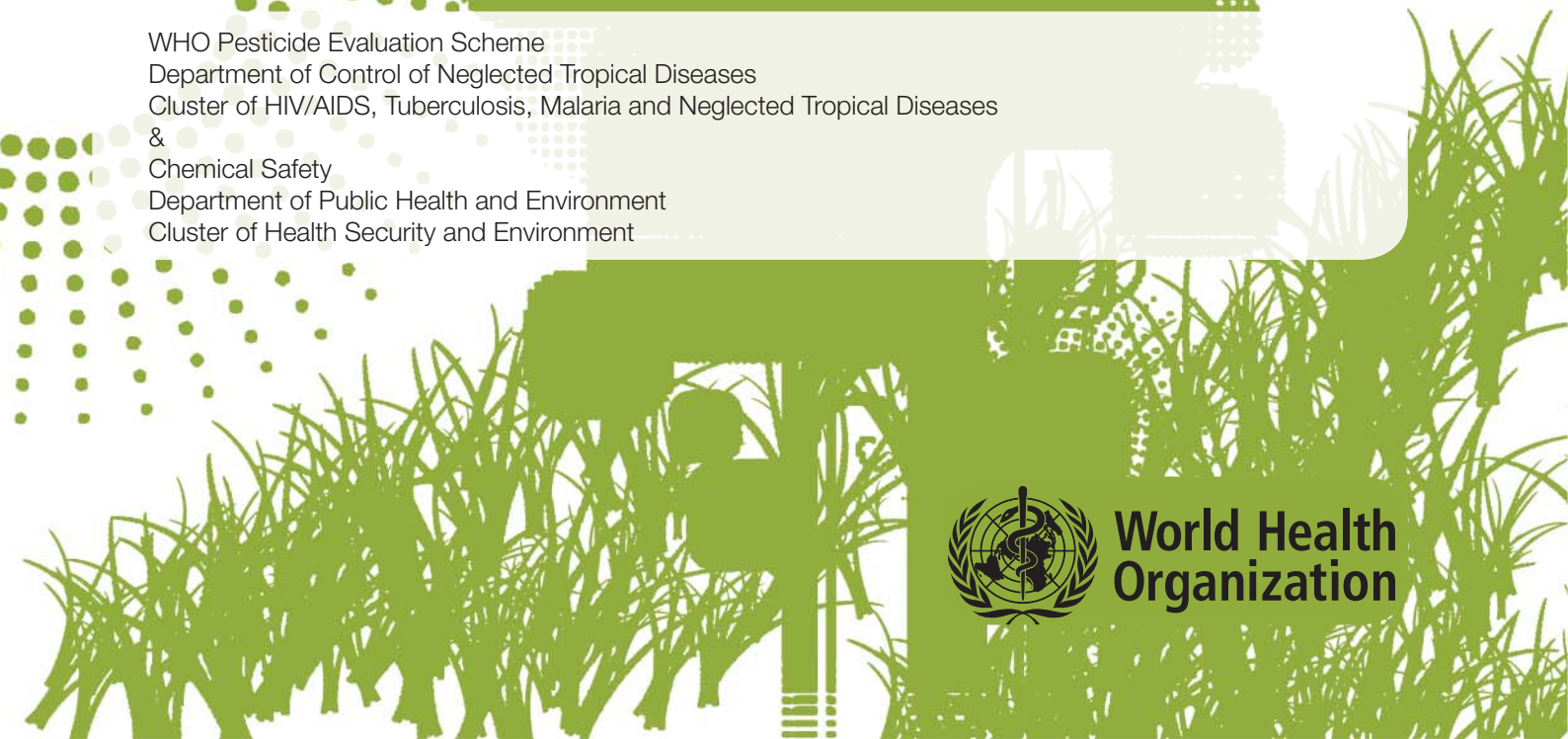
GENERIC RISK ASSESSMENT MODEL FOR INSECTICIDES USED FOR LARVICIDING

First Revision (February 2011)

WHO Pesticide Evaluation Scheme
Department of Control of Neglected Tropical Diseases
Cluster of HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases
&
Chemical Safety
Department of Public Health and Environment
Cluster of Health Security and Environment



World Health Organization

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WHO PESTICIDE EVALUATION SCHEME
&
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Contents

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The first draft of these generic models was prepared by a drafting committee appointed by the World Health Organization (WHO) and composed of Dr M. Mäkinen, Finnish Institute of Occupational Health, Kuopio, Finland; Dr T. Santonen, Finnish Institute of Occupational Health, Helsinki, Finland; Dr A. Aitio, private consultant, Helsinki, Finland; Dr S. Dobson OBE, Birchtree Consultants Ltd., Peterborough, UK; and Dr M. Zaim, WHO Pesticide Evaluation Scheme (WHOPES), Geneva, Switzerland. None of the drafting committee members declared an interest in the subject matter of these guidelines.

The first draft of the guidelines was peer reviewed by individuals and institutions known for their expertise in the subject. The peer review group comprised Dr M. Baril, Institut de recherche Robert-Sauvé en santé et en sécurité au travail (IRSST), Montreal, Canada; Dr N. Besbelli, United Nations Environment Programme (UNEP), Geneva, Switzerland; Dr M. Birchmore, Syngenta Ltd., Basel, Switzerland; Dr L. Blake, Syngenta Ltd., Surrey, UK; Dr R. Brown, WHO Programme on Chemical Safety, Geneva, Switzerland; Dr H. Bouwman, School of Environmental Sciences and Development, North-West University, Potchefstroom, South Africa; Dr R. S. Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA; Dr O. Hänninen, National Institute for Health and Welfare (THL), Kuopio, Finland; Dr M. Latham, Manatee County Mosquito Control District, Palmetto, FL, USA; Professor Dr G. A. Matthews, Imperial College, Ascot, UK; Dr D. J. Miller, Dr M. Crowley and Dr J. Evans, United States Environmental Protection Agency (USEPA), Office of Pesticide Programs, Health Effects Division, Washington DC, USA; Dr L. Patty, Bayer Environmental Science, Lyon, France; Dr L. Tomaska and Dr M. Bulters, Australian Commonwealth Department of Health, Office of Chemical Safety, Canberra, Australia; Dr C. Vickers, WHO Programme on Chemical Safety, Geneva, Switzerland; and Dr O. Yamada, French Agency for Environmental and Occupational Health Safety (Afsset), Maisons-Alfort, France.

The above-mentioned drafting committee considered all comments received and prepared a second draft. This revised draft was reviewed and discussed at a WHO consultation held at the Finnish Institute of Occupational Health in Helsinki (Finland) on 23–25 June 2009. The experts appointed by WHO were Dr N. Besbelli, Dr H. Bouwman, Dr O. Hänninen, Dr M. Latham and Professor Dr G. A. Matthews. Dr C. Vickers (WHO Programme on Chemical Safety) and Dr M. Zaim (WHOPES) took part in reviewing the revised draft. None of the experts participating in the consultation declared an interest in the subject matter of these guidelines.

Based on experience from use gathered since 2009, and also to make use of emerging new information, the document was revised in February 2011 by the original drafting committee.

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The Department welcomes feedback on the guidelines and suggestions for improvement from national programmes, research institutions and industry in order to improve future editions.

Acronyms and abbreviations

ADI	acceptable daily intake
a.i.	active ingredient
ARfD	acute reference dose
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BMD	benchmark dose
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
ETR	exposure–toxicity ratio
EU	European Union
EUROPOEM	European Predictive Operator Exposure Model
GLP	good laboratory practice
guideline scenario	exposure scenario which assumes that the insecticide 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
JMPR	Joint Meeting on Pesticide Residues
lax standard scenario	tropical conditions are accommodated and no personal protective equipment other than light clothing covering the trunk only is assumed
LC_{50}	concentration killing 50% of the test organisms
LOAEL	lowest-observed-adverse-effect-level
LOEC	lowest-observed-effect concentration
MRL	minimal risk level
NOAEL	no-observed-adverse-effect-level
NOEC	no-observed effect concentration
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
PSD	Pesticides Safety Directorate
RfC	reference concentration
RfD	reference dose
RPE	respiratory protective equipment
TSD	tolerable systemic dose
TWAC	time-weighted average concentration
UF	uncertainty factor
UKPOEM	UK Predictive Operator Exposure Model
USEPA	United States Environmental Protection Agency

1. Introduction

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 usually complementary to other integrated vector control measures, such as environmental management, and is used to control malaria and other mosquito-borne diseases, including dengue, as well as nuisance mosquitoes (Najera & Zaim, 2002; WHO, 2006).

In addition to chemical insecticides, petroleum and other types of oil, monomolecular surface films, biological substances (e.g. bacterial endotoxins) and insect growth regulators are used for larviciding. Organophosphates are commonly used, despite problems of resistance in some areas. Larviciding may also be employed for water used in irrigation of food crops and has been used to treat drinking-water. Pyrethroids are not recommended – they are considered to have too wide an impact spectrum on non-target species.

The most commonly used liquid formulations of chemical insecticides used for larviciding are aqueous suspensions and emulsifiable concentrates. Solid formulations include active ingredients formulated either on solid granules or sand (as a carrier) for immediate release to the water body or on a specialized solid matrix to provide a slow, prolonged release giving residual action of weeks or months (Najera & Zaim, 2002; WHO, 2006).

The equipment used for application of the liquid formulations of mosquito larvicides are typically compression- and lever-operated back-pack 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 by gloved hand. Details of WHO-recommended larvicides for mosquito control and the procedure for their application have been published elsewhere (WHO, 2006), as have the requirements, procedures and criteria for testing and evaluation of mosquito larvicides (WHO, 2005b).

2. Purpose

This document provides a generic model that can be used for risk assessment of mosquito larvicides; it aims to harmonize the risk assessment of such insecticides for public health use. The assessment considers both adults and children (all age groups) as well as people in the following specific categories:

- those preparing the spray;
- those applying the spray or other formulations; and
- residents who may come into contact with or use the treated waters.

Assessments of human health risk should consider the use of mosquito larvicides in potable water. Aspects of ecological risk also need to be assessed because of the direct application of larvicides into the aquatic environment – 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 treatment and subsequent use of mosquito nets* (WHO, 2004). 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 the risk assessments proposed for larvicide treatments are not conducted de novo; risk assessments that have already been generated for the pesticides in the regulatory context of crop protection can be used as a starting point. 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 mosquito control.

3.1 Probabilistic vs deterministic risk assessment models

Historically, exposure models have been based on point estimates. This deterministic approach has the advantage of simplicity and consistency. Risk characterization is relatively straightforward: the exposure estimate is compared with a health-based guidance value. One of the drawbacks of this approach is that it incorporates no information about the variability of real exposures. Likewise, there is no assessment of, or information about, the uncertainty in the exposure estimate.

The probabilistic technique offers a complementary modelling approach that incorporates variability of exposure. Probabilistic modelling uses distributions of values rather than single values. The advantage of probabilistic technique is that it provides the probability of occurrence of exposure, which offers a sophisticated way of characterizing and communicating 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 estimations of dietary exposure (for example, in estimates produced by the United States Environmental Protection Agency). Over 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 Pesticides Safety Directorate). 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 appear to be easy to understand and "user-friendly" will be published 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 could, however, be used as a special technique in more complex situations or when deterministic assessments have identified exposures of concern (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 human health risk assessment model

Comprehensive presentations on the principles of risk assessment can be found elsewhere in the scientific literature (e.g. WHO, 1999); only a short 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. The entire process of hazard assessment, exposure estimation and risk characterization is known as *risk assessment*. Management of *uncertainties* related to all natural processes, including processes related to risk assessment, is an essential part of a valid, good-quality risk assessment.

The subsequent process of *risk management* considers the risk assessment in parallel with any potential benefits, socioeconomic and political factors, the possibilities for risk reduction, and other issues that are relevant 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 pesticide operators (applicators), residents of treated dwellings, bystanders, domestic animals, wildlife and the environment. Exposure should be assessed in a "**guideline scenario**", which assumes that the insecticide is used according to the instructions given on the product label and in WHO guideline information. A "**lax standard scenario**" takes into account the fact that in reality these instructions are not necessarily followed completely. Accidental exposures, misuse related to fundamental misunderstanding of instructions and intentional misuse are not considered.
3. *Risk characterization*. In the risk characterization step, estimates of exposure are compared with acceptable exposure levels previously defined in hazard assessment in all relevant exposure situations.

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

4. The human health risk assessment model

4.1 Hazard assessment

The purpose of 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); they are largely the same, regardless of the class of chemical or its use pattern, differing only in, for example, data requirements. These principles have been summarized in an earlier WHO publication (WHO, 2004), which describes a generic risk assessment model for insecticide treatment and subsequent use of mosquito nets and which, with some updating, forms the basis for the current text.

4.1.1 Sources of data

Hazard identification is based on gathering and analysing relevant data on the possible effects of the insecticide on humans. These data may include both toxicological (animal testing) and human data. It is recommended that, when available, risk assessments that have already been generated for the insecticides, e.g. in the regulatory context of crop protection, can be used as a starting point. These risk assessments usually contain all the relevant health hazard data available for the insecticide 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 kind of authoritative evaluation are given in Table 1. Many can be accessed on the Internet, for example via OECD's eChemPortal (http://webnet3.oecd.org/echemportal/).

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

In the case of insecticides that 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 pesticide formulations in question, or general population studies;
- ethically approved volunteer studies examining mild, temporary effects of short-term 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 insecticide 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**

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/
USEPA – Pesticide evaluations	http://www.epa.gov/pesticides/regulating/index.htm, or http://www.epa.gov/pesticides/reregistration/status.htm
Agency for Toxic Substances and Disease Registry (ATSDR) – Toxicological Profiles	http://www.atsdr.cdc.gov/toxpro2.html
European Food Safety Authority (EFSA) – Pesticide Risk Assessments	http://www.efsa.europa.eu/EFSA/ScientificPanels/efsa_locale-1178620753812_PRAPER.htm

Experimental toxicity data

For many pesticides, the human database is very limited. In these cases hazard assessment is dependent on information from experimental animals and on in-vitro studies. For insecticides 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 (OECD, 1987; http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788), or USEPA (latest update 2007: http://www.epa.gov/ocspp/pubs/frs/home/guidelin.htm). For older pesticides animal toxicity data may be limited and may not encompass modern requirements (unless they have been recently evaluated in regulatory programmes intended to review old pesticides).

Like other chemicals, public health pesticides used in larviciding have the potential to cause a wide range of toxic effects. To identify the critical effects of the insecticide 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 pesticide, the range of 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 pure substances, that is, for the active ingredients or solvents used in insecticide formulations rather than for the pesticide formulations themselves. Sometimes, however, some acute toxicity tests may also be performed with an insecticide formulation to ensure that the acute toxicity does not differ from that predicted on the basis of the tests or its individual components.

4.1.3 Range of toxicity tests normally required for pesticide approval

In addition to these general requirements, information on dermal absorption is valuable in assessing the health risks of insecticides used in mosquito larviciding because of the possible repeated dermal exposure of inhabitants of treated areas. Inhalation toxicity studies may 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 give 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**
- **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' duration, may sometimes be required.
- **Genetic toxicity studies**, in vitro for gene mutation and chromosomal damage. If any in-vitro tests indicative 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.
- For more recently approved substances, studies on developmental neurotoxicity, dermal penetration and immunotoxicology and other specialized studies* may have been performed.

Absorption of the insecticide by inhalation, ingestion and through the skin should be estimated in the hazard assessment. If no chemical-specific data exist, default values of 100% for inhalation and ingestion and 10% for the

dermal route can be used. It should be noted that while residents are usually exposed to the product as sprayed, which is as a diluted solution, operators may be exposed to both the diluted product, and the undiluted formulation. Dermal absorption may be different for these two. Thus, for mixing and loading, the absorption rate of the non-diluted formulation is to be used, while for other dermal exposure, that of the diluted spray is more appropriate (EC, 2002; WHO 2004a).

4.1.4 Evaluation of the toxicity information

An experienced toxicologist should evaluate the range and quality of 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 an insecticide used for larvidicing, 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, relevance 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 Insecticides not recommended for use in larviciding

Compounds meeting the criteria for carcinogenicity, mutagenicity or reproductive toxicity categories 1A and 1B of the *Globally harmonized system of classification and labelling of chemicals* (United Nations, 2009; http://live.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html) 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 (JMPM, 2008).

It is suggested that this recommendation be followed in the case of larvicides 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 assessment. Moreover, an insecticide of high acute toxicity, meeting the criteria of classes Ia or Ib of the WHO recommended classification of pesticides by hazard (WHO, 2010), is not recommended for use in larviciding. However, it is the acute toxicity of the *formulation*, not just of the active ingredient, that should be taken into account, based on data relating to the formulation itself.

If both the active insecticide ingredient and the formulation have shown a high incidence of severe or irreversible adverse effects on human health or the environment, use of that particular insecticide may not be acceptable (JMPM, 2008).

4.1.6 Other special considerations in hazard assessment

Interactions between insecticides and other constituents of the formulation

If two or more insecticides are used concurrently, possible toxicological interactions between those insecticides should be considered. Insecticides of the same class may produce additive toxic effects; organophosphates, for example, reduce acetylcholinesterase activity. 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. Unfortunately, reliable information is often unavailable, but knowledge of metabolic pathways or of receptor binding may sometimes help in identifying possible interactions.

Interactions may also occur between the active ingredient and the solvent used in the technical product. Moreover, impurities present in the technical product, e.g. in organophosphate products, may interact with the product and affect its final toxicity. Comprehensive specification of technical material (see http://www.who.int/whopes/quality) is thus of the utmost importance.

4.1.7 Dose–response assessment and setting of tolerable 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 some end-points, however, such as endocrine disruption, the shape of the dose–response curve is not very well understood, which limits use of these data in the risk assessment.

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 to be linear, meaning that risk cannot be excluded at any exposure level.

The NOAEL and LOAEL values are study-specific dose levels at which no effects or minimal 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 the identification of the critical end-point and the critical study (WHO, 2004). 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 critical effects may not always be the same for different exposure scenarios. For example, for scenarios involving high-level acute exposure to acutely toxic insecticide, such as spraying of the insecticide, acute effects and irritation may be taken as critical effects, whereas effects from long-term/chronic studies should be considered in setting of reference value 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/LOAEsL for insecticides (WHO, 2010):

- 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 of 20% or more of brain or red blood cell acetylcholinesterase is considered to be of clear toxicological significance (JMPR, 1998a).
- 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 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 single dose assumed to be without appreciable effect, a benchmark dose 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 of acceptable exposure levels in the same way as a NOAEL is used to apply similar uncertainty factors as to the NOAEL. A benchmark dose 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 considered 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 doses (TSDs), critical NOAELs/LOAELs (or benchmark doses) are divided by uncertainty factors (UFs) to account for variability and uncertainties:

TSD = 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, 2005b), 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 for 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 lower 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, 2005b).

In some cases, the use of additional UFs is justified (Dourson, Knauf & Swartout, 1992; Herrman & Younes, 1999; Vermeire, 1999; WHO, 1999; Dorne & Renwick, 2005; 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 (often 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).

Types of acceptable exposure limits needed for the risk assessment of larviciding

Different reference values/TSDs may be needed according to the type of insecticide; a TSD based on repeated or long-term exposure is usually the most relevant. For insecticides with marked acute toxicity, it is important, however, also to verify that the maximal daily exposure is acceptable; for this purpose, the tolerable systemic dose for acute exposure, TSD_{AC} (based on *e.g.* 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/kg body weight per day. For most insecticides, 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 the European Union, reference doses or concentrations (RfDs, RfCs) set by the USEPA, and minimal risk levels (MRLs) set by the ATSDR. While preference in the risk assessment for larviciding 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 generally 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 inhabitants of insecticide-treated dwellings are also exposed via skin contact and – especially when spraying does not follow the recommended procedures – by inhalation. All exposure routes must therefore be taken into account in estimating the total systemic

exposure. Specifically, it should be noted that the JMPR/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. On the other hand, it is important that TSDs set 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 be at risk of inhalation exposure, it is critical to ensure that the insecticide has no significant local respiratory effects and that TSDs for long-term systemic exposure are also protective against possible respiratory effects. However, when larvicides 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 indoor residual spraying (IRS), and respiratory effects should be negligible. With dry products, such as granules, dust particles may be formed and become airborne.

Regional and national occupational exposure levels (OELs) may be available for public health pesticides. However, it should be noted that these values do not take into account skin exposure, which may be more significant than inhalation exposure in pesticide application. In the case of larviciding, 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 OELs therefore tend to be much smaller than those used in setting guidelines for population exposure.

For these reasons, the same systemic TSD is recommended for operators as for the general population.

Short-term exposure

A guidance value for short-term (24-hour) dietary exposure to agricultural plant protection products has been set by JMPR especially 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 (ARfD).

The acute reference dose (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, 1998a; Solecki et al., 2005). It is derived similarly to the long-term ADI, using relevant human or animal studies of acute or short-term 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 quite

commonly used unless chemical-specific information is available that supports the use of a lower UF (see above).

For organophosphates and carbamates, inhibition of acetylcholinesterase in either red blood cells or brain, measured minutes to hours after dosing, is an appropriate parameter on which to base the guidance value for short-term exposure. For example, the ARfD for chlorpyriphos is based on a study in human volunteers, in which an NOAEL of 1 mg/kg was identified for the inhibition of erythrocyte acetylcholinesterase activity. Since the study was carried out in humans, no interspecies extrapolation was needed and an ARfD of 0.1 mg/kg was set using a UF of 10.

For larviciding, a tolerable systemic dose for acute exposure, TSD_{AC}, derived from *e.g*. the ARfD may be used in the risk assessment, notably for insecticides with significant acute toxicity, to take account of acute risks related to, for example, insecticide application, and spillages.

For several insecticides used for larviciding, 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, 2010) JMPR has also laid down principles for the derivation of ARfDs for agricultural pesticides (Solecki et al., 2005); these can be adjusted for insecticides used for larviciding when no authoritative acute reference dose is available.

4.2 Human exposure assessment

Exposure algorithms, default values and unit exposures, which describe the relationship between operational conditions and exposure, are taken from *Standard operating procedures for residential exposure assessments* (USEPA, 1997a, 2009), *Exposure factors handbook* (USEPA, 1997b) *and Child-specific exposure factors handbook* (USEPA, 2008), different agricultural field-study databases and modelling approaches (European Predictive Operator Exposure Model (EUROPOEM, 2003); UK Predictive Operator Exposure Model (PSD, 2007)). The defaults should be modified by the user of the models on a case-by-case basis and replaced with appropriate measured or otherwise improved point values or distributions, when applicable.

The ability of a pesticide 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 insecticide, and the inherent sensitivity of the exposed person. Exposure has also been seen to be strongly related to the actual amount of product or active ingredient handled and applied. Exposure assessment of larviciding therefore consists of several different scenarios for different target groups.

For the risk characterization, a total exposure 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. WHO has published guidance on exposure models and communicating uncertainties (WHO, 2005a; WHO, 2008).

Among the residents of the treated areas or users of treated water, unborn and newborn babies and 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 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, sweating of 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. Moreover, the model does not take account of concurrent use of the insecticides 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 in:

- optimal conditions, i.e. the guideline scenario; and
- a lax standard scenario, which allows for some common deviations from the instructions (tropical conditions are accommodated and no personal protective equipment other than light clothing covering the trunk is assumed)

4.2.1 General parameters for exposure assessment

1. Operators are considered to weigh 62 kg (16-21 years old female median, Table 3, USEPA, 2008). In specific circumstances, it may be appropriate to lower the default weight, but this is a realistic assumption in most cases and also covers most females.
2. Adult residents are assumed to weigh 62 kg. Risks are also estimated for children aged 11-16 years (32 kg), and toddlers, i.e., children aged 2-3 years (14 kg) as well as newborns (4.8 kg; median, less than 1 month olds; USEPA, 2008).
3. 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

9.3 mL is the maximum amount of liquid on hands (total surface area of hands 930 cm^2 (Table 3; USEPA, 1997, 2008)

Table 3. **Anthropometric and physiological characteristics used in the model**[a]

	Adult[1]	Child (6-11 years)	Toddler (2-3 years)	Newborn[2]
Weight kg	62	32	14	4.8
Body surface m^2				
total	1.69	1.08	0.61	0.29
hands	0.093	0.054	0.032	0.015
arms	0.264	0.137	0.072	0.040
forearms	0.111[3]	0.058[3]		
legs	0.556	0.301	0.142	0.060
lower legs	0.189[4]	0.102[4]		
feet	0.123	0.078	0.043	0.019
head	0.135	0.136	0.087	0.053
Respiration rate m^3/h [5]				
sleep/nap	0.40	0.38	0.38	0.28[6]
sedentary	0.40	0.38	0.40	0.28[6]
light activity	0.89	0.90	1.0	0.66[6]
moderate activity	1.9	1.7	1.7	1.3[6]
Food consumption g/d	1100	1100	1000	
Water consumption L/d	2	1	1	

[a] Source: USEPA 2008.
[1] (16-21 year, female)
[2] Birth to 1 month
[3] 42% of the surface of the arms (USEPA 1997b)
[4] 34% of the surface of the arms (USEPA 1997b)
[5] 95th percentile of short term exposure value
[6] birth to 1 year

Parameters for exposure assessment – operator exposure

The procedure for mosquito larviciding is detailed elsewhere (WHO, 2006). Typically, the equipment used for application of the liquid formulations of mosquito larvicides consists of compression- and lever-operated back-pack sprayers fitted with either a fan or a cone nozzle. Solid formulations are dispersed by an applicator (e.g. for granules) and by gloved hand. WHO has published specifications for the equipment used in such applications (WHO, 2006).

In this exposure assessment for the guideline scenarios, it is assumed that WHO recommendations are being followed.

In the lax standard scenario: tropical conditions are accommodated and no personal protective equipment other than light clothing covering the trunk is assumed.

The tasks that are considered to cause exposure to the operators are:

– mixing and loading; and

– application of the insecticide product by spraying and washing and maintenance of the equipment.

- Contamination 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. Inhalation exposure is considered negligible during mixing and loading.
- For the assessment of operator exposure to larvicides applied as liquid sprays, it is assumed that the inhalation exposure of the sprayman 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.
- The insecticide formulations commonly used in mosquito larviciding are emulsifiable concentrates and granules and other solid formulations. Some formulations (e.g. tablets) are used only in certain applications, e.g. for water-storage containers.
- Mosquito larviciding includes the treatment of manmade 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).
- For exposure assessment of spraymen, it is assumed that the spray operator works six days a week, over a six-month period.
- It is assumed that correct maintenance procedures for the equipment are followed to ensure that no leakages occur during the spraying operations; for example, leakages from the trigger valve will specifically affect the hands.
- It is assumed that a single sprayman could apply a maximum of 12 tank-loads of insecticide spray 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.
- The concentration of the spray liquid is to be checked from product labels of 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.

- Most insecticides used in vector control have low volatility, and exposure to gaseous insecticide is therefore usually negligible (USEPA, 1997a; WHO, 2004). Dust from dry formulations, especially during mixing and loading, and aqueous aerosols from compression sprayers may, however, cause inhalation exposure of the operator. Because of the large droplet size generated in larviciding, this exposure, however, is considerably smaller than that used in space spraying and even IRS.
- In the guideline scenario, it is assumed that operators wear appropriate personal protective equipment (PPE), i.e. gloves, other protective clothing and respirators, according to the label instructions and the relevant WHO manual – both when mixing and loading and when spraying. In the lax standard scenario it is assumed that no PPE is used, which may be quite common in view of the likely climatic conditions. When full PPE (respirator, protective gloves, long-sleeved protective clothes) is used, an overall reduction coefficient of 0.1 (10%) is applied (EUROPOEM, 2003).

Parameters for exposure assessment – residents

Larviciding of a target is performed at 7-day intervals during a season of 6 months.

Exposure of adults and children, through ingestion of treated water, or through bathing with or swimming in treated water, is similar. No inhalation exposure is assumed in any circumstances.

It has been stated that larviciding should not be used for the treatment of 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, 1 litre/day for children (USEPA, 2008); accidental ingestion exposure may also occur.

For dermal exposure due to bathing, body surface areas are assumed to be 1.69 m^2 for adults 1.08 m^2 for children, 0.61 m^2 for toddlers, and 0.29 for newborns (USEPA, 2008). It is assumed that one bath is taken per week, plus daily body washing which is equivalent to one weekly bath – a total of 2 x 52 = 104 bathing (or swimming) events per year (USAID, 2006). During a 6-month spraying season, 52 events of whole body dermal exposure are thus assumed.

Improper disposal of pesticide containers may contaminate soil, groundwater and surface water, and this 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 insecticides 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 are available for estimating the concentration of contaminants in the groundwater.

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

Operator exposure

Mixing and loading insecticide formulation

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

The formulations used in larviciding include emulsifiable concentrate, which is a liquid formulation. There are no solid (granule or tablet) formulations of chemical larvicides that need mixing. Table 4 deals with dermal exposure to liquid products.

$$Predicted\ dose = \frac{VF_{dermal} \times CF \times PPE \times AbsD \times EF}{BW \times AT}$$

where:

- predicted dose = TWA systemic dose due to dermal exposure from liquid formulations, in mg active ingredient/kg body weight per day
- VF_{dermal} = volume of formulation on hands (from Table 4) × no. of daily operations (12)
- *CF* = concentration of active ingredient in the formulation
- *PPE* = Protection by PPE; guideline scenario = 0.1, lax standard scenario = 1
- *EF* = exposure frequency, 6 days/week for a 6-month spraying period (156 days)

- *AbsD* = dermal absorption, percent (default = 10%)
- *BW* = body weight (60 kg)
- *AT* = averaging time, 1 year (365 days)

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

Inhalation exposure

Inhalation exposure can be assumed to be negligible. The large droplet size, downward spraying direction, working outdoors and the recommended use of PPE justify the assumption of low inhalation exposure in guideline scenario conditions

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 and hat) and appropriate gloves are used during both spraying and washing or maintenance of the equipment. Dermal exposure under these conditions is considered to be 10% of that estimated in the lax standard scenario because of the protection provided by the gloves.

$$Predicted\ \ dose = \frac{VS_{\text{dermal}} \times CS \times PPE \times EF \times AbsD}{BW \times AT}$$

where:

- predicted dose = TWA systemic dose due to dermal exposure, mg active ingredient/kg body weight per day
- VS_{dermal} = volume of spray on hands = 9.3 mL/day
- *CS* = 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 by PPE; guideline scenario= 0.1, lax standard scenario = 1
- *EF* = exposure frequency, 6 days/week for a 6-month spraying period = 156 days
- *AbsD* = dermal absorption, percent (default = 10%)
- *BW* = body weight (62 kg)
- *AT* = averaging time, 1 year (365 days)

To estimate the maximal daily dose (for the assessment of acute toxicity by comparison to the TSD_{AC}), the TWA total operator exposure is multiplied by AT/EF = 365/156 = 2.34.

Residential exposure

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

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.

Ingestion exposure, drinking contaminated water

$$Predicted\ dose = \frac{CDW \times WIR \times AbsO \times EF}{BW \times AT}$$

where:

- predicted dose = TWA systemic dose due to ingestion exposure, mg active ingredient/kg body weight per day
- *CDW* = concentration in drinking water, mg active ingredient/litre. For products with a dissipation half-time, $T_{½} \leq 5$ 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 $T_{½} > 5$ days, *CDW* is calculated from target concentration $\times$ $T_{½}$ /ln2. If a second-tier estimation is needed for a product with a dissipation $T_{½} \leq 5$ days, actual dissipation data are used.
- *WIR* = water ingestion rate (2 litres/day for adults, 1 litre/day for children and toddlers)
- *AbsO* = gastrointestinal absorption, default = 100%
- *EF* = exposure frequency, 7 days/week for a 6-month spraying period = 183 days
- *BW* = body weight (62 kg for adults, 32 kg for children, 14 kg for toddlers)
- *AT* = averaging time, 1 year (365 days)

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

Dermal exposure, bathing/swimming in contaminated water

$$Predicted\ dose = \frac{VS_{\text{dermal}} \times CW \times AbsD \times EF}{BW \times AT}$$

where:

- Predicted dose = TWA systemic dose due to dermal exposure, mg active ingredient/kg body weight per day

- VS_{dermal} = volume of water on skin, 0.01 cm (0.0001 m) film on skin after run-off (default volume for adults is 1.69 m^2 x 0.0001 m = 169 mL, for children 108 mL, for toddlers 61 mL, for newborns 29 mL)
- *CW* = concentration in bathing/swimming water, mg active ingredient/litre. For products with a dissipation $T_{½} \leq 5$ days, the first-tier *CW* is the estimated target concentration = spraying rate g/ha $\times 10^{-4}$ divided by the depth of the waterbed (metres); the default value is 0.5. For products with a dissipation $T_{½} > 5$ days, CW is calculated from target concentration × dissipation $T_{½}$/ln2. If a second-tier estimation is needed for a product with a dissipation T½ ≤ 5 days, actual dissipation data are used.
- *AbsD* = dermal absorption (default = 10%)
- *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 2 x 52 = 104 events). The treatment season is assumed to be 6 months; 104/2 = 52 events/year.
- *BW* = body weight (62 kg adults, 32 kg for children, 14 kg toddlers, 4.8 kg newborns)
- *AT* = averaging time, 1 year (365 days)

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

The maximal daily dose (for the assessment of acute toxicity by comparison to the TSD_{AC}), is the sum of the oral dose (TWA oral dose multiplied by AT/EF = 365/183 = 2) and dermal dose (TWA dermal dose multiplied by AT/EF = 365/52 = 7).

Exposure via breast milk

Calculations for exposure via breast milk are presented here for both lipid-soluble and water-soluble active ingredients. No highly biopersistent insecticides are recommended for larviciding applications.

Infant exposure from breast milk can be estimated from the equation:

$$Predicted\ dose = \frac{C \times IR \times AbsO}{BW}$$

where:

- *IR* = ingestion rate of milk, kg/day; upper percentile default for a newborn is 950 mL/day (USEPA, 2008), thus if relative density is assumed to be 1 kg/litre, daily consumption would be 0.95 kg/day
- *AbsO* = fraction absorbed (default, 100%)
- *BW* = body weight (newborn 4.8 kg; USEPA, 2008)
- *C* = concentration of active ingredient in breast milk, mg/litre, estimated from the from the body burden of the mother at steady state.

For water-soluble insecticides, the body burden is assumed to be concentrated in the water compartment of the body, and the concentration in breast milk equals this concentration, i.e. the concentration in breast milk is

C = 1.4 × body burden.

Lipid-soluble insecticides ($pK_{ow} \geq 2$) are concentrated in the adipose tissue, and the concentration in adipose tissue is 5 × body burden mg/kg (assuming 20% fat content of the body). The average fat content of breast milk is assumed to be 50 g/litre, and the insecticide concentration in breast milk is thus (WHO, 2001):

$$C = \frac{D \times T_{1/2} \times 5 \times 0.05}{0.693}$$

where:

- C = concentration of the insecticide in breast milk, mg/litre
- D = daily dose to the mother, mg/kg body weight
- $T_{½}$ = first-order kinetics half-time of the insecticide in the body, days

The estimate of the systemic dose from exposure from breast feeding is based on the steady-state body burden of the mother; it thus also represents the maximal daily dose of the infant.

The accuracy of this default value may be considerably increased if chemical-specific data are available.

Ingestion exposure from contaminated foodstuffs grown in an area contaminated from irrigation with larvicide-treated water – adults and children

Exposure due to ingestion of contaminated foodstuff may be a significant source of human exposure. If the pesticide present in treated water used for irrigation of edible plants (vegetables, etc.) is both persistent and bioaccumulative, actual levels in these media and in food items should be measured.

4.2.3 Total exposure assessment

Total exposure is calculated by summing the contributions via different routes. The default absorption rates for ingestion, inhalation and dermal exposure are 100%, 100% and 10%, respectively. 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 the area that is being sprayed who are using the treated water for different household purposes.

4.2.4 Uncertainties in exposure-determining factors and risk calculations

Default values used in the risk assessment models are often obtained from sources representing North American or European situations. African and Asian circumstances – body dimensions, for example – are often different. When available, values specific of 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 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 exposure with TSDs defined in hazard assessment in all relevant exposure situations.

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

When this ratio is <1, the health risk is considered to be acceptable. When it is >1, there are possible health risks, and the planned use for larviciding may be unacceptable. In the case of operators, however, 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.

When the insecticide has significant acute toxicity (*e.g.*, JMPR or another organization has set an ARfD), the risk is also estimated for short-term exposure:

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

In the publication *Generic risk assessment model for insecticide treatment and subsequent use of mosquito nets*, (WHO, 2004), another approach to risk characterization, based on MOE (margin of exposure) [called margin of safety, MOS, in that document], is described. However, this alternative approach has not been used to any significant extent in the context of public health pesticides and has therefore been omitted from the current document.

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 use for public health purposes.

In the two areas of disease vector control covered in the generic models being published concurrently - larviciding and space spraying - 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 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.

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:

- 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 can be used to address four issues:

- the absolute risk to non-target organisms for each type of insecticide used;
- the relative risk of different pesticides;
- the number of repeat applications likely to lead to risk to organisms in the environment;
- 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 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 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, 2006). 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 and 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. 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 *acute* exposures of soil organisms would use this value. It is likely that input to soil from application as an aquatic larvicide 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; go to 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 biodegration 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)

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

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

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

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 judgment 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 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 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 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 *acute* 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, 1987) 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 larvidical 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:

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

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 acute 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 time-weighted average concentration 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 – 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 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; 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 acute 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 >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 aquatic organisms section. 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, 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, 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.

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 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 insecticides used as aquatic larvicides.

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 acute 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 • dog oral 2-year studies. •

Generic risk assessment model	Worked example
1.8 Identify critical NOAEL(s) from pivotal studies for acute 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 • subchronic oral NOAEL, rat, based on cholinesterase inhibition, 1 mg/kg • chronic oral NOAEL, dog, based on cholinesterase inhibition, 1 mg/kg • 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 is taken to represent tolerable systemic dose (TSD) (EU 2006). Available dermal studies support these values which are based on oral data.
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 defaults and other data used in the assessments should not be limited to those presented as examples in this document. Searches should be made for case-specific, valid and scientifically sound data. *Aim:* • to estimate operator exposure via dermal and inhalation routes during mixing, loading and application of larvicide products, and during washing and maintenance of the spray equipment; • to estimate residential exposure of adults and children, i.e. dermal and ingestional exposure (to contaminated or intentionally treated water), and exposure of infants via breast milk.	**2. Exposure assessment** In this worked example, an emulsifiable concentrate formulation of an organophosphate insecticide, product "X", is assumed. The active ingredient content of the product is 500 mg/mL; the container size 5L, and closure size of the container 45 mm. A guideline scenario (label and WHO instructions are followed) and a lax standard scenario (which takes account, for example, the effect of tropical weather conditions on the use of PPE).

Generic risk assessment model	Worked example
2.1 Operator exposure during mixing and loading, application, and equipment maintenance *a) Exposure during mixing and loading* It is assumed that inhalation exposure of the operator during mixing and loading is negligible. For liquid formulations, dermal exposure during mixing/loading is estimated by using unit exposures from a database. In the lax standard scenario, it is assumed that there is no use of PPE (gloves); in guideline scenario, gloves are used. When ready-to-use products (tablets, etc.) are employed, there is no mixing or loading Body weight of an adult operator is 62 kg, exposure frequency EF = 156 days, averaging time, AT = 365 days. Predicted systemic dose $= \frac{VF_{\text{dermal}} \times CF \times PPE \times EF \times AbsD}{BW \times AT}$ *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. Dermal exposure consists of contamination of hands (930 cm^2). The thickness of the liquid layer on the skin is 0.01 cm, the body weight of an adult, 62 kg. Exposure frequency is 156 days, and averaging time 365 days. Predicted systemic dose = $\frac{VS_{\text{dermal}} \times CS \times PPE \times EF \times AbsD}{BW \times AT}$	***2.1 Operator exposure during mixing and loading, application, and equipment maintenance*** *a) Exposure during mixing and loading* The hand contamination (Table 3) is 0.01 mL/operation; a maximum number of 12 tank-loads per day is assumed. VF_{dermal} = 0.01 mL/operation x 12 = 0.12 mL *CF* = 500 mg/mL As no chemical-specific data are available for dermal absorption, the default of 10% is used. • In the lax standard scenario, systemic dose during mixing and loading is 0.12 mL × 500 mg/mL × 0.1 × 156/(62 × 365) **= 0.0414 mg/kg bw**. • In the guideline scenario the use of gloves is assumed to give 90% protection; the predicted dose is **=0.0041 mg/kg bw** .. *b) Exposure during application and washing and maintenance of the equipment* The spray liquid contains 0.5 mg a.i./mL (0.1% spray liquid, i.e. 500 mg/mL x 0.001) For dermal absorption, the default 10% is used. • In the lax standard scenario, the predicted systemic dose from dermal exposure is 0.5 mg/mL × 9.3 mL × 156 × 0.1 / (62 kg × 365) = **0.0032 mg/kg bw**. • In the guideline scenario, gloves are assumed to assumed to give 90% protection, the predicted dose is **0.0003 mg/kg bw**.
c) total operator predicted dose, exposures are combined:	*c) total operator predicted dose* • guideline scenario: $dose_{M/L}$ dermal + $dose_A$ dermal = 0.0041mg a.i./kg bw + 0.0003 mg a.i./kg bw **=0.0045 mg/kg bw per day** • Lax standard scenario: $dose_{M/L}$ dermal + $dose_A$ dermal = 0.0414 mg a.i./kg bw + 0.0032 mg a.i./kg bw **=** **0.0446 mg/kg bw per day**. The maximal systemic daily dose in the guideline scenario is 0.011 mg/kg bw and 0.10 mg/kg bw in the lax standard scenario.

Generic risk assessment model	Worked example
2.2 Residential exposure *2.2.1 Drinking treated water* Exposure is predicted from the concentration of active ingredient in the water and the water ingestion rate. The water ingestion rate is assumed here to be 2 litres/day for adults, and 1 litre/day for children and toddlers. The body weight is 62 kg for adults, 32 kg for children, and 14 kg for toddlers Exposure duration is 183 days and averaging time of 365 days.	***2.2 Residential exposure*** *2.2.1 Drinking treated water* 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. Ingestion exposure due to drinking treated water: • adults: 5 µg/L × 2 L × 183 /(62 × 365) **= 0.081 µg/kg bw per day** • children: 5 µg/L × 1 L × 183 /(32 × 365) **= 0.078 µg/kg bw per day** • toddlers: 5 µg/L × 1 L × 183 /(14 × 365) **= 0.179 µg /kg bw per day**
2.2.2 Bathing and swimming in treated water, dermal exposure Thickness of the liquid film on skin is 0.001 dm, skin surface exposed 169, 108, 61, and 29 dm^2 for adults, children, toddlers and newborns. An application rate of 11–25 g a.i./ha is recommended for larvicidal use of X. This 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 average water concentration over the period of 6 months. As exposure is to both suspended and dissolved X, partition is not considered. Number of exposures is 52/yr. Averaging time is 365 d. Dermal absorption is 10%	*2.2.2 Bathing and swimming in treated water, dermal exposure* Dermal exposure due to contact with treated water: • adults is 5 × 169 ×10^{-3} × 52 × 0.1/(62 × 365) **= 0.0002 µg/kg bw per day** • children is 5 × 108 ×10^{-3} × 52 × 0.1/(32 × 365) **= 0.0002 µg/kg bw per day** • toddlers is 5 × 61 ×10^{-3} × 52 × 0.1/(14 × 365) **= 0.0003 µg/kg bw per day** • newborns is 5 × 29 ×10^{-3} × 52 × 0.1/(4.8 × 365) **= 0.0004 µg/kg bw per day**
2.2.3 Ingestion exposure via breast milk The breast milk exposure calculation presented here is a very rough estimation. Use of chemical-specific data is highly recommended. Default absorbed fraction is 100%. Concentration in breast milk is calculated using the exposure of the mother at steady state as a starting point. Body burden = daily systemic dose (mg a.i./day) x $T_{1/2}$ (days)/ln2. For water-soluble insecticides, body burden is assumed to be concentrated in the water compartment, and the concentration in breast milk equals this concentration. For lipid-soluble insecticides (pK_{ow} ≥2), the concentration in breast milk (mg/kg milk fat) = 5 x body burden (assuming 20% fat content of the body). Average fat content of breast milk is assumed to be 50 g/litre. Ingestion rate for newborn = 950 mL/day = 0.95 kg/day (relative density 1 kg/litre). Bw. of a newborn is assumed to be 4.8 kg.	*2.2.3 Ingestion exposure via breast milk* The concentration of a lipid-soluble insecticide in breast milk = body burden (mg a.i./kg bw) x 5 x 0.05 kg/litre x $T_{½}$/ln2. For X, the biological $T_{½}$ = 0.5 day For a mother who is a resident of the treated area, using treated water for household purposes, the predicted dose for th suckling infant is: 1 × (0.081 + 0.0002) × 5 × 0.5 × 0.05 × 0.95 / (0.693 × 4.8) = **0.003 µg/kg bw per day**. For the infant of a mother who also works as a larviciding operator, the predicted doses are: • Guideline operator scenario: 1 × (0.081 + 0.0002 + 4.45) × 5 × 0.5 × 0.05 × 0.95 / (0.693 × 4.8) = **0.16 µg/kg bw per day**. • Lax standard operator scenario: 1 × (0.081 + 0.0002 + 44.5) × 5 × 0.5 × 0.05 × 0.95 / (0.693 × 4.8) = **1.59 µg/kg bw per day**.

Generic risk assessment model	Worked example
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, 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.	**3. Risk characterization** ***3.1 Comparison of exposure estimates with TSDs for operator risk characterization*** The irritation capacity and acute toxicity of X are low. Thus local effects and acute toxicity are not important aspects in the risk assessment, which is based on comparison with long-term toxicity and the long-term TSD. From 1.11, TSD used in subsequent risk characterization is 0.01 mg/kg bw per day. Predicted doses to be used in subsequent risk characterization: *Total TWA operator predicted doses:* • Guideline scenario: $dose_{M/L}$ dermal + $dose_A$ dermal **=0.0046 mg/kg bw**. • Lax standard scenario: $dose_{M/L}$ dermal + $dose_A$ dermal **= 0.046 mg/kg bw** In the guideline scenario, the exposure is considered to be acceptable. The predicted dose is 46% of the TSD. The TSD is exceeded in the lax standard scenarios, 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, 0.011 mg/kg bw, which is 11% of the TSD_{AC}; in the lax standard scenario the maximal daily dose, 0.1 mg/kg bw, is 100% of the TSD_{AC}. *Total resident predicted TWA doses:* • Adults Dose from drinking treated water + dose from bathing in treated water = **0.08 µg/kg bw** • Children Dose from drinking treated water + dose from bathing in treated water = **0.08 µg/kg bw** • Toddlers Dose from drinking treated water + dose from bathing in treated water = **0.2 µg/kg bw** Residential exposure is considered to be acceptable in all cases. The predicted dose represents ≤ 2% 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 1.59 µg/kg bw, exposure due to bathing 0.0004 µg/kg bw, and total predicted dose, **= 1.6 µg/kg bw.** In lax standard operator exposure scenario, the predicted exposure of the infant is 16% of the TSD.

Generic risk assessment model	Worked example
	If the mother is exposed only residentially, the exposure of the newborn is less than 0.1% of the TSD. The predicted maximal daily dose is < 4% of TSD_{AC} for all age groups and exposure scenarios of residents.

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 focussing 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 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 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 acute ETR for earthworms using the initial concentration in soil. Classify concern for soil organisms. If acute concern is indicated, calculate 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. 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 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 48h) 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.

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