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A GENERIC RISK ASSESSMENT MODEL FOR INSECTICIDE TREATMENT AND SUBSEQUENT USE OF MOSQUITO NETS

World Health Organization
Communicable Disease Control, Prevention
and Eradication
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&
Protection of the Human Environment
Programme on Chemical Safety (PCS)

Contents

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1. Purpose

The aim of this report is to develop a generic model that can be used for risk assessment of exposure to insecticides during the various stages in the production and use of insecticide-treated bednets. The model proposed covers the assessment of any risks to those treating bednets with insecticide in a domestic setting (operators) and to those sleeping under insecticide-treated bednets (users). While it is recognized that there is increasing interest in the commercial production of pretreated bednets, the generic model proposed is for the simplest situation of domestic treatment and use of nets; it does not include the special situation of commercial production of nets in a factory environment.

2. Background

2.1 Need for a generic risk assessment model

Pyrethroid insecticides have been used for several years for the treatment of bednets to protect against malaria-carrying mosquitoes. The effectiveness of such bednets in reducing morbidity and mortality from malaria has been documented elsewhere (WHO, 2000). The WHO Roll Back Malaria (RBM) project has made insecticide-treated bednets one of the cornerstones of the effort to reduce malaria, setting the goal in October 1999 of ensuring coverage of 60 million African families with insecticide-treated mosquito nets over a five-year period.

The present consensus is that pyrethroids – at the levels currently employed – are generally of low risk to human health, both for operators and for users of treated bednets. The WHO Pesticide Evaluation Scheme (WHOPES) currently recommends a number of insecticides, all pyrethroids, for the treatment of bednets (Najera & Zaim, 2002). A review of the safety of pyrethroid-treated bednets has been published (Zaim et al., 2000), and in a detailed risk assessment on the use of deltamethrin on bednets, Barlow; Sullivan & Lines (2001) support the safety-in-use of this particular

insecticide. However, detailed assessments of the other WHOPES-approved compounds have yet to be published.

Because of the development of insect resistance to the commonly used pyrethroids, there is now a need to consider the use of alternative insecticide classes for vector control in the treatment of bednets. Alternatives under consideration include organo-phosphates and carbamates, which differ from the pyrethroids in their mode of action and are inherently more acutely toxic and less stable. Thus there is an urgent need for safety assessment of such treatments before they are used in the field. There is also a need to assess the risks from the various methods of bednet treatment that may be used, including the types of insecticide formulation used and the newer, more persistent insecticide treatments. A generic risk assessment model is therefore needed, based on typical scenarios for the preparation and use of insecticide-treated bednets and on average or "worst case" values for environmental and human parameters, and applicable to any insecticide.

2.2 Essential elements of a risk assessment model

In the context of this report it is important to distinguish between "hazard" and "risk". *Hazard* is defined as the inherent capacity of a chemical/exposure to cause adverse effects in animals or humans. *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 effect(s) associated with a particular exposure in a given population, together with any attendant uncertainties. The entire process of hazard assessment, exposure estimation, and risk characterization is known as *risk assessment*. The subsequent process of *risk management* considers the risk assessment alongside any potential benefits, socioeconomic and political considerations, the possibilities for risk reduction, and other

factors that are relevant in making operational decisions on the acceptability of a particular level of risk.

This report sets out the information requirements necessary to enable adequate risk assessments for the use of any insecticide in the treatment of bednets and for subsequent use of the nets to be performed in a transparent manner. The report does not deal with risk management considerations.

Risk assessment of insecticide use on bednets involves three steps:

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

2. Exposure assessment: This involves estimation of potential exposure to the insecticide of operators and users, with emphasis on subgroups of the population who may be especially at risk either because of higher exposures or because of vulnerability associated with their inherited properties, life-stage or state of health. It includes estimation of both likely and worst-case exposures to the insecticide via dermal, inhalational, and oral routes. Exposure is usually defined as the amount of substance that comes into contact with a person – that is, the amount present on the skin, the amount inhaled, or the amount ingested. Risk assessments can sometimes be based on these (external) exposure estimates. More usually it is necessary to calculate the internal absorbed dose – that is the amount absorbed into the systemic circulation – in which case information about various absorption factors is required. The extent and rate of absorption vary with route of exposure and depend on physiological properties of the individual and physicochemical characteristics of the insecticide.

3. Risk characterization: In the context of insecticide-treated bednets, risk characterization can be based on either a comparison of exposure estimates with previously defined acceptable exposure levels, or a comparison of no-effect or low-effect levels with exposure estimates to assess the margin of safety for particular activities and exposure scenarios. Risk characterization should include discussion of the nature, severity, and reversibility of the toxicity that may be produced in different exposure scenarios, the likelihood of detection of adverse effects at an early stage, any identified vulnerable groups, and any uncertainties in the hazard or exposure assessments.

Each of the above steps is considered in detail and the information required for each step is defined. Under real-life conditions it is unusual for all the information elements of a risk assessment to be available. Frequently, “default” values have to be used for some of the parameters in the exposure assessment: decisions then have to be made on whether to use average values, defined percentile values, or “worst-case” values. Similarly, uncertainties in the toxicity information and in the extrapolation of animal data to humans necessitate the use of uncertainty factors to derive acceptable exposure levels. Default values for uncertainty factors are available. The more conservative the default values selected, the more conservative the risk assessment becomes. Whatever default values are used, it is important that all the assumptions made are clearly stated, so that the validity and limitations of the risk assessment can be appreciated by those involved in the risk management process.

It should be noted that, in making a choice about a suitable insecticide for safe use on bednets, consideration must also be given to the disposal of waste insecticide – both from the treatment process and from the washing of the nets. Some insecticides are toxic to fish as well as to beneficial insects and mammals, and these environmental aspects must be taken into account. The present model only deals with risk assessment for human health, not with environmental risks.

3. The risk assessment model

The detailed requirements for the three essential elements of the risk assessment model for insecticide use on bednets, i.e. the hazard assessment, the exposure assessment, and the risk characterization, are developed below.

3.1 Hazard assessment (hazard identification and hazard characterization)

3.1.1 Sources of data

The first step in hazard assessment is to conduct a thorough search of the published literature on the particular insecticide under consideration. This should include both toxicological and medical literature and any relevant information published by national and supranational agencies involved in pesticide evaluations and approvals. The manufacturer(s) of a particular insecticide may also be prepared to release unpublished information or study reports to assist in the risk assessment. If reviews are used, rather than original papers, this should be explicitly stated in the risk assessment and the provenance of the reviews should be cited. Sources of authoritative reviews on pesticide toxicity include the Joint FAO/WHO Meeting on Pesticide Residues (JMPR), WHO International Programme on Chemical Safety (IPCS), International Agency for Research on Cancer (IARC), US Environmental Protection Agency (USEPA), US Agency for Toxic Substances and Disease Registry (ATSDR), the US National Toxicology Program (NTP), the European Commission Scientific Committee on Plants and the United Kingdom Department for Environment, Food and Rural Affairs, Pesticides Safety Directorate. If reliance is placed on reviews, the original study report or publication should ideally also be consulted if it is identified as critical to the risk assessment.

For assessing human health risks from exposure to insecticides, data from humans would be most appropriate, but for many insecticides the human database may be limited and hazard

identification and hazard characterization will be dependent on information from experimental animals and test results in vitro. Conversely, for some insecticides, especially those that have been in use for many years, the available animal toxicology studies may be very limited. In such cases there is usually human evidence of safe (and unsafe) use, from case reports of accidental and deliberate poisonings, occupational studies on those manufacturing or using the insecticide or its formulations, or other epidemiological studies. Where reliable human data do exist for particular aspects of toxicity, they should take precedence over animal data in the risk assessment.

Insecticides that have been approved or reregistered as active substances by a regulatory authority in recent years will be expected to have a fairly complete package of experimental toxicology studies, conducted to modern standards, according to Good Laboratory Practice (GLP), and using internationally accepted protocols such as those published by the Organisation for Economic Co-operation and Development (OECD, 1987), the European Commission (EC, 2002a) or the USEPA (2002a). Extensive regulatory programmes are also under way, in both the USA and the European Union (EU), to review older pesticides, including the pyrethroids and organophosphorus and carbamate insecticides; the review procedures carry a requirement for the pesticides to be supported by up-to-date studies if they are to continue in use. Better data are consequently becoming available.

Most insecticides currently used or being considered for use on bednets have existing agricultural and/or biocide uses and will therefore have been through a regulatory approval process. The types of studies required by regulatory authorities will depend on the precise uses of the insecticide, and requirements may vary on points of detail from country to country or region to region. However, the range of tests normally required for approval in Europe or the USA is very similar. The essential studies required for placing plant protection products (CEC, 1991) or biocidal products (CEC, 1998) on the EU market are set out below.

3.1.2 Range of toxicity tests normally required for pesticide approval

Studies marked with an asterisk(*) are those that may provide useful dose–response information (see section 3.1.3).

- **Toxicokinetic studies**, usually in the rat, using single and repeat oral dosing, to give information on absorption, metabolism, distribution, and excretion of the parent compound and its metabolites.
- **Acute toxicity studies** to define the approximate lethal doses by oral, percutaneous, and sometimes inhalation routes, and the effects on body weight, clinical signs, and gross pathology produced at lower dose levels following single-dose administration.
- **Skin irritation studies.**
- **Eye irritation studies.**
- **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' duration 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.

3.1.3 Evaluation of the toxicity information

An experienced toxicologist should review the range and quality of the human and animal toxicity studies available. All the toxicity tests described in section 3.1.2 are useful for assessment of the hazard potential of an insecticide for use on bednets, although it is recognized that not all such tests may have been performed. Particular note should be made of missing information. In the context of hazard assessment of insecticide use on bednets, in addition to the normally required studies, repeat-dose dermal and inhalation toxicity studies are of value, if available. If the database is poor, information on chemically related compounds may be useful.

The following points are of particular importance in evaluating the studies:

- The nature of the toxicities observed, their severity and whether they would be reversible on cessation of exposure.
- The steepness of the dose–response curves.
- For each type of toxicity identified by an asterisk (*) above, the doses without adverse effect, i.e. no-observed-adverse-effect levels (NOAELs), and the doses causing just- measurable adverse effects, i.e. lowest-observed-adverse-effect levels (LOAELs).
- The quality of the pivotal study that identifies the critical toxic effect, which is usually the effect occurring at the lowest dose among all the doses and types of toxicity examined.
- If irreversible toxicity is noted in any organs at higher dose levels than that at which the critical effect occurs, these should also be noted in case they may be relevant to the setting of acceptable exposure limits (see section 3.3.2.1) or may assist in predicting what possible additional risks may be present if certain exposures are exceeded.

- In the case of insecticides such as carbamates and organophosphates, which act on specific and nonspecific cholinesterases, the dose levels that cause measurable effects, even if those effects are not considered “adverse”, should be noted. For example, while inhibition of plasma or brain butyrylcholinesterase serves mainly as an indicator of internal exposure, a statistically significant inhibition of 20% or more of brain or red blood cell acetylcholinesterase is considered to be of clear toxicological significance (JMPR, 1998a).
- Insecticides that are both genotoxic and carcinogenic would normally be regarded as unacceptable for use in situations where the general public would be exposed. Such compounds are generally recognized to have the potential to exert effects at very low doses, particularly where there would be daily exposure for a considerable portion of an individual’s lifetime. Even if the studies indicate apparent NOAELs, these should not be used for risk assessment. In exceptional cases, mathematical modelling might be used to determine a level of risk deemed acceptable for a particular exposure scenario in which it is considered that the benefits would justify the potential risks. If the insecticide is of high acute toxicity, it may be unacceptable for use on bednets. Consultation of the WHO recommended classification of pesticides by hazard (WHO, 2002) is recommended. This lists pesticides in five categories based primarily on the acute oral and dermal LD_{50} values of the active ingredients – extremely hazardous, highly hazardous, moderately hazardous, slightly hazardous, or unlikely to present acute hazard in normal use. However, the acute toxicity of the formulation, not just of the active ingredient, should be taken into account, based on data on the formulation itself.

It is suggested that the NOAELs and LOAELs for each type of toxicity are tabulated (see Table 1 for an example of format). However, there may be studies in which the lowest dose tested is a clear effect level (EL) and in which it is not possible to identify either an NOAEL or an LOAEL. In these cases, the EL should be tabulated instead. Conversely, the highest dose tested may be

without any effect and this should be tabulated as the NOAEL, noting that the true NOAEL may be higher. From such a table, the importance of the specific organs or systems affected can be considered and the selection of the pivotal study (or studies) that identifies the critical NOAEL/LOAEL can be made, for incorporation into the subsequent stages of the risk assessment. In some regions of the world, the use of bednets for malaria prevention may be seasonal whereas continual use may be necessary in other regions. Thus the critical studies may not always be the same for different exposure scenarios, and this may have to be considered in the overall assessment.

Table 1. Tabulation of results from toxicity studies

Type of study (species, duration, route of exposure)	No-observed-adverse-effect levels (NOAEL)	Lowest-observed-adverse-effect level (LOAEL) or effect level (EL)	Description of effect (nature, severity)

3.2 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 has to 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 whether this is intermittent or continuous. These considerations may indicate different scenarios for the different groups of people involved in the preparation and use of bednets. These groups comprise:

- those involved in the manufacture and distribution of the insecticide (not further considered here)
- those treating bednets with insecticide
- those cleaning treated bednets by washing
- those sleeping under treated bednets
- those who might accidentally ingest concentrated insecticide.

Different scenarios must be considered to cover the several different possibilities for insecticide exposure during these situations.

3.2.1 Treating bednets with insecticide

3.2.1.1 Methods of net treatment

Three methods are currently available for treatment of nets:

- "'Do-it-yourself" treatment kits are available for home use. The pesticide is supplied in liquid, powder, or tablet form to be dissolved or dispersed in water. The nets are dipped in the resulting pesticide solution/suspension, then dried.
- A central service may be run by trained personnel. Net owners can bring their nets for treatment or re-treatment, thus reducing the risks of exposure of untrained members of the public.
- Factory-pretreated nets are supplied for sale, whose effectiveness may be longer lasting (up to 3–4 years). These reduce problems, such as the preparation, use, and disposal of insecticide-containing solutions, associated with the need to dip and re-dip nets,.

This report considers only exposures likely to be associated with the "do-it-yourself" type of home-based net treatment, since this is likely to give rise to the worst-case exposure scenarios. The other systems are more amenable to control, although the larger amounts of insecticide used will necessitate careful control programmes to minimize exposure, both of production personnel, who may be exposed daily, and of the environment.

In order to estimate the exposure of those treating bednets with insecticide, the proposed formulation of the insecticide to be used, its type of packaging, and the frequency of application need to be known at the outset – these factors influence the degree of exposure to the insecticide. Instructions for net treatments should give clear information on the amount of insecticide formulation to be used for each net and the volume of water in which it should be dissolved or dispersed. If there is no direct experimental evidence relating to levels of exposure, assumptions must be made about the likely volumes of powder or liquid concentrate formulation and of dilute solutions or suspensions that will get onto the skin and be available for absorption, the duration of contact, and the degree of skin penetration of the insecticide. The possibilities for oral and inhalation exposure during dipping of bednets also have to be considered. Taken together, these will allow estimates to be made of the expected levels of exposure that may occur during the different phases of production of insecticide treated nets on each occasion when they are treated.

3.2.1.2 Variability in contamination/exposure

Studies on pesticide operators have revealed that huge variations in the amount of skin contamination can occur during different parts of the work cycle. For example, when working with a liquid concentrate formulation before dilution, one small drop of concentrate on the skin may cause exposure exceeding the total resulting from all processes using diluted material, such as spraying and waste disposal. There is also a large variation between workers in the care they take when working, so that exposure can vary by orders of magnitude between workers. Thus, for each exposure scenario, there will be a distribution of exposures within a population, and attention should be given to the extent of variation that may be expected between individuals exposed to the same scenario. The use of any personal protective equipment would also have an influence on the exposures. There are statistical methods for dealing with probability distributions, and probabilistic exposure assessments give estimates of the variability and uncertainty of the range of exposures that may be expected in different scenarios. Deterministic exposure

assessments are based on point estimates of input variables, and some idea of potential variability in exposure can be obtained by estimating both likely average and worst-case exposures.

For simplicity – because of the many factors to be considered in performing a risk assessment for insecticide treatment of bednets under relatively unsophisticated conditions, and the probability that exposure will not follow a normal distribution pattern – this generic risk assessment model is based on a deterministic methodology, using a ranges of scenarios that may be expected.

3.2.1.3 Exposure during “do-it-yourself' home-based net treatment

The following factors should be considered in assessing the likely exposure scenarios during home-based treatment of bednets:

- who will do it
- how often
- whether training/instruction is given
- nature of the insecticide formulation supplied and its packaging
- method and volume of dissolution or dispersion
- use of protective clothing, (it may be that only gloves will be available)
- reuse of contaminated protective clothing (e.g. gloves)
- extent of skin contamination during dipping, hanging out to dry, and disposal of waste insecticide
- extent of absorption via the skin
- additional direct exposure via the oral route
- additional direct exposure via inhalation.

- **Who will do it**

  Both adults and children may be involved in dipping nets. Worst-case exposure scenarios are likely to involve children: they may be untrained and less able than adults to follow written or pictorial instructions, and they are of lower body weight than adults, with a greater surface area per kg body weight, resulting in greater exposure on a body weight basis from contact with a chemical on the same proportion of the skin surface. Separate exposure estimates are therefore needed for adults and children.

Box 1
Default values for body weight

Examples of default values are:

adult 60 kg (average female)
child 40 kg (average 11-year-old)

Further typical values for adults and children of different ages can be found elsewhere (USEPA, 1997a, 2002c; ECETOC, 2001). In specific situations in which actual body weights are known, the default values should be replaced by actual values.

- **How often**

  Estimates for the frequency with which nets need to be retreated vary. Ideally, the retention characteristics of the pesticide under consideration should be known and used to determine the re-treatment schedule. However, some studies on nets dipped in pyrethroids at home or by a central service show that, with monthly net washing, the insecticide washes out over a period as short as 1–3 months (USAID, 2002). Other studies on pyrethroids show little or no decline in insecticidal activity after 5 washes or 6–7 months of domestic

use (Maxwell et al., 1999; Curtis, personal communication). Thus, it could be assumed that home-based re-treatment of nets may take place at 3-monthly intervals (supposing that the actual re-treatment is in line with the recommended practice). The dipping of nets for a family is likely to be completed in one day, and the exposure should therefore be considered as an acute exposure.

- **Training or instruction**
  Under the safest scenario, training or instruction (verbal, written, and/or pictorial) would be available and followed. For a worst-case scenario, however, it should be assumed that no initial training is available and that any precautionary instructions supplied (e.g. to wear gloves or to pour liquids carefully to avoid splashes) are not necessarily followed.

- **Nature of the insecticide formulation supplied and its packaging**
  The insecticide as supplied by the manufacturer may be in the form of a liquid concentrate, a powder, or a solid tablet. Considering the likelihood of operator exposure, a solid tablet is generally the safest formulation; the least safe is generally a liquid concentrate, because splashing of concentrate onto skin deposits the active insecticide in a form that may be easily absorbed. Powder may pose an intermediate risk because of the possibility of inhalation. Similarly, the size and design of the packaging/container in which the formulation is supplied will influence the likelihood of exposure. Pouring a small amount of liquid concentrate from a large-volume container is likely to result in more skin contamination from splashes (and accidents) than if the required amount of concentrate for treatment of a net is supplied in a small, treatment-sized container. Similarly, powder supplied in water-soluble, treatment-sized sachets is likely to result in less exposure than taking a quantity of powder from a larger container. Thus each type of formulation needs a different exposure scenario, which takes account of the type of packaging in which it is supplied.

Where liquid concentrates are used, Box 2 gives nominal values for the volume of hand contamination from emptying containers of liquid concentrate of different volumes. The values are derived from test data using containers of the appropriate design and are the 75th percentile value from pouring tests on each type of container (Pesticides Safety Directorate, 1992). Neck aperture is a critical design feature and where wide-necked containers are used the volume of hand contamination is less as shown in Box 2.

Box 2

Values for hand contamination from emptying containers of different volume

Container size (litres)	*Contamination (ml/operation)*
1 unspecified design	0.01
5 unspecified design	0.20
10 unspecified design	0.50
20 unspecified design	0.50
1 wide-necked	0.01
2 wide-necked	0.01
5 wide-necked	0.01

(Pesticides Safety Directorate, 1992)

- **Method and volume of dilution or dispersion**
  The required target dose, i.e. the concentration of the insecticide per unit area of the freshly-treated bednet, determines the quantity of insecticide in the formulation supplied for dilution and the recommended dilution volume.

This information must be factored in to the exposure scenario and should be available from manufacturers or from those conducting field trials; it depends on the method used to dilute the formulation, which will also influence the extent of possible operator contamination. Variables include the type of container used for dilution (bucket, shallow basin), the way in which the formulation is added to the water, and the method used for mixing (e.g. stirring with the (un)gloved hand or with a stick), all of which may influence the degree of splashing and amount of liquid deposited on the skin.

- **Use of protective clothing**
  Gloves are likely to be supplied and/or used (see Boxes 3 and 4 for default contamination values). However, for a worst-case scenario it should be assumed that gloves are not used (see Box 6). It is unlikely that any other type of protective clothing (e.g. face protection or coveralls) will be used. It should also be borne in mind that in a hot climate the skin of the arms and legs may be less protected by the normal clothing than in cooler climates.

- **Reuse of contaminated protective clothing**
  If gloves are to be reused, they should be washed at the end of the operation while still on the hands, but it cannot be assumed that this will be done. Gloves may also be removed and put on again during the same operation. Both scenarios are likely to result in higher contamination of the hands of operators than use of new gloves or gloves previously unused for insecticide treatments.

- **Extent of skin contamination during dipping, hanging out to dry, and disposal of waste insecticide**
  Deposition of dilute insecticide on the skin will occur during dipping of the net, wringing it out, and hanging it out to dry. Net materials (cotton, or polyester or other synthetic fibre) vary in their absorbency. Some dipping operations recommend that the net is turned in the container until all the liquid is absorbed, which will reduce the extent of skin contamination from drips when nets are hung outside or laid on beds to dry.

In the absence of measurements of actual contamination, default values must be used to estimate the extent of skin contamination during dipping and drying of the nets. There are two possible ways of estimating dermal exposure (amount of active ingredient per unit body weight deposited on the skin):

- by using an estimate of the volume of solution/suspension contaminating the skin (see Box 3)
- by using an estimate of the amount of active ingredient contaminating the skin (see Box 4).

These two methods can be applied to various exposure scenarios. Examples of scenarios at either end of the likely exposure spectrum are given below (safest scenario – Boxes 3 and 4; least safe scenario – Box 5). If a liquid concentrate formulation is used, the amount of insecticide contamination from splashes during emptying of the container, using the volumes shown in Box 2, should be added to the calculations shown below.

In the safest scenario, it is assumed that:

- gloves are worn, used once, and discarded;
- the solution/suspension is made up, and the nets are dipped and dried according to any instructions provided with the dipping kit;
- the face is not touched by contaminated gloves;
- any left over liquid is disposed of safely without splashing onto skin;
- hands and any contaminated clothing are washed thoroughly when dipping is finished.

The amount deposited on the skin can be calculated in two different ways, i.e. by using the volume of suspension in contact with the hands (as shown in Box 3) or by using the amount of active insecticide in the solution in contact with the hands (as shown in Box 4).

In Box 3, the default value of 4 ml for contamination of the hands is an estimate for this scenario. It is an extrapolation from the figure of 8.4 ml, which is considered to be the maximum amount of a non-viscous liquid likely to be in contact with hands that have been immersed ungloved in a liquid, after run-off (EC, 2003). The figure of 8.4 ml is derived by multiplying the total surface area of both hands (840 cm^2) by an assumed film thickness of 0.01 cm. If previously uncontaminated gloves and careful operating technique are used, the amount in contact with the hands could be much less than 4ml.

It should be noted that the value for contamination inside the glove for the scenario in Box 4 has been taken from the work of Garrod, Phillips & Pemberton (2001), in which data from 190 measurements of contamination inside gloves by non-volatile components of pesticide products were collated. The applications were insecticide, remedial, antifoulant, and preservative products, and the tasks included diluting product concentrates, spraying, using solvent- or water-based products, applying pesticide dusts, and handling wet-treated articles. The 95th percentile figure of 72 mg/min used in Box 4 clearly represents a worst case of contamination when gloves are worn, given that the 75th percentile and median values from their data were 4.21 mg/min and 1.36 mg/min respectively. Garrod, Phillips & Pemberton (2001) point out that comparison of the median values for deposition on the glove exterior and interior (not shown) suggests that wearing gloves offers a better than 20-fold protection.

Box 3

Dermal exposure during dipping of one net (safest scenario) estimated by volume of suspension on the skin

It is assumed that:

- A maximum of 4 ml of dipping suspension could contaminate the hands (2 ml/hand) via drips, splashes and spills getting inside the gloves, via penetration through the gloves, or via temporary removal of contaminated gloves.

- An amount, *A* mg, insecticide is evenly distributed in *B* ml of dipping solution/suspension, giving a concentration of $A/B = C$ mg/ml.

The amount deposited on the skin (*D*) would be:

$4 \times C$ mg

equivalent to:

$4C/60$ mg/kg body weight for a 60-kg adult

$4C/40$ mg/kg body weight for a 40-kg child

i.e.

$0.067C$ mg/kg body weight for a 60-kg adult

$0.1C$ mg/kg body weight for a 40-kg child

Both of the above approaches give estimates of the amount of dermal exposure on a body weight basis for the safest scenario. These may then be compared directly with an acceptable exposure level (AEL) for the dermal route (dermal AEL) or the NOAEL for the dermal route, if available (see section 3.3.2). However, the more usual situation is that no values are available for the dermal AEL or dermal NOAEL because dermal toxicity data are often lacking.

Under these circumstances skin penetration (percutaneous absorption) values must be used to convert the amounts deposited on the skin into systemic absorption values for comparison with the oral AEL or oral NOAEL (see "Extent of absorption via the skin" below).

Box 4

Dermal exposure during dipping of one net (safest scenario) estimated by amount of active ingredient on the skin, using data provided by Garrod, Phillips & Pemberton (2001)

It is assumed that:

- For product densities of 1.0 g/ml (water-based products), the 95th percentile rate of exposure inside protective gloves is 72 mg/min, which equates to 0.072 mg/min for a product concentration of 1 mg/ml.

- An amount, *A* mg, of insecticide is evenly distributed in *B* ml of dipping solution/suspension, giving a concentration of *A*/*B* = *C* mg/ml.

- Potential contact time for dipping one net is 10 minutes (EC, 2002c).

The amount deposited on the skin (D) would be:

$0.072 \times 10 \times C = 0.72C$ mg

equivalent to:

$0.72C/60$ mg/kg body weight for a 60-kg adult
$0.72C/40$ mg/kg body weight for a 40-kg child

i.e.

$0.012C$ mg/kg body weight for a 60-kg adult
$0.018C$ mg/kg body weight for a 40-kg child

In the least safe scenario, it is assumed that:

- no gloves are worn;
- the solution is made up by stirring with an ungloved hand, and the nets are dipped and dried without reference to any instructions provided with the dipping kit;
- the face may be touched by contaminated hands;
- there is splashing onto the skin (e.g. legs and feet) during disposal of used solution;
- hands and any contaminated clothing are not washed when dipping is finished.

The amount deposited on the skin can be calculated as shown in Box 5. The volume of 8 ml (4 ml/hand) is considered to be the maximum amount of a non-viscous liquid likely to be in contact with the hand after run-off (EC, 2003). The amounts splashed onto the arms and feet are assumed to be similar to that on the hands.

These estimated amounts deposited on the skin before absorption for the least safe scenario may be compared with the dermal AEL or dermal NOAEL if available (see section 3.3.2), or the amounts deposited on the skin may be converted into systemic absorption values for comparison with the oral AEL or oral NOAEL (see "Extent of absorption via the skin" below).

- **Extent of absorption via the skin**

  Data on skin penetration (percutaneous absorption) from human trials or from experiments using in vitro skin preparations are rarely available. Where such data are not available, a commonly used default assumption for absorption via the skin is 10% of the amount deposited on the skin, provided that the molecular mass is more than 500 and the octanol–water partition coefficient (log P_{ow}) is <–1 or >4 (EC, 2002b). However, if the physicochemical properties of the insecticide and its formulation fall outside these limits, a default assumption of 100% should be used. Expert judgement can be used to determine whether the 100% default should be

used or modified on the basis of other data, e.g. comparison of toxicities via the dermal and oral routes. In addition, it should be noted that there is an inverse relationship between concentration of pesticide on the skin per unit area and percentage absorption. At low concentrations, the amount absorbed expressed as a percentage of applied dose is, in general, higher than the percentage absorbed at higher concentrations (EC, 2002b).

Box 5

Dermal exposure during dipping of one net (least safe scenario) estimated by volume of suspension on the skin

It is assumed that:

- 8 ml of solution is in immediate contact with the hands.
- 8 ml of solution is in contact with the lower arms.
- 8 ml of solution is spilled onto the legs and feet.
- An amount, *A* mg, of insecticide is evenly distributed in *B* ml of dipping solution/suspension, giving a concentration of $A/B = C$ mg/ml.

The amount deposited on the skin (D) would be:

$24 \times C$ mg

equivalent to:

$24C/60$ mg/kg body weight for a 60-kg adult
$24C/40$ mg/kg body weight for a 40-kg child

i.e.

$0.4C$ mg/kg body weight for a 60-kg adult
$0.6C$ mg/kg body weight for a 40-kg child

An example calculation of systemic exposure via skin penetration is shown in Box 6.

Box 6

Systemic exposure during dipping estimated by skin penetration

It is assumed that:

- Absorption via the skin is 10% of the amount deposited on the skin.

Using the estimate *D* for the amount deposited on the skin, from the scenarios in Box 3, 4, or 5, the amount absorbed systemically would be:

0.1*D* mg

For example:

From scenario in Box 3,

D = 0.067*C* (60-kg adult) or 0.1*C* (40-kg child)

So systemic exposure is:

0.0067*C* mg/kg body weight for a 60-kg adult
0.010*C* mg/kg body weight for a 40-kg child

The estimate of systemic exposure via skin contamination may then be compared with the oral AEL or oral NOAEL (see section 3.3.2).

- **Exposure via the oral route**

  Direct exposure via the oral route would be relatively unusual during treatment of nets, but the possibility of transfer of insecticide via hand-to-mouth contact should be borne in

mind. Additional oral exposure should not pose a problem if the risk characterization for dermal exposure (see section 3.3) shows that estimated dermal exposures are below an acceptable exposure level or that there is an acceptable margin of safety between the estimated exposure and the relevant NOAEL. This is because, for both these approaches, a factor is built in to cover for a certain amount of variability in exposures. However, if the risk characterization indicates that estimated exposures are close to AELs or that there is little or no margin of safety, the possibility of oral exposure should be taken into account in the risk assessment, particularly if children may be dipping nets. A possible default estimate for hand-to-mouth transfer might be 5% of the total amount of 8 ml on the hands in the least safe scenario (Box 5), i.e. 0.4 ml.

- **Exposure via inhalation**

  It is likely that the majority of bednet treatments will be conducted in the open air rather than indoors, and most insecticides are of low volatility. In these circumstances, exposure via inhalation has generally been shown to be negligible and need not be taken into account. If bednet treatments are performed indoors in unventilated or poorly ventilated areas, then, depending on the vapour pressure of the insecticide, additional exposure via inhalation may need to be estimated. Insecticides with vapour pressures above 0.01 Pa (see 3.2.3.1) may need this kind of evaluation.

3.2.2 Washing of treated nets

It should be assumed that both adults and children may carry out the washing of nets. Nets may be washed as often as once a month (Jones & Miller, undated). The washing of nets for a family is likely to be completed in one day and the exposure should therefore be considered as an acute exposure.

Estimates for how quickly the insecticide washes out vary (see section 3.2.1.3, under “How often”). Given that the insecticide may, at worst, wash out over a period of 3 months (Duffield & Hordle, 1997), exposure to insecticide from the washing of nets

can be estimated as follows. Assuming approximately the same volume of water is used for washing as for dipping, exposure will be approximately one-third of that estimated for the least safe scenario for original treatment by dipping, i.e. without the use of gloves, but no addition needs to be made for splashes from the use of liquid concentrate. Provided that reasonable precautions are taken, it can be assumed that, if the risk assessment shows that the insecticide is considered safe for dipping of nets, it will also be safe for washing nets where the exposure will be less, provided that the volume of washing water is not significantly less than that used for dipping.

The amount deposited on the skin during washing can be calculated as shown in Box 7.

The dermal exposure (or dermal exposure converted to systemic exposure as shown in Box 6) from washing of the net(s) should then be compared with the dermal (or oral) AEL or oral NOAEL (see section 3.3.2). Since the exposure from washing of nets will be less that the exposure from dipping (unless a large number of nets are washed with a prolonged contact time), the scenario of washing can be ignored if the dipping of nets is deemed safe. However, if washing and re-dipping are done on the same day, the two exposures should be added together.

3.2.3 Sleeping under treated nets

The potential routes of exposure that need to be taken into account in risk assessments for those sleeping under treated nets are inhalation, dislodgeable residues from the net being deposited on skin in contact with the net, and, in the case of infants and young children, the additional possibility that the net may be mouthed, chewed, or sucked. In the risk assessment scenarios that follow, the examples of a young child aged around 1 year and weighing 10 kg and a newborn infant weighing 3 kg are used (rounded averages for body weights taken from USEPA, 2002c, ECETOC, 2001).

Box 7

Dermal exposure during washing of a single batch of nets as estimated by volume of suspension on the skin

It is assumed that:

- Gloves are not worn; the volumes of water used for dipping and washing are similar.
- 8 ml of washing water is in immediate contact with the hands.
- 8 ml of washing water is in contact with the lower arms.
- 8 ml of washing water is spilled onto the legs and feet.
- Washing of contaminated skin is not carried out immediately after dipping.
- The exposure is equivalent to one-third (see section 3.2.2) of the total dermal exposure during dipping with the least safe scenario (see Box 5).

The amount deposited on the skin during washing would be:

$$\frac{24}{3} \times C \text{ mg}$$

equivalent to:

8*C*/60 mg/kg body weight for a 60-kg adult
8*C*/40 mg/kg body weight for a 40-kg child

i.e.

0.13*C* mg/kg body weight for a 60-kg adult
0.2*C* mg/kg body weight for a 40-kg child

3.2.3.1 Inhalation

Many attempts have been made to model the indoor air environment, all of which have shown that this is extremely complex and not readily amenable to mathematical modelling. Even the simplest models have to take account of the rate of emission from the pesticide-treated source, diffusion into the room air, presence of sinks, such as furniture and carpets, that can adsorb and desorb the pesticide, and the rate of air exchange in the room. The volatilization of an insecticide from bednets depends on its vapour pressure, its diffusion coefficient in air, its diffusion coefficient in the bednet material, the ambient temperature, and other factors such as water solubility. Of these, the diffusion coefficient of the dried insecticide within the solid material of the bednet is particularly important. However, such coefficients are difficult to determine experimentally and are very rarely available. Because of the variety of conditions that will prevail in the field use of treated bednets, no single mathematical model would be appropriate for estimating the amount of insecticide present in the air under treated bednets.

Fortunately, in most situations involving use of insecticide-treated bednets, the contribution of inhalation to total body exposure is so small that, in practice, it can be ignored. This is in agreement with the recommendation of the USEPA standard operating procedure (SOP) for residential exposure estimates, dealing with post-application doses from materials impregnated with pesticides (USEPA, 1997b). This SOP states that, in the absence of actual field data, the inhalation dose is not of concern because (i) the pesticide is generally contained within the material, (ii) pesticides generally have low vapour pressures, and (iii) concentrations are generally low.

It is also in agreement with EU guidance on data requirements for biocides, which state that the vapour pressure need not be measured when calculations show that it is likely to be $<10^{-5}$ Pa, and that methods for analysis in air need be submitted only “if the substance is volatile (i.e. if the vapour pressure is $\geq$0.01 Pa)…”

(EU, 2000). Vapour pressures of typical insecticides at room temperature are shown in Table 2.

It can be seen that most insecticides, including those currently recommended by WHO for bednet treatment (Najera & Zaim, 2002), have low or very low vapour pressures. Experimental data on deltamethrin concentrations in the air under bednets also showed that the inhalation exposure was negligible (0.07–2.0%) compared with the exposure via oral and dermal routes(Barlow, Sullivan & Lines, 2001) . Studies on occupationally exposed pesticide workers also show that inhalation exposure is usually a small percentage of the dermal exposure (Hayes, 1975).

Of course, if field or experimental data are available on concentrations of insecticide in air under treated bednets at room temperature, these data can be used to calculate the probable inhaled dose using standard values for respiratory volume as shown in Box 8.

Table 2. Vapour pressure of selected pesticides at room temperatures (20–25 °C) [a]

Chemical	Vapour pressure (Pa)
Organochlorines	
Gamma-HCH (Lindane)	5600×10^{-6}
Endrin	36×10^{-6}
DDT	25×10^{-6}
Pyrethroids	
Tetramethrin (racemic mixture)	4.7×10^{-6}
Deltamethrin	2.0×10^{-6}
Permethrin	2.5×10^{-6}
Cyfluthrin (most volatile isomer)	0.96×10^{-6}
Lambda-cyhalothrin	0.2×10^{-6}
Alpha-cypermethrin	0.17×10^{-6}
Organophosphates and carbamates	
Dichlorvos	1.6
Fenitrothion	18×10^{-3}
Chlorpyrifos methyl	5600×10^{-6}
Chlorpyrifos	2500×10^{-6}
Azinphos-methyl	180×10^{-6}
Carbosulfan	41×10^{-6}

[a] Data taken from *The pesticide manual* (Worthing, 1991) or from IPCS Environmental Health Criteria for the specific substances.

Box 8

Inhalation of insecticide while sleeping under a treated net

This may be calculated as follows:

$C \times RV \times H = I$

where

C = concentration of insecticide in breathing zone ($\mu g/m^3$)

RV = respiratory volume (m^3/h)

H = average time spent under net each day (h)

I = amount of insecticide inhaled (µg/day)

Data on respiratory volumes *at rest* for adults and children indicate that the following values can be used for *RV*:

adult (>18 years)	$0.4 m^3/h$
child ($\leq$18 years)	$0.3 m^3/h$
infant ($\leq$3 years)	$0.2 m^3/h$ (USEPA, 1997a, 2002c)

Reasonable estimates of average sleeping times are:

adult 8 hours; child 10 hours; infant 12 hours

3.2.3.2 Skin contact

For anyone sleeping under a treated bednet, contact between the net and bare skin is to be expected. It is difficult to estimate how much of the insecticide might be transferred to the skin, and the quantity may vary with the type of insecticide, type of bednet material, shape of the bednet, and humidity. Data published on dislodgeable particles of deltamethrin following treatment of carpets (Maxey, Murphy & Berbrick, 1996) have shown that, for dry carpets, the transfer coefficient was stable at 2.5%. The amount of insecticide on a net when the net is first treated is

known as the target dose, usually expressed in mg/m^2. In the absence of better data, it can be assumed that 2.5% of the target dose might be transferred to the skin in contact with the net each night. This would be a worst-case estimate since it assumes that 2.5% of the target dose is dislodgeable every night, even though the body is likely to make contact with the same part of the net each night and the amount of insecticide on the net diminishes over time and with washing. The figures for potential surface area in contact with the net shown in Table 3 have been estimated using data on skin surface areas of parts of the body adapted from USEPA (1997a, 2002c), assuming that the trunk, hands, arms, lower legs and feet are uncovered and that 30% of their total surface area could be in contact with the net.

Table 3. Skin surface area potentially in contact with the net

Region	Surface area potentially in contact with net (m^2) [a]		
	Adult [b]	Child [c]	Newborn [d]
Trunk	0.167	0.069	0.0248
Hands	0.027	0.009	0.0035
Arms	0.076	0.022	0.0097
Lower legs	0.070	0.020	0.0069
Feet	0.038	0.013	0.0045
Total (*A*)	0.378	0.133	0.0494

[a] Assumes 30% of surface area of body part is in contact with the net.
[b] Adapted from data in USEPA, 1997a, assuming total body surface area of 1.8 m^2 and percentage of total body surface area for trunk is 31%, hands 5%, arms 14%, lower legs 13%, feet 7%.
[c] Adapted from data in USEPA, 2002c, for child 2 < 3 years of age, assuming total body surface area of 0.6 m^2 and percentage of total body surface area for trunk is 38.5%, hands 5%, arms 12%, lower legs 11%, feet 7%.
[d] Adapted from USEPA (2002c) and *British National Formulary* (BMA/RPSGB, 2002), assuming total body surface area of 0.23 m^2 and percentage of total body surface area for trunk is 36%, hands 5%, arms 14%, lower legs 10%, and feet 6.5%.

If dermal penetration data are available, the percentage of the transferred material that will be absorbed into the body can be calculated. In the absence of penetration data, the usual default value is 10%, unless there are indications that it should be adjusted down to 1% or up to 100%. (See section 3.2.1.3, under "Extent of absorption via the skin", for explanation of modifications.)

The potential daily dermal exposure may be calculated as shown in Box 9.

These estimated worst-case dermal exposures may be compared with the dermal AEL for the insecticide, if available. If it is assumed that 10% of the amount dislodged onto the skin could be absorbed, the estimated daily amount absorbed (adult $0.0157 \times 10^{-3}T$ mg/kg body weight; child $0.0222 \times 10^{-3}T$ mg/kg body weight; newborn $0.0412 \times 10^{-3}T$ mg/kg body weight) can be compared with the oral AEL, or with the oral NOAEL to estimate the margin of safety (see section 3.3.2).

3.2.3.3 Oral exposure

In addition to dermal exposure, oral exposure from hand-to-mouth transfer and bednet mouthing, chewing, and sucking must also be considered in the case of infants and young children. Maximum estimated amounts on the hands can be calculated using the equation in Box 9 and the surface area of the hands shown in Table 3. For hand-to-mouth transfer it is assumed that 10% of the amount present on the hand is transferred to the mouth and swallowed. Oral exposure via this route can be calculated as shown in Box 10.

Box 9

Potential daily dermal exposure from sleeping under a treated net

It is assumed that:

- The target dose of insecticide for treated nets is T mg/m^2.
- The transfer coefficient for the amount of dislodgeable insecticide from net to skin is 2.5%.
- The total area of skin potentially in contact with the net (A m^2) is as shown in Table 3 above

Potential daily dermal exposure (D) is:

$$T \times \frac{2.5}{100} \times A = D \text{ mg/day}$$

For adult, child and newborn these are:
Adult:

$$T \times \frac{2.5}{100} \times 0.378 = 0.00945 \times T \text{ mg/day}$$

equivalent to $0.157 \times 10^{-3} T$ mg/kg body weight per day for a 60-kg adult

Child:

$$T \times \frac{2.5}{100} \times 0.133 = 0.00325 \times T \text{ mg/day}$$

equivalent to $0.222 \times 10^{-3} T$ mg/kg body weight per day for a 2 < 3-year-old child weighing 15 kg

Newborn:

$$T \times \frac{2.5}{100} \times 0.0494 = 0.0001235 \times T \text{ mg/day}$$

equivalent to 0.412 x $10^{-3} T$ mg/kg body weight per day for a newborn infant weighing 3 kg

Box 10

Oral exposure via hand-to-mouth transfer

It is assumed that:

- The target dose of insecticide for treated nets is T mg/m^2.
- The transfer coefficient for the amount of dislodgeable insecticide from net to skin is 2.5%.
- The total area of hand in m^2 potentially in contact with the net is as shown in Table 3 above.
- 10% of the amount on the hand is transferred to the mouth.

Potential daily oral exposure from hand to mouth transfer is:

$$T \times \frac{2.5}{100} \times \frac{\text{Hand area}}{10} \quad \text{mg/day}$$

Child:

$$T \times \frac{2.5}{100} \times \frac{0.009}{10} = 0.023 \times 10^{-3}\ T \quad \text{mg/day}$$

equivalent to 0.0015 x $10^{-3}T$ mg/kg body weight per day for a 2 < 3-year-old child weighing 15 kg

Newborn:

$$T \times \frac{2.5}{100} \times \frac{0.035}{10} = 0.0088 \times 10^{-3}\ T \quad \text{mg/day}$$

equivalent to 0.0029 x $10^{-3}T$ mg/kg body weight per day for a newborn infant weighing 3 kg

In addition, children may mouth, chew, and suck the nets during the night. It is assumed as a worst case that an area of 50 cm^2 (0.005 m^2) of the net is in contact with the mouth overnight and that 30% of the insecticide in that area is transferred into the mouth (i.e. the same amount as can be washed out), swallowed, and absorbed. In practice, the section of bednet in contact with the mouth each night will tend to be the same, so exposure from this source will decrease significantly after a few nights' use. Oral exposure via this route can be calculated as shown in Box 11.

Box 11

Oral exposure from direct mouth contact with the net

It is assumed that:

- The target dose of insecticide for treated nets is T mg/m^2.
- An area of 0.005 m^2 is in contact with the mouth.
- 30% of the target dose is transferred into the mouth.

Potential daily oral exposure from direct mouth contact is:

$$T \times 0.005 \times \frac{30}{100} \text{ mg/day}$$

Child:

$$T \times 0.005 \times \frac{30}{100} = 1.5 \times 10^{-3}\ T \quad \text{mg/day}$$

equivalent to 0.1 x $10^{-3}T$ mg/kg body weight per day for a 2 < 3-year-old child weighing 15 kg

Newborn:

$$T \times 0.005 \times \frac{30}{100} = 1.5 \times 10^{-3}\ T \quad \text{mg/day}$$

equivalent to 0.5 x $10^{-3}T$ mg/kg body weight per day for a newborn infant weighing 3 kg

3.2.3.4 Total exposure from all routes while sleeping under a treated net

A worst case for total daily systemic exposure to insecticide while sleeping under a net from inhalation, skin contact, and oral contact can be calculated, assuming 10% of that deposited on the skin and 100% of that inhaled or swallowed is absorbed. Table 4 below collates all the critical formulae derived in Boxes 9–11 for estimating total exposure via the systemic route. The amount absorbed can then be compared with the oral AEL, or with the critical NOAEL for systemic exposure to determine the margins of safety for adults, young children and newborns (see section 3.3.2).

Table 4. Total daily systemic exposure (in mg/kg body weight per day) from all routes while sleeping under a treated bednet

	Skin contact [a]	Oral from hand-to-mouth transfer	Oral from chewing net	Total
Adult	$0.0157 \times 10^{-3}T$	~0	~0	$0.016 \times 10^{-3}T$ [b]
Child	$0.0222 \times 10^{-3}T$	$0.0015 \times 10^{-3}T$	$0.1 \times 10^{-3}T$	$0.124 \times 10^{-3}T$
Newborn	$0.0412 \times 10^{-3}T$	$0.0029 \times 10^{-3}T$	$0.5 \times 10^{-3}T$	$0.544 \times 10^{-3}T$

[a] Assumes 10% of dermal dose is absorbed systemically; 2.5% of target dose (*T*) on net is transferred to skin in contact with net; 30% of area of trunk, hands, arms, lower legs, and feet is in contact with the net; 10% of hand exposure is transferred to the mouth; 30% of insecticide in 50 cm^2 of net is transferred to the mouth and all absorbed.

[b] *T* is target dose of insecticide on the net in mg/m^2.

3.2.4 Accidental swallowing of concentrated formulations

When dipping is done in a domestic environment, it is possible that young children may get hold of a concentrated insecticide formulation (tablets, powder, or liquid) and accidentally swallow it. Depending on the acute toxicity of the insecticide, such situations may be life-threatening.

For the exposure scenario, if the insecticide formulation is packaged in single-net treatment size, it should be assumed that the whole of a single tablet or sachet of powder is ingested. If a multi-dose formulation is used, it should be assumed that a mouthful (say, 20 ml) is ingested. The amount of insecticide in the formulation will be available from the manufacturer or indicated on the label or accompanying instructions. To assess the likelihood of severe toxicity or death, the estimated exposure in mg/kg body weight should be compared with either an oral acute reference dose (see section 3.3.2.2) or the NOAEL from an oral acute toxicity test.

3.3 Risk characterization

3.3.1 Essential elements

The essential elements of the risk characterization are:

- evaluation of the overall quality of the data and its adequacy for risk assessment;
- comparison of the estimated exposures with *either* acceptable exposure levels derived from the total toxicological data, *or* NOAELs from the critical toxicity studies to give margins of safety;
- recommendation on whether exposures are acceptable or the margins of safety adequate;
- explanation of any uncertainties in the data and how these have been taken into account;
- identification of unacceptable scenarios, susceptible “at risk” groups, or groups requiring special attention.

3.3.2 Methods for assessing the safety of estimated exposures

In principle, there are three methods that may be used to assess the safety of the estimated insecticide exposure levels during treatment, washing and use of treated bednets:

i. An AEL for repeated exposure to a particular insecticide via a particular route of exposure, (oral, dermal, or inhalation) is derived. The AEL is then compared with the estimate of actual exposure via that same route. Any exposure at or below the AEL is considered to be without significant long-term risk to health.

ii. An acute reference dose (ARfD), i.e. the acceptable upper limit for exposure during one day, to an insecticide via a particular route of exposure, (oral, dermal, or inhalation), is derived. The ARfD is then compared with the estimate of acute exposure via that same route. Any exposure at or below the ARfD is considered to be without significant acute risk to health.

iii. The critical NOAEL for a particular route of exposure is divided by the estimated exposure via that route to give a margin of safety (MOS). An MOS of $\geq$100, when determined by comparison of estimated exposure with a NOAEL identified from animal data, is generally considered to be without significant risk to health, although higher and lower values may be appropriate in specific situations.

3.3.2.1 Comparison with an acceptable exposure level

Where possible, the toxicity information should be used to derive an AEL for each route of exposure. An AEL is usually derived by dividing the critical NOAEL by an uncertainty factor (UF).

$$AEL = \frac{NOAEL}{UF}$$

An AEL is usually expressed in units of mg/kg body weight per day for oral and dermal routes and in mg/m^3 for the inhalation route.

AELs should be derived only when the toxicity database is sufficiently extensive to give confidence that the major types of toxicity have been investigated by an appropriate route of exposure. In cases where there is an incomplete database, the MOS approach should be used (see section 3.3.2.3). For risk assessment of insecticides on bednets, AELs for oral and dermal routes of exposure are the most useful; AELs for the inhalation route are often unnecessary because inhalation exposures are usually negligible.

The critical NOAEL is usually the lowest NOAEL (in mg/kg body weight per day) from the toxicity studies (animal or human) conducted. However, in cases where the NOAEL for serious, irreversible toxicity is close to the lowest NOAEL, consideration should be given to taking this higher NOAEL as the critical value and applying a larger UF.

The size of the UF should take account of uncertainties in the database, including the possibility of inter-species differences and of human inter-individual differences. If the critical NOAEL is derived from an animal study, a default UF of 100 is usually used, representing a 10-fold factor for both inter-species and inter-individual differences. The contributors to the overall UF are normally multiplied because they are considered to relate to independent factors. Reviews generally support the use of a default value of 100 for the UF (Dourson & Stara, 1983; Calabrese, 1985; Lewis, 1993; Dourson, Felter & Robinson,1996; Renwick & Lazarus, 1998; Dorne, Walton & Renwick, 2001a, 2001b; Walton, Dorne & Renwick, 2001). If the critical NOAEL is derived from human data, the default UF can be reduced by a factor of 10 since inter-species differences do not have to be taken into account. If there is chemical-specific information on the toxicokinetics or toxicodynamics of the insecticide in either animals or humans, this may also allow the default UF of 100 to be modified to reflect the chemical-specific data. The UF would

generally be reduced to below 100, although the data could in rare cases indicate an increase (see WHO, 1999, for details).

There may also be reasons for rasing the default UF above 100. For example, when an LOAEL is used, rather than an NOAEL, an additional UF (often 3 or 10) is usually incorporated. In the absence of a chronic study, if an NOAEL from a sub-chronic study is used to derive an AEL for long-term exposure, an additional UF (often 10) is usually incorporated to take account of the attendant uncertainties (Dourson, Knaug & Swartout, 1992). An additional UF (often 10) may also be incorporated if the critical NOAEL relates to serious, irreversible toxicity, such as developmental abnormalities or cancer induced by a non-genotoxic mechanism. The above-suggested modifications of the default UF have been derived from extensive reviews of available toxicity databases (Dourson & Stara, 1983; Vermeire et al., 1999).

For some insecticides, the literature search will reveal that guidance values for AELs for the general public have already been set by other bodies. These include acceptable daily intakes (ADIs) set by the JMPR, reference doses or concentrations (RfDs, RfCs) set by the USEPA, and minimal risk levels (MRLs) set by the ATSDR. Some of these (ADIs, RfDs) relate to long-term oral exposure, others(RfCs) to long-term inhalational exposure; MRLs are specific for acute, intermediate, or chronic exposures. There may also be published AELs for occupational exposure via the inhalational route. However, occupational guidance values should be used with caution since they may be set assuming use of the pesticide by fit, trained personnel, wearing suitable protective clothing and exposed only for the duration of the working day or shorter periods of time, and may reflect only the need to protect against irritation. They may be set using an uncertainty factor of less than 100. They can be useful for extrapolation to the general public if account is taken of the differences in exposure conditions and vulnerability. Where any guidance values set by authoritative bodies are available, they can be used in the risk assessment, provided that they are not compromised by the results of studies appearing they were set.

3.3.2.2 Comparison with an acute reference dose

In the particular case of insecticides with significant acute toxicity, acute exposure over a short period may be potentially as hazardous as longer-term exposure. Examples include some of the chemicals with anticholinesterase activity, such as the organophosphates and carbamates, and chemicals that cause developmental toxicity. In such cases, the upper limit for acceptable exposure during any one day, known as the acute reference dose (ARfD), may need to be calculated, especially for the situation of acute exposure during dipping of bednets. 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, 1998b). It is derived in an analogous way to the AEL, using relevant human or animal studies of acute or short-term dosing. The critical NOAEL from such studies is used to derive the ARfD by application of an uncertainty factor – usually 100 if the NOAEL is based on animal data (see section 3.3.2.1).

$$\text{ARfD} = \frac{\text{NOAEL}_{\text{acute}}}{\text{UF}}$$

For organophosphate and carbamate compounds, inhibition of acetylcholinesterase in either red blood cells or brain, measured minutes to hours after dosing, is an appropriate parameter on which to base the ARfD.

3.3.2.3 Estimating the margin of safety

In cases where guidance values for acceptable exposure are not already available, or cannot be derived from the existing toxicity data, an alternative approach is to estimate the margin of safety (MOS). The MOS is the ratio of the NOAEL in mg/kg body weight per day (or mg/m^3 for the relevant route of exposure) divided by the estimated exposure in mg/kg body weight per day (or mg/m^3) for that route.

$$MOS = \frac{NOAEL_{oral/dermal/inhalation}}{EXPOSURE_{oral/dermal/inhalation}}$$

Unlike AELs (described in section 3.3.2.1), which apply generically to routes of exposure irrespective of the precise exposure scenario, an MOS applies only to a specific exposure scenario (e.g. sleeping under a treated bednet). Once an MOS has been calculated, consideration must be given to whether the MOS is of an acceptable magnitude. Generally an MOS of 100 or more for total daily exposure would be regarded as sufficient to take account of inter-species and inter-individual human differences in cases where the NOAEL is derived from animal data. If the MOS is less than 100, consideration should be given to the nature and severity of the critical effect, the likelihood of inter- and intra-species variation, how close the LOAEL is to the NOAEL, the slope of the dose–response curve, the nature of the human population exposed, etc. These considerations will aid the risk manager to make a judgement on the acceptability of the MOS. For example, if the critical effect comes from human data, an MOS as low as 10 may be acceptable. If, the critical effect comes from animal data, is of marginal toxicological significance and is reversible, or if the LOAEL is a long way away from the NOAEL or the dose–response curve is shallow, an MOS lower than 100 may be acceptable. Conversely, if the critical effect is serious and irreversible, if the LOAEL is close to the NOAEL, or if the dose–response curve is steep, an MOS of 100 or more may be considered necessary.

3.3.3 Special considerations in relation to insecticide-treated bednets

3.3.3.1 Route-to-route extrapolation

Where toxicity via specific routes of exposure has not been studied, it may be possible, using other data, to estimate the doses that by other routes would give similar systemic exposures to those actually studied. For example, in the absence of toxicity data via the dermal route, data on skin penetration may be used to

estimate systemic exposure (see “Extent of absorption via the skin” in section 3.2.1.3). The estimated systemic exposures from a particular dermal exposure can then be compared with that resulting from oral exposure, provided that the extent of oral absorption is known. The data from the repeat-dose oral toxicity studies can then be used to “read across” to the dermal exposure situation. However, if this is done, and if toxicity is attributable to the parent compound, some consideration must also be given to the possibility of a first-pass effect in oral exposure situations. Parent compounds absorbed into the circulation of the gut are rapidly transported to the liver and metabolized. Thus, systemic concentrations of parent compound may be higher and may persist for longer following dermal exposure than following oral exposure. Similarly, in the absence of toxicity data for the inhalation route, “read across” from oral studies may be possible, again with consideration being given to the possibility of a first-pass effect reducing parent compound toxicity from exposure via the oral route compared with the inhalational route. If data on systemic bioavailability following dermal, inhalational, or oral exposure do not exist, default values can be used to estimate the possible systemic exposure (see section 3.2.3.4).

3.3.3.2 Early warning of undesirable exposures

Information on toxicity may be available from human case reports and from occupational and epidemiological studies, which may indicate the levels of exposure that are known to be toxic for humans and the type of toxicity to be observed. The nature of the first signs of toxicity in humans is important to the risk assessment. It is an advantage if the first signs are easily recognized, benign, and reversible on stopping exposure, since it will help to avoid excessive exposure. If, on the other hand, the first signs of excessive exposure are serious, prolonged, or life-threatening, much larger margins of safety may have to be applied to arrive at an acceptable exposure level. With pyrethroids, for example, an early sign of excessive exposure is tingling sensations in the face. This seems to occur at exposure levels below those that cause other types of toxicity, and is reversible on stopping exposure. Persistence of such effects provides a warning

sign overexposure could be occurring and that steps to reduce exposure should be taken. With anticholinesterase exposure, changes in visual acuity or pupil size may indicate overexposure. Such benign, reversible warnings are valuable in preventing overexposure in general use situations, and may be taken into account in determining acceptable margins of safety.

3.3.3.3 Interactions between insecticides and/or vehicles

Possible toxicological interactions between different insecticides may have to be considered if the use of more than one insecticide on a single net is proposed or if bednets are used in conjunction with house spraying of insecticides. Insecticides of the same class may produce additive toxic effects and insecticides of different classes may, rarely, produce supra-additive or synergistic toxic effects, and this will have to be taken into account in the risk assessment. If the use of more than one insecticide on a net is contemplated, it is important that mechanisms of action and toxicokinetics are taken into consideration in assessing whether an interaction is possible, and what type. Much more information is available on drug interactions than pesticide interactions. Some interactions can be predicted from a knowledge of metabolic pathways and receptor specificities; many, however, are not predictable but may nonetheless be serious and life-threatening. For example, considerable national and international effort is currently being devoted to assessing the effects of aggregate and cumulative exposure to organophosphates (USEPA, 2001, 2002b; COT, 2002). To date, most insecticide treatments of bednets have involved aqueous vehicles; if a non-aqueous vehicle is considered, toxicological assessment of the vehicle itself, and of possible interactions with insecticides, would be required.

3.3.3.4 Health and nutritional status of individuals

Under the conditions in which insecticide-treated bednets will be used, consideration may also need to be given to the role of other factors, such as nutrition and intercurrent disease, that may influence of toxic reactions to pesticides. Animal studies are normally carried out on healthy, well nourished animals, and these may be more resistant to the toxic effects of a pesticide then individuals who are malnourished, suffer from specific nutritional deficiencies, or have infections that might impair liver or renal function. For example, the metabolism of some chemicals depends on adequate folate or glutathione reserves being available for detoxification. The traditional safety margins built into the derivation of AELs would be expected to take account of much of these inter-individual differences. In the case of small MOS estimates, however, these factors may need to be borne in mind in assessing the acceptability of those estimates.

Pregnancy is another factor that may need separate consideration. Since the embryo and fetus may be more susceptible than adults and children, special attention should be paid to any potential risks in pregnancy and should be reflected in the data on reproductive toxicity. If no such data are available, no conclusions can be drawn about the safety of exposure during pregnancy.

3.3.3.5 Chemicals unsuitable for use on bednets

Insecticide that are both genotoxic and carcinogenic may cause irreversible toxicity, even at very low exposures. Such substances are generally considered unsuitable for bednet use, irrespective of the likely exposure.

It is relatively unusual for chemicals to be absorbed through the skin in sufficient amounts to cause death. However, some pesticides have acute dermal LD_{50} values in animals which indicate that mortality has been induced following dermal application (see WHO, 2002). For such substances it is important to determine whether there may be circumstances in which severe

toxicity could be induced as a result of accidental dermal exposure or careless handling. The risk–benefit considerations may well preclude the use of such substances as insecticides for bednets because of the potential risks to those dipping nets.

In the particular case of accidental swallowing of concentrated insecticide formulations, there may be little or no margin of safety for infants. If the estimated exposure exceeds the oral ARfD (where appropriate) or the highest dose causing no severe toxicity in acute oral toxicity tests, consideration may need to be given to the suitability of the particular formulation for domestic use. The possibility for risk reduction measures, such as child-resistant packaging and the incorporation of bittering agents into formulations may also need to be considered.

3.3.3.6 Consideration of long-term, low-dose exposure

While repeat-dosing studies in laboratory animals address organ and tissue toxicity in detail, their focus on histopathology may well preclude the detection of subtle changes in neurological function. Possible neurological damage following long-term low-dose exposure of humans to organophosphates has been a subject of concern, particularly following reports of such effects in those using organophosphates in sheep dips. The topic was considered in 1999 by the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. The Committee concluded that the evidence did not support the view that low-dose exposure to organophosphates caused clinically significant neurophysiological effects or peripheral neuropathy. The available data indicated that any risks involved in using sheep dips arose predominantly from exposure to the concentrated formulation (COT, 1999). Nevertheless, studies are continuing on long-term, low-dose human exposures, and the findings would need to be taken into account in assessing any risks from the possible use of organophosphates on bednets.

3.3.3.7 Risk–benefit considerations

When aspects of a risk assessment of a particular insecticide are unfavourable, risk managers will want to give consideration to such risk–benefit aspects as the nature of the potential for toxicity compared with the potential benefits of malaria prevention.

3.3.4 Possibilities for refining the risk characterization

With the exception of accidental swallowing of insecticide formulation, the highest exposures will affect those treating bednets by dipping. If the initial risk characterization for a particular insecticide indicates that these short-term exposures are unacceptable in relation to AELs developed using repeat-dose data or NOAELs derived from repeat-dose data, consideration can be given to whether short-term exposures actually pose a lesser risk than that indicated from repeat-dose data. This can be ascertained only by detailed examination of the toxicity database. In the case of insecticides with anticholinesterase activity, it should be borne in mind that acute exposures may be just as hazardous as longer-term exposures.

For example, if the AEL initially used is set on the basis of the NOAEL from a long-term study, consideration should be given to whether it might be more appropriate to set a separate AEL for short-term exposure, based on the (probably higher) NOAELs from short-term studies, such as sub-acute and developmental studies.

The generic model has been developed using a range of scenarios, but workers experienced in malaria control should modify the suggested scenarios if local factors indicate that alternatives may be more appropriate. For example, rectangular nets are usually more spacious than conical nets and may result in less skin contact with the net (PATH Canada, 1998). Even better would be to collect actual exposure data under normal use conditions, so that the model can be improved and made more relevant to local conditions.

3.4 Conclusions

The proposed generic model for risk assessment of production and use of insecticide-treated bednets is relatively simple in that the application of the model to any specific insecticide requires knowledge of three parameters:

- the critical AELs/NOAELs for systemic exposure (ideally via dermal, oral and inhalation routes);
- the concentration (*C*)of the insecticide in the dipping solution;
- the target concentration (*T*)of the insecticide on the bednet.

It should be recognized, however, that derivation of AELs and NOAELs from toxicity data is time-consuming and requires toxicological expertise. In cases where internationally agreed AELs for exposure of the general public are already available for a particular insecticide (e.g. from JMPR, IPCS, USEPA, ATSDR, etc.), these may be used in the model.

4. Summary of the model and a worked example

Below is a summary of the generic model together with a worked example on deltamethrin, the details of which have been published previously (Barlow, Sullivan & Lines, 2001).

Generic model for treated bednets and worked example (deltamethrin)

Generic risk assessment model	Worked example: deltamethrin
1. Toxicity data	**1. Toxicity data**
Aim: To assess available toxicity data and derive acceptable exposure levels	*Aim: To assess available toxicity data and derive acceptable exposure levels*
1.1 Conduct literature search for human, animal and in vitro toxicity data and any necessary physicochemical data on the insecticide.	1.1 Literature search on deltamethrin conducted on MEDLINE, TOXLINE and sources of reviews (WHO IPCS, JMPR, USEPA, PSD, IARC, ATSDR, etc).
1.2 Obtain relevant reviews and key original papers.	1.2 Comprehensive reviews available from IPCS and IARC. Key repeat-dose rat dermal study available from manufacturer. Key human occupational and poisoning papers obtained.
1.3 Tabulate types of study, toxic effects observed, no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs).	1.3 All available relevant animal and human studies tabulated.
1.4 Assess whether quality of database is adequate for risk assessment (range of studies, conduct of studies, adequacy of dose–response data, etc).	1.4 Studies available on all relevant types of toxicity, most via oral route, with some inhalation and dermal studies. Most conducted to acceptable standards with adequate dose–response data.

Generic risk assessment model	Worked example: deltamethrin
1.5 If database is adequate, identify critical toxic effect(s).	1.5 In humans, first toxic symptom is facial paraesthesia, reversible on cessation of exposure. Critical toxic effect in animals is neurotoxicity.
1.6 If the insecticide is genotoxic or extremely acutely toxic via dermal or oral routes, consider whether it is worth proceeding with risk assessment.	1.6 Deltamethrin not genotoxic and has low acute toxicity. Proceed with risk assessment.
1.7 If 1.6 does not apply, identify pivotal study/studies giving dose–response data for critical effect(s).	1.7 Pivotal studies were human occupational studies (for paraesthesia), 21-day rat dermal study, 2-year dog dietary study, and 90-day rat gavage study (for neurotoxicity).
1.8 Identify critical NOAEL(s) from pivotal studies for acute exposure and for longer-term (repeat-dose) exposure.	1.8 Critical NOAELs for deltamethrin: Acute oral exposure human: 1.75 g/day. 21-day dermal, rat: 1000 mg/kg bw per day. 90-day gavage, rat, 2-year-dietary, dog: 1 mg/kg bw per day.
1.9 Assess whether the database allows the setting of acceptable exposure levels (AELs) for short-term and long-term exposure via oral, dermal and inhalational routes.	1.9 Database adequate to allow setting of AELs for long-term dermal and oral exposure. Not adequate for acute exposure. Inhalation exposure is negligible (see 2.3).

Generic risk assessment model	Worked example: deltamethrin
1.10 Set AELs 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): $AEL = \frac{NOAEL}{UF}$ A default UF of 100 is recommended for NOAELs derived from animal studies. A default UF of 10 for NOAELs derived from human studies. (See main text, section 3.3.2.*1* for variations on these defaults.)	1.10 The following AELs were set from the toxicity data: Dermal AEL = $\frac{1000}{100} = 10$ mg/kg bw per day Although derived from 21-day dermal animal toxicity study, no additional UF used for sub-chronic study because no toxicity observed at highest dose tested. Default UF of 100 used. Oral AEL = $\frac{1}{100} = 0.01$ mg/kg bw per day Derived from sub-chronic and chronic studies, so default UF of 100 used.
1.11 Where other reputable bodies have set ADIs, RfDs, ARfDs, MRLs, etc, for various routes of exposure, use these as AELs for bednet scenarios.	1.11 The ADI of 0.01 mg/kg bw per day set by JMPR in 1982 used as AEL for oral exposure. Inspection of up-to-date database confirmed critical oral NOAEL remains at 1 mg/kg bw per day.
1.12 Tabulate AELs for use in subsequent risk characterization.	1.12 AELs used in risk characterization: Dermal AEL 10 mg/kg bw per day Oral AEL, 0.01 mg/kg bw per day

Generic risk assessment model	Worked example: deltamethrin
2. Exposure assessment	**2. Exposure assessment**
Aim: To estimate exposure via dermal, oral and inhalation routes during dipping, washing and use of nets.	*Aim: To estimate exposure via dermal, oral and inhalation routes during dipping, washing and use of nets.*
2.1 Estimate dermal and systemic exposure during dipping of nets – of an adult and a child (suggested defaults 60 kg for adult, 40 kg for 11-year-old child) – using both safest and least safe scenarios – by either (a) volume of suspension on skin, or (b) amount of active ingredient on skin	2.1. Estimate dermal and systemic exposure during dipping of nets
(a) Dermal exposure during dipping (safest scenario), estimated by volume of suspension on the skin	*(a) Dermal exposure during dipping (safest scenario), estimated by volume of suspension on the skin*
It is assumed that: • A maximum of 4 ml of dipping suspension could contaminate the hands (2 ml/hand) • An amount, *A* mg, of insecticide, is evenly distributed in *B* ml of dipping solution/suspension, giving a concentration of $A/B = C$ mg/ml.	• 400 mg of deltamethrin is evenly distributed in 500 ml of dipping solution / suspension, giving a concentration of $\frac{400}{500} = 0.8$ mg/ml

Generic risk assessment model	Worked example: deltamethrin
The amount deposited on the skin would be: 0.067*C* mg/kg bw for a 60-kg adult 0.1*C* mg/kg bw for a 40-kg child *See Box 3 for details.*	The amount deposited on the skin is: 0.067*C* = 0.05 mg/kg bw for a 60-kg adult 0.1*C* = 0.08 mg/kg bw for a 40-kg child
(b) Dermal exposure during dipping (safest scenario) estimated by amount of active ingredient on the skin	*(b) Dermal exposure during dipping (safest scenario) estimated by amount of active ingredient on the skin*
It is assumed that: • For product concentration of 1.0 mg/ml, the 95th percentile rate of exposure inside protective gloves is 0.072 mg/min of diluted product • An amount, *A* mg, of insecticide is evenly distributed in *B* ml of dipping solution/suspension, giving a concentration of *A*/*B* = *C* mg/ml. • Potential contact time is 10 minutes	• 400 mg of deltamethrin is evenly distributed in 500 ml of dipping solution/suspension, giving a concentration of $\frac{400}{500}$ = 0.8 mg/ml
The amount deposited on the skin would be: 0.012*C* mg/kg bw for a 60-kg adult 0.018*C* mg/kg bw for a 40-kg child *See Box 4 for details.*	The amount deposited on the skin is: 0.012*C* = 0.0096 mg/kg bw for a 60-kg adult 0.018*C* = 0.0144 mg/kg bw for a 40-kg child

Generic risk assessment model	Worked example: deltamethrin
(c) Dermal exposure during dipping (least safe scenario) estimated by volume of suspension on the skin It is assumed that: • 8 ml of solution is in immediate contact with the hands. • 8 ml of solution is in contact with the lower arms. • 8 ml of solution is spilled onto the legs and feet. • An amount, *A* mg, of insecticide is evenly distributed in *B* ml of dipping solution/suspension, giving a concentration of *A*/*B* = *C* mg/ml The amount deposited on the skin would be: 0.4*C* mg/kg bw for a 60-kg adult 0.6*C* mg/kg bw for a 40-kg child *See Box 5 for details*	*(c) Dermal exposure during dipping (least safe scenario) estimated by volume of suspension on the skin* • 400 mg of deltamethrin is evenly distributed in 500 ml of dipping solution / suspension, giving a concentration of $\frac{400}{500}$ = 0.8 mg/ml The amount deposited on skin is: 0.4*C* = 0.32 mg/kg bw for a 60-kg adult 0.6*C* = 0.48 mg/kg bw for a 40-kg child
(d) Systemic exposure during dipping estimated by skin penetration It is assumed that: • Absorption via the skin is 10% of the amount deposited on the skin	*(d) Systemic exposure during dipping estimated by skin penetration* • 400 mg of deltamethrin is evenly distributed in 500 ml of dipping solution/suspension, giving a concentration of

Generic risk assessment model	Worked example: deltamethrin
• An amount, *A* mg, of insecticide is evenly distributed in *B* ml of dipping solution/suspension, giving a concentration of *A*/*B* = C mg/ml	$\frac{400}{500}$ = 0.8 mg/ml
The amount absorbed systemically would be:	The amount absorbed systemically is:
For scenario (a) in 2.1: 0.0067*C* mg/kg bw for a 60-kg adult 0.010*C* mg/kg bw for a 40-kg child	For scenario (a) in 2.1: 0.0067*C* = 0.005 mg/kg bw for a 60-kg adult 0.010*C* = 0.008 mg/kg bw for a 40-kg child
For scenario (b) in 2.1: 0.0012*C* mg/kg bw for a 60-kg adult 0.0018*C* mg/kg bw for a 40-kg child	For scenario (b) in 2.1: 0.0012*C* = 0.001 mg/kg bw for a 60-kg adult 0.0018*C* = 0.0014 mg/kg bw for a 40-kg child
For scenario (c) in 2.1: 0.04*C* mg/kg bw for a 60-kg adult 0.06*C* mg/kg bw for a 40-kg child	For scenario (c) in 2.1 0.04*C* = 0.032 mg/kg bw for a 60-kg adult 0.06*C* = 0.048 mg/kg bw for a 40-kg child
See Box 6 for details.	

Generic risk assessment model	Worked example: deltamethrin
(e) Hand contamination from splashes during emptying of container of liquid concentrate	*(e) Hand contamination from splashes during emptying of container of liquid concentrate*
If the insecticide formulation is in the form of a liquid, skin contamination from splashes during emptying of the container into the bucket or bowl used for dipping must be added to the above estimates, using the values for volume of contamination (*V*) given in Box 2 of the main text and the concentration of insecticide per ml in the formulation (*F*). Amount = *V* x *F* mg	The formulation of deltamethrin is a solid tablet. It is assumed there is no exposure to the undiluted formulation.
2.2 Estimate dermal and systemic exposure during washing of nets	2.2 Estimate dermal and systemic exposure during washing of nets
Dermal exposure during washing of a single batch of nets as estimated by volume of suspension on the skin	*Dermal exposure during washing of a single net as estimated by volume of suspension on the skin*
It is assumed that: • 8 ml of washing water is in contact with the hands. • 8 ml of washing water is in contact with the lower arms. • 8 ml of washing water is spilled onto the legs and feet. • Washing of contaminated skin is not carried out immediately after dipping.	

Generic risk assessment model	Worked example: deltamethrin
• The exposure is equivalent to one-third of the total dermal exposure during dipping with the least safe scenario (scenario (c) in 2.1).	• The exposure is equivalent to one-third of 19.2 mg, the total dermal exposure during dipping with the least safe scenario.
The amount deposited on the skin during washing would be: 0.13*C* mg/kg bw for a 60-kg adult 0.2*C* mg/kg bw for a 40-kg child *See Box 7 for details*	The amount deposited on the skin is: 0.13*C* = 0.10 mg/kg bw for a 60-kg adult 0.2*C* = 0.16 mg/kg bw for a 40-kg child
2.3 Estimate inhalation, dermal, and oral exposures from sleeping under treated nets For clarity, separate calculations of exposures via inhalation, dermal, and oral routes are shown earlier in the text in Boxes 8–11. In practice only the short formulae shown below, which are derived from Boxes 8–11, need be used to estimate total systemic exposure.	2.3 Estimate inhalation, dermal, and oral exposures from sleeping under treated nets
Estimate total systemic exposures for adults, children, and newborns via dermal, oral, and inhalation routes and convert to total systemic exposure	*Estimate total systemic exposures for adults, children, and newborns via dermal, oral, and inhalation routes and convert to total systemic exposure*

Generic risk assessment model	Worked example: deltamethrin
It is assumed that: • The target dose for treated nets is *T* mg/m^2 • 10% of amount deposited on skin is absorbed systemically • 100% of the amount ingested is absorbed systemically • Inhalation is negligible	 • The target dose for deltamethrin-treated nets is 25 mg/m^2
Using the formulae in Table 4, the total systemic absorption is: Adult: 0.016 x 10^{-3}*T* mg/kg bw per day Child: 0.124 x 10^{-3}*T* mg/kg bw per day Newborn: 0.544 x 10^{-3}*T* mg/kg bw per day	Using the formulae in Table 4, the total systemic absorption is: Adult: 0.016 x 10^{-3} x 25 = 0.0004 mg/kg bw per day Child: 0.124 x 10^{-3} x 25 = 0.003 mg/kg bw per day Newborn: 0.544 x 10^{-3} x 25 = 0.014 mg/kg bw per day
If measured inhalation data are available or if inhalation could be significant (high vapour pressure) add amount for inhalation, using formula in (a) above, and assuming 100% of amount inhaled is absorbed systemically.	Deltamethrin has a low vapour pressure (2.0 x 10^{-6} Pa) so inhalation negligible and can be ignored.
2.4 Accidental ingestion of concentrated insecticide formulation The consequences of accidental ingestion of any concentrated formulation by infants and young children can be assessed by:	2.4 Accidental ingestion of concentrated insecticide formulation

Generic risk assessment model	Worked example: deltamethrin
• Assuming that the entire contents of a single net treatment formulation (before dilution) is swallowed. The amount (*Q*) of active insecticide in a single tablet, sachet of powder, or bottle of liquid concentrate should be ascertained from the manufacturer if not stated on the packaging or in the accompanying instructions.	• For deltamethrin the formulation is marketed as a single net treatment in the form of a solid tablet. The amount of active insecticide in a single tablet is 400 mg.
The amount of oral exposure would be: *Q* mg equivalent to: *Q*/15 mg/kg bw for a 2 < 3-year-old, 15-kg child	The amount of oral exposure is: 400 mg equivalent to: 400/15 = 26.6 mg/kg bw for a 2 < 3-year-old, 15-kg child
3. Risk characterization	
3.1 Compare each of the exposure estimates obtained in section 2 for each of the scenarios: *Either:* with the Acceptable Exposure Level (AEL) for the same route of exposure (see section 3.3.2. of main text for details); *or:* with the no-observed-adverse-effect level (NOAEL) for the same route of exposure to obtain the margin of safety (MOS).	3.1 Comparison of estimated exposures with AELs or NOAELs *Dipping of nets, safest scenario* Dermal exposure: Adult: 0.05 mg/kg bw per day Child: 0.08 mg/kg bw per day These are below the dermal AEL of 10 mg/kg bw perday. Equivalent systemic exposure: Adult: 0.005 mg/kg bw per day Child: 0.008 mg/kg bw per day These are below the oral AEL of 0.01 mg/kg bw per day.

Generic risk assessment model	Worked example: deltamethrin
	Dipping of nets, least safe scenario Dermal exposure: Adult: 0.48 mg/kg bw per day Child: 0.72 mg/kg bw per day These are below the dermal AEL of 10 mg/kg bw per day; exposures acceptable. Equivalent systemic exposure: Adult: 0.048 mg/kg bw per day Child: 0.072 mg/kg bw per day These are above the oral AEL of 0.01 mg/kg bw per day. MOSs are 20 for adult and 13 for child, compared with the oral NOAEL of 1 mg/kg bw per day.
3.2 Using the AEL comparison, if an exposure is below the relevant AEL, it can be reasonably assumed that the worst-case conditions for exposure are without appreciable risk to human health. Using the NOAEL comparison, if the MOS is 100 or more, it can be reasonably assumed that the worst-case conditions for exposure are likely to be without appreciable risk to human health.	3.2 Exposures are below the relevant AELs, so can be assumed to be safe, except for estimated systemic exposure in the least safe scenario.

Generic risk assessment model	Worked example: deltamethrin
3.3 If an exposure is above the relevant AEL, consider refining the risk assessment or whether any remedial measures could be taken to reduce exposure. If an exposure gives an MOS of less than 100, consider refining the risk assessment or whether any remedial measures could be taken to reduce exposure.	3.3 An MOS of less than 100 for estimated systemic exposure in least safe scenario emphasizes needto use gloves, for example, and to minimize spills of liquid onto skin. *Sleeping under nets* Total systemic exposure: Adult: 0.0004 mg/kg bw per day Child: 0.003 mg/kg bw per day Newborn: 0.014 mg/kg bw per day These are below the oral AEL of 0.01 mg/kg bw per day, except for newborn. MOS for newborn is 71 compared with the oral NOAEL of 1 mg/kg bw per day. Exposures are below the relevant AEL, so can be assumed safe, except for estimated systemic exposure in the newborn. An MOS of less than 100 for estimated systemic exposure of newborns emphasizes the need, for example, to use nets suspended so that skin and oral contact for newborns are minimized.

Generic risk assessment model	Worked example: deltamethrin
3.4 If the initial risk assessment indicates that exposures are unacceptable and neither refinement of the risk assessment nor additional remedial measures to reduce exposure are possible, it should be concluded that the insecticide is unsuitable for “do-it-yourself” home-based use. In some cases, the risks to home-based dippers may unacceptable, but the risks to those washing or sleeping under nets are acceptable. In such cases, the possibility of using the insecticide only on commercially pretreated nets could be considered.	3.4 No unacceptable exposures found

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6. List of abbreviations and acronyms

ADI	acceptable daily intake
AEL	acceptable exposure level
ARfD	acute reference dose
ATSDR	United States Agency for Toxic Substances and Disease Registry
C	concentration of insecticide after dilution ready for net treatment
CEC	Commission of the European Communities
EL	effect level
EU	European Union
GLP	Good Laboratory Practice
IARC	International Agency for Research on Cancer
IPCS	International Programme on Chemical Safety jointly sponsored by the United Nations Environment Programme, the International Labour Organization and the World Health Organization
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
MOS	margin of safety
LOAEL	lowest-observed-adverse-effect level
MRL	minimal risk level

NOAEL	no-observed-adverse-effect level
OECD	Organisation for Economic Co-operation and Development
PSD	Pesticides Safety Directorate of the United Kingdom
RfD	reference dose
SOP	standard operating procedure
T	Target dose of insecticide on treated nets
DEFRA	United Kingdom Department for Environment, Food and Rural Affairs
UF	uncertainty factor
USAID	United States Agency for International Development
USEPA	United States Environmental Protection Agency
WHO	World Health Organization
WHOPES	World Health Organization Pesticide Evaluation Scheme