0.084 µg/kg bw** Children Dose from drinking treated water + dose from bathing in treated water = **0.105 µg/kg bw** Toddlers Dose from drinking treated water + dose from bathing in treated water = **0.25 µg/kg bw** Residential exposure is considered acceptable in all cases. The predicted dose represents ≤ 3% of the TSD. Newborn babies – dermal exposure + breast-milk exposure When the mother is larviciding operator (lax standard scenario), predicted systemic exposure of newborns via breast milk is 1.47 µg/kg bw per day, exposure due to bathing 0.0001 µg/kg bw, and total predicted dose, **= 1.47 µg/kg bw.** If the mother is exposed only residentially, the exposure of the newborn is less than 0.1% of the TSD. If the mother is also an operator, the predicted TWA dose is 1.5% of the TSD in the guideline scenario, and 15% of the TSD in the lax standard scenario. The predicted maximal daily doses of the operator similarly are approx. 4.3% of the TSD_{AC} in the guideline scenario, and 43% in the lax standard scenario.

8. Summary of the environmental risk assessment model and a worked example

Generic risk assessment model	Worked example
1. Identify source documents on risk assessment of the substance State reliability for source documents used. Conduct literature search for additional studies focusing on field estimations relevant to malarial vector control.	**1. Identify source documents on risk assessment of the substance** Two national peer-reviewed risk assessments (Odenkirchen & Eisler, 1988; ATSDR, 1997) were identified and two reviews and risk assessments in a peer-reviewed scientific journal (Barron & Woodburn, 1995; Giesy et al., 1999) were also used.
2. Exposure estimation ***Air*** Determine likely spray drift from intended application area and likely "application rates" to non-target areas. Establish volatility class for the active ingredient; obtain maximum daily loss by volatilization.	**2. Exposure estimation** ***Air*** An application rate of 11–25 g a.i./ha is recommended for larvicidal use of insecticide X (WHO, 2006). A likely spray drift of 4% of the applied dose (direction application) has been assumed (Ganzelmeier et al., 1995; EPPO, 2003) as the "application rate" for terrestrial habitats adjacent to the spraying area. Vapour pressure has been reported as 2.4×10^{-3} Pa at 25 °C and a dimensionless Henry's Law constant (air-water partition coefficient) at 3.5×10^{-8}).
Soil Calculate initial concentration in soil (worst case). State assumptions made for interception by vegetation, soil depth and soil density. Obtain value(s) for half-life in soil DT_{50} and correct for temperature as appropriate. Calculate TWAC in soil over the time period used in chronic toxicity tests available to the risk assessment. Take account of repeated applications and calculate likely concentrations in a time series. Estimate whether the pattern of application will lead to build-up of residues in soil. Calculate the number of applications required to reach soil concentrations of concern to soil organisms and time for recovery to non-damaging concentrations.	***Soil*** A classification of **medium** has been assigned for volatilization from water and **low** for volatilization from soil. Maximum daily losses would be 25% and 1% respectively. An initial concentration in soil of 0.33 µg/kg was calculated based on input of 4% of the applied dose as spray drift and a soil depth of 10 cm. Interception by vegetation was assumed to be 50% (typical for patchy groundcover vegetation). The default soil density value of 1500 kg/m^3 was used. A DT_{50} in soil of 30–60 days at a temperature of 25 °C was reported, which was not corrected. This is the largest reported value and has been selected as worst-case (reported values range between 15 and 60 days). Soil TWACs were calculated for 14 days following "application" at 0.3 µg/kg (initial concentration at application of the larvicide was 0.33 µg/kg). The time period was the duration of the chronic test used for earthworms. Because risk to soil organisms is low for both acute and chronic exposure (see later), no further calculations are necessary here.

Generic risk assessment model	Worked example
Surface water and aquatic sediments Calculate initial concentration in surface water Estimate partition between aquatic media (water body and sediment) and establish likely concentrations in each if relevant. Obtain values for sources of dissipation from water/sediment: – biodegradation – hydrolysis – photodegradation. Estimate the importance of other dissipation factors: – advection – sedimentation – resuspension. Calculate dissipation rate from surface water and derive a TWAC appropriate for comparison with chronic toxicity test results. Calculate dissipation rate from aquatic sediment and derive a TWAC appropriate for comparison with chronic sediment toxicity test results.	***Surface water and aquatic sediments*** Initial concentration from direct application to surface water is 5 µg/litre. Partition has been reported only in general terms (fraction in water is 20% and in sediment 80%). Field studies measuring total dissipation in surface waters in semitropical conditions were identified, giving a DT_{50} of 2 days. This measured result was used in calculations. Laboratory studies gave biodegradation DT_{50} as 2 days, hydrolysis DT_{50} as 53 days, photodegradation DT_{50} as 30 days and volatilization DT_{50} as 9 days. Results suggest that the major factor in dissipation is biodegradation and partitioning to sediment from the water body. Advection (dilution by water flow), sedimentation and resuspension were not considered. TWACs were calculated for 7, 21 and 216 days, corresponding to the duration of toxicity test results used later at 0.3, 0.2 and 0.002 µg/litre respectively. TWAC in sediment at 7 weeks after application was calculated at 0.16 µg/kg.
3. Effects estimation and risk calculation ***Aquatic organisms*** Identify acute aquatic toxicity test results. Determine the lowest reported LC_{50}/EC_{50} values for algae, invertebrates and fish; add other groups of organisms as available. Calculate ETRs from initial concentration in surface water and lowest acute toxicity results. Classify each ETR as low, medium or high acute risk to aquatic organisms. If only low acute risk is found for any group of organisms, no further risk assessment is required for that group. Repeat the ETR calculations for chronic exposure using the TWAC in surface water and results of chronic toxicity tests. Classify each ETR as low, medium or high chronic risk to aquatic organisms. Calculate the ETR for sediment-dwelling organisms using the concentration in sediment, adjusted for degradation over the exposure period of the tests, and chronic toxicity test results for sediment organisms. Classify the ETR for risk to sediment-dwelling organisms as low, medium or high. Fit a distribution curve to toxicity results if they are sufficient in number and quality. Derive a probabilistic guidance value (95% protection with an uncertainty of 50%) for target/target-related organisms and non-target organisms. Establish bioaccumulation potential either from the octanol/water partition coefficient log K_{ow} or preferably from a bioaccumulation study with fish. Classify bioaccumulation. Apply results of field or semi-field studies from the literature to refine risk assessment.	**3. Effects estimation and risk calculation** ***Aquatic organisms*** Results for lowest reported acute toxicity for algae, invertebrates (*Gammarua)* and fish (*Lepomis*) were 148, 0.07 and 2 µg/litre respectively. ETR acute algae = 0.003: class **low** ETR acute invertebrates = 7.1: class **high** ETR acute fish = 0.25: class **medium** No further consideration was given to algae. ETR chronic invertebrates = 1.22: class **high** (over 21 days) ETR chronic fish = 0.01: class **low** (over 216 days) Long-term risks to fish populations over a season are considered low from a single application of insecticide X as a larvicide. ETR from a 7-week test on juvenile copepods with an LOEC of 5 µg/kg was 0.031: class **low**. There were Insufficient data to allow a distribution to be calculated. From the physicochemical properties of insecticide X, bioaccumulation potential is high at an estimated BCF of 4800 based on log K_{ow} of 5. Measured BCF in fish is substantially lower at 1700. No relevant field studies on aquatic organisms were identified.

Generic risk assessment model	Worked example
Soil organisms Obtain toxicity results for acute exposure of earthworms (LD_{50}). Calculate the acute ETR for earthworms using the initial concentration in soil. Classify concern for soil organisms. If acute concern is indicated, calculate the chronic ETR using the TWAC for the duration of the chronic test and the NOEC for reproduction in earthworms. Establish bioaccumulation potential for terrestrial organisms from log K_{ow} or preferably from measured bioconcentration factors for earthworms. Classify bioaccumulation potential for terrestrial organisms. Classify risk to soil function using results from function tests on carbon/nitrogen transformation in soil. Apply results of field or semi-field studies from the literature to refine risk assessment.	***Soil organisms*** An acute LD_{50} of 104 mg/kg soil was reported for earthworms. The ETR acute for earthworms is 0.000 003 and is considered **low.** Although no consideration would need to be given to chronic effects on earthworms, a chronic NOEC for reproductive effects of 4.6 mg/kg soil has been reported, giving a chronic ETR of 0.000 07 and confirming **low** risk for earthworms. A measured BCF value of 9.7 for worms has been reported (compared with a theoretical BCF calculated at 50 from the log K_{ow}). Bioaccumulation potential is considered **low**. No field studies of relevance to soil organisms were identified.
Terrestrial vertebrates Calculate the ETR for fish-eating and earthworm-eating species if bioaccumulation potential indicates the possibility of secondary poisoning. Take repeat applications into account. Calculate ETRs based on acute or chronic toxicity test results as appropriate for succeeding time periods Apply results of field or semi-field studies from the literature to refine risk assessment.	***Terrestrial vertebrates*** While the pK_{ow} 5 would indicate bioaccumulation potential, the metabolism in mammals is fast (complete excretion in 48 h) and the bioaccumulation potential is thus **low**.
4. Risk classification Tabulate all calculated risk factors and assess the overall pattern, nature and degree of risk.	**4. Risk classification** Significant risk of the use of insecticide X as a mosquito larvicide is confined to non-target aquatic invertebrates. High risk to these organisms is both acute and chronic. Medium risk to fish in the short term does not extend to long-term exposure.

References

ATSDR (1997). Toxicological profile for chlorpyrifos. Atlanta (GA): United States Department of Health & Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Barron MG, Woodburn KB (1995). Ecotoxicology of chlorpyrifos. Reviews of Environmental Contamination and Toxicology. 144:1–93.

Becker FA et al. (1999). The degree of ground coverage by arable crops as a help in estimating the amount of spray solution intercepted by the plants. Nachrichtenblatt des deutschen Pflanzenschutzdienstes. 51:237–42.

Bhat VS et al. (2017). Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience; Increasing utility and facilitating regulatory acceptance. Crit Rev Toxicol. 47:729–49.

Bilanin AJ et al. (1989). AGDISP: The aircraft spray dispersion model, code development and experimental validation. Trans ASABE. 32:327–34.

De Souza DP (1995) Molluscicide control of snail vectors of schistosomiasis. Mem Inst Oswaldo Cruz. 90:165–8.

Dorne JLCM, Renwick AG (2005). The refinement of uncertainty/safety factors in risk assessment by the incorporation of data on toxicokinetic variability in humans. Toxicol Sci. 86:20–26.

Dourson ML, Knauf LA, Swartout JC (1992). On reference dose (RfD) and its underlying toxicity data base. Toxicol Ind Health. 8(3):171–89.

EC (2002). Technical Notes for Guidance on Annexes I, IA and IB – inclusion. Technical Notes for Guidance in Support of Directive 98/8/EC of the European Parliament and the Council concerning the placing of biocidal products on the market. Principles and practical procedures for the inclusion of active substances in Annexes I, IA and IB. Ispra, Italy. Brussels: European Commission (available at: https://echa.europa.eu/documents/10162/16960215/tnsg-annex-i-inclusion_en.pdf, accessed 22 November 2018).

EC (2006). Guidance for the setting and application of Acceptable Operator Exposure Levels (AOELs) [working document]. Brussels: European Union (http://ec.europa.eu/food/plant/docs/pesticides_ppp_app-proc_guide_tox_accpt-exp-levs-2006.pdf, accessed 22 November 2018).

EFSA (2007). Scientific Opinion of the Panel on plant protection products and their residues on a request from EFSA related to the default Q10 value used to describe the temperature effect on transformation rates of pesticides in soil. EFSA Journal. 622:1–32 (http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2008.622/epdf, accessed 22 November 2018).

EFSA (2012). Guidance on dermal absorption. Scientific opinion. EFSA Panel on plant protection products and their residues (PPR). Parma, Italy: European Food Safety Authority (EFSA) (http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2665/epdf, accessed 22 November 2018).

EPPO (2003). European and Mediterranean Plant Protection Organization: Environmental risk assessment scheme for plant protection products. EPPO Bulletin. 33(2):147-244 (https://onlinelibrary.wiley.com/toc/13652338/2003/33/2, accessed 22 November 2018).

EUROPOEM II (2003). The development, maintenance and dissemination of a European Predictive Operator Exposure Model (EUROPOEM) database. A EUROPOEM II Database and Harmonised Model, FAIR3-CT96-1406. Carshalton, England, TNO-BIBRA International.

FAO/WHO (2014) The International Code of Conduct on Pesticide Management. Rome: Food and Agriculture Organization of the United Nations (http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Code/CODE_2014Sep_ENG.pdf, accessed 22 November 2018).

Ganzelmeier H et al. (1995). Studies on the spray drift of plant protection products: results of a test program carried out throughout the Federal Republic of Germany. Berlin: Blackwell Wissenschafts Verlag.

Giesy JP et al. (1999). Chlorpyrifos: ecological risk assessment in North American aquatic environments. *Reviews of Environmental Contamination and Toxicology*, 160:1–129.

Hayes WJ (1975). Toxicology of pesticides. Baltimore (MD): Williams & Wilkins.

HEEG (2013a) HEEG Default human factor values for use in exposure assessments for biocidal products. European Commission Joint Research Centre, Institute for health and consumer protection. Chemical assessment and testing. HEEG opinion (endorsed at TM II 2013).

HEEG (2013b) HEEG opinion on Assessment of inhalation exposure of volatilized biocide active substances. European Commission Joint Research Centre, Institute for health and consumer protection. Chemical assessment and testing. HEEG opinion 13 (endorsed at TM IV and amended after TM III 2013 to take into account changed default human factor values; Ispra, 12/10/2011).

Herrman JL, Younes M (1999). Background to the ADI/TDI/PTWI. Regul Toxicol Pharmacol. 30:S109–S113.

Hewitt AJ et al. (2001). Development of the AgDrift model for aerial application from helicopters and fixed-wing aircraft. In: Proceedings, EnviroTox. Canberra: Environment Australia:121–29.

Hewitt AJ et al. (2002). Development of the spray drift task force database for aerial applications. Environ Toxicol Chem. 21:648–658.

JECFA (2002). Safety evaluation of certain food additives and contaminants. Prepared by the fifty-seventh meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Geneva: World Health Organization (ftp://ftp.fao.org/es/esn/jecfa/jecfa57c.pdf, accessed 22 November 2016).

JMPM (2008). Recommendations of the 2nd FAO/WHO Joint Meeting on Pesticide Management and 4th Session of the FAO Panel of Experts on Pesticide Management, Geneva, 6–8 October 2008. Rome: Food and Agriculture Organization of the United Nations (http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/Code/Recommendations08_01.pdf, accessed 22 November 2018).

JMPR (1982). Bendiocarb. PESTICIDE RESIDUES IN FOOD – 1982. Sponsored jointly by FAO and WHO (http://www.inchem.org/documents/jmpr/jmpmono/v82pr05.htm, accessed 22 November 2018).

JMPR (1984) Bendiocarb. PESTICIDE RESIDUES IN FOOD – 1984. Sponsored jointly by FAO and WHO (http://www.inchem.org/documents/jmpr/jmpmono/v84pr45.htm, accessed 22 November 2018).

JMPR (1998). Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues and the Environment and the WHO Core Assessment Group, Rome 21–30 September 1998. Geneva: World Health Organization (http://www.who.int/foodsafety/publications/jmpr-reports/en/): Section 2.14, Interpretation of cholinesterase inhibition:17–19, accessed 22 November 2018).

JMPR (1999). Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and the WHO Core Assessment Group, Rome, 20–29 September 1999 (http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Reports_1991-2006/REPORT1999.pdf, accessed 22 November 2018).

JMPR (2008). Safety factors for acute C_{max}-dependent effects: specific considerations with respect to carbamates such as carbofuran. In: Pesticide residues in food – 2008. Joint FAO/WHO meeting on

pesticide residues. Evaluations 2008 Part II Toxicological:7–10 (http://whqlibdoc.who.int/publications/2010/9789241665247_eng.pdf, accessed 22 November 2018).

JMPR (2012). Inventory of evaluations performed by the Joint Meeting on Pesticide Residues (JMPR (http://apps.who.int/pesticide-residues-jmpr-database, accessed 22 November 2018).

Matthews GA (2001). Dermal exposure of hands to pesticides. In: Maibach HI, editor. Toxicology of skin. Philadelphia, USA, Taylor and Francis:179–182.

Meek ME et al. (2011). Risk assessment of combined exposure to multiple chemicals: a WHO/IPCS framework. Regul Toxicol Pharmacol. 60:S1–S14.

Mineau P et al. (1994). A critique of the avian 5-day dietary test (LC_{50}) as the basis of avian risk assessment. Ottawa: Canadian Wildlife Service (Technical Report Series 215).

Najera JA, Zaim M (2002). Malaria vector control - decision-making criteria and procedures for judicious use of insecticides. Geneva: World Health Organization (http://whqlibdoc.who.int/hq/2003/WHO_CDS_WHOPES_2002.5_Rev.1.pdf, accessed 22 November 2018).

Nordic Council of Ministers (2007). Probabilistic exposure assessment methods in chemical safety assessments (REACH). Copenhagen: Nordic Council of Ministers (TemaNord 2007:563; http://whqlibdoc.who.int/hq/2003/WHO_CDS_WHOPES_2002.5_Rev.1.pdf, accessed 22 November 2018).

Odenkirchen EW, Eisler R (1988). Chlorpyrifos hazards to fish, wildlife and invertebrates: a synoptic review. Laurel (MD): United States Fish and Wildlife Service, Patuxent Wildlife Research Center (Contaminant Hazard Reviews, Report No. 13).

OECD (2011). Guidelines for the testing of chemicals (and subsequent revisions). Paris: Organisation for Economic Cooperation and Development (http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals_chem_guide_pkg-en;jsessionid=j73j4wz0ptk0.delta, accessed 22 November 2018).

PSD (2007). UK Predictive Operator Exposure Model (POEM): a user's guide. York, England: Pesticides Safety Directorate (available at: http://www.pesticides.gov.uk/approvals.asp?id=2427, accessed 22 November 2018).

SCHER (2011). Toxicity and assessment of chemical mixtures. Scientific Committee on health and environmental risks SCHER. Brussels: European Commission Directorate-General for Health and Consumers (http://ec.europa.eu/health/scientific_committees/environmental_risks/docs/scher_o_155.pdf, accessed 22 November 2018).

Solecki R, Davies L, Dellarco V, Dewhurst I, van Raaij M, Tritscher A (2005). Guidance on setting of acute reference dose (ARfD) for pesticides. Food Chem Toxicol. 43:1569–93. doi:10.1016/j.fct.2005.04.005.

Teske ME, Bird SL, Esterly DM, Curbishley TB, Ray SL, Perry SG (2002). AgDrift: a model for estimating near-field spray drift from aerial applications. Environ Toxicol Chem. 21:659–71. doi:10.1002/etc.5620210327.

UN (2015). Globally harmonized system of classification and labelling of chemicals, 6th edition. New York (NY): United Nations (http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev06/English/ST-SG-AC10-30-Rev6e.pdf, accessed 22 November 2018).

USAID (2006). Integrated vector management programs for malaria vector control. Programmatic environmental assessment. Washington (DC): United States Agency for International Development (prepared by RTI International; http://pdf.usaid.gov/pdf_docs/PNACP696.pdf, accessed 22 November 2016).

USEPA (2008). Child-specific exposure factors handbook (final report). Washington, DC, United States Environmental Protection Agency, Office of Research and Development (http://cfpub.epa.gov/ncea/CFM/recordisplay.cfm?deid=199243, accessed226 November 2018).

USEPA (2010). Final test guidelines for pesticides and toxic substances. Washington (DC): United States Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention (https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/final-test-guidelines-pesticides-and-toxic, accessed 22 November 2018).

USEPA (2011). Exposure factors handbook: 2011 edition. Washington (DC): United States Environmental Protection Agency, Office of Research and Development C (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=236252, accessed 22 November 2018).

USEPA (2012). Standard operating procedures for residential pesticide exposure assessments. Washington (DC): Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention, United States Environmental Protection Agency (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedure-residential-exposure, accessed 22 November 2018).

Vermeire T, Stevenson H, Pieters MN, Rennen MAJ (1999). Assessment factors for human health risk assessment: a discussion paper. Crit Rev Toxicol. 29:439–90.

WHO (1965). Snail control in the prevention of bilharziasis. Geneva: World Health Organization (WHO Monograph Series No. 50; http://apps.who.int/iris/bitstream/10665/41772/1/WHO_MONO_50.pdf. accessed 22 November 2018).

WHO (1992). The role of molluscicide in schistosomiasis control. Geneva: World Health Organization (http://apps.who.int/iris/bitstream/10665/62295/1/WHO_SCHISTO_92.107.pdf, accessed 22 November 2018).

WHO (1994). Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. Geneva: World Health Organization (Environmental Health Criteria, 170; http://www.inchem.org/documents/ehc/ehc/ehc170.htm, accessed 22 November 2018).

WHO (1999). Principles for the assessment of risks to human health from exposure to chemicals. Geneva: World Health Organization (Environmental Health Criteria, 210; available at: www.inchem.org/documents/ehc/ehc/ehc210.htm, accessed 22 November 2018).

WHO (2003). Space spray application of insecticides for vector and public health pest control: a practitioner's guide. Geneva: World Health Organization (whqlibdoc.who.int/hq/2003/WHO_CDS_WHOPES_GCDPP_2003.5.pdf, accessed 22 November 2018).

WHO (2004). Generic risk assessment model for insecticide treatment and subsequent use of mosquito nets. Geneva: World Health Organization (http://whqlibdoc.who.int/hq/2004/WHO_PCS_04.1.pdf, accessed 22 November 2018).

WHO (2005a). Chemical-specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment. Geneva: World Health Organization (IPCS Harmonization Project Document, No. 2; http://whqlibdoc.who.int/publications/2005/9241546786_eng.pdf, accessed 22 November 2018).

WHO (2005b). Guidelines for laboratory and field testing of mosquito larvicides. Geneva: World Health Organization (http://apps.who.int/iris/bitstream/10665/69101/1/WHO_CDS_WHOPES_GCDPP_2005.13.pdf, accessed 22 November 2018).

WHO (2005c). Principles of characterizing and applying human exposure models. Geneva: World Health Organization (Harmonization Project Document No. 3; http://apps.who.int/iris/bitstream/10665/43370/1/9241563117_eng.pdf, accessed 22 November 2018).

WHO (2006). Pesticides and their application for the control of vectors and pests of public health importance, 6th edition. Geneva: World Health Organization (http://www.who.int/iris/handle/10665/69223, accessed 22 November 2018).

WHO (2008). Part 1: Guidance document on characterizing and communicating uncertainty in exposure assessment. Geneva: World Health Organization (Harmonization Project Document No. 6; http://www.who.int/ipcs/methods/harmonization/areas/uncertainty%20.pdf, accessed 22 November 2018).

WHO (2009a). Principles for modelling dose–response for the risk assessment of chemicals. Geneva: World Health Organization (Environmental Health Criteria 239; http://whqlibdoc.who.int/publications/2009/9789241572392_eng.pdf), accessed 22 November 2018).

WHO (2009b). Principles and methods for the risk assessment of chemicals in food. Geneva: World Health Organization (Environmental Health Criteria 240; (http://www.who.int/foodsafety/publications/chemical-food/en/, accessed 22 November 2018).

WHO (2017a). Field use of molluscicides in schistosomiasis control programmes: an operational manual for programme managers. Geneva: World Health Organization (http://apps.who.int/iris/bitstream/10665/254641/1/9789241511995-eng.pdf, accessed 22 November 2018).

WHO (2017b). WHO Guidelines for drinking-water quality, 4th edition, incorporating the 1st addendum. Geneva: World Health Organization. http://apps.who.int/iris/bitstream/10665/254637/1/9789241549950-eng.pdf, accessed 22 November 2018).

WHO (2018a). Equipment for vector control specification guidelines, second edition. Geneva: World Health Organization. http://apps.who.int/iris/bitstream/handle/10665/272410/9789241513821-eng.pdf, accessed 22 November 2018).

WHO (2018b). A generic risk assessment model for insecticide-treated nets, 2nd edition. Geneva: World Health Organization (http://apps.who.int/iris/bitstream/10665/260305/1/9789241513586-eng.pdf, accessed 22 November 2018).

Annex: Risk assessment of vector traps

Introduction

Vector traps are used for vector surveillance and/or vector control.

Vector traps are structures or devices unto which vectors enter and/or make contact with, which ultimately result in their death and/or sterilization. Traps may work by capturing and retaining mosquitos inside a physical structure ("capture–kill") or by attracting and releasing mosquitos exposed to an insecticide or autodisseminant that will kill, sterilize or otherwise reduce vector populations after individuals leave the trap ("capture–release").

Some types of vector traps may use larvicides or adulticides. A first-tier human health risk assessment for the use of these types of traps can be performed using similar elements to those used in the generic risk assessment model for larviciding and molluscicide.

An environmental risk assessment is not proposed; the quantity of pesticide used in vector traps is expected to be very small compared with other forms of vector control such as larviciding or space spraying, and hence environmental impact should be limited.

Background

Vector traps could potentially be used by both professional vector control personnel or consumers/households. This model will focus on professional users since their handling of traps (and hence their exposure) is expected to be higher than that of household users.

The scenario considered in this model is devices which contain a larvicide or adulticide (the generic term "pesticide" will be used), in solid form or liquid form (diluted or ready to use), where the user is required to set up, maintain and dispose of the trap or its contents.

Exposure scenarios included in the model

Trap assembly involves the user placing the pesticide in the trap. The hands of the user may be exposed to the pesticide in this process. It is assumed that traps are designed to be carried and placed in position without exposing the user to the contents.

Trap servicing (maintenance) involves replenishing the contents of the trap – the exposure scenario is assumed to be the same as that during trap assembly. Exposure in both scenarios is based on the number of handling operations.

The disposal scenario involves disposal of the material within the trap and/or the trap itself. For traps using liquid, the exposure scenario covers all liquid in the trap – whether liquid pesticide or water used within the trap.

Assumptions

Due to few data being available, the model is based on simple first-tier and worst-case situations. Specific data for the product and situation should be used if available.

The exposure of trap users is assumed to represent the worst-case since pesticide products will be handled directly by users. Secondary exposure of residents of areas where traps are in use is assumed to be minor by comparison with the exposure of users. Traps are expected to be designed to restrict exposure only to vectors once the

trap is in place (as far as reasonably possible). Exposure to material removed from traps by vectors over the course of use is anticipated to be very low.

The risk assessment model assumes that gloves are not worn while handling traps. Handling traps is a task requiring manual dexterity and is not amenable to wearing protective gloves.

Exposure to solids

This scenario covers products which are in solid form during use, such as dust, powder or solid bait, and are not diluted in water.

Exposure is only via the dermal route, and only hands are exposed. Hands can be exposed whenever a trap is filled, re-filled or emptied and the exposure scenario is the same for each – a separate assessment for disposal is not needed. When calculating the number of traps expected to be handled in a working day and the number of days when traps are handled (scenario-specific information), the disposal of traps should be included. Exposure assessment is based on the parameters recommended by the Netherlands Centre for Substances and Integrated Risk Assessment (Bremmer et al., 2006[1]) for exposure to solid baits placed within boxes or feeding stations. The unit dermal exposure is 0.5% of the amount of product per occasion handled. Dermal exposure can be calculated as shown in Box A1.

Box A1. Dermal exposure; solids

$SysD_{TWA} = UE_{SOL} \times WT \times CF \times NOD \times ABS_D \times EF / (BW \times AT)$

$SysD_{MAX} = UE_{SOL} \times WT \times CF \times NOD \times ABS_D / BW$

where:

$SysD_{TWA}$	=	TWA systemic dose mg/kg bw per day
$SysD_{MAX}$	=	Maximal daily systemic dose mg/kg bw
UE_{SOL}	=	Unit exposure for solids, 0.5% of weight of product per trap
WT	=	Weight of formulated product added per trap (from product or trap instructions)
CF	=	Concentration of formulated product (from product label)
NOD	=	Number of traps expected to be handled in a working day
ABS_D	=	Dermal absorption (see section 4.1.3)
EF	=	Exposure frequency (number of days that workers will handle traps in a year)
BW	=	Body weight (60 kg; Table 3)
AT	=	Averaging time (365 days)

Exposure to liquids

This scenario covers products which are added to traps in liquid form. If formulated products require to be diluted before use, then this can be calculated using the method for mixing and loading of liquid formulations for larviciding (section 4.2.2).

Inhalation exposure from using traps outdoors is assumed to be negligible. If required, guidance on determining the need to consider inhalation exposure from pesticides used for public health protection can be found in the WHO generic risk assessment model for

[1] Bremmer HJ, Blom WM, van Hoeven-Arentzen PH, Prud'homme de Lodder LCH, van Raaij MTM, Straetmans EHFM, et al. Pest control products fact sheet. RIVM report 320005002/2006. RIVM: Bilthoven; 2006 (https://www.rivm.nl/en/Topics/C/ConsExpo/Fact_sheets, accessed 16 November 2018).

insecticide-treated nets.[1] The use of the *Inhalation – evaporation from a constant surface* model in ConsExpo[2] could be considered if necessary.

Exposure assessment (dermal) while handling traps (filling or re-filling) is based on parameters recommended by the Netherlands Centre for Substances and Integrated Risk Assessment (Bremmer et al., 2006) for dermal exposure to liquid concentrate while mixing and loading biocides for indoor use. This scenario, which involves handling of relatively small volumes and small containers, is considered to be an adequate surrogate for the vector trap situation. The unit dermal exposure is 0.01 mL per operation (or 10 mg (assuming density of 1 g/cm^3) per operation).

Dermal exposure during filling or re-filling of traps with liquid can be calculated as shown in Box A2.

Box A2. Dermal exposure; liquids (filling or re-filling)

$SysD_{TWA} = UE_{SOL} \times CF \times NOD \times ABS_D \times EF / (BW \times AT)$

$SysD_{MAX} = UE_{SOL} \times CF \times NOD \times ABS_D / BW$

where:

$SysD_{TWA}$	=	TWA systemic dose mg/kg bw per day
$SysD_{MAX}$	=	Maximal daily systemic dose mg/kg bw
UE_{SOL}	=	Unit exposure for liquids, 0.01 mL per operation
CF	=	Target concentration of liquid in trap (from product label and instructions)
NOD	=	Number of traps expected to be filled in a working day
ABS_D	=	Dermal absorption (see section 4.1.3)
EF	=	Exposure frequency (number of days that workers will fill traps in a year)
BW	=	Body weight (60 kg; Table 3)
AT	=	Averaging time (365 days)

Unlike with solids, the exposure scenario with liquids is calculated separately. Exposure assessment (dermal) during disposal of traps and/or their contents can be calculated using similar parameters to exposure to spray solution during larviciding. The same conservative assumption of maximum volume of liquid on adult hands is used. Total exposure of users with traps using liquids is obtained by adding together the results from Box A2 and A3.

[1] A generic risk assessment model for insecticide-treated nets, 2nd edition. Geneva: World Health Organization; 2018 (http://apps.who.int/iris/bitstream/10665/260305/1/9789241513586-eng.pdf, accessed 16 November 2018).

[2] www.consexpo.nl

Dermal exposure during disposal of traps containing liquid can be calculated as shown in Box A3.

Box A3. Dermal exposure; liquids (disposal)

$SysD_{TWA} = VS_{dermal} \times CF \times EF \times Abs_D / (BW \times AT)$

$SysD_{MAX} = VS_{dermal} \times CF \times Abs_D / BW$

$SysD_{TWA}$	=	TWA systemic dose mg/kg bw per day
$SysD_{MAX}$	=	Maximal daily systemic dose mg/kg bw
VS_{dermal}	=	Volume of spray on hands = 8.2 mL (see section 4.2.1)
CF	=	Target concentration of liquid in trap (from product label and instructions)
EF	=	Exposure frequency (number of days that workers will dispose of traps in a year)
ABS_D	=	Dermal absorption of the spray (see section 4.1.3)
BW	=	Body weight (60 kg)
AT	=	Averaging time, 1 year (365 days)

Other considerations

Due to wide variations in practice, product-specific data and information from local situations should be used, whenever possible.

Misuses, such as handling of traps by children, are not covered in this risk assessment.

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