

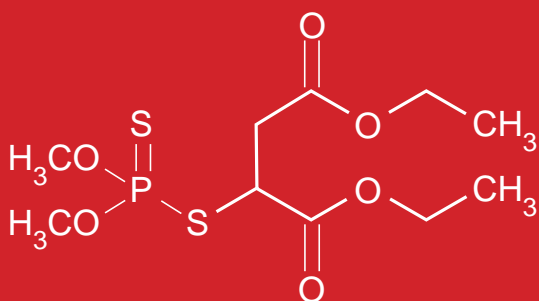
USE OF MALATHION FOR VECTOR CONTROL

REPORT OF A WHO MEETING GENEVA, 16–17 MAY 2016

WHO PESTICIDE EVALUATION SCHEME,
DEPARTMENT OF CONTROL OF NEGLECTED TROPICAL DISEASES

GLOBAL MALARIA PROGRAMME

DEPARTMENT OF PUBLIC HEALTH, ENVIRONMENTAL
AND SOCIAL DETERMINANTS OF HEALTH



World Health
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1. INTRODUCTION

The World Health Organization (WHO) convened a group of experts to review the risk of malathion used in public health and discuss the implications of WHO's recommendations on the use of malathion in vector control following the evaluation of malathion as "*probably carcinogenic to humans*" by the International Agency for Research on Cancer (IARC). A particular concern was the potential implication of the availability or non-availability of malathion for vector control in the context of Zika virus disease.

The IARC monograph concluded that there was "*limited evidence*" in humans for carcinogenicity, based on observations of positive associations with the incidence of non-Hodgkin lymphoma and aggressive cancer of the prostate. It also concluded that there was "*sufficient evidence*" for carcinogenicity in experimental animals, and mechanistic and other relevant data supported the classification of malathion in Group 2A ("*probably carcinogenic to humans*").

In consideration of the IARC's classification and the availability of a significant number of new studies, an extraordinary Joint FAO/WHO Meeting on Pesticide Residues (JMPR) was held on 9–13 May 2016 at WHO headquarters in Geneva, Switzerland. The outcome of this meeting, at which the risk to consumers from exposure to malathion via residues in food following its agricultural use was assessed, informed the assessment by the experts of the risk from its vector control uses.

The JMPR reaffirmed the acceptable daily intake (ADI) of 0–0.3 mg/kg bw and the acute reference dose (ARfD) of 2 mg/kg bw established in 1997 and 2003 respectively on the basis of inhibition of acetylcholinesterase activity in both cases. Inhibition of acetylcholinesterase activity was the most sensitive, relevant adverse effect of malathion identified.

The meeting reviewed two formulations of malathion: emulsion, oil in water (EW) and ultra-low volume (UL). Both formulations are currently recommended by WHO for outdoor space spraying via vehicle-mounted and hand-held equipment. It was noted that these malathion products are not recommended by WHO for indoor space spraying and this scenario was therefore not considered further at the meeting.

Malathion wettable powder (WP) formulation is recommended by WHO for malaria vector control by indoor residual spraying (IRS). No specification of a malathion WP formulation, including toxicologically significant impurities¹ such as malaaxon and isomalathion, has been proposed to WHO by any manufacturer² and therefore it was not possible to undertake a risk assessment for this IRS scenario.

The health-based guidance values for malathion established by the JMPR are for the oral route of exposure. As the oral absorption of malathion is extensive (80%) and the ADI and ARfD are based on a systemic end-point, the experts concluded that the ADI and ARfD

¹ Joint FAO/WHO meeting on pesticide residues. Geneva: World Health Organization; 2016 (http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/, accessed May 2016).

² The current WHO specification is available for the technical material and EW and UL formulations, but not for WP (http://who.int/entity/whopes/quality/en/Malathion_specs_eval_WHO_March_2013.pdf, accessed May 2016).

without adjustment for oral absorption would be applicable for other routes of exposure, following adjustment for absorption by those routes, if necessary.

The JMPR noted that the only two tumours considered to be treatment-related following dietary exposure of rodents to malathion were liver adenomas in one study in mice and nasal adenomas in one study in rats. The JMPR concluded that these tumours were secondary to other toxicological effects in the target tissues and had a clear threshold and were secondary to other effects in the target tissues. The upper-bound of the ADI provided a margin of exposure of three orders of magnitude for the doses causing these tumours, and hence the experts concluded that the risk to humans from these carcinogenic effects was unlikely at exposures below the ADI.

The JMPR concluded that the genotoxic effects observed in some test systems with both malathion and malaoxon occur secondary to the formation of reactive oxygen species which will exhibit a threshold, and therefore malathion and malaoxon are unlikely to be genotoxic at anticipated dietary exposures.

The meeting of experts was opened by Dr Dirk Engels, Director, WHO Department of Control of Neglected Tropical Diseases. He welcomed participants and recalled that the extraordinary meeting of the JMPR (Geneva, 9–13 May 2016) had re-assessed the risk of malathion, as well as of glyphosate and diazinon, and that the conclusions from that meeting would be discussed in this specific meeting. He noted that IARC's classification of malathion as probably carcinogenic could have some implications on continuing the use of malathion for vector control, especially in the control of *Aedes* spp. in the context of the Zika virus outbreak. WHO is committed to recommending the use of low-risk pesticide products for public health and vector control, and Dr Engels hoped that the advice given to WHO would help the Organization in making an evidence-informed decision to advise Member States on the use of malathion.

Dr Raman Velayudhan, Coordinator, Vector Ecology and Management, further briefed the group on the current usage of malathion in the control of dengue and Zika virus diseases.

Dr Rajpal Yadav, Scientist in charge of the WHO Pesticide Evaluation Scheme, summarized the interests declared by the invited experts and explained the procedures of the meeting.

Professor Alan Boobis, Imperial College London, UK was appointed as Chairperson and Dr Antero Aitio, Helsinki, Finland as Rapporteur.

Five invited experts, one staff member representing the IARC, and eight staff members representing the WHO Secretariat attended the meeting (see Annex 1 – List of participants; Annex 2 – Agenda).

Declarations of interest

All the five invited experts completed a *Declaration of interests for WHO experts* before the meeting for assessment by the WHO Secretariat. The meeting requires the participation of high-level experts who are therefore involved in international meetings and working groups dealing with chemical risk assessment; these experts are also involved in improving the methodology of chemical risk assessment. The following interests were declared:

Dr Alan Boobis, Imperial College London, UK has provided advice to various governmental institutions and international organizations about pesticides in general. He has participated in several working groups of the International Life Sciences Institute (ILSI) dealing with the development or improvement of the methodology used to assess chemical risk. He is also a member of the ILSI Health and Environmental Sciences Institute Board of Trustees, chair of the ILSI Board of Trustees and vice-president of ILSI Europe. These positions are not remunerated and are directly due to the scientific excellence of Dr Boobis and to his international recognition. In 2014, Dr Boobis provided consultancies to two private companies for a fee, but these were not related to the topic of the meeting. He has also received research support from GSK/MRC for a PhD studentship and from Cefic LRI for a study about cross-species comparison of animal and human NOAELS. Neither study was directly related to pesticides.

Dr **Matthew O'Mullane** declared that he has been Director of the Chemical Review Programme of the **Australian Pesticides and Veterinary Medicines Authority** responsible for regulating pesticides and veterinary medicines since 2013, and that his organization is reevaluating malathion.

The WHO Secretariat assessed the interests declared by the experts, which it determined not to be directly related to the topics under discussion at the meeting. It was therefore decided that those declarations did not constitute conflicts of interest and that the considered experts could participate in the meeting.

2. MALATHION UL 1186 g/L

Summary and conclusions

Assuming that

- malathion ultra-low volume application is used for outdoor space spraying only;
- the product complies with the WHO specification, notably with reference to the impurity profile;
- guidelines for the space spraying of insecticides for vector and public health pest control,¹ and label instructions are strictly followed, especially that the hands are protected with suitable gloves and that the arms are covered; and
- the application rate is no more than 260 g/ha;

the *WHO generic risk assessment model for indoor and outdoor space spraying of insecticides* predicts that

- the systemic dose of malathion received by the operators is very likely to exceed acceptable levels if the operating guidelines (described in the model as the “guideline scenario”) are not strictly adhered to;
- the systemic dose of malathion may reach 270% of the acceptable systemic time weighted average (TWA) dose (described in the model as the long-term tolerable systemic dose (TSD), and 94% of the TSD for acute exposure (TSD_{AC}), in operators of hand-held sprayers even when complying with the operating instructions;
- the systemic dose in vehicle-mounted spraying is predicted to reach 39% of the long-term TSD and 10% of the TSD_{AC} when complying with the operating instructions;
- the exposure to malathion does not exceed the TSD for bystanders of different ages (8%, 10% and 20% of the TSD, and 29%, 37% and 72% of the TSD_{AC} in adults, children and toddlers, respectively), 0.3% and 1.4% of the TSD_{AC} of newborns of resident mothers, and of resident operator mothers; and
- the exposure to malathion does not cause untoward effects on the aquatic environment, soil organisms, birds or herbivorous mammals.

As the operator exposure is mainly through dermal absorption, in order to ensure that the exposure remains below the TSD in all cases, operators must wear gloves that provide effective (no less than 97%) protection.

¹ Space spray application of insecticides for vector and public health pest control – a practitioner’s guide. Geneva: World Health Organization; 2003 (WHO/CDS/WHOPES/GCDPP/2003.5; whqlibdoc.who.int/hq/2003/WHO_CDS_WHOPES_GCDPP_2003.5.pdf, accessed May 2016).

Excessive exposure to malathion will cause a decrease in red blood cell acetylcholinesterase activity, which is more likely to occur in the operators of hand-held sprayers than vehicle-mounted sprayers. Red blood cell acetylcholinesterase activity levels of operators of hand-held sprayers should be regularly monitored as part of an occupational health monitoring scheme, and the operators should be removed from further exposure if the levels drop 25% or more below baseline level.^{1,2}

In the guideline scenario assessed using this risk assessment model, the operators should wear appropriate personal protective equipment (gloves, long-sleeved protective clothes and respirators), according to the label instructions and the relevant WHO manual both when mixing and loading and when spraying. In the lax standard scenario described in the risk assessment model (results not presented because all operator exposures are very likely to exceed acceptable levels), no personal protective equipment is used.

¹ Pesticides and their application for the control of vectors and pests of public health importance. Geneva: World Health Organization; 2006 (WHO/CDS/NTD/WHOPES/GCDPP/2006.1); http://apps.who.int/iris/bitstream/10665/69795/1/WHO_CDS_NTD_WHOPES_GCDPP_2006.1_eng.pdf, accessed May 2016).

² Cholinesterase monitoring of agricultural pesticide applicators. California: USA; Office of Environmental Health Hazard Assessment (OEHHA) (<http://oehha.ca.gov/pesticides/program/cholinesterase-monitoring-agricultural-pesticide-applicators>, accessed May 2016).

3. MALATHION EW 440 G/L

Summary and conclusions

Assuming that

- malathion EW formulation is used for outdoor space spraying only;
- the product complies with the WHO specification, notably with reference to the impurity profile;
- guidelines for the space spraying of insecticides for vector and public health pest control¹ and label instructions are strictly followed, especially that the hands are protected with suitable gloves and that the arms are covered; and
- the application rate is no more than 352 g/ha;

the *WHO generic risk assessment model for indoor and outdoor space spraying of insecticides* predicts that

- the systemic dose of malathion received by the operators is very likely to exceed acceptable levels if the operating guidelines (described in the model as the “guideline scenario”) are not strictly adhered to;
- the systemic dose of malathion may reach 63% of the acceptable systemic TWA (long-term) dose (TSD), and 22% of the TSD for acute exposure (TSD_{AC}) in operators of hand-held sprayers when complying with the operating instructions;
- the systemic dose in vehicle-mounted spraying is predicted to reach 29% of the TSD and 11% of the TSD_{AC} when complying with the operating instructions;
- exposure to malathion does not exceed the TSD or TSD_{AC} in bystanders of different ages (0.6%, 1.1% and 2.8% of the TSD, and 2%, 4% and 10% of the TSD_{AC} in adults, children and toddlers, respectively), 0.02% and 0.1% of the TSD_{AC} of newborns of resident mothers, and of resident operator mothers; and
- exposure to malathion does not cause untoward effects on the aquatic environment, soil organisms, birds or herbivorous mammals.

¹ Space spray application of insecticides for vector and public health pest control – a practitioner’s guide. Geneva: World Health Organization; 2003 (WHO/CDS/WHOPES/GCDPP/2003.5; whqlibdoc.who.int/hq/2003/WHO_CDS_WHOPES_GCDPP_2003.5.pdf, accessed May 2016).

4. CONCLUSIONS ON CARCINOGENICITY

The JMPR evaluated published studies on cancer outcomes following occupational exposure to malathion (from agricultural uses). The JMPR concluded that overall, there is some weak evidence of a positive association between malathion exposure and non-Hodgkin lymphoma from case-control studies and an overall meta-analysis. However it was notable that the Agricultural Health Study (AHS), which was the only cohort study and was large and of high quality, found no evidence of an association at any exposure level. The meeting also concluded that overall, the evidence is suggestive of a positive association between malathion exposure and risk of aggressive prostate cancer; however, the evidence base was limited to the one large AHS cohort study.

Overall, JMPR concluded that, based on a consideration of the results of animal bioassays, genotoxicity assays and epidemiological data from occupational exposures, malathion and its metabolites are unlikely to pose a carcinogenic risk to humans from exposure via the diet (following use of malathion according to good agricultural practices (GAP)).

The experts concluded that any carcinogenic effect would be a consequence of systemic exposure and hence any carcinogenic risk from non-oral routes of exposure is likely to be comparable with that by the oral route, at similar levels of systemic exposure. As it was concluded that exposure to malathion and its metabolites at levels which would occur via the diet at the ADI would be unlikely to present a carcinogenic risk to humans, a similar conclusion should apply to those exposures occurring following use for outdoor space spraying which were below the TSD.

The experts recognized that there is some uncertainty regarding the exposure matching between those involved with space spraying of malathion for vector control and those involved in its application for agricultural use. The IARC concluded that there is “limited evidence” for carcinogenicity in humans following occupational exposure and this introduces some uncertainty; however, this uncertainty has to be balanced against the public health benefit of space spraying with malathion for vector control.

Similar conclusions would apply to indoor residual spraying for malaria vector control, if performed with a formulation with a WHO specification, provided that exposure was below the TSD.

5. RECOMMENDATIONS

1. The generic model for outdoor space spraying should be updated based on experience obtained during the current evaluation. This should include consideration of the appropriate default factor(s) for excretion in breast milk.
2. Additional guidance should be prepared on the importance of product stewardship regarding bystander exposure; this could form part of the practitioner's guide.¹
3. The model-predicted exposures should be verified by direct measurements of exposure of operators and bystanders during and after application.
4. Guidance on measurement of cholinesterase activity should be developed by WHO to assist jurisdictions with managing occupational exposure to organophosphate pesticides.
5. Results from epidemiological, occupational health and other such observational studies of human exposure would be useful for the continued evaluation of the use of malathion in vector control.
6. Consideration should be given to the potential additional risks that would be associated with dilution of malathion UL formulation with organic solvents such as fuel oil.

¹ Space spray application of insecticides for vector and public health pest control – a practitioner's guide. Geneva: World Health Organization; 2003 (WHO/CDS/WHOPES/GCDPP/2003.5; whqlibdoc.who.int/hq/2003/WHO_CDS_WHOPES_GCDPP_2003.5.pdf, accessed May 2016)

ANNEX 1. LIST OF PARTICIPANTS

Invited experts

Dr Antero Aitio, Helsinki, Finland

Dr Alan Boobis, Imperial College London, UK

Dr Matthew O'Mullane, Australian Pesticides and Veterinary Medicines Authority, Kingston, Australia

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Dr Simon Scarrott, Exposure Branch, Health & Safety Executive, Chemicals Regulation Directorate, York, UK

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Dr Richard Brown, Chemical Safety, Department of Public Health, Environmental and Social Determinants of Health, World Health Organization, Geneva, Switzerland

Dr Anna Drexler, Vector Ecology and Management, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

Dr Dirk Engels, Director, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

Dr Abraham Mnzava, Entomology and Vector Control, Global Malaria Programme, World Health Organization, Geneva, Switzerland

Dr Emmanuel Temu, Entomology and Vector Control, Global Malaria Programme, World Health Organization, Geneva, Switzerland

Dr Raman Velayudhan, Vector Ecology and Management, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

Dr Philip Verger, Risk Assessment and Management, Food Safety, Zoonoses and Foodborne Diseases, World Health Organization, Geneva, Switzerland

Dr Rajpal Yadav, Vector Ecology and Management, Department of Control of Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland

ANNEX 2. AGENDA

Monday, 16 May 2016 (09:00–17:30)

1. Opening of the meeting
– *WHO Director, NTD*
2. Introductions
– *Including declarations of interests and confidentiality undertakings*
– *Election of Chair and Rapporteur*
3. Objectives of the meeting
– *Dr Richard Brown (PHE)*
4. The use of malathion in vector control (control of malaria, Zika, dengue, etc.)
 - Status of WHOPES/NTD recommendations and WHO/GMP position on the use of malathion WP formulation for indoor residual spraying for control of malaria
– *Dr Rajpal Yadav (WHOPES/NTD) and Dr Emmanuel Temu (GMP)*
 - NTD position on the use of malathion EW and UL formulations for space-spraying for control of *Aedes* spp. (dengue, Zika, chikungunya, yellow fever)
– *Dr Raman Velayudhan (NTD)*
5. **2016 JMPR assessment of malathion**
– *JMPR experts to present the conclusions of the JMPR extraordinary meeting of 9–13 May 2016*
6. WHO generic risk assessment for malathion UL and EW for space spraying exposures and health and environmental risks
– *Dr Antero Aitio on behalf of the WHO Secretariat*

Tuesday, 17 May 2016 (09:00–12:30)

7. Discussion and development of recommendations
– *Meeting experts to agree on recommendations to make to the WHO Secretariat*
8. Closure

ANNEX 3. RISK ASSESSMENT FOR MALATHION UL

Exposures and health and environmental risks associated with outdoor space spraying using FMC malathion UL (revision May 2016)¹

Background

The World Health Organization (WHO) has published a *Generic risk assessment model for indoor and outdoor space spraying of insecticides* in 2011 (1). FMC Corporation, USA had presented an assessment of their product malathion UL following the guidelines given in the generic model to the WHO Pesticide Evaluation Scheme (WHOPES) (2). WHO has published a practitioner's guide for the space spray application of insecticides for vector and public health pest control (3).

Product and its toxicity and ecotoxicity

Malathion UL is an ultra-low volume formulation containing 1186 mg/mL malathion. The product is used for outdoor space spraying without further dilution. The recommended application rate is $0.00719 \text{ mL}/139 \text{ m}^3 = 8.53 \text{ mg a.i./m}^3$ which corresponds to $0.022 \text{ mL spray/m}^2 = 26.0 \text{ mg a.i./m}^2$ (2). The product is sold in different vessels ranging from 5-gallon containers (19 L) to 22 gallon (208 L) drums. The highest default unit exposure, 0.5 mL/mixing and loading operation (1), is used in this document.

The molecular mass of malathion is 330.36, solubility in water 148 mg/L, and the octanol–water partition coefficient $\log P_{OW}$, 2.75. The vapour pressure at 25 °C is 4.5×10^{-4} Pa and Henry's law constant, 4.1×10^{-7} . The half-time of malathion in soil is 1 day, that in water and sediment, 8 h (4,5).

Absorption and distribution

Urinary excretion of malathion + metabolites was 53–82% (mean, 65%) of the administered dose in human volunteers. The balance may have been metabolites not analysed (e.g. glutathione conjugates), or unabsorbed malathion (6). In this assessment, a value 100% is adopted for gastrointestinal absorption.

The default dermal absorption for malathion would be 100% (1). However, the cumulative dermal absorption of malathion in human volunteers of 50% malathion EC was 2.3–9% (mean 3.1%), that of malathion neat 2.5–18.4% (6.2%), malathion 1% aqueous mixture, 9.9–20.4% (4.8%) and 10% aqueous mixture 3.1–10.0% (5.5%) (6). In this assessment, a value 10% is adopted for dermal absorption.

No malathion or malathion metabolites were detected ($< 0.05 \text{ mg/L}$) in the milk of goats fed $3.3\text{--}3.8 \text{ mg} \times \text{kg}_{bw}^{-1} \times \text{d}^{-1}$ ^{14}C -malathion for five days (4). Excretion of ^{32}P in milk after an oral dose of ^{32}P -malathion was 0.2% of the dose in lactating cows (7). It should be noted that it is likely that a major proportion of this represents metabolites of malathion rather than unchanged malathion. Assuming the IPCS interspecies variation in kinetics ($10^{0.6}$) (8), which is likely to be conservative when used in this way, excretion in mother's milk in this assessment is estimated to be $0.2 \times 10^{0.6} = 0.8\%$ of the dose.

¹ This assessment was submitted to WHOPES on 20 May 2016 by Dr Antero Aitio.

Toxicity

The JMPR acceptable daily intake (ADI) for malathion is $0\text{--}0.3 \text{ mg}\times\text{kg}_{\text{bw}}^{-1}$ and the acute reference dose (ARfD), $2 \text{ mg}\times\text{kg}_{\text{bw}}^{-1}$ (9,10). In 2015, a Working Group of the International Agency for Research on Cancer (IARC) reevaluated the carcinogenicity of malathion (11), and – based on *limited evidence* in humans for the carcinogenicity and *sufficient evidence* for carcinogenicity in experimental animals supported by mechanistic data – concluded that malathion is *probably carcinogenic to humans* (2A). At its extraordinary meeting in May 2016, the JMPR considered existing and new data on the carcinogenicity in humans and in experimental animals as well as on the genotoxicity of malathion, and concluded that malathion and its metabolites are unlikely to pose a carcinogenic risk to humans from exposure via the diet (following use of malathion according to good agricultural practices (GAP)). The JMPR extraordinary meeting confirmed the ADI and ARfD values above.

On 16–17 May 2016, an expert meeting to consider malathion exposures and health risks following its use for vector control, in the light of the available evidence, concluded that any carcinogenic effect would be a consequence of systemic exposure and hence any carcinogenic risk from non-oral routes of exposure are likely to be comparable with that by the oral route at similar levels of systemic exposure. As it was concluded that exposure to malathion and its metabolites at levels which would occur via the diet at the ADI would be unlikely to present a carcinogenic risk to humans, a similar conclusion should apply to those exposures occurring following use for outdoor space spraying which were below the TSD, and they are used in the present risk assessment. In the present assessment, the JMPR ADI and ARfD are used as the basis of the risk assessment. Assuming 100% gastrointestinal absorption, the tolerable systemic dose, $\text{TSD} = \text{ADI}$, and the tolerable systemic dose for acute exposure, $\text{TSD}_{\text{AC}} = \text{ARfD}$.

The most prominent adverse effect of malathion, both in short-term and long-term studies, is the inhibition of acetylcholinesterase. Such an effect can be assessed by the analysis of red blood cell cholinesterase activity (6). It has been extensively used to monitor humans potentially exposed to organophosphates.

Malathion is of low acute and chronic toxicity, but malathion products may contain **impurities** that are more toxic than malathion, and also impurities that increase the toxicity of malathion, such as isomalathion, malaoxon, methyl-OOSPS-triester, and methyl OOOPS-triester. Upper limits for the concentrations of these impurities (4, 1, 15, and 5 g/kg for isomalathion, malaoxon, methyl-OOSPS-triester, and methyl OOOPS-triester, respectively) in malathion have been established in WHO pesticide specifications (5).

Ecotoxicity

Malathion is very toxic to *aquatic* environments. Of fish species, the lowest LC_{50} is for three-spined stickleback (*Gasterosteus aculeatus*), $21.7 \text{ }\mu\text{g/L}$. In standard tests, malathion is even more toxic to *Daphnia magna* with an EC_{50} of $0.7 \text{ }\mu\text{g/L}$. However, from higher-tier mesocosm studies it has been determined that the NOAEC for daphnids is $5.0 \text{ }\mu\text{g/L}$, and an environmentally acceptable concentration of $30 \text{ }\mu\text{g/L}$ for aqueous environments has been established. Malathion is considerably less toxic to aquatic algae ($\text{EC}_{50} \geq 4 \text{ mg/L}$) (12).

An acute LD₅₀ for bobwhite quail (*Colinus virginianus*) (a mainly seed-eating bird, in this evaluation used to represent all birds) is 214 mg×kg_{bw}⁻¹. The LD₅₀ for rats (representing terrestrial vertebrates) is 1485 mg×kg_{bw}⁻¹ (12).

An LD₅₀ of 116 mg×kg⁻¹ soil for earthworms (*Eisenia foetida*) has been reported for malathion (12).

Exposure and risk assessment using the generic model assumptions

Operator exposure and risk

The model (1) presents an exposure assessment for operators of hand-held sprayers. The operator of the hand-held sprayer is assumed to walk at a speed of 600 m/min as specified in the Practitioner's guide (3) and aim at a target concentration of 260 g malathion/ha. The model assumes that outdoor vehicle-mounted sprayer operation does not expose the operator who is protected by the cab of the vehicle and working upwind of the spray. Exposure may, however, take place in the *mixing and loading* and *washing and maintenance* of the equipment.

In the *lax standard scenario*,¹ acute and time-weighted average (TWA) exposure of operators to malathion far exceed the TSD and TSD_{AC} both in mixing and loading and in spraying. Therefore below, only the guideline exposure scenario is discussed.

Hand-held sprayer

In the *guideline scenario*, the predicted TWA exposure of the operator in *mixing and loading* is 0.04 mg×kg_{bw}⁻¹×d⁻¹ (14% of TSD).

Assuming that during the *spraying* the operator of a hand-held sprayer spends 30 min/d (moderate physical work load) within the spray cloud, the predicted *inhalation* exposure of a hand-held sprayer is 0.006 mg×kg_{bw}⁻¹×d⁻¹ (2% of TSD).

The predicted *dermal* exposure from spraying with and washing/maintenance of the hand-held equipment is high: 0.76 mg×kg_{bw}⁻¹×d⁻¹ for the TWA exposure, and 1.8 mg×kg_{bw}⁻¹×d⁻¹ for maximal daily exposure. These represent 253% and 89% of the TSD and TSD_{AC}, respectively. These estimates are based on 0.01 mL layer of the spray on hands, i.e., an area of 9.3 cm² (1).

The predicted total exposure of an operator of a hand-held sprayer in the guideline scenario is 0.81 mg×kg_{bw}⁻¹×d⁻¹ for the TWA exposure, and 1.9 mg×kg_{bw}⁻¹×d⁻¹ for maximal daily exposure. These represent 270% and 94% of the TSD and TSD_{AC}, respectively.

Vehicle-mounted sprayer

Exposure from *mixing and loading* is assumed to be similar in operators of hand-held and vehicle-mounted sprayers, that is, 0.04 mg×kg_{bw}⁻¹×d⁻¹.

¹ For descriptions of lax standard and guideline scenarios, see (1).

The inhalation exposure of the operator in vehicle-mounted *spraying* from the spray application is predicted to be negligible. The model similarly predicts that dermal exposure during spraying using vehicle-mounted sprayer is negligible (1). The model does not present estimates for exposure from washing and maintenance of the equipment separately; the contribution of this activity is here estimated to be 10% of the dermal exposure of the hand-held operators (including spraying, and washing and maintenance of the equipment), *i.e.*, $0.076 \text{ mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ for the TWA exposure, and $0.18 \text{ mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ for maximal daily exposure. These represent 25% and 9% of the TSD and TSD_{AC}, respectively.

The total exposure of operators in vehicle-mounted spraying in the guideline scenario is estimated to be $0.12 \text{ mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ for the TWA exposure, and $0.19 \text{ mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ for maximal daily exposure. These represent 39% and 10% of the TSD and TSD_{AC}, respectively.

Bystander exposure and risk

The model assumes that bystanders **may stay within the spray cloud for 15 minutes**, and be **exposed 15 times a year** (1). Total exposure, from inhalation exposure outdoors, dermal exposure from touching the surfaces indoors and outdoors (exposed skin area being that of head, hands, arms, lower legs and feet), oral exposure from contaminated food items, as well as hand-to-mouth exposure for toddlers, is predicted to be 0.02, 0.03, and 0.06 $\text{mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ (8, 10, and 20% of the TSD) for adults, children, and toddlers. The maximal daily exposure is predicted at 0.6, 0.7, and 1.4 mg/kg bw, or 29, 37, and 72% of the TSD_{AC}. Exposure of a newborn infant from the milk of a resident mother is predicted to remain below $1 \mu\text{g} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ (0.3% of the TSD_{AC}) and that of a resident-operator (guideline scenario) mother, below $4 \mu\text{g} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ (1.4% of the TSD_{AC}).

The **overwhelmingly most important route of exposure is inhalation from staying in the spray cloud (> 99% of the total)**. Dermal exposure from touching surfaces, oral exposure from contaminated food, and from hand-to-mouth behaviour is less than 0.1% of the TSD.

Environmental exposure and ecotoxicology

In the first-tier evaluation, volatilization from the soil and vegetation need not be taken into account in the environmental assessment (1). The half-time of malathion is short both in water and soil; and no accumulation is predicted when the spray interval is 7 days (1). Ecotoxicological data indicate that toxicity is not increased with extended exposure time. Thus assessment of chronic ecotoxicity is not considered.

In the *aquatic environment*, highest acute toxicity is expressed toward fish; the acceptable concentration, 30 $\mu\text{g}/\text{L}$. The worst case initial concentration of malathion is 5 $\mu\text{g}/\text{L}$, a concentration fully acceptable (4).

The initial *soil* concentration of malathion is estimated to be 0.12 mg/kg . The exposure to toxicity ratio (ETR), noting the reported LD₅₀ for earthworms of 116 mg/kg soil, is 0.001. The risk is thus *low* (1).

Malathion is very toxic to *terrestrial arthropods* including honey bees, but the generic model does not require an assessment of this risk.

Short-term daily dietary exposures of malathion for *terrestrial vertebrates* (herbivorous mammals, herbivorous birds, insectivorous birds, and fruit-eating birds) are estimated to be $6\text{--}50 \text{ mg}\times\text{kg}_{\text{bw}}^{-1}\times\text{d}^{-1}$, and the estimated toxicity ratios, 0.03–0.08. Thus the risk to terrestrial vertebrates can be considered to be low (1), and estimates for long-term exposure and risk need not be performed.

The generic model does not require an assessment of the risk to *higher terrestrial plants*.

Summary and conclusions

Assuming that

- malathion ultra-low volume application (UL) is used for outdoor space spraying only;
- the product complies with the WHO specification, notably with reference to the impurity profile;
- guidelines for the space spraying of insecticides for vector and public health pest control (3), and label instructions are strictly followed – especially that the hands are protected with suitable gloves and that the arms are covered; and
- the application rate is no more than 260 g/ha;

the *WHO generic risk assessment model for indoor and outdoor space spraying of insecticides* predicts that:

- the systemic dose of malathion received by the operators is very likely to exceed acceptable levels if the operating guidelines (described in the model as the “guideline scenario”) are not strictly adhered to;
- the systemic dose of malathion may reach 270% of the acceptable systemic time weighted average (TWA) dose (described in the model as the long-term tolerable systemic dose or TSD), and 94% of the tolerable systemic dose for acute exposure (TSD_{AC}), in operators of hand-held sprayers even when complying with the operation instructions;
- the systemic dose in vehicle-mounted spraying is predicted to reach 39% of the long-term tolerable systemic dose (TSD); and 10% of the tolerable systemic dose for acute exposure, TSD_{AC} when complying with the operation instructions;
- the exposure to malathion does not exceed the TSD for bystanders of different ages (8%, 10%, and 20% of the TSD, and 29%, 37%, and 72% of the TSD_{AC} in adults, children and toddlers, respectively), 0.3% and 1.4% of the TSD_{AC} of newborns of resident mothers, and of resident operator mothers; and
- the exposure to malathion does not cause untoward effects on the aquatic environment, soil organisms, birds or herbivorous mammals.

As the operator exposure is mainly through dermal absorption, in order to ensure that the exposure remains below the TSD in all cases, operators must use gloves which provide effective (no less than 97%) protection.

Excessive exposure to malathion will cause a decrease in red cell acetylcholinesterase activity, which is more likely in the operators of hand-held sprayers. Red cell acetylcholinesterase activity levels of operators of hand-held sprayers should be regularly

monitored as part of an occupational health monitoring scheme, and the operators should be removed from further exposure if the levels drop 25% or more below baseline level (13,14).

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ANNEX 4. RISK ASSESSMENT FOR MALATHION EW

Exposures and health and environmental risks associated with outdoor space spraying using FMC malathion EW (revision May 2016)¹

Background

The World Health Organization (WHO) has published a *Generic risk assessment model for indoor and outdoor space spraying of insecticides* in 2011 (1). Cheminova had presented an assessment of their product malathion EW following the guidelines given in the generic model to the WHO Pesticide Evaluation Scheme (WHOPES) (2). WHO has published a practitioner's guide for the space spray application of insecticides for vector and public health pest control (3).

Product and its toxicity and ecotoxicity

Malathion EW is an emulsion, oil in water formulation containing 440 g/L malathion. The recommended rate of application is 600–800 mL/ha, corresponding to 264–352g/ha; in the worst case situation, 750 mL of the formulation is diluted to 2L of water, giving a spray concentration of 165 g/L (2).

The molecular mass of malathion is 330.36, solubility in water 148 mg/L, and the octanol–water partition coefficient $\log P_{OW}$, 2.75. The vapour pressure at 25 °C of malathion is 4.5×10^{-4} Pa and Henry's law constant, 4.1×10^{-7} . The half-time of malathion in soil is 1 day, that in water and sediment, 8 h (4,5).

Absorption and distribution

Urinary excretion of malathion + metabolites was 53–82% (mean, 65%) of the administered dose in human volunteers. The balance may have been metabolites not analysed (e.g. glutathione conjugates), or unabsorbed malathion (6). In this assessment, a value 100% is adopted for gastrointestinal absorption.

The default dermal absorption for malathion would be 100% (1). However, the cumulative dermal absorption of malathion in human volunteers of 50% malathion EC was 2.3–9% (mean 3.1%), that of malathion neat 2.5–18.4% (6.2%), malathion 1% aqueous mixture, 9.9–20.4% (4.8%) and 10% aqueous mixture 3.1–10.0% (5.5%) (6). In this assessment, a value 10% is adopted for dermal absorption.

No malathion or malathion metabolites were detected (< 0.05 mg/L) in the milk of goats fed $3.3\text{--}3.8 \text{ mg} \times \text{kg}_{bw}^{-1} \times \text{d}^{-1}$ ^{14}C -malathion for five days (4). Excretion of ^{32}P in milk after an oral dose of ^{32}P -malathion was 0.2% of the dose in lactating cows (7). It should be noted that it is likely that a major proportion of this represents metabolites of malathion rather than unchanged malathion. Assuming the IPCS interspecies variation in kinetics ($10^{0.6}$) (8), which is likely to be conservative when used in this way, excretion in mother's milk in this assessment is estimated to be $0.2 \times 10^{0.6} = 0.8\%$ of the dose.

¹ This assessment was submitted to WHOPES on 20 May 2016 by Dr Antero Aitio.

Toxicity

The JMPR acceptable daily intake (ADI) for malathion is $0\text{--}0.3 \text{ mg}\times\text{kg}_{\text{bw}}^{-1}\times\text{d}^{-1}$ and the acute reference dose (ARfD), $2 \text{ mg}\times\text{kg}_{\text{bw}}^{-1}$ (9,10).

In 2015, a Working Group of the International Agency for Research on Cancer (IARC) reevaluated the carcinogenicity of malathion (11), and – based on *limited evidence* in humans for the carcinogenicity and *sufficient evidence* for carcinogenicity in experimental animals supported by mechanistic data – concluded that malathion is *probably carcinogenic to humans* (2A).

At its extraordinary meeting in May 2016, the JMPR considered existing and new data on the carcinogenicity in humans and in experimental animals as well as on the genotoxicity of malathion and concluded that malathion and its metabolites are unlikely to pose a carcinogenic risk to humans from exposure via the diet (following use of malathion according to good agricultural practices (GAP)). The JMPR extraordinary meeting confirmed the ADI and ARfD values above.

On 16–17 May 2016, an expert meeting to consider malathion exposures and health risks following its use in vector control, in the light of the available evidence concluded that any carcinogenic effect would be a consequence of systemic exposure and hence any carcinogenic risk from non-oral routes of exposure are likely to be comparable with that by the oral route, at similar levels of systemic exposure. As it was concluded that exposure to malathion and its metabolites at levels which would occur via the diet at the ADI would be unlikely to present a carcinogenic risk to humans, a similar conclusion should apply to those exposures occurring following use for outdoor space spraying which were below the TSD, and they are used in the present risk assessment. In the present assessment, the JMPR ADI and ARfD are used as the basis of the risk assessment. Assuming 100% gastrointestinal absorption, the tolerable systemic dose, $\text{TSD} = \text{ADI}$, and the tolerable systemic dose for acute exposure, $\text{TSD}_{\text{AC}} = \text{ARfD}$.

The most prominent adverse effect of malathion, both in short-term and long-term studies, is the inhibition of acetylcholinesterase. Such an effect can be assessed by the analysis of red blood cell cholinesterase activity (6). It has been extensively used to monitor humans potentially exposed to organophosphates.

Malathion is of low acute and chronic toxicity, but malathion products may contain impurities that are more toxic than malathion, and also impurities that increase the toxicity of malathion, such as isomalathion, malaoxon, methyl-OOSPS-triester, and methyl OOOPS-triester. Upper limits for the concentrations of these impurities (4, 1, 15, and 5 g/kg for isomalathion, malaoxon, methyl-OOSPS-triester, and methyl OOOPS-triester, respectively) in malathion have been established in WHO pesticide specifications (5).

Ecotoxicity

Malathion is very toxic to *aquatic* environments. Of fish species, the lowest LC_{50} is for three-spined stickleback (*Gasterosteus aculeatus*), $21.7 \text{ }\mu\text{g/L}$. In standard tests, malathion is even more toxic to *Daphnia magna* with an EC_{50} of $0.7 \text{ }\mu\text{g/L}$. However, from higher-tier mesocosm studies it has been determined that the NOAEC for daphnids is $5.0 \text{ }\mu\text{g/L}$, and an

environmentally acceptable concentration of 30 µg/L for aqueous environments has been established. Malathion is considerably less toxic to aquatic algae ($EC_{50} \geq 4$ mg/L) (12).

An acute LD_{50} for bobwhite quail (*Colinus virginianus*) (a mainly seed-eating bird, in this evaluation used to represent all birds) is $214 \text{ mg} \times \text{kg}_{bw}^{-1}$. The LD_{50} for rats (representing terrestrial vertebrates) is $1485 \text{ mg} \times \text{kg}_{bw}^{-1}$ (12).

An LD_{50} of $116 \text{ mg} \times \text{kg}^{-1}$ soil for earthworms (*Eisenia foetida*) has been reported for malathion (13).

Exposure and risk assessment using the generic model assumptions

Operator exposure and risk

The model (1) presents an exposure assessment for operators of hand-held sprayers. The operator of the hand-held sprayer is assumed to walk at a speed of 600 m/min as specified in the Practitioner's guide (3) and aim at a target concentration of 352 g malathion/ha. The model assumes that outdoor vehicle-mounted sprayer operation does not expose the operator who is protected by the cab of the vehicle and working upwind of the spray. Exposure may, however, take place in the *mixing and loading* and *washing and maintenance* of the equipment.

In the *lax standard scenario*,¹ the time-weighted average (TWA) exposure of operators to malathion far exceeds the TSD both in mixing and loading and in spraying. Therefore below, only the guideline exposure scenario is discussed.

Hand-held sprayer

In the *guideline scenario*, the predicted TWA exposure of the operator in *mixing and loading* is $0.08 \text{ mg} \times \text{kg}_{bw}^{-1} \times \text{d}^{-1}$ (25% of TSD).

Assuming that during *spraying* the operator of a hand-held sprayer spends 30 min/d (moderate physical work load) within the spray cloud, the predicted *inhalation* exposure of a hand-held sprayer is $0.0076 \text{ mg} \times \text{kg}_{bw}^{-1} \times \text{d}^{-1}$ (2.5% of TSD).

The predicted *dermal* exposure from spraying with and washing/maintenance of the hand-held equipment is $0.11 \text{ mg} \times \text{kg}_{bw}^{-1} \times \text{d}^{-1}$ for the TWA exposure, and $0.25 \text{ mg} \times \text{kg}_{bw}^{-1} \times \text{d}^{-1}$ for maximal daily exposure. These represent 35% and 12% of the TSD and TSD_{AC} , respectively. These estimates are based on 0.01 mL layer of the spray on hands, i.e. an area of 9.3 cm^2 (1).

The predicted total exposure of an operator of a hand-held sprayer in the guideline scenario is $0.19 \text{ mg} \times \text{kg}_{bw}^{-1} \times \text{d}^{-1}$ for the TWA exposure, and $0.44 \text{ mg} \times \text{kg}_{bw}^{-1} \times \text{d}^{-1}$ for maximal daily exposure. These represent 63 and 22% of the TSD and TSD_{AC} , respectively.

¹ For descriptions of lax standard and guideline scenarios, see (1).

Vehicle-mounted sprayer

Exposure from *mixing and loading* is assumed to be similar in operators of hand-held and vehicle-mounted sprayers, that is, $0.08 \text{ mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$.

The inhalation exposure of the operator in vehicle-mounted *spraying* from the spray application is predicted to be negligible. The model similarly predicts that dermal exposure during spraying using vehicle-mounted sprayer is negligible (1). The model does not present estimates for exposure from washing and maintenance of the equipment separately; the contribution of this activity is here estimated to be 10% of the dermal exposure of the hand-held operators (including spraying, and washing and maintenance of the equipment), i.e. $0.011 \text{ mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ for the TWA exposure, and $0.025 \text{ mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ for maximal daily exposure. These represent 3.5% and 1.2% of the TSD and TSD_{AC}, respectively.

The total exposure of operators in vehicle-mounted spraying in the guideline scenario is estimated to be $0.086 \text{ mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ for the TWA exposure, and $0.22 \text{ mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ for maximal daily exposure. These represent 29 and 11% of the TSD and TSD_{AC}, respectively.

Bystander exposure and risk

The model assumes that bystanders may stay within the spray cloud for 15 minutes, and be exposed 15 times a year (1). Total exposure, from inhalation exposure outdoors, dermal exposure from touching surfaces indoors and outdoors (exposed skin area being that of head, hands, arms, lower legs and feet), oral exposure from contaminated food items, as well as hand-to-mouth exposure for toddlers, is predicted to be 0.002 , 0.003 , and $0.008 \text{ mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ (0.6, 1.1, and 2.8% of the TSD) for adults, children, and toddlers. The maximal daily exposure is predicted at 0.04, 0.08 and 0.21 mg/kg bw , 2, 4 and 10% of the TSD_{AC}. Maximal exposure of a newborn infant from the milk of a resident mother is predicted to remain below $0.07 \text{ } \mu\text{g} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ (0.02% of the TSD_{AC}) and that of a resident-operator (guideline scenario) mother, below $0.3 \text{ } \mu\text{g} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$ (0.1% of the TSD).

Environmental exposure and ecotoxicology

In the first-tier evaluation, volatilization from the soil and vegetation need not be taken into account in the environmental assessment (1). The half-time of malathion is short both in water and soil; and no accumulation is predicted when the spray interval is 7 days (1). Ecotoxicological data indicate that toxicity is not increased with extended exposure time. Thus assessment of chronic ecotoxicity is not considered.

In the *aquatic environment*, highest acute toxicity is expressed toward fish; the acceptable concentration, 30 $\mu\text{g/L}$. The worst case initial concentration of malathion is 7 $\mu\text{g/L}$, a concentration fully acceptable (4).

The initial *soil* concentration of malathion is estimated to be 0.11 mg/kg . The exposure to toxicity ratio (ETR), noting the reported LD₅₀ for earthworms of 116 mg/kg soil , is 0.001. The risk is thus *low* (1).

Malathion is very toxic to *terrestrial arthropods* including honey bees, but the generic model does not require an assessment of this risk.

Short-term daily dietary exposures of malathion for *terrestrial vertebrates* (herbivorous mammals, herbivorous birds, insectivorous birds, and fruit-eating birds) are estimated to be $8\text{--}70 \text{ mg} \times \text{kg}_{\text{bw}}^{-1} \times \text{d}^{-1}$, and the estimated toxicity ratios, 0.04–0.10. Thus the risk to terrestrial vertebrates can be considered to be low (1), and estimates for long-term exposure and risk need not be performed.

The generic model does not require an assessment of the risk to *higher terrestrial plants*.

Summary and conclusions

Assuming that

- malathion oil-in-water formulation (EW) is used for outdoor space spraying only;
- the product complies with the WHO specification, notably with reference to the impurity profile;
- guidelines for the space spraying of insecticides for vector and public health pest control (3), and label instructions are strictly followed – especially that the hands are protected with suitable gloves and that the arms are covered; and
- the application rate is no more than 352 g/ha;

the WHO generic risk assessment model for indoor and outdoor space spraying of insecticides predicts that:

- the systemic dose of malathion received by the operators is very likely to exceed acceptable levels if the operating guidelines (described in the model as the “guideline scenario”) are not strictly adhered to;
- the systemic dose of malathion may reach 63% of the acceptable systemic TWA (long-term) dose TSD, and 22% of the acute dose, TSD_{AC} in operators of hand-held sprayers when complying with the operation instructions;
- the systemic dose in vehicle-mounted spraying is predicted to reach 29% of the TSD and 11% of the TSD_{AC} when complying with the operation instructions;
- exposure to malathion does not exceed the TSD or TSD_{AC} in bystanders of different ages (0.6%, 1.1%, and 2.8% of the TSD, and 2%, 4% and 10% of the TSD_{AC} in adults, children, and toddlers, respectively), 0.02% and 0.1% of the TSD_{AC} of newborns of resident mothers, and of resident operator mothers; and
- exposure to malathion does not cause untoward effects on the aquatic environment, soil organisms, birds or herbivorous mammals.

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