GENERIC RISK ASSESSMENT MODEL FOR INDOOR AND OUTDOOR SPACE SPRAYING OF INSECTICIDES
Generic risk assessment model for indoor and outdoor space spraying of insecticides

2nd Edition
Contents

Acknowledgements

Terminology, abbreviations and acronyms

1. Introduction

2. Purpose

3. Background

3.1 Probabilistic vs deterministic risk assessment models

3.2 Essential elements of a health risk assessment model

4. The health risk assessment model

4.1 Hazard assessment

4.1.1 Sources of data

4.1.2 Types of health hazard data

4.1.3 Range of toxicity tests normally required for pesticide approval

4.1.4 Evaluation of the toxicity information

4.1.5 Insecticides not recommended for use in space spraying

4.1.6 Mixtures of insecticides and insecticides with other constituents of the formulation

4.1.7 Dose–response assessment and setting of acceptable exposure levels

4.2 Exposure assessment

4.2.1 General parameters for exposure assessment

4.2.2 Algorithms used to estimate exposure and absorbed dose caused by indoor or outdoor space spraying of insecticides

4.2.3 Total exposure assessment

4.3 Risk characterization

5. The environmental risk assessment model

5.1 Environmental exposure assessment

5.1.1 Air

5.1.2 Soil

5.1.3 Surface water and aquatic sediment

5.2 Effects

5.2.1 Aquatic organisms

5.2.2 Soil organisms and soil function

5.2.3 Non-target terrestrial arthropods including honeybees

5.2.4 Terrestrial vertebrates

5.2.5 Higher terrestrial plants

6. Conclusions

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

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

References
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The Secretariat revised the document based on these comments; advice was then sought on open questions during an expert consultation from Health Canada of the Government of Canada, the British Health and Safety Executive, the Finnish Institute of Occupational Health and the Dutch National Institute for Public Health and the Environment (RIVM). The document was then finalized by the Secretariat as the second edition. Comments received during peer review and the views of experts consulted during the expert consultation were advisory in nature, and the contents of the document are the responsibility of the Secretariat.
### Terminology, abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADI</td>
<td>acceptable daily intake</td>
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<tr>
<td>a.i.</td>
<td>active ingredient</td>
</tr>
<tr>
<td>ARfD</td>
<td>acute reference dose</td>
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<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry</td>
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<tr>
<td>AUC</td>
<td>area under curve</td>
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<tr>
<td>BCF</td>
<td>bioconcentration factor</td>
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<tr>
<td>BMD</td>
<td>benchmark dose</td>
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<tr>
<td>CICAD</td>
<td>Concise International Chemical Assessment Document</td>
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<tr>
<td>Cmax</td>
<td>peak plasma concentration</td>
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<tr>
<td>DDD</td>
<td>daily dietary dose</td>
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<tr>
<td>DFI</td>
<td>daily food intake</td>
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<tr>
<td>EC</td>
<td>European Commission</td>
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<tr>
<td>EC50</td>
<td>concentration having a 50% effect on test populations against a specific end-point</td>
</tr>
<tr>
<td>EFSAs</td>
<td>European Food Safety Authority</td>
</tr>
<tr>
<td>EPPO</td>
<td>European and Mediterranean Plant Protection Organization</td>
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<tr>
<td>ETR</td>
<td>exposure–toxicity ratio</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>EUROPOEM</td>
<td>European Predictive Operator Exposure Model</td>
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<tr>
<td>GHS</td>
<td>Globally Harmonized System of Classification and Labelling of Chemicals (UN, 2015)</td>
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<tr>
<td>GLP</td>
<td>good laboratory practice</td>
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<tr>
<td>guideline scenario</td>
<td>exposure scenario which assumes that the insecticide is used according to the instructions given on the product label and in WHO guideline information.</td>
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<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
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<td>IPCS</td>
<td>International Programme on Chemical Safety</td>
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<tr>
<td>JECFA</td>
<td>Joint FAO/WHO Expert Committee on Food Additives</td>
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<tr>
<td>JMPM</td>
<td>Joint Meeting on Pesticide Management</td>
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<tr>
<td>JMPR</td>
<td>Joint Meeting on Pesticide Residues</td>
</tr>
<tr>
<td>lax standard scenario</td>
<td>exposure scenario in which no personal protective equipment other than light clothing covering the trunk is assumed</td>
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<tr>
<td>LC50</td>
<td>concentration killing 50% of the test organisms</td>
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<tr>
<td>LOAEL</td>
<td>lowest-observed-adverse-effect-level</td>
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<tr>
<td>LOEC</td>
<td>lowest-observed-effect concentration</td>
</tr>
<tr>
<td>MRL</td>
<td>minimal risk level</td>
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<tr>
<td>NOAEL</td>
<td>no-observed-adverse-effect-level</td>
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<tr>
<td>NOEC</td>
<td>no-observed effect concentration</td>
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<tr>
<td>NOED</td>
<td>no-observed effect dose (terminology used in environmental risk assessment (EPPO, 2003))</td>
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<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
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<tr>
<td>OEL</td>
<td>occupational exposure level</td>
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<td>PEC</td>
<td>predicted environmental concentration</td>
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<tr>
<td>PNEC</td>
<td>predicted no-observed-effect concentration</td>
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<tr>
<td>PPE</td>
<td>personal protective equipment</td>
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<tr>
<td>RFC</td>
<td>reference concentration</td>
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<tr>
<td>RfD</td>
<td>reference dose</td>
</tr>
<tr>
<td>RPE</td>
<td>respiratory protective equipment</td>
</tr>
<tr>
<td>TSD</td>
<td>tolerable systemic dose</td>
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<tr>
<td>TSDac</td>
<td>tolerable systemic dose, acute exposure</td>
</tr>
<tr>
<td>TWA</td>
<td>time-weighted average</td>
</tr>
<tr>
<td>TWAC</td>
<td>time-weighted average concentration</td>
</tr>
<tr>
<td>UF</td>
<td>uncertainty factor</td>
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<tr>
<td>UKPOEM</td>
<td>UK Predictive Operator Exposure Model</td>
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<tr>
<td>USEPA</td>
<td>United States Environmental Protection Agency</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>WHOPES</td>
<td>World Health Organization Pesticide Evaluation Scheme</td>
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1. **Introduction**

Space spraying is an application for the dissemination of insecticides in the form of small droplets (of less than 30 µm volume mean diameter) that will remain airborne sufficiently long (but usually not more than 30 min) to make contact with flying target insect species such as mosquito vectors of disease. Because this type of treatment is not intended to leave a residual deposit, space spraying involves application of a very low dosage of insecticide. Sequential space-spray applications of insecticides in the same area are usually needed to control the emerging adult populations and are commonly recommended for rapid containment of outbreaks of *Aedes*-borne diseases such as dengue and Chikungunya and to some extent of malaria. Space spraying may also have value in public health pest control programmes against nuisance mosquitoes and flies.

There are essentially three types of application of space spraying: cold fogging, thermal fogging using carrier oil and ultra-low volume treatment using ground equipment (namely portable (hand/shoulder-carried) and vehicle-mounted foggers) as well as aerial equipment mounted on aircrafts.

The formulations commonly used for such applications are hot fogging concentrates, ultra-low-volume liquids, oil-in-water emulsions and emulsifiable concentrates. Formulations such as wettable powders, suspension concentrates and water-dispersible granules are unsuitable for space spraying. An appropriate formulation must be chosen and the label instructions carefully followed for all applications. WHO specifications for pesticides for quality control and international trade are available at: http://www.who.int/pq-vector-control/en/.

WHO has published procedures for space-spray application of insecticides in public health (WHO, 2003, 2011), specification guidelines for equipment for vector control that include space spraying (WHO, 2018a), and requirements, procedures and criteria for testing and evaluation of insecticides for space spraying (WHO, 2009a).

2. **Purpose**

The purpose of this document is to provide a generic model that can be used for risk assessment of exposure to insecticide products applied as space treatments, both indoors and outdoors, against flying insect vectors and pests of public health importance. It aims to harmonize the risk assessment of such insecticides for public health use. The assessment considers exposures for both adults and children (all ages) as well as people in the following specific categories:

- those handling insecticides and preparing/loading the spray liquid in application equipment;
- those applying the spray indoors and outdoors;
- residents who return to treated houses after a specified time following treatments; and
- bystanders who are present during an outdoor application.

In addition to human health risk assessment, aspects of ecological risk assessment must be considered. In contrast to the former, ecological risk assessment characterizes the risk to populations of non-target organisms other than to humans.

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

It is recommended that the risk assessments proposed for space spraying are not conducted de novo; rather, 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 judgement 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 space spraying of insecticides indoors or outdoors.

3.1 **Probabilistic vs deterministic risk assessment models**

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

The probabilistic technique offers a complementary modelling approach that incorporates variability of exposure between individuals and at different points in time and allows an assessment of the uncertainty of the assessment outcome (uncertainty of data, such as limited availability of empirical information, as well as limitations in the measurements, models or techniques used to develop representations of complex physical, chemical and biological processes) (WHO, 2008). Probabilistic modelling uses distributions of values rather than single values. The advantage of the technique is that it provides the probability of occurrence and/or amount of exposure, which offers a realistic and informative way of characterizing risk. Just as for deterministic models, however, the validity of the exposure estimate depends on the quality and extent of the input data and the reliability of the estimation algorithm.

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

– the difficulty of using the models,
– algorithm development;
– collection of good-quality input distributions;
– criteria for decision-making (what is an acceptable risk and what is not); and
– communicating the results to stakeholders.

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

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

3.2 Essential elements of a health risk assessment model

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

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

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

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

*Risk assessment* refers to the entire process of hazard assessment, exposure estimation and risk characterization. Consideration of any *uncertainties* in the hazard assessment, exposure assessment and risk characterization is an essential part of a valid, good-quality risk assessment.

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

1. *Hazard assessment*. Hazard assessment comprises hazard identification and hazard characterization, i.e. identification of the possible toxic effects of a substance, the dose/exposure levels at which those effects occur, and the dose/exposure levels below which no adverse effects are observed.

2. *Exposure assessment*. Exposure assessment may concern insecticide operators (applicators), residents of treated dwellings and users of other treated buildings, as well as 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 (WHO, 2003; WHO, 2011). A "*lax standard scenario*", however, takes into account the reality that these instructions are not necessarily followed completely. Conservative, high end-point estimates of the default distributions are used as defaults. No account is taken of intentional misuse. All relevant routes of exposure are covered.


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

4. **The health risk assessment model**

4.1 **Hazard assessment**

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

- whether an agent may pose a health hazard to human health;
- 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 level below which the effects are no longer observed. The principles of human health hazard assessment are discussed in greater detail elsewhere (e.g. WHO, 1999; WHO 2009d); they are generally applicable to all chemical classes and patterns of use, although there may be some differences, e.g. in data requirements.

4.1.1 **Sources of data**

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

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

### 4.1.2 Types of health hazard data

**Human data**

If insecticides 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 insecticide formulations in question, or general population studies; and
- ethically approved volunteer studies examining mild, temporary effects of acute exposure or toxicokinetics of the substance in a limited number of subjects.

#### Table 1. Examples of authoritative evaluations that may be used as starting points for the risk assessment of insecticides for space spraying

<table>
<thead>
<tr>
<th>Source</th>
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<tbody>
<tr>
<td>Joint Meeting on Pesticide Residues (JMPR) – Monographs and Evaluations</td>
<td><a href="http://www.inchem.org/pages/jmpr.html">http://www.inchem.org/pages/jmpr.html</a></td>
</tr>
<tr>
<td>United States Environmental Protection Agency (USEPA) – Pesticide evaluations</td>
<td><a href="https://iaspub.epa.gov/apex/pesticides/?p=chemicalsearch:1">https://iaspub.epa.gov/apex/pesticides/?p=chemicalsearch:1</a></td>
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</tbody>
</table>
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.

**Experimental toxicity data**

For many pesticides, the human database is very limited. In these cases, hazard assessment relies 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 (2011) or USEPA (2010). 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 older, regulated insecticides).

Like all substances, insecticides used in space spraying 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 insecticide, the range of toxicity tests normally needed for health risk assessment, for example in regulatory approval of pesticides and biocides in OECD countries, is very similar (see Table 2).

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

### 4.1.3 Range of toxicity tests normally required for pesticide approval

In addition to the general requirements outlined in the previous section, information on dermal absorption is valuable in assessing the health risks of insecticides used in space spraying. Although space treatment is not expected to leave any residual deposit (surfaces are not intentionally sprayed), small droplets may be deposited on some surfaces within the dwellings to which inhabitants will be subsequently exposed. Inhalation toxicity studies may also be of value in the assessment of risks to operators who are subject to potential acute and repeated inhalation exposure.

Absorption of the insecticide by inhalation, ingestion or through the skin should be estimated in the hazard assessment. If no chemical-specific data exist, default values of 100% for inhalation and ingestion are used. For dermal absorption of insecticides with molecular mass > 500 and octanol/water partition coefficient (log $P_{OW}$) < −1 or > 4, 10% is used as the default.

Since dermal absorption of several pyrethrins and pyrethroids has been shown to be in the order of 1%, it is reasonable to apply a default dermal absorption value of 10% rather than 100% for pyrethrins and pyrethroids when chemical-specific data are not available. However, it must be emphasized that if the assessor is aware that specific data exist for a pyrethroid, those data should be used in preference to the default value. A similar bridging approach could be developed for other chemical groups of
pesticides. For insecticides other than pyrethroids when no data are available, the concept of an inverse relationship between concentration and dermal absorption is applied: for pesticide formulations with the active ingredient (a.i.) content > 5%, a default dermal absorption value of 25% is used, whereas for mixtures with a concentration ≤ 5%, the default used is 75% (EFSA, 2012). In the absence of good-quality data on dermal absorption of dry insecticides deposited on the skin or transferred from surfaces, the higher estimate (concentrated or diluted) of the active ingredient is used (EFSA, 2011, 2014). It should be noted that while residents are usually exposed to the product as sprayed, i.e. a diluted solution, operators may be exposed to both the diluted product and the undiluted formulation. Thus, for mixing and loading, the absorption rate of the non-diluted formulation is to be used, whereas for other dermal exposure, that of the diluted spray is more appropriate (EFSA, 2012).

Table 2. Range of toxicity tests normally required for pesticide approval

Note: Studies marked with an asterisk (*) may provide useful dose–response data.

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

4.1.4 Evaluation of the toxicity information

An experienced toxicologist should evaluate the range and quality of the human and animal toxicity information available. Although all the toxicity tests described in the previous section are useful for assessment of the hazard potential of an insecticide used for space spraying, 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 particularly important when evaluating the relevance of toxicological studies to hazard identification and risk assessment:

- Experimental design and quality of the critical study or studies. This includes, for example, purity of the active ingredient tested, physicochemical properties (stability, etc.), size of the study (number of exposure groups, group sizes, sex, etc.), suitability of the exposure levels used, duration of exposure, extent of toxicological and statistical evaluation, relevancy of the route of exposure to humans, and whether the study adhered to established guidelines and GLP (WHO, 1999).

- Nature of the effects seen, their severity and sites, and whether they would be reversible on cessation of exposure.

- Is it possible to identify dose–response relationship, no-observed-adverse-effect-level (NOAEL) and lowest-observed-adverse-effect-level (LOAEL)?

4.1.5 Insecticides not recommended for use in space spraying

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

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

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

4.1.6 Mixtures of insecticides and insecticides with other constituents of the formulation

If two or more insecticides are used concurrently, possible interactions between those insecticides should be considered. Insecticides with similar action may produce additive toxic effects (dose/concentration addition); organophosphates, for example, decrease acetylcholinesterase activity. For toxicants with dissimilar (independent) action, the combined effect can be estimated directly from the probability of responses to the individual components (response addition) or the sum of biological effects (effects addition). Other forms of interaction include synergistic (supra-additive) and antagonistic effects, which may be caused by different classes of insecticides, for example because of metabolic interactions. Synergism is usually only noted at high exposure levels and may be considered unlikely at levels acceptable for the individual components (SCHER, 2011). In this document, the conservative recommendation of the International Programme on Chemical Safety
(IPCS) to consider effects of mixtures as dose/concentration additive (Meek et al., 2011) is adopted as the default, except in cases in which a different mode of action has been demonstrated for the two components of the mixture.

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

4.1.7 Dose–response assessment and setting of acceptable exposure levels

Dose–response assessment is an essential part of hazard assessment for deriving health-based guidance values and for the assessment of risks. Different methods are available (WHO, 2009b). 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, 2009b). 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, 2009b). Use of these approaches in the setting of acceptable exposure levels requires knowledge of the assumed shape of the dose–response curve. For endocrine-mediated toxicity, however, the shape of the dose–response curve may not be well defined, which poses problems for the risk assessment of substances with such activity.

NOAEL approach

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

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

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

The following additional points should be noted when identifying NOAELs/LOAELs for insecticides (WHO, 2009b):
• If irreversible toxicity is noted in any organs at higher dose levels than those 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.

• For insecticides such as carbamates and organophosphates, which act on specific and nonspecific cholinesterases, the dose levels that cause measurable effects – even if those effects are not considered “adverse” – should be noted. For example, while inhibition of plasma or brain butyrylcholinesterase serves mainly as an indicator of internal exposure, a statistically significant inhibition ≥ 20% of brain or red blood cell acetylcholinesterase is considered to be of clear toxicological significance (JMPR, 1998).

• There may be studies in which the lowest dose tested is a clear effect level and in which it is not possible to identify either an NOAEL or an LOAEL. In these cases, this lowest dose should be tabulated, noting that LOAEL and NOAEL may be significantly lower. Alternatively, the method for the derivation of benchmark dose can be used (see below).

• If the highest dose tested is without any effect, it 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, 2009b). Whereas a NOAEL represents a dose level assumed to be without appreciable effect, a BMD is based on data from the entire dose–response curve of the critical effect (WHO, 2009b). For end-points with an assumed threshold level, a BMD model can be used as a point of departure for setting acceptable exposure levels in the same way as an NOAEL is used by applying similar uncertainty factors. A BMD model may also be helpful in situations where there is a need for low-dose extrapolation, such as occurs in carcinogenicity mediated by a genotoxic mechanism, when it is assumed that the dose–response is linear. Usually, BMD10 – representing a level with 10% response – is used as a starting point for low-dose linear extrapolation in these situations (WHO, 2009b).

**Setting tolerable systemic doses: the use of uncertainty factors**

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

\[ TSD = \text{Abs}_{\text{oral}} \times \frac{\text{NOAEL}}{\text{UF}} \]

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

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

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

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

- When LOAEL is used instead of NOAEL, an additional UF (e.g. 3 or 10) is usually incorporated.

- When an NOAEL from a sub-chronic study (in the absence of a chronic study) is used to derive a TSD for long-term exposure, an additional UF (e.g. 3–10) is usually incorporated to take account of the attendant uncertainties.

- If the critical NOAEL relates to serious, irreversible toxicity, such as developmental abnormalities or cancer induced by a non-genotoxic mechanism, especially if the dose–response is shallow (WHO, 1999).

- When there are exposed subgroups, which may be extra-sensitive to the effects of the compound (e.g. neonates because of the incompletely developed metabolism).

- If the database is limited.

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

- If the NOAEL/LOAEL is derived from human data, the UF for interspecies differences need not be taken into account.

- If chemical-specific data on the toxicokinetics or toxicodynamics of the insecticide in either animals or humans are available, the default UF of 100 may be modified to reflect these data (see WHO, 2005a).
• The effect is not cumulative and is related to peak plasma concentration, not AUC (see above).

**Types of tolerable exposure limits needed for the risk assessment of space spraying**

Different reference doses/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, however, it is also important to verify that the maximal daily exposure is acceptable; for this purpose, the tolerable systemic dose for acute exposure, \( \text{TSD}_{\text{AC}} \) (based on, for example, the acute reference dose, ARfD) is used (Solecki et al., 2005).

**Repeated exposure**

The long-term TSD is usually based on systemic effects observed in long-term studies and is expressed as mg per kg body weight per day (mg kg\( _{\text{bw}}^{\text{-1d}} \)). 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 by the European Union, and reference doses or concentrations (RfDs, RfCs) set by the USEPA. While preference in the risk assessment for space spraying should be the ADIs set by WHO, guidance values set by other authoritative bodies can be used, especially in the absence of WHO guidelines or when WHO guidelines no longer represent current knowledge.

Long-term TSDs are set on the basis of oral studies: chronic studies most commonly use the oral route and many values, such as the ADIs set by JMPR, are intended primarily to control pesticide residue intake through the diet. However, operators and inhabitants of insecticide-treated dwellings are exposed also 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 Joint FAO/WHO Expert Committee on Food Additives (JECFA) ADIs usually presume 100% gastrointestinal absorption; if actual data are available, the TSD (representing absorbed dose) should be derived from the ADI by considering the gastrointestinal absorption. However, it is important that TSDs also protect against possible local effects, for example on the respiratory tract.

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

Regional and national occupational exposure levels (OELs) may be available for pesticides used for public health protection. However, it should be noted that these values do not take into account absorption via the skin which, for exposure to insecticides, may be more significant than that via inhalation (Hayes, 1975). 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 UF\( s \) applied in setting acceptable exposure levels for space spraying thus usually need to be significantly larger than those applied in setting OELs.

It is recommended that the same systemic TSD be applied for space spray operators as for the general population.
Acute exposure
Guidance values for acute (24-hour) dietary exposure to agricultural plant protection products have been set by JMPR for insecticides with significant acute toxicity such as acutely neurotoxic insecticides, including those with anticholinesterase activity (organophosphates and carbamates); these values are called acute reference doses (ARfDs).

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

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

For space spraying, a tolerable systemic dose for acute exposure, TSD\text{AC}_1, derived from e.g. the ARfD, may be used in the risk assessment, notably for insecticides with significant acute toxicity, to take into account the acute risks related to, for example, insecticide application and exposure to treated surfaces.

For most of the common insecticides used for space spraying, an ARfD from JMPR is available for the derivation of the TSD\text{AC}_1, or JMPR has concluded that because of lack of significant acute toxicity, no ARfD is needed (JMPR, 2012). JMPR has also laid down principles for the derivation of ARfDs for agricultural pesticides (Solecki et al., 2005); these can be adjusted for insecticides used for space spraying when no authoritative acute reference dose is available.

4.2 Exposure assessment

The second step in performing a risk assessment is to estimate exposure to the insecticide in the various groups of people potentially at risk. Exposure must take account of various parameters, including the route of exposure, the actual amounts of material involved, the duration of exposure in terms of both daily and annual exposure and seasonality, and the periodicity of exposure (intermittent or continuous).

The following groups of people may be exposed to insecticide through space spraying:

- spray operators; and
- residents and bystanders
  - adults
  - children (including breastfed infants).

Exposure algorithms, default values and unit exposures, which describe the relationship between operational conditions and exposure, are taken from Standard operating procedures for residential pesticide exposure assessments (USEPA, 2012), and Exposure factors handbook: 2011 edition (USEPA, 2011); different agricultural
field-study databases and modelling approaches (European Predictive Operator Exposure Model (EUROPOEM II, 2003); UK Predictive Operator Exposure Model (PSD, 2007). The 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. Similarly, application of anthropometric and physiological datasets derived from the true target population, when available, is likely to yield more accurate exposure predictions.

The ability of an insecticide 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 is also strongly related to the actual amount of product or active ingredient handled and applied. Exposure assessment of space spraying therefore consists of several different scenarios for different target groups.

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

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

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

Another important area of uncertainty is the risk assessment of bioaccumulative active ingredients; 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 spraying and that instructions – including safety precautions – are strictly followed, the exposure in space spraying should generally be low. However, optimum conditions do not always prevail during the spraying operations, and risk assessments that assume appropriate equipment and strict compliance with instructions may lead to an underestimation of the level of exposure. Unintentional misuse, however, is very difficult to take into account in models, and similar problems arise in trying to include the effect of contaminated clothing, perspiration on the skin, use of contaminated rags or towels to wipe the skin, etc. in the risk assessments. In most cases, these parameters are impossible to quantify. Situations related to misuse or accidents are mostly not covered by this document. Reusing pesticide containers is mentioned. The possibility of lactating mothers working as operators should be considered where relevant. These scenarios are to be taken into account in specific cases. They can be more reliably quantified than misuse or accident situations. 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 to spray operators and residents and bystanders in treated areas, in:

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

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

4.2.1 General parameters for exposure assessment

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

- Risks for residents are estimated for adults, children (aged 6–11 years), toddlers (aged 12–24 months) and infants (aged < 12 months), as recommended by the European Human Exposure Expert Group (HEEG, 2013a). Exposure via mother’s milk is estimated for infants and newborns (birth to 1 month).

- Anthropometric and physiological input parameters (weight, skin surface area and ventilation rate) have an effect on the risk estimates. Ideally, data from the target population should be used. However, it is also important that the database is internally consistent: all needed parameters for all age groups are available and are derived from the same population. The database produced by the USEPA (2011) is extensive and up-to-date, covering all age groups and all relevant anthropometric and physiological data-points. It is also recommended for use by the European Human Exposure Expert Group (HEEG, 2013a), and was therefore used in this document (Table 3). For body weight, the 25th percentiles are applied; for respiration rate, the HEEG recommendations are used. When appropriate anthropometric data are available for the population for which the risk assessment is made, these should be used.

- Adult spray operators and residents are assumed to weigh 60 kg. Risks are also estimated for children aged 6–11 years (assumed to weigh 23.9 kg), toddlers aged 12–24 months (10 kg) and infants from birth to 12 months of age (8 kg). Exposure via mother’s milk is assessed also for newborns (birth to 1 month, weight 4.2 kg (USEPA, 2011; HEEG, 2013a).

- The film thickness of a non-viscous liquid likely to be in contact with unprotected, immersed skin is assumed to be 0.01 cm after run-off; thus 8.2 mL is the maximum amount of the liquid on the hands of an adult (total surface area of hands 820 cm²; for children this volume is 4.3 mL – see Table 3) (USEPA, 2011; HEEG, 2013a).

- In most instances, exposure assessment consists of multiplication of several estimated parameters with an inherent variability (e.g. transfer from wall to hand skin, fraction of hand surface area mouthed, salivary extraction rate). If for each such parameter a high percentile of the distribution, say 95th percentile, is used, this leads to an exposure estimate that is unrealistically conservative. Therefore, when available, a lower percentile is applied, usually the 75th percentile.
Table 3. Anthropometric and physiological characteristics used in the model (USEPA, 2011; HEEG, 2013a)

<table>
<thead>
<tr>
<th></th>
<th>Adult</th>
<th>Child 6–11 yr</th>
<th>Toddler 12–24 mo</th>
<th>Infant ≤ 12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight(^a) (kg)</td>
<td>60</td>
<td>23.9</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Body surface(^a) (m(^2))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>1.660</td>
<td>0.9200</td>
<td>0.4800</td>
<td>0.4100</td>
</tr>
<tr>
<td>hands</td>
<td>0.0820</td>
<td>0.0428</td>
<td>0.0230</td>
<td>0.0197</td>
</tr>
<tr>
<td>arms</td>
<td>0.2270</td>
<td>0.1270</td>
<td>0.0619</td>
<td>0.0582</td>
</tr>
<tr>
<td>forearms</td>
<td>0.1129</td>
<td>0.0497</td>
<td>0.0269</td>
<td>0.0230</td>
</tr>
<tr>
<td>legs</td>
<td>0.5330</td>
<td>0.2742</td>
<td>0.1219</td>
<td>0.1041</td>
</tr>
<tr>
<td>lower legs</td>
<td>0.230(^c)</td>
<td>0.1070(^d)</td>
<td>0.054(^e)</td>
<td>0.046(^e)</td>
</tr>
<tr>
<td>feet</td>
<td>0.1130</td>
<td>0.0605</td>
<td>0.0288</td>
<td>0.0246</td>
</tr>
<tr>
<td>head</td>
<td>0.1110</td>
<td>0.0529</td>
<td>0.0403</td>
<td>0.0344</td>
</tr>
<tr>
<td>trunk</td>
<td>0.5710</td>
<td>0.3376</td>
<td>0.1795</td>
<td>0.1533</td>
</tr>
<tr>
<td>Respiration rate(^b)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>short-term(^b) (m(^3)/h)</td>
<td>1.25</td>
<td>1.32</td>
<td>1.26</td>
<td>0.84</td>
</tr>
</tbody>
</table>

\(^a\) Weight and body surface are 25th percentiles based on females (aged 30–40 years, 6–11 years, 12–24 months, and 6–12 months (representing infants ≤ 12 months)) (USEPA, 2011; as recommended by HEEG, 2013a).

\(^b\) These values represent mean values under moderate physical work load, recommended by HEEG to be used as default values in exposure assessments (USEPA, 2011; HEEG, 2013a).

\(^c\) Source: USEPA, 2011.

\(^d\) 11.6% of the total skin surface (USEPA, 2011).

\(^e\) 11.2% of the total skin surface of a 2-year old (USEPA, 2011).

Parameters for exposure assessment – operator exposure

There are three methods of creating space spray: cold fogging, thermal fogging using carrier oil, and ultra-low volume treatment. Spraying is carried out using portable (hand/shoulder-carried) or vehicle-mounted foggers or aerial equipment. The formulations commonly used for such applications are hot-fogging concentrates, ultra-low-volume liquids, emulsions, oil-in water formulations and emulsifiable concentrates. Some formulations may be marketed uniquely for indoor or outdoor application. Therefore, estimates of exposure and risk are carried out for both. For outdoor spraying, exposures are quite different for operations performed using hand-held equipment and vehicle-mounted equipment. The differences are considered in the model.

A practitioner’s guide for space spraying published by WHO details the appropriate spraying equipment and other issues that must be considered for safe and effective application of space-spray products (WHO, 2003). WHO has also published specifications for quality control of equipment used in such applications (WHO, 2018a). In the guideline scenario exposure assessment, it is assumed that WHO recommendations and product label instructions are followed, including the use of overalls. In the lax standard scenario, no personal protective equipment other than light clothing covering the trunk is assumed.

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

– mixing and loading;
– application of the insecticide product by spraying with manually carried equipment (exposure during spraying with vehicle-mounted equipment is not considered significant – see below); and
– washing and maintenance of the spray equipment (applies to both hand-held and vehicle-mounted equipment).
Only adults are assumed to do work as spray operators.

For operator exposure, the exposure duration is assumed to be 6 hours per day, 6 days a week, for a period of 6 months; 2 working hours per day are presumed to be spent in activities without exposure. This pattern is evident, for example, dengue epidemics and is based on information provided to WHO by selected national vectorborne disease control programmes.

It is assumed that the correct maintenance procedures for the spray equipment are followed to ensure that no leakages occur during the spraying operations. For example, that no leakages occur on the hands from the tap or valve which has to be handled when starting and finishing the work.

Frequency of exposure in mixing and loading can be described by the number of tanks prepared per day. Tank size is assumed to be 5 litres. As an example, the tank is filled with a premixed insecticide formulation consisting of 1 part concentrate to 99 parts diluent oil (e.g. diesel oil). The label specifies a maximum of 200 mL of spray solution to be used per house, which is assumed to be 200 m³. Treatment of 60 houses per day – which is standard for this application – would require 12 L of spray, meaning that the 5-L tank is filled by an operator three times during the day.

For outdoor spraying using hand-held sprayer, the operator is assumed to cover 36 hectares/hour, i.e. 200 hectares/day. The number of daily mixing/loading tasks should be calculated from the target application rate and concentration of the (diluted) spray liquid, assuming that the sprayer volume is 5 L (WHO 2003). For outdoor spraying using vehicle-mounted sprayer, the default number of daily operations is 2.

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

Hand contamination during filling of the tank is assumed to depend on the size of the insecticide 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 (UK POEM data: PSD, 2007); see Table 4.

Inhalation exposure to insecticides used in vector control is often low due to the low volatility of the insecticides used (WHO 2018b; USEPA, 2012; HEEG, 2013b). However, space spraying is intended to produce large amounts of aerosol.
in the treated dwelling or area, and inhalation must therefore be considered a relevant route of exposure in some situations during space spraying.

In the guideline case 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, however, it is assumed that no PPE is used, which may be quite common in view of the likely climatic conditions in which space spraying is carried out. When full PPE (respirator, protective gloves, long-sleeved protective clothes) is used, an overall reduction coefficient of 0.1 (10%) is applied (EUROPOEM II, 2003).

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

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

In outdoor spraying with hand-held equipment, the operator is assumed to stay outside the fog as far as possible, but still be exposed for 30 min/day.

When vehicle-mounted equipment meeting WHO recommendations is used (closed cabin (with air filter), with controls for the spray system operated from inside the cabin) then neither inhalation nor dermal exposure is expected to occur during the spraying, the operator staying within the cabin. The operator is, however, assumed to be exposed in mixing and loading, and in the washing and maintenance of the equipment.

**Parameters for exposure assessment – residents and bystanders**

Use of empty product packages to store food items or drinking-water may lead to high exposures and even acute intoxications. The variability of such practices is large and the risks involved cannot be modelled meaningfully. Such misuses are not covered in this risk assessment. Since space spraying is mostly organized by authorities, it can be assumed that residents will seldom have access to empty containers.

**Indoor space spraying**

The frequency of indoor treatments can vary widely with the exposure scenario and by country or geographical area, from annual or occasional treatment to repeated treatments in epidemic situations and disease outbreaks. The WHO recommendation in an emergency situation is spraying every 2–3 days for a week, followed by sprays 1–2 times a week (WHO, 2009c). In this document, the Pakistani Health Ministry recommendation of spraying every second day during the first week, every third day thereafter during the first month, and a weekly spray during the second month (Mukhtari, 2009), i.e. altogether 15 spraying incidents in a year, is used as the default but, because of the wide variations in practice, it is strongly recommended that local, case-specific data be used as well, whenever possible.

It is assumed that recommendations given in WHO's practitioner's guide (WHO, 2003) are complied with: that is, residents are not in the house during the spraying, they will stay out of the house until the spray has settled or degraded, and all food items were removed before spraying began.
It is assumed that exposure of resident adults and children occurs via the dermal route (touching contaminated surfaces in treated houses) or by ingestion of contaminated foodstuffs or water.

For surface contamination, and subsequent post-treatment dermal exposure to settled residue, it is assumed that surfaces are not intentionally sprayed but that the total volume of spray is ultimately deposited on horizontal surfaces of the house, including tables, work surfaces and the floor. For example, if the product label calls for 1 mL/m² of diluted formulation (1 part formulation to 99 parts oil) to be sprayed in a room of 40 m³ (4 m x 4 m x 2.5 m), the resulting deposition is 2.5 mL of diluted formulation/m² of horizontal surface. This would be the worst case scenario, with all material sprayed depositing onto the horizontal surfaces (40 mL of spray in the room depositing onto the 4m x 4m =16 m² surface). In practice, especially with any wind outside the building, only about 50% of the droplets are eventually deposited on horizontal surfaces; most small droplets tend to escape through any openings. It is expected that the residue on the surfaces will decay or be carried away rapidly, so that the exposure is characteristically acute.

Outdoor space spraying
For outdoor space spraying, it cannot be assumed that bystanders will not be exposed; the assumed exposure time is 15 min.

4.2.2 Algorithms used to estimate exposure and absorbed dose caused by indoor or outdoor space spraying of insecticides

Operator exposure

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

Dermal exposure of operators during mixing and loading must be considered. The formulations used in indoor and outdoor space spraying are all liquids – hot-fogging concentrates, ultra-low-volume liquids, emulsions, oil-in-water formulations and emulsifiable concentrates. In the absence of formulation-specific data, default values for dermal exposure to liquid formulations during each mixing and loading session presented in Table 4 are used.

Estimation of systemic dose from mixing and loading is presented in Box 1.

<table>
<thead>
<tr>
<th>Box 1. Mixing and loading; dermal exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>SySD\textsubscript{TWA} = ( UE\text{\textsubscript{LIQ}} \times PPE \times CF \times NOD \times ABS_D \times EF / (BW \times AT) )</td>
</tr>
<tr>
<td>SySD\textsubscript{MAX} = ( UE\text{\textsubscript{LIQ}} \times PPE \times CF \times NOD \times ABS_D / BW )</td>
</tr>
<tr>
<td>where:</td>
</tr>
<tr>
<td>SySD\textsubscript{TWA} = TWA systemic dose mg/kg bw per day</td>
</tr>
<tr>
<td>SySD\textsubscript{MAX} = Maximal daily systemic dose mg/kg bw</td>
</tr>
<tr>
<td>UE\text{\textsubscript{LIQ}} = Unit exposure for a liquid formulation mL/operation (see Table 4)</td>
</tr>
<tr>
<td>PPE = PPE efficacy 0.1 in guideline scenario, 1 in lax standard scenario</td>
</tr>
<tr>
<td>CF = Concentration of formulation mg/mL (product label)</td>
</tr>
<tr>
<td>NOD = Number of operations per day (see section 4.2.1)</td>
</tr>
<tr>
<td>ABS_D = Dermal absorption for concentrated products (see section 3.1.3)</td>
</tr>
<tr>
<td>EF = Exposure frequency, 6 days/week for a 6-month spraying period = 156 days (default)</td>
</tr>
<tr>
<td>BW = Body weight (60 kg; see Table 3)</td>
</tr>
<tr>
<td>AT = Averaging time (365 days)</td>
</tr>
</tbody>
</table>
Application of insecticide formulation, and washing and maintenance of the spray equipment

Inhalation exposure

In the lax standard scenario, it is assumed that no respiratory protective equipment (RPE) is used, despite recommendations. In the guideline scenario, efficient RPE and good work practices (operator moves away from the spray fog) can be assumed to provide 90% protection. In indoor spraying, the operator stays in the contaminated area during application of the spray; in outdoor spraying using hand-held equipment, the operator is assumed to stay outside the fog as far as possible, but still be within the fog for 30 minutes/day. In vehicle-mounted spraying, a closed cabin with air filtering and internal controls for the spray system is assumed and no inhalation exposure is assumed.

The inhalation exposure during application for indoor space spraying may be calculated as shown in Box 2. The inhalation exposure during application for outdoor space spraying using a hand-held sprayer may be calculated as shown in Box 3.

Box 2. Application, inhalation exposure, indoor space spraying

\[
\begin{align*}
\text{SysD}_{\text{TWA}} &= TC_{\text{Air}} \times RPE \times BV \times ED \times ABS_p \times EF \times (BW \times AT) \\
\text{SysD}_{\text{MAX}} &= TC_{\text{Air}} \times RPE \times BV \times ED \times ABS_p / BW \\
\text{where:} \\
\text{SysD}_{\text{TWA}} &= \text{TWA systemic dose mg/kg bw per day} \\
\text{SysD}_{\text{MAX}} &= \text{Maximal daily systemic dose mg/kg bw} \\
TC_{\text{Air}} &= \text{Target concentration of the active ingredient in the air mg/m}^3 \\
RPE &= \text{Protection provided by the respiratory protective equipment, 0.1 for the guideline scenario, 1.0 for the lax standard scenario} \\
BV &= \text{Breathing volume (total amount of air inhaled during the exposure): moderate activities, adults = 1.25 m}^3/\text{hour (see Table 3; USEPA, 2012); thus, a total of 7.5 m}^3 \text{of contaminated air is breathed.} \\
ED &= \text{Exposure duration, 6 hours of spraying during the 8-h working day} \\
ABS_p &= \text{Absorption from the respiratory tract. The default value is 100\%} \\
EF &= \text{Exposure frequency, 6 days/week for a 6-month spraying period = 156 days} \\
BW &= \text{Body weight (60 kg)} \\
AT &= \text{Averaging time, 1 year (365 days)}
\end{align*}
\]

Box 3. Application, inhalation exposure, outdoors space spraying, hand-held sprayer

\[
\begin{align*}
\text{SysD}_{\text{TWA}} &= TAR \times RPE \times BV \times ED \times EF \times ABS_p / (HSC \times BW \times AT) \\
\text{SysD}_{\text{MAX}} &= TAR \times RPE \times BV \times ED \times ABS_p / (HSC \times BW) \\
\text{where:} \\
\text{SysD}_{\text{TWA}} &= \text{TWA systemic dose mg/kg bw per day} \\
\text{SysD}_{\text{MAX}} &= \text{Maximal daily systemic dose mg/kg bw} \\
TAR &= \text{Target application rate mg active ingredient/m}^2 \text{ (= 0.1 \times rate in grams active ingredient/ha; this divided by HSC gives concentration of active ingredient in mg/m}^3) \\
RPE &= \text{Protection provided by the respiratory protective equipment, 0.1 for the guideline scenario, 1.0 for the lax standard scenario} \\
BV &= \text{Breathing volume (moderate activity; default 1.25 m}^3/\text{hour (see Table 3)} \\
ED &= \text{Exposure duration, 30 min = 0.5 hours/day} \\
EF &= \text{Exposure frequency, 6 days/week for a 6-month spraying period = 156 days} \\
ABS_p &= \text{Absorption from the respiratory tract. The default value is 100\%} \\
HSC &= \text{Height of spray cloud (default, 3 m)} \\
BW &= \text{Body weight (60 kg)} \\
AT &= \text{Averaging time, 1 year (365 days)}
\end{align*}
\]
Dermal exposure

In a **lax standard scenario**, hands are exposed to the spray during application and to the spray liquid 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/maintenance of the equipment. Dermal exposure under these conditions is considered to be 10% that in the lax standard scenario.

Dermal exposure is considered similar in indoor and outdoor space spraying using hand-held equipment. In the use of vehicle-mounted spraying equipment, exposure is not considered significant in the application, and the exposure in washing and maintenance of the equipment is considered to represent 1/10 of the exposure in application, washing and maintenance of the equipment in indoor and outdoor/hand-held equipment activity as calculated in Box 4.

**Box 4. Application, washing and maintenance. Dermal exposure, indoor and outdoor space spraying**

\[
\begin{align*}
\text{SysD}_{\text{TWA}} &= VLH \times C_{\text{spray}} \times \text{PPE} \times \text{EF} \times \text{Abs}_D / (BW \times AT) \\
\text{SysD}_{\text{MAX}} &= VLH \times C_{\text{spray}} \times \text{PPE} \times \text{Abs}_D / BW \\
\text{where:} & \\
\text{SysD}_{\text{TWA}} &= \text{TWA systemic dose mg/kg bw per day} \\
\text{SysD}_{\text{MAX}} &= \text{Maximal daily systemic dose mg/kg bw} \\
VLH &= \text{Volume of liquid on hands} = 8.2 \text{ mL (see section 4.2.1)} \\
C_{\text{spray}} &= \text{Concentration of the active ingredient in the spray in mg/mL, derived from the concentration of the active ingredient in the formulation and its dilution for spraying} \\
\text{PPE} &= \text{Protection provided by the protective equipment, 0.1 for the guideline scenario, 1.0 for the lax standard scenario} \\
\text{EF} &= \text{Exposure frequency, 6 days/week for a 6-month spraying period = 156 days} \\
\text{ABS}_D &= \text{Dermal absorption of the spray (see section 4.1.3)} \\
BW &= \text{Body weight (60 kg)} \\
AT &= \text{Averaging time, 1 year (365 days)}
\end{align*}
\]

**Resident and bystander exposure**

Residential exposure is assumed to result from dermal exposure to spray residues dislodging from furniture, shelves and floors on which they were deposited (having settled following spraying – surfaces are not intentionally sprayed). The sprayed insecticide may be transloqued to food items, and also be lost from walls, ending up in house dust and leading to ingestion by toddlers. For products that are toxic and are extensively excreted in mother's milk, mother's milk may be an important source of exposure to newborns.

*Inhalation exposure – residents and bystanders (adults, children, toddlers, infants)*

Residents are instructed not to enter houses during or immediately after spraying; it is therefore assumed that they are not exposed via inhalation to space spraying indoors and that residential exposure via inhalation is limited to outdoor applications. It is assumed that a bystander or a resident of the area could spend 15 min in the spray.
The inhalation exposure of residents and bystanders from outdoor space spraying may be calculated as shown in Box 5.

**Box 5. Residents and bystanders, inhalation exposure, outdoor space spraying**

\[
\begin{align*}
\text{SysD}_{\text{TWA}} &= TAR \times BV \times ED \times EF \times ABS_p / (HSC \times BW \times AT) \\
\text{SysD}_{\text{MAX}} &= TAR \times BV \times ED \times ABS_p / (HSC \times BW)
\end{align*}
\]

where:

- \(\text{SysD}_{\text{TWA}}\) = TWA systemic dose mg/kg bw per day
- \(\text{SysD}_{\text{MAX}}\) = Maximal daily systemic dose mg/kg bw
- \(TAR\) = Target application rate mg active ingredient/m\(^2\) (= 0.1 \ times rate in grams active ingredient/ha; this divided by HSC gives concentration of active ingredient in mg/m\(^3\))
- \(BV\) = Breathing volume (see Table 3)
- \(ED\) = Exposure duration, 15 min, 0.25 hours/day
- \(EF\) = Exposure frequency, 15 days/year
- \(ABS_p\) = Absorption from the respiratory tract. The default value is 100%
- \(HSC\) = Height of spray cloud (default, 3 m)
- \(BW\) = Body weight (adults 60 kg, older children 23.9 kg, toddlers 10 kg, infants 8 kg)
- \(AT\) = Averaging time, 1 year (365 days)

**Dermal exposure – touching of contaminated surfaces (floors, tables, other furniture); potential residues on toddlers’ hands leading to hand-to-mouth ingestion exposure**

Space spraying is intended to knock down flying insects, but the spray is likely to reach surfaces inside dwellings. The concentration of the active ingredient in space spraying is low and it is assumed that this contamination is not long-lasting and that the insecticide will degrade rapidly; thus, exposure resulting from a single treatment is assumed to last for one day after application (and is considerably lower on the second day than on the first day. In a 2.5 m high room, the amount deposited on horizontal surfaces = 2.5 \ times concentration/m\(^3\). The USEPA default proportion transloqted onto skin is 8% of the amount present on the surfaces (USEPA, 2012). The very small droplets of space spraying tend to remain airborne, and any settling is on horizontal surfaces down-wind. Therefore, exposure from the insecticide settling on surfaces is only considered significant after indoor spraying.

The body part surface areas are given in Table 3. For adults and children, it is assumed that hands, forearms and feet are exposed; the area exposed is thus 0.308 m\(^2\) for adults and 0.153 m\(^2\) for children. For toddlers (aged 1–2 years), the hands, forearms, lower legs and feet (0.133 m\(^2\)) are assumed to be exposed. Infant floor mobility increases from the age of 3–6 months (USEPA, 2012); the exposed skin area for infants aged 0–12 months is assumed to include the head, hands, arms, trunk, legs and feet, i.e. 0.394 m\(^2\).
The dermal exposure from residents touching contaminated surfaces may be calculated as shown in Box 6.

### Box 6. Residents; dermal exposure from touching contaminated surfaces

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Equation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SysDTWA</td>
<td>( C_{Sur} \times Transl \times ESA \times EF \times AbsD / (BW \times AT) )</td>
<td>TWA systemic dose due to dermal exposure from indoors space spraying, mg a.i./kg bw per day</td>
</tr>
<tr>
<td>SysDMAX</td>
<td>( C_{Sur} \times Transl \times ESA \times AbsD / BW )</td>
<td>Maximal daily systemic dose due to dermal exposure after a spraying episode, mg a.i./kg bw</td>
</tr>
<tr>
<td>( C_{Sur} )</td>
<td></td>
<td>Concentration on the horizontal surfaces mg/m(^2), i.e. 2.5 x concentration in the air mg/m(^3).</td>
</tr>
<tr>
<td>Transl</td>
<td></td>
<td>Fraction translodged onto skin; default 8% of the amount on the surface (USEPA 2012; hard surfaces)</td>
</tr>
<tr>
<td>ESA</td>
<td></td>
<td>Skin areas (0.308 m(^2) for adults, 0.153 m(^2) for older children, 0.133 m(^2) for toddlers), 0.394 m(^2) for infants</td>
</tr>
<tr>
<td>EF</td>
<td></td>
<td>Exposure frequency (default 15 times/year)</td>
</tr>
<tr>
<td>AbsD</td>
<td></td>
<td>Dermal absorption (see section 4.1.3)</td>
</tr>
<tr>
<td>BW</td>
<td></td>
<td>Body weight (adults 60 kg, older children 23.9 kg, toddlers 10 kg, infants 8 kg)</td>
</tr>
<tr>
<td>AT</td>
<td></td>
<td>Averaging time (1 year = 365 days)</td>
</tr>
</tbody>
</table>

**Ingestion exposure**

Ingestion exposure results from consuming contaminated foodstuff. It is assumed that food is not directly sprayed; rather, the contamination of food items results from transfer of the insecticide from the sprayed surfaces to the food items. The default assumptions are that the amount available for transfer from contaminated shelf surfaces to food items is 8% (USEPA, 2012); the concentration of the active ingredient on the surfaces is calculated as above for household surfaces. The surface area of food (daily intake) can be calculated from the daily volume of food eaten (2202, 1417, 1378, and 1074 g/day) for adults, children, toddlers and infants respectively (USEPA, 2011). The density of food is approximately 1 g/cm\(^3\), assuming that “food” is a cube of which one surface, i.e. volume to the power \( \frac{1}{3} \), is in contact with the shelf: the contaminated surface of food is 0.0169 m\(^2\) for adults, 0.0126 m\(^2\) for children, 0.0124 m\(^2\) for toddlers and 0.0105 m\(^2\) for infants. Half of the food is in contact with contaminated surfaces (the rest is assumed to be either in bags or other wrappings, or peeled before use). Exposure is continuous.
The exposure from ingestion of contaminated food may be calculated as shown in Box 7.

**Box 7. Residents; ingestion exposure from contaminated food**

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{SysD}<em>{\text{TWA}} = 0.5 \times C</em>{\text{Sur}} \times Transl \times SAF \times EF \times Abs_{\text{O}} / (BW \times AT)$</td>
<td>TWA systemic dose due to oral exposure from eating contaminated food after indoor space spraying, mg a.i./kg bw per day</td>
</tr>
<tr>
<td>$\text{SysD}<em>{\text{MAX}} = 0.5 \times C</em>{\text{Sur}} \times Transl \times SAF \times Abs_{\text{O}} / BW$</td>
<td>Maximal daily systemic dose due to oral exposure from eating contaminated food after a spraying episode, mg a.i./kg bw</td>
</tr>
<tr>
<td>$C_{\text{Sur}}$</td>
<td>Concentration on the surface mg/m$^2$, i.e. $2.5 \times$ the amount of a.i./m$^3$ air (target concentration)</td>
</tr>
<tr>
<td>Transl</td>
<td>Fraction translodged onto food. Default = 8% of the amount present on the surfaces (USEPA, 2012; hard surfaces)</td>
</tr>
<tr>
<td>SAF</td>
<td>Surface area of food in contact with the shelf, m$^2$. The surface area of food is 0.0169, 0.0128, 0.0124 and 0.0105 m$^2$ for adults, children, toddlers and infants respectively. Half of food items are in contact with contaminated surfaces (parameter 0.5)</td>
</tr>
<tr>
<td>EF</td>
<td>Exposure frequency (default 15 times/year)</td>
</tr>
<tr>
<td>Abs$_{\text{O}}$</td>
<td>Gastrointestinal absorption (default 100%)</td>
</tr>
<tr>
<td>BW</td>
<td>Body weight (adults 60 kg, children 23.9 kg, toddlers 10 kg, infants 8 kg)</td>
</tr>
<tr>
<td>AT</td>
<td>Averaging time (1 year = 365 days)</td>
</tr>
</tbody>
</table>

**Hand-to-mouth activity of the toddler**

Toddlers frequently put different objects in their mouths and ingest soil or dust from contaminated hands. Insecticide is thus transferred to the hands from the surfaces contacted (see above); the hand area for toddlers is 0.023 m$^2$ (Table 3). The default fraction of the pesticide translodged on the skin is 8% (default hard surface value; USEPA, 2012). For some pesticides, chemical-specific values are available (pyrethrins 8%, permethrin 3%, deltamethrin 6%, chlorpyrifos 13%, piperonyl butoxide 5%; 75th percentiles). The fraction of the hand surface actually mouthed is 16.4%, and the fraction of the pesticide extracted by saliva is 57% (USEPA, 2012; 75th percentiles).
The ingestion exposure of toddlers from hand-to-mouth activity may be calculated as shown in Box 8.

**Box 8. Resident toddler; hand-to-mouth activity**

\[
\text{SysD}_{\text{TWA}} = \frac{C_{\text{Sur}} \times \text{Transl} \times \text{ESA} \times F_{\text{HM}} \times F_{\text{EXS}} \times EF \times Abs_{\text{O}}}{(BW \times AT)}
\]

\[
\text{SysD}_{\text{MAX}} = \frac{C_{\text{Sur}} \times \text{Transl} \times \text{ESA} \times F_{\text{HM}} \times F_{\text{EXS}} \times Abs_{\text{O}}}{BW}
\]

where:

- \( \text{SysD}_{\text{TWA}} \) = TWA systemic dose due to oral exposure from hand-to-mouth activity, mg a.i./kg bw per day
- \( \text{SysD}_{\text{MAX}} \) = Maximal daily systemic dose due to oral exposure from hand-to-mouth activity, mg a.i./kg bw
- \( C_{\text{Sur}} \) = Concentration on the surface mg/m\(^2\), i.e. 2.5 \times \text{the amount of a.i.} / m^3 \text{ air (target concentration)}
- \( \text{Transl} \) = Fraction translodged onto hands. Default = 8\% of the amount present on the surfaces (USEPA, 2012)
- \( \text{ESA} \) = Exposed skin area (0.023 m\(^2\); see Table 3)
- \( F_{\text{HM}} \) = Fraction of hand area mouthed; default 0.164 (USEPA, 2012)
- \( F_{\text{EXS}} \) = Fraction extracted in saliva; default 0.57 (USEPA, 2012)
- \( EF \) = Exposure frequency (default 15 times/year)
- \( Abs_{\text{O}} \) = Gastrointestinal absorption (default 100\%)
- \( BW \) = Body weight (toddlers 10 kg)
- \( AT \) = Averaging time (1 year = 365 days)
Exposure via breast milk

Exposure via breast milk is estimated for a newborn, representing a worst-case scenario. If the estimated dose for the newborn is significant, exposure is estimated also for an infant.

When information is available on the fraction of the mother’s dose excreted in her milk, this can be used to estimate the dose of the breast-fed infant. When extrapolating from animal data, the IPCS default variability factor for kinetics, $10^{0.6} = 3.98$, is applied (WHO, 1999), as shown in Box 9.

**Box 9. Exposure via breast milk estimated from fraction of dose excreted in milk**

$$\text{SysD}_{\text{TWA}} = 3.98 \times Fr_{\text{milk}} \times Abs_{O} \times Dose_{M} / BW$$

where:

- $\text{SysD}_{\text{TWA}}$ = Systemic dose of the breast-fed infant due to the excretion of the pesticide in mother’s milk mg/kg bw per day
- $Fr_{\text{milk}}$ = Fraction of the dose excreted in milk in an experimental animal
- $Abs_{O}$ = Oral absorption rate (default, 100%)
- $Dose_{M}$ = Dose the mother has received mg [estimated dose mg/kg bw x body weight of the mother kg]
- $BW$ = Body weight (newborn, 4.2 kg (USEPA, 2011 – 25th percentile; HEEG, 2013a); infant, 8 kg)

When data on actual excretion in milk are not available, an upper bound of the exposure from mother’s milk can be roughly estimated from the physicochemical characteristics, and kinetics of the insecticide as follows (Box 10).

Concentration of the insecticide in breast milk is estimated from the exposure of the mother at steady state. Body burden = daily dose mg/kg bw × $T_{1/2}$ (days)/ln(2) (JECFA, 2002). 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; that is, the concentration in breast milk (mg/L) is $1.4 \times$ body burden = $1.4 \times$ daily dose mg/kg bw × $T_{1/2}$ (days)/ln(2) ($\text{SolC} = 2.02$ in Box 10). For lipid-soluble compounds ($pK_{ow} \geq 2$), the insecticide is concentrated in the adipose tissue, and the concentration in adipose tissue is (20% fat content of the body) $5 \times$ body burden mg/kg. The average fat content of breast milk is assumed to be 50 g/L. Thus the concentration in mother's milk for a fat-soluble chemical is $5 \times$ mother’s daily dose × 0.05 / ln(2) = 0.361 × dose of the mother ($\text{SolC}$ in Box 10).

**Box 10. Exposure via breast milk estimated from kinetic properties**

$$\text{SysD}_{\text{TWA}} = \text{SolC} \times Dose_{Mbw} \times T_{1/2} \times IR \times Abs_{O} / BW$$

where:

- $\text{SysD}_{\text{TWA}}$ = Systemic daily dose from mother’s milk mg/kg bw
- $\text{SolC}$ = Solubility constant; 2.02 for water-soluble and 0.361 for lipid soluble insecticides
- $Dose_{Mbw}$ = Daily dose to the mother mg/kg bw
- $T_{1/2}$ = First-order kinetics half-time in the body of the insecticide, days. Chemical-specific data to be used, as no meaningful default can be given
- $IR$ = Ingestion rate of milk, kg/day, based on 660 mL/day (average of mean values for the first 12 months; 510 mL for the first month; USEPA, 2011); 0.68 kg/day and 0.53 kg/day respectively using a relative density of milk of 1.03
- $Abs_{O}$ = Fraction absorbed (default is 100%)
- $BW$ = Body weight (newborn, 4.2 kg (USEPA, 2011 – 25th percentile; HEEG, 2013a); infant, 8 kg)
Ingestion exposure from contaminated foodstuffs grown in an area contaminated from space spraying – adults, children and toddlers

Insecticide sprayed in the air of a house or household area (e.g. garden) will also contaminate house dust, house floor materials and soil. Sweeping the house will transfer this contaminated material to the surrounding soil where vegetables and animals such as chickens might take up the insecticide. This could pose a significant route of human exposure if the insecticide is both persistent and bioaccumulative. If these properties apply, measurements should be made of actual levels in these media and food items.

4.2.3 Total exposure assessment

Total systemic dose is calculated by summing the contributions via different routes. Exposure and risk should be calculated for operators, for residents (adults and children of different age groups) of the area that is being sprayed and for bystanders (visiting the area).

4.3 Risk characterization

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

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

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

\[
\text{Ratio} = \frac{\text{Estimated maximal daily systemic dose}}{\text{TSD}_{\text{AC}}}
\]

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

When aspects of a risk assessment of a specific insecticide are unfavourable, risk managers will want to consider risk–benefit aspects, such as the potential for toxicity compared with the potential benefits of preventing the vector-borne disease in question, alternative insecticides and other vector control options (see http://www.who.int/neglected_diseases/vector_ecology/en/ and http://www.who.int/malaria/areas/vector_control/en/).
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 the risk from outdoor space spraying.

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

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

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

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 insecticides for space spraying:

- With the exception of granules applied to surface waters, all pesticides can become airborne during application and may become airborne following application 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.
- For outdoor space spraying, the pesticide will be intercepted by vegetation and then reach the soil. The mobility of the pesticide in soil determines the exposure of soil organisms; its presence in soil (together with residues on vegetation) determines the exposure of terrestrial vertebrates, both directly and indirectly via their food. Vertical movement through soil profiles determines the possible contamination of groundwater, and vertical and horizontal movement and surface run-off determine the indirect contamination of surface water.
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 different levels of food chains (from primary vegetation, through herbivore prey to predators). 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 for outdoor space spraying 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; and
- current best practice for the application of pesticides to minimize risk.

5.1 Environmental exposure assessment

5.1.1 Air

Pesticides may become airborne during the spraying process and, following application, by volatilization from soil, water and vegetation surfaces. The degree of spray drift is dependent on the physical characteristics of the spray application – the equipment used, the droplet size and the height above ground at which the spray is applied. Drift is usually expressed as a percentage of the applied dose of active ingredient that is likely to move outside the intended spraying area. If equipment and conditions remain constant for different insecticides, this proportion will remain constant.

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

However, outdoor space spraying for vector and public health pest control differs significantly from agricultural usage in that it is intended for spray droplets to stay airborne for as long as possible to kill flying insects. Aerial application over rice
paddies will give wider drift; 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 and public health pest 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. As a default for spray drift for space spraying, 10% is suggested (truck spraying, 8 km/h wind speed; AGDISP, Bilanin et al., 1989).

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.

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

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

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

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

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

<table>
<thead>
<tr>
<th>Relative volatility (class)</th>
<th>Henry’s Law constant at 20 °C</th>
<th>Vapour pressure (Pa) at 20 °C</th>
<th>Maximum daily loss (% of applied dose) in first 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>For soil</td>
<td>For plants</td>
<td>For soil</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 10^{-3}</td>
<td>&gt; 10^{-1}</td>
<td>&gt; 10^{-3}</td>
</tr>
<tr>
<td>Medium</td>
<td>10^{-6} – 10^{-3}</td>
<td>10^{-3} – 10^{-1}</td>
<td>10^{-6} – 10^{-3}</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 10^{-6}</td>
<td>&lt; 10^{-3}</td>
<td>&lt; 10^{-5}</td>
</tr>
</tbody>
</table>

*Source: EPPO, 2003.*

For bare soil, the classification should be based on Henry’s Law constant and for vegetation surfaces it should be based on vapour pressure.

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. In the first-tier risk assessment for public health space spraying, the volatility classification is not used and need not be performed. Deposition from the air would also be estimated over time and distance from the applied source to give estimated concentrations in the receiving medium (soil or water). There is no standardization of such models and each has advantages and disadvantages depending on the medium from which volatilization occurs (soil or water) and the conditions of transport.

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

5.1.2 Soil

Applicability
Outdoor space spraying is an exceptional activity likely to be undertaken only in emergency epidemic situations. The most likely scenario is spraying of interim camps for displaced people. It is not necessary to conduct an environmental risk assessment for such spraying unless there are key natural habitats within the limit of significant spray drift (section 5.1.1). Wider spraying of the natural environment, or aerial application, warrants an assessment for soil organisms.

Given the emergency nature of the situations in which such spraying would take place, the sole aim of the assessments would be choice of least damaging insecticide (rather than a choice between spraying or not spraying). That choice must be based on risk assessments of all possible pesticides, using basic worst-case comparisons between active ingredients.

Soil will receive doses of insecticide directly from outdoor space spraying; areas not directly sprayed may also be affected by spray drift or by redeposition after volatilization from soil or water.

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/m³); suggested default 1500 kg/m³

The application rate (\( A \)) would be the recommended application rate for the formulation in direct overspray of the natural environment. If direct overspray can be excluded, default spray drift 10% (see above) may be used (Bilanin et al., 1989).

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

Risk for short-term exposures of soil organisms would use this value.

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 biodegradation 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 increased temperature 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) after a single application

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

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 according from the equation in the following section.
**Calculation of concentration at time \( t \) after a single application**

\[
C_t \text{ (mg/kg soil)} = C_i \times \exp\left(-\frac{\ln(2)}{DT_{50}} \times t\right)
\]

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)

**Repeat applications**

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.

Repeat applications cause significantly increased (doubling) soil concentrations if the trough concentration (the concentration immediately before the next application) is \( \geq 0.5 \times C_i \) (i.e. if the total dissipation half-time is \( \geq 2 \times \) application interval, the worst-case default of which is 7 days).

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

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

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

where:

- \( R_{\text{low}} \) = 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 following application of A (kg/ha)
- \( n \) = the number of applications. As a contingency measure in dengue epidemics, WHO recommends space spraying every 7–10 days (WHO, 2011). As the dengue season may extend over 6 months, \( n \) in the worst-case scenario is approximately 25; this can therefore be used as the default number of applications.

Upper plateau concentration:

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

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 either expressed as $K_{OM}$ (for organic matter) or $K_{OC}$ (for organic carbon). The normalized value should be taken unless there is indication that organic material content of the relevant soils differs significantly from the default/measured values used in its calculation.

Residues of pesticides from the soil may be moved by rainfall and be carried by run-off to adjoining surface water. In the case of outdoor space spraying, where the objective is immediate knock-down of flying insects with no residual effect expected, the amount of insecticide deposited on soil will be much lower than that associated with agricultural spraying, so any run-off will be negligible. If it is considered that run-off could occur because of soil slope, there are models that might be used to assess the likelihood and extent of run-off (Beinat & van den Berg, 1996). If a risk is perceived, further information may be required to refine the risk assessment.

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

Outdoor space spraying is clearly imperative as a means of preventing epidemics; the benefits therefore outweigh any risk to the environment. However, it is clearly an advantage to know the degree to which such environmental damage will occur and the time likely to be needed for environmental recovery. In such circumstances, it is suggested that a calculation be performed to predict the number of repeat applications that would lead to 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 would be 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**

Outdoor space spraying might overspray surface water or lead to exposure through spray drift; regular reapplication with, typically, daily intervals could lead to significant exposure.

Run-off from soil/vegetation application would represent another source of exposure for surface waters following outdoor space spraying, and this exposure might persist if high soil residues had built up from successive regular sprays.
Initial concentrations in surface water from spray drift during outdoor space spraying applications are given below.

**Estimation of initial concentration in water from outdoor space spraying (worst case) – spray drift**

\[ C_{\text{drift}} = 100 \times E \times X/D \]

where:

- \( C_{\text{drift}} \) = initial concentration in water, µg/L
- \( E \) = proportion of drift (default = 10%)
- \( X \) = application rate (kg/ha)
- \( D \) = water depth (metres; default = 0.5 m)

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

As stated in section 5.1.2, run-off is usually not a problem in the case of space spraying for public health purposes; run-off need only be considered in cases in which the rainfall is heavy, the slope of the terrain is steep, and the soil is susceptible to run-off (clay, loam, silt). When needed, run-off estimates may be estimated as in Beinat & van den Berg (1996). Estimation should express potential run-off in percentage terms and lead to a calculation of concentration. Initial concentration following outdoor space spraying would then be the value from spray drift plus the value from run-off. For pesticides classified as highly volatile (see Table 5), an additional estimate of active ingredient in rainfall would be made.

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:*

\[ K_{s/l} = C_{\text{sed}} / C_{\text{water}} \]

where:

- \( K_{s/l} \) = sediment/water distribution coefficient (litres/kg)
- \( C_{\text{sed}} \) = concentration in sediment (mg/kg)
- \( C_{\text{water}} \) = concentration in water (mg/litre)

*Fractions dissolved and sorbed:*

\[ F_{\text{dissolved}} = 1/(1 + K_{s/l}) \] and \[ F_{\text{sorbed}} = K_{s/l}/(1 + K_{s/l}) \]

*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. Factors that may be relevant are: 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).

Hydrolysis may be an important factor in dissipation and might also 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 pKₐ value for the substance is close to (within 1 unit) of the pH of the water; this might 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.

Concentration in the water body will dissipate as a result of any or all of these processes. The processes can be summed as rate constants, $K_x$, which can be calculated from half-life $DT_{50}$ according to the general formula:

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

Total dissipation may then be estimated according to the following equation:

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

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

where:

- $K_{total\_dissipation} = total\ reaction\ rate\ constant\ for\ all\ processes\ together\ assuming\ first-order\ kinetic\ in\ days^{-1}$
- $K_b = rate\ constant\ for\ biodegradation\ (days^{-1})$
- $K_s = rate\ constant\ for\ sedimentation\ (days^{-1})$
- $K_r = rate\ constant\ for\ resuspension\ (days^{-1})$
- $K_v = rate\ constant\ for\ volatilisation\ (days^{-1})$
- $K_h = rate\ constant\ for\ hydrolysis\ (days^{-1})$
- $K_p = rate\ constant\ for\ photodegradation\ (days^{-1})$
- $F_w = fraction\ of\ dissolved\ substance$
- $K_a = rate\ constant\ for\ advection\ (days^{-1})$

Then:

$$C_t = C_i \cdot e^{-K_{total\_dissipation} \times t}$$

$$C_t = C_i \times \exp(-K_{total\_dissipation} \times t)$$
where:

\[ C_t = \text{concentration at time } t \ (\text{mg/litre}) \]
\[ C_i = \text{initial concentration from all sources} \ (\text{mg/litre}) \]
\[ t = \text{time (days)} \]

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 over \( t \) days calculated as:

\[
TWAC = \frac{C_i \times (1-e^{-kt_{\text{total dissipation/\text{total}}}})}{k_{\text{total dissipation/\text{total}}}}
\]

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 on 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 the new tests show lower sensitivity than the existing ones; 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.

It is suggested that ETRs are calculated for all three types of organism likely to be represented in the dataset – algae, fish and daphnids – plus other invertebrates if test
results area available. Classification of the insecticide against unrelated organisms might then distinguish between different insecticides. Larvicidal application is likely to classify insecticides as high risk; outdoor space spraying is less likely to do so because of much lower exposure.

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

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

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

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

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

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

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

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

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

The strict definition of “chronic” would be “over the lifetime of the organism”. Algal tests cover multiple generations of the algae, even for short-term exposure (typically 3–4 days), and these are often used in both acute and chronic toxicity assessments. The end-points in algal tests (growth or biomass) are indications of population-level effects and would conform to an alternative definition of chronicity – of relevance to population level. Chronic tests on daphnids are typically run over 28 days and would include two generations, fulfilling both definitions of chronicity. Some daphnid species can achieve the same number of generations in a much shorter time. "Chronic effects" on fish are commonly derived from tests conducted over shorter periods than would meet either definition. The decision on whether a fish test would 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 space spraying; they should be examined for evidence of higher toxicity at higher temperature. It is unlikely that the dataset will be sufficiently large for confident predictions in this respect.

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

**Exposure–toxicity ratios for chronic exposure**

The ETR is derived by dividing the TWAC in surface water over the time period of the chronic test by the lowest reported NOEC for algae, invertebrates and fish, plus any other group of organisms for which chronic toxicity test results are available to derive the ETR. 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 tests 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 used 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 log $K_{ow}$: $BCF = 0.048 \times P_{ow}$
  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. Input of 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 conducted 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 has 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 acute LD$_{50}$ from an earthworm test corrected for soil organic matter (normally a factor of 2 is used but this should be determined by expert input).
- If the ETR is > 0.2 (equivalent to a safety margin of 5), acute toxicity for earthworms is of concern.

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

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

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

**Establish bioaccumulation potential for terrestrial organisms**

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

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

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 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 public health use of pesticides. Outdoor space spraying is carried out for public health pest control as well as prevention/control of other vector-borne diseases such as dengue. Outdoor space spraying for knock-down and control of adult mosquitoes may inevitably kill some non-target arthropods that are flying at the same time as mosquitoes.

**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 conducted on acute LD$_{50}$/LC$_{50}$ test result; 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, this would include: vegetation for herbivorous birds and mammals (different types of vegetation would be relevant according to the type of application and the local habitat), insects for insectivorous
birds and mammals, and prey items such as worms, fish, birds or small mammals for predators.

Standard calculations to estimate residue levels in food items are included in regulatory systems for pesticides; see Tables 6–8. These are based on application of pesticides to crops and are therefore not directly applicable to public health use of pesticides. The body weights assumed for the type of species in Tables 6–8 are worst-case: a small mammal is likely to consume food in amounts equivalent to a greater proportion of its body weight than a larger one eating the same food items. Insectivorous birds are generally small, while herbivorous ones are generally large. Seed-eaters are not included in the table; significant contamination of seed is normally from treatment of seeds with pesticide and is considered an unlikely scenario for insecticide spraying.

Table 7. Generalized calculation of residue levels in food items for birds and mammals for short-term exposure (minutes to hours) following spraying (calculate in all cases)

<table>
<thead>
<tr>
<th>Body weight (g)</th>
<th>Short-cut value (worst case)</th>
<th>Short-cut value (most likely case)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbivorous mammal</td>
<td>25</td>
<td>197</td>
</tr>
<tr>
<td>Herbivorous bird</td>
<td>3000</td>
<td>63</td>
</tr>
<tr>
<td>Insectivorous bird</td>
<td>10</td>
<td>54</td>
</tr>
<tr>
<td>Fruit-eating bird</td>
<td>80</td>
<td>24</td>
</tr>
</tbody>
</table>

*The “most likely case” scenario is based on the 50th percentile of the distribution of residues (90th percentile for worst case) and assumes only 50% of time is spent feeding in the contaminated area.

To calculate daily dietary dose (DDD) (mg/kg body weight per day):

\[ \text{DDD} = \text{short-cut value} \times \text{application rate in kg/ha} \]

Table 8. Generalized calculation of residue levels in food items for birds and mammals for medium-term exposure (days to weeks) following spraying (calculate if short-term risk ETR > 1)

<table>
<thead>
<tr>
<th>Body weight (g)</th>
<th>Short-cut value (worst case)</th>
<th>Short-cut value (most likely case)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbivorous mammal</td>
<td>25</td>
<td>86</td>
</tr>
<tr>
<td>Herbivorous bird</td>
<td>3000</td>
<td>27</td>
</tr>
<tr>
<td>Insectivorous bird</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>Fruit-eating bird</td>
<td>80</td>
<td>5</td>
</tr>
</tbody>
</table>

ETR, exposure toxicity ratio

For worst case, medium-term risk assessment, use the initial values directly from Table 7. For the “most likely case” scenarios, use TWAC. The fraction of the DDD for the correction (f) is calculated as:

\[ f = \frac{1 - e^{-kt}}{kt} \]

where:

\[ k = \frac{\ln(2)}{DT_{50}} \]

\[ t = \text{averaging time (days)} \]

In addition, if significant bioaccumulation was indicated in the aquatic organisms or soil sections:
For fish-eating species, whole body residues will have been calculated from the bioaccumulation studies in the section on aquatic organisms.

For birds consuming earthworms, whole body residues will have been obtained in the soil organisms section.

Table 9. Generalized calculation of residue levels in food items for birds and mammals for long-term exposure (weeks to months) following spraying (calculate if medium-term risk ETR > 1)

<table>
<thead>
<tr>
<th>Body weight (g)</th>
<th>Short-cut value (worst case)</th>
<th>Short-cut value (most likely case)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbivorous mammal</td>
<td>25</td>
<td>45</td>
</tr>
<tr>
<td>Herbivorous bird</td>
<td>3000</td>
<td>14</td>
</tr>
<tr>
<td>Insectivorous bird</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>Fruit eating bird</td>
<td>80</td>
<td>3</td>
</tr>
</tbody>
</table>

ETR, exposure toxicity ratio

a Use the lower value outside, and the higher value during, the breeding season.

Use TWACs for both worst-case and most-likely case scenarios.

Where multiple applications are made, factors to apply to the DDDs are calculated as follows:

- Factor = \((1 - e^{-0.069ni})/(1 - e^{-0.069i})\)

where:

- \(i\) = interval
- \(n\) = number of applications

The equation assumes a default value of 10 days for \(DT_{50}\).

The relationship between body weight and food consumption for birds and mammals has been comprehensively studied. If particular local species are likely to be exposed through contaminated food, and there is general knowledge of their diet, their body weights can be estimated and specific calculations can be made for risk if the generalized assessment indicates concern. The short-cut values given in Tables 6–8 are for short-term exposure and are “reasonable worst case” for the likely distribution of residue concentrations (90th percentile). More realistic values, and values covering medium- to long-term exposure, are available to refine the risk assessment if needed.

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 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 $P_{ow} > 3$ or $BCF > 1000$.

**Calculation of exposure–toxicity ratios for birds and mammals**

**Short-term exposure**

The DDD values obtained above are divided by acute toxicity $LD_{50}$ values.\(^1\)

**Medium-term exposure**

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

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

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

**Note:** Applicability of the short-term dietary toxicity test in birds (5 days) for risk assessment has been called into question (Mineau et al., 1994). Results of the test are often a consequence of starvation because of repellency of the diet and should therefore be used with caution.\(^2\)

**Long-term exposure**

The DDD values obtained above 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 in public health.

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\(^1\) The selection of the appropriate toxicity value to use is the responsibility of the assessor.

\(^2\) Interpretation of the results of the test is the responsibility of the assessor.
6. Conclusions

The models described in this document are intended for first-tier risk assessments; when better validated models are available, they should be used. The default values presented here are intended as examples. Case-specific or substance-specific defaults or distributions for default parameters should be applied whenever available. In the interests of the transparency of the process, it is of utmost importance that the process is transparent and that the risk assessor can justify 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 a synthetic pyrethroid insecticide "X" is used as a model compound. This product is sold in a 10-L can with a 45-mm closure. The product is used exclusively for indoor space spraying. The target concentration in the air is 0.5 mg a.i./m$^3$; the concentration of the formulation is 50 mg/mL. For use, it is diluted 1:100 and the concentration of X in the spray is thus 0.5 mg/mL. The spraying rate is 1 mL/m$^3$.

<table>
<thead>
<tr>
<th>Generic risk assessment model</th>
<th>Worked example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Toxicity data</strong>&lt;br&gt;Aim: To assess available toxicity data and derive acceptable exposure levels.</td>
<td><strong>1. Toxicity data</strong>&lt;br&gt;Aim: To assess available toxicity data and derive acceptable exposure levels.</td>
</tr>
<tr>
<td>1.1 Conduct literature search for human, animal and in-vitro toxicity data and any necessary physicochemical data on the insecticide.</td>
<td>1.1 Literature search on insecticide X conducted on MEDLINE, TOXLINE and sources of reviews (WHO/IPCS reviews (EHCs, CICADs), JMPR, USEPA, IARC, ATSDR, EFSA, etc.).</td>
</tr>
<tr>
<td>1.2 Obtain relevant reviews and key original papers.</td>
<td>1.2 Comprehensive reviews available from IPCS, JMPR and IARC. Original key papers obtained.</td>
</tr>
<tr>
<td>1.3 Tabulate types of study, toxic effects observed, NOAEs and LOAELs.</td>
<td>1.3 All available relevant animal and human studies tabulated.</td>
</tr>
<tr>
<td>1.4 Assess whether quality of database is adequate for risk assessment (range of studies, conduct of studies, adequacy of dose–response data, etc.).</td>
<td>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.</td>
</tr>
<tr>
<td>1.5 If database is adequate, identify critical toxic effect(s).</td>
<td>1.5 In humans, first toxic symptom is facial paraesthesia, reversible on cessation of exposure. Critical toxic effect in animal tests is neurotoxicity. No dose–response data for humans are available but database for animals is adequate.</td>
</tr>
<tr>
<td>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.</td>
<td>1.6 The substance is not genotoxic, and it has not shown carcinogenic or specific reproductive toxic effects. It has moderate acute toxicity. Toxicokinetic data suggest good oral absorption (default 100% oral absorption is used in this assessment). Proceed with risk assessment.</td>
</tr>
<tr>
<td>1.7 If 1.6 does not apply, identify pivotal study/studies giving dose–response data for critical effect(s).</td>
<td>1.7 Pivotal studies were:&lt;br&gt;• 21-day rat inhalation study&lt;br&gt;• 1- and 2-year dog dietary studies&lt;br&gt;• 2-year rat dietary study&lt;br&gt;• acute oral neurotoxicity study (single dose, gavage)</td>
</tr>
</tbody>
</table>
1.8 Identify critical NOAEL(s) from pivotal studies for short-term exposure and for longer-term (repeat-dose) exposure.

1.8 Critical NOAELs for insecticide X in space spraying scenarios:
- acute oral neurotoxicity, rat, NOAEL = 5 mg/kgbw⁻¹
- 21-day inhalation (6 hours/day, 5 days/week), rat, NOAEL = 9.6 mg/m³ (equivalent to 2.6 mg/kgbw⁻¹·d⁻¹)
- 1-year and 2-year dietary studies, dog, NOAEL = 1 mg/kgbw⁻¹·d⁻¹
- 2-year rat dietary study, NOAEL = 1 mg/kgbw⁻¹

1.9 Assess whether the database allows the setting of TSDs for short- and long-term exposure

1.9 Database is adequate for the setting of TSDs, both for long-term and short-term exposure, for the substance.

1.10 Set TSDs for oral, dermal, or inhalation exposure by dividing NOAEL for the critical effect from the pivotal study via that route by an uncertainty factor (UF):

\[ \text{TSD} = \frac{\text{NOAEL}}{\text{UF}} \]

A default UF of 10 is recommended for NOAELs derived from animal studies.

A default UF of 10 is recommended for NOAELs derived from human studies.

(See section 4.1.7 for variations on these defaults.) Where other reputable bodies have set ADIs, RfDs, ARfDs, MRLs (minimal risk levels), etc., for various routes of exposure, use these to derive TSDs for space spraying scenarios.

1.11 Conclusion on final TSD(s).

2. Exposure assessment

The defaults used should be replaced by case-specific, valid and scientifically sound data.

**Aim:** To estimate operator exposure via dermal and inhalation routes during mixing and loading, and applying space spray indoors and outdoors, and during washing and maintenance of the spray equipment; and to estimate residential or bystander exposure of adults, children, toddlers and infants, during and after spraying.

2.1 Operator exposure

a) Exposure during mixing and loading

During mixing and loading, inhalation exposure is negligible.

For liquid formulations, dermal exposure is estimated by using unit exposures from a database. In lax standard estimations, it is assumed that there is no use of PPE (gloves); in guideline scenario estimations, gloves are used.

Body weight of an adult operator is 60 kg.

Predicted TWA dose \( \text{SysD}_{\text{TWA}} = \frac{\text{UE}_{\text{UQ}} \times \text{PPE} \times \text{CF} \times \text{NOD} \times \text{ABSD} \times \text{EF}}{(\text{BW} \times \text{AT})} \)

Predicted maximal daily dose \( \text{SysD}_{\text{MAX}} = \frac{\text{TWA}}{24} \)

TWA systemic dose during mixing and loading from dermal exposure in the guideline scenario is
\[
0.1 \times 0.1 \times 50 \times 3 \times 0.1 \times 156 / (60 \times 365) = 0.1 \times 0.1 \times 50 \times 3 \times 0.1 \times 156 / (60 \times 365) = 0.04 \times 10^{-3} \text{mg/kgbw·d} \]

in the lax standard scenario is
\[
0.1 \times 0.1 \times 50 \times 3 \times 0.1 \times 156 / (60 \times 365) = 0.1 \times 0.1 \times 50 \times 3 \times 0.1 \times 156 / (60 \times 365) = 0.04 \times 10^{-3} \text{mg/kgbw·d} \]

Maximal daily systemic dose during mixing and loading from dermal exposure in the guideline scenario is
\[
0.1 \times 0.1 \times 50 \times 3 \times 0.1 \times 60 = 2.5 \text{mg/kgbw} \]

in the lax standard scenario it is
\[
0.1 \times 0.1 \times 50 \times 3 \times 0.1 / 60 = 0.05 \text{mg/kgbw} \]
\[ \text{UE}_i \times \text{PPE} \times \text{CF} \times \text{NOD} \times \text{ABS}_D / \text{BW} \], where:

- \( \text{UE} \) = 0.1 mL/operation;
- \( \text{PPE} \) = 0.1 in guideline scenario, 1 in lax standard scenario;
- \( \text{NOD} \) = 3;
- \( \text{CF} \) = 50 mg/mL;
- \( \text{AbsD} \) = dermal absorption. X is a pyrethroid; in addition, the MW of X > 500 and \( \log P_{\text{OW}} > 4 \); thus \( \text{AbsD} = 0.1 \);
- \( \text{EF} \) = 156/year;
- \( \text{BW} \) = 60 kg;
- \( \text{AT} \) = 365 days

b) Inhalation exposure during indoors application, and washing and maintenance of the equipment

\[
\text{SysD}_{\text{TWA}} = \text{TC}_{\text{air}} \times \text{RPE} \times \text{BV} \times \text{ED} \times \text{AbsP} \times \text{EF} \times \frac{\text{AbsD}}{(\text{BW} \times \text{AT})}
\]

Predicted maximal daily dose \( \text{SysD}_{\text{MAX}} = \text{TC}_{\text{air}} \times \text{RPE} \times \text{BV} \times \text{ED} \times \text{AbsP} / \text{BW} \), where:

- \( \text{TC}_{\text{air}} \) = 0.5 mg/m³;
- \( \text{RPE} \) = 0.1 for guideline scenario, 1 for lax standard scenario;
- \( \text{BV} \) = 1.25 m³/h;
- \( \text{ED} \) = 6 h;
- \( \text{AbsP} \) = 1.0;
- \( \text{EF} \) = 156 d/yr;
- \( \text{BW} \) = 60 kg;
- \( \text{AT} \) = 365 days

TWA systemic dose is in the guideline scenario:
0.5 \( \times \) 0.1 \( \times \) 1.25 \( \times \) 6 \( \times \) 1 \( \times \) 156 / (60 \( \times \) 365)
= 2.7 \( \mu \)g/kgbw \( \cdot \) d⁻¹
in the lax standard scenario:
0.5 \( \times \) 1 \( \times \) 1.25 \( \times \) 6 \( \times \) 1 \( \times \) 156 / (60 \( \times \) 365)
= 26.7 \( \mu \)g/kgbw \( \cdot \) d⁻¹

Maximal daily systemic dose is in the guideline scenario:
0.5 \( \times \) 0.1 \( \times \) 1.25 \( \times \) 6 \( \times \) 1 / 60
= 6.3 \( \mu \)g/kgbw
in the lax standard scenario:
0.5 \( \times \) 1 \( \times \) 1.25 \( \times \) 6 \( \times \) 1 / 60
= 62.5 \( \mu \)g/kgbw

c) Dermal exposure during application and washing and maintenance of the equipment

In lax standard estimations, it is assumed that there is no use of PPE (gloves); in guideline scenario estimations, gloves are used.

**Predicted TWA dose** \( \text{SysD}_{\text{TWA}} = \)

\[
\text{VLH} \times \text{C}_{\text{spray}} \times \text{PPE} \times \text{EF} \times \text{AbsD} / (\text{BW} \times \text{AT})
\]

**Maximal daily exposure** \( \text{SysD}_{\text{MAX}} = \)

\[
\text{VLH} \times \text{C}_{\text{spray}} \times \text{PPE} \times \text{AbsD} / \text{BW}
\]

\( \text{VLH} \) = volume of liquid on hands = 8.2 mL
\( \text{C}_{\text{spray}} \) = concentration in the spray = 0.5 mg/mL
\( \text{PPE} \) = protection device efficiency = 0.1 for guideline scenario, 1 for lax standard scenario;
\( \text{EF} \) = exposure frequency = 156 days
\( \text{AbsD} \) = dermal absorption, 0.1 (default for pyrethroids)
\( \text{BW} \) = body weight, 60 kg
\( \text{AT} \) = averaging time, 365 days

t) Total operator predicted dose

Dermal and inhalation exposure from mixing, loading, spraying, and washing and maintenance of the equipment added together.

\[
\text{TWA systemic dose}
\]

Guideline scenario:
1.07 \( + \) 2.7 \( + \) 0.29 = 1.07 + 2.7 + 0.29
2.2 Bystanders and residents

a) Inhalation exposure
Residential exposure via inhalation is assumed to be negligible in indoors space spraying.

b) Dermal exposure due to touching contaminated surfaces

\[
\text{SysD}_{TWA} = C_{\text{Sur}} \times \text{Transl} \times \text{ESA} \times \text{EF} \times \text{AbsD} / (\text{BW} \times \text{AT})
\]

\[
\text{SysD}_{\text{MAX}} = C_{\text{Sur}} \times \text{Transl} \times \text{ESA} \times \text{AbsD} / \text{BW},
\]

where:
- \(C_{\text{Sur}}\) = concentration on horizontal surfaces = 2.5 x 0.5 mg/m³ = 1.25 mg/m²
- \(\text{Transl}\) = translodgeable fraction = 8%
- \(\text{ESA}\) = exposed skin surface area; (0.308 m² for adults, 0.153 m² for children, 0.133 m² for toddlers, 0.394 m² for infants)
- \(\text{EF}\) = exposure frequency, 15/year
- \(\text{AbsD}\) = dermal absorption, 0.1 (default for pyrethroids)
- \(\text{BW}\) = body weight (adults 60 kg, children 23.9 kg, toddlers 10 kg, infants 8 kg)
- \(\text{AT}\) = averaging time, 365 days

Predicted TWA systemic dose in adults:
\[
= 1.25 \times 0.08 \times 0.153 \times 0.0169 \times 15 \times 1 / (23.9 \times 365)
= 0.0021 \mu g/\text{kgbw}^{-1} \text{d}^{-1}
\]

in children:
\[
= 1.25 \times 0.08 \times 0.153 \times 0.1 / (23.9 \times 365)
= 0.0026 \mu g/\text{kgbw}^{-1} \text{d}^{-1}
\]

in toddlers:
\[
= 1.25 \times 0.08 \times 0.133 \times 0.1 / (10 \times 365)
= 0.0055 \mu g/\text{kgbw}^{-1} \text{d}^{-1}
\]

in infants:
\[
= 1.25 \times 0.08 \times 0.394 \times 0.1 / (8 \times 365)
= 0.020 \mu g/\text{kgbw}^{-1} \text{d}^{-1}
\]

Predicted maximal daily systemic dose in adults:
\[
= 1.25 \times 0.08 \times 0.153 \times 0.0169 / 60
= 0.0014 \mu g/\text{kgbw}^{-1}
\]

in children:
\[
= 1.25 \times 0.08 \times 0.153 / 23.9
= 0.0027 \mu g/\text{kgbw}^{-1}
\]

\[
= 0.014 \mu g/\text{kgbw}^{-1}
\]

TWA systemic daily dose due to ingestion exposure through eating contaminated foodstuff:

\[
= 0.5 \times 1.25 \times 0.08 \times 0.0169 \times 15 \times 1 / (60 \times 365)
= 0.00058 \mu g/\text{kgbw}^{-1} \text{d}^{-1}
\]

in children:
\[
= 0.5 \times 1.25 \times 0.08 \times 0.0126 \times 15 \times 1 / (23.9 \times 365)
= 0.0011 \mu g/\text{kgbw}^{-1} \text{d}^{-1}
\]

in toddlers:
\[
= 0.5 \times 1.25 \times 0.08 \times 0.0105 \times 15 \times 1 / (8 \times 365)
= 0.0027 \mu g/\text{kgbw}^{-1} \text{d}^{-1}
\]

c) Ingestion exposure due to contaminated foodstuffs

\[
\text{SysD}_{TWA} = 0.5 \times C_{\text{Sur}} \times \text{Transl} \times \text{SAF} \times \text{EF} \times \text{AbsO} / (\text{BW} \times \text{AT})
\]

\[
\text{SysD}_{\text{MAX}} = 0.5 \times C_{\text{Sur}} \times \text{Transl} \times \text{SAF} \times \text{AbsO} / \text{BW},
\]

where:
- \(C_{\text{Sur}}\) = concentration on the surface mg/m², 2.5 x 0.5 = 1.25 mg/m²
- \(\text{Transl}\) = fraction translocated onto hands, 0.08
- \(\text{SAF}\) = contaminated surface of food, 0.0169, 0.0126, 0.0124, and 0.0105 m² for adults, children, toddlers, and infants respectively
- \(\text{EF}\) = exposure frequency, 15/year
- \(\text{AbsO}\) = gastrointestinal absorption, 1.0
- \(\text{BW}\) = body weight; adults 60 kg, children 23.9 kg, toddlers 10 kg, infants 8 kg
- \(\text{AT}\) = averaging time, 365 days

Predicted maximal daily systemic dose due to ingestion exposure through eating contaminated foodstuff:

in adults:
\[
= 0.5 \times 1.25 \times 0.08 \times 0.0169 \times 15 \times 1 / (60 \times 365)
= 0.00058 \mu g/\text{kgbw}^{-1} \text{d}^{-1}
\]

in children:
\[
= 0.5 \times 1.25 \times 0.08 \times 0.0126 \times 15 \times 1 / (23.9 \times 365)
= 0.0011 \mu g/\text{kgbw}^{-1} \text{d}^{-1}
\]

in toddlers:
\[
= 0.5 \times 1.25 \times 0.08 \times 0.0124 \times 15 \times 1 / (10 \times 365)
= 0.0025 \mu g/\text{kgbw}^{-1} \text{d}^{-1}
\]

in infants:
\[
= 0.5 \times 1.25 \times 0.08 \times 0.0105 \times 15 \times 1 / (8 \times 365)
= 0.0027 \mu g/\text{kgbw}^{-1} \text{d}^{-1}
\]

in adults:
\[
= 0.5 \times 1.25 \times 0.08 \times 0.0169 \times 1 / 60
= 0.014 \mu g/\text{kgbw}^{-1}
\]
in children:  
= 0.5 x 1.25 x 0.08 x 0.0126 / 23.9  
= 0.026 µg/kgbw

in toddlers:  
= 0.5 x 1.25 x 0.08 x 0.0124 / 10  
= 0.062 µg/kgbw

in infants:  
= 0.5 x 1.25 x 0.08 x 0.0105 / 8  
= 0.066 µg/kgbw

For toddlers, the systemic TWA daily dose from hand-to-mouth exposure is:  
1.25 x 0.08 x 0.23 x 0.164 x 0.57 x 1 / 10 x 365  
= 0.00088 µg/kgbw

For toddlers, the maximal daily systemic dose from hand-to-mouth exposure is:  
1.25 x 0.08 x 0.23 x 0.164 x 0.57 x 1 / 10  
= 0.022 µg/kgbw

e) Total exposure of residents
Sum of inhalation exposure from dermal and oral exposure from indoors spraying

2.3 Exposure of resident operators
Exposure in mixing, loading, application and equipment maintenance + residential exposure

2.4 Ingestion exposure via breast milk – infants and newborns
SysDTWA = SolC x DoseM x T½ x IR x AbsO / BW  
SolC = solubility constant, 0.361  
DoseM = daily dose of the mother, 0.0027, 4.06 and 40.3 µg/kgbw  
T½ = half-time in the body, 1 day  
IR = ingestion rate of milk, (newborn 0.53 kg/day)  
AbsO = oral absorption, 100%

For a suckling newborn, whose mother is a resident of a treated dwelling, the predicted TWA daily dose is not more than:  
0.361 x 0.0027 x 1 x 0.53 x 1 / 4.2  
= 0.00012 µg/kgbw

When the mother also works as a spray operator indoors, the predicted doses are:  
 guideline scenario operator:  
0.361 x 4.06 x 1 x 0.53 x 1 / 4.2  
= 0.18 µg/kgbw

lax standard scenario:  
0.361 x 40.3 x 1 x 0.53 x 1 / 4.2 kg  
= 1.84 µg/kg bw

As the estimate is based on the steady-state body burden of the mother, these estimates also represent
BW = body weight, newborn 4.2 kg

3. Risk characterization

3.1 Compare exposure estimates with the TSD. For products with appreciable acute toxicity or irritative properties, consideration should be given to TSDAC.

3.2 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.

3.3 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.

3.4 In some cases the exposure is found unacceptable. Other methods of vector control should be considered.

3. Risk characterization

**Operator**

The irritation capacity of insecticide X is low. The risk assessment is based on comparison of the long-term exposure with the long-term TSD and of the maximal daily exposure with the TSDAC.

From 1.11, TSD used is 0.01 mg/kg\text{bw}^{-1}\text{d}^{-1}.

Short-term guidance value TSDAC is 0.05 mg/kg\text{bw}^{-1}.

**LONG-TERM (TWA) EXPOSURE**

In the guideline scenario, operator exposure is considered acceptable, as the total predicted dose is approximately 40% of the TSD. In the lax standard scenario, the TSD may be exceeded 4-fold. It is therefore important to make sure that safe practices are implemented, that adequate PPE is used and that the equipment is kept in good working condition.

**MAXIMAL DAILY EXPOSURE**

In the guideline scenario, operator exposure is considered acceptable, as the maximal daily systemic dose is 19% of the TSDAC. In the lax standard scenario, the TSDAC may be exceeded 1.9-fold. It is therefore important to make sure that safe practices are implemented, that adequate PPE is used and that the equipment is kept in good working condition.

**Resident operator**

Exposure of resident adults is less than 1% of that of the operators and thus the exposure of resident operator is not significantly higher than that of non-resident operators.

**Resident**

ADULT RESIDENT exposure is considered acceptable. The predicted TWA dose is 0.03% of the TSD and the daily maximal dose 0.13% of the TSDAC. RESIDENT CHILD exposure is considered acceptable. The predicted TWA dose is 0.04% of the TSD and the maximal daily dose 0.18% of the TSDAC. RESIDENT TODDLER exposure is considered acceptable. The predicted TWA dose is 0.09% of the TSD and the maximal daily dose 0.43% of the TSDAC. RESIDENT INFANT exposure is considered acceptable. The predicted TWA dose is 0.23% of the TSD and the maximal daily dose 1.1% of the TSDAC. Exposure of NEWBORN BABIES is considered acceptable. The predicted dose does not exceed 0.002% of the TSD in infants of resident mothers not working as spray operators. The dose of infants of resident mothers working as operators (guideline scenario) is 1.8% of the TSD. Infants of mothers applying the lax working standard may receive a TWA dose of 18% of TSD.
8. Summary of the environmental risk assessment model and a worked example

<table>
<thead>
<tr>
<th>Generic environmental risk assessment model</th>
<th>Worked example</th>
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</thead>
<tbody>
<tr>
<td><strong>1. Identify source documents on risk assessment of the substance</strong> State reliability for source documents used. Conduct literature search for additional studies focusing on field estimations relevant to malarial vector control.</td>
<td><strong>1. Identify source documents on risk assessment of the substance</strong> One international review and one regional (EU) assessment summary were identified. A national registration summary for use of insecticide X as a wood preservative and one article published in a peer-reviewed scientific journal were also used.</td>
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<tr>
<th><strong>2. Exposure estimation</strong></th>
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<tr>
<td><strong>Air</strong></td>
<td><strong>Air</strong></td>
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<tr>
<td>Determine likely spray drift from intended application area and likely &quot;application rates&quot; to on-target areas. Establish volatility class for the active ingredient; obtain maximum daily loss by volatilization.</td>
<td>An application rate of up to 1 g/ha is recommended for outdoor space spraying of insecticide X (WHO, 2006). A likely spray drift of 10% at 100 metres distance – based on truck-based application and a wind speed of 8 km/hour – has been assumed as the “application rate” for surface waters. Vapour pressure has been reported as $1.2 \times 10^{-8}$ Pa at 25 °C and a dimensionless Henry’s Law constant (air–water partition coefficient) at $6.14 \times 10^{-5}$.</td>
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<tr>
<th><strong>Soil</strong></th>
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<tr>
<td>Calculate initial concentration in soil (worst-case scenario). 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. Obtain value for adsorption coefficient in soil $K_d$. Establish the degree of concern for leaching to groundwater and adjacent surface water.</td>
<td>A classification of medium has been assigned for volatilization from soil and water and low for volatilization from plants. Note that volatilization from the surface of water can be very high but dissipation into the water body is quite rapid. An initial concentration in soil of 0.033 µg/kg was calculated based on direct application to 50% vegetation cover and a soil depth of 10 cm. The default soil density of 1500 kg/m³ was used. A $DT_{50}$ in soil (field soil study) of 21 days was reported. Soil TWACs were calculated for 14 days, the time period for the toxicity test on earthworms at 0.011 µg/kg. Regular spraying at weekly intervals for 7 weeks would lead to an upper plateau concentration of 0.13 µg/kg soil. Since the acute LD₅₀ for earthworms (see below) is 1290 mg/kg soil, a concentration of concern would never be reached. Reported values of $K_{oc}$ are extremely high; a value of 460 000 was used in the calculations to maximize expected bioaccumulation. (This was the lowest value reported.)</td>
</tr>
</tbody>
</table>
Generic environmental 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 in surface water from 10% of drifted spray was 0.002 µg/litre.

Based on radioactive tracers:
- on day 0, 38% water/60% sediment,
- on day 4, 20% water/75% sediment,
- on day 28, 0.25% water/82% sediment.

Field studies measuring total dissipation from water were identified, giving a $DT_{50}$ of 1.6 days. This measured result was used in calculations.

Laboratory studies gave biodegradation $DT_{50}$ as 0.7 days, hydrolysis $DT_{50}$ as 13 000 days (negligible hydrolysis) and photodegradation $DT_{50}$ as 47.7 days. Volatilization from the surface film is rapid; a half-life of 0.1 days indicates significant losses within the short period on the water surface (estimated at up to 70% in one study). Results suggest that partitioning and biodegradation are the major factors in dissipation from the water body.

TWACs were calculated for 21 and 28 days, corresponding to the duration of the toxicity test results used later at 0.000 22 µg/litre and 0.000 16 µg/litre, respectively.

TWAC was calculated on the basis of initial concentration in sediment at 0.013 µg/kg over 28 days, giving a predicted concentration in sediment of 0.0011 µg/kg.

Given the short half-time, no significant build-up of the concentration in water is expected in repeated applications.

3. Effects estimation and risk calculation

Aquatic organisms

Identify acute aquatic toxicity test results. Determine the lowest reported LC50/EC50 values for algae, invertebrates and fish; add other groups of organisms as available.

Calculate ETRs from the initial concentration in surface water and the 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.

Calculate the ETR for sediment-dwelling organisms using the concentration in sediment (adjusted for degradation over the exposure period of the test) and chronic toxicity test results for sediment organisms.

3. Effects estimation and risk calculation

Aquatic organisms

Lowest reported toxicity results for algae, invertebrates (Gammarus) and fish (Cyprinus) were 23, 0.003 and 0.07 µg/litre respectively. The fish study is one identified from the scientific literature but not previously used in risk assessments for insecticide X.

ETR acute algae = 0.0001: class low
ETR acute invertebrates = 0.67: class medium
ETR acute fish = 0.028: class low.

No further consideration was given to algae or fish. Risk to both groups from indirect exposure through spray drift of outdoor space spraying is considered to be low.

ETR chronic invertebrates after single application = 0.01: class low.

Chronic risk to aquatic invertebrates is considered low.

ETR for sediment-dwelling organisms is 0.0001 for Chironomus riparius in a 28-day test (LC50) in artificial sediment (organic matter 4%). In natural
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<td>Classify the ETR for risk to sediment-dwelling organisms. 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 $P_{ow}$ 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.</td>
<td>Sediment (organic matter 12.5%) there was no toxicity because the insecticide X was bound to the sediment. Chronic risk to sediment dwellers is low. Insufficient data were available for calculation of distribution. From the physicochemical properties of insecticide X, bioaccumulation potential is moderate to high at an estimated BCF of 1910 based on $P_{ow}$ of 4.6. Measured BCF in fish of 1400 confirms the classification.</td>
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<th>Soils organisms</th>
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<tr>
<td>Obtain toxicity results for short-term exposure of earthworms (LD$<em>{50}$). Calculate the acute ETR for earthworms using the initial concentration in soil. Classify concern for soil organisms. If acute concern is indicated, calculate the chronic ETR using the soil TWAC for the duration of the chronic test and the NOEC for reproduction in earthworms. Establish bioaccumulation potential for terrestrial organisms from $P</em>{ow}$ or preferably from measured BCFs 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.</td>
<td>An acute LD$<em>{50}$ of 1290 mg/kg soil was reported for earthworms. ETR acute for earthworms is 0.000 003 and is considered low. There is no chronic toxicity concern for earthworms. The theoretical BCF for earthworms is 0.04 based on the $P</em>{ow}$ of 4.6 and a $K_{oc}$ value of 460 000. This is low and probably overestimates BCF since most reported $K_{oc}$ values are much higher. No field studies of relevance to soil organisms were identified.</td>
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<tr>
<th>Terrestrial vertebrates</th>
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<tr>
<td>Calculate residue levels in food items for terrestrial vertebrates (birds and mammals) for “worst-case” and “most-likely-case” and short-term exposure. Calculate ETRs. Calculate residue levels for medium- and long-term exposure scenarios based on cut-off values for ETRs at lower time periods. 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.</td>
<td>Short-term residue levels in food items were calculated for both worst-case and most-likely-case scenarios. These ranged from 0.0025 mg/kg diet for fruit to 0.2 mg/kg for herbage. This gives short-term (minutes to hours) ETRs of: – herbivorous bird = 0.000 03 – insectivorous bird = 0.000 02 – fruit-eating bird = 0.000 001 This indicates low risk to birds from use of insecticide X for outdoor space spraying, either ground-applied or aerially applied. No relevant field studies on terrestrial vertebrates were identified.</td>
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<tr>
<td>Generic environmental risk assessment model</td>
<td>Worked example</td>
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<tr>
<td><strong>4. Risk classification</strong>&lt;br&gt;Tabulate all calculated risk factors and assess the overall pattern, nature and degree of risk.</td>
<td><strong>4. Risk classification</strong>&lt;br&gt;Significant risk of the use of insecticide X as an outdoor space spray for the control of adult mosquitoes is confined to non-target aquatic invertebrates exposed by spray drift. The medium risk is acute but does not persist to chronic exposure.</td>
</tr>
</tbody>
</table>
References

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


GENERIC RISK ASSESSMENT MODEL FOR INDOOR AND OUTDOOR SPACE SPRAYING OF INSECTICIDES