Australian Government
Australian Pesticides and Veterinary Medicines Authority

3 July 2014

Mr Tim Watling
Committee Secretary
Senate Rural and Regional Affairs and Transport References Committee
PO Box 6100
Parliament House
CANBERRA ACT 2600

Dear Mr Watling

Inquiry into the Implications of the use of Fenthion on Australia's horticultural industry

Thank you for the opportunity to provide additional information to assist the Rural and Regional Affairs Transport References Committee *Inquiry into the Implications of the use of Fenthion on Australia's horticultural industry*.

In response to the Committee's request for additional information to be provided in relation to scientific concerns regarding fenthion, please find enclosed an additional submission from the APVMA.

The APVMA can address any queries regarding this submission in its appearance at the hearing on Monday 7 July 2014.

Yours sincerely

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Australian Government

Australian Pesticides and Veterinary Medicines Authority

Senate Rural and Regional Affairs and Transport Reference Committee – Inquiry into the Implications of the use of Fenthion on Australia's horticultural industry

AUSTRALIAN PESTICIDES AND VETERINARY MEDICINES AUTHORITY
ADDITIONAL SUBMISSION

JULY 2014

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Executive Summary

The Australian Pesticides and Veterinary Medicines Authority (APVMA) is providing this additional submission in response to a request from the Rural and Regional Affairs and Transport References Committee for further detail on scientific concerns regarding fenthion as part of its *Inquiry into the Implications of the use of Fenthion on Australia's horticultural industry*.

The key matters which the APVMA has included in this submission are as follows:

1. There are many studies demonstrating the harmful health effects of fenthion. These studies have been independently reviewed by European, North American and Australian pesticide regulators, in addition to expert panels of the World Health Organisation.

2. Fenthion is a nerve poison that causes a spectrum of adverse health effects ranging from effects on biochemical parameters at low levels of exposure, to clinical signs (nausea, vomiting, diarrhoea, salivation, muscle twitching, laboured breathing, lethargy and coma) to death at higher levels of exposure. These effects can occur following a single exposure.

3. It is important that members of the public eating food containing fenthion residues and workers using fenthion products are protected from these harmful effects. This is achieved by setting dietary exposure limits (or health standards) and worker exposure limits, plus exposure reduction measures, where applicable.

4. The APVMA's statutory criteria specify that the continued use of any chemical under review according to the approved product label can only be allowed if that use:
    i. Would not be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residue; and
    ii. Would not be likely to have an effect that is harmful to human beings.

5. The dietary risk assessment undertaken by the APVMA as part of the fenthion review determined that the short-term dietary health standard for fenthion (the acute reference dose) was exceeded by a large margin (up to 10-fold) in children and adults, which poses a significant <u>public health concern</u>.

6. The worker risk assessment undertaken by the Office of Chemical Safety determined that a number of use patterns would lead to workers exceeding the occupational safety limit for fenthion. Where these limits cannot be mitigated by engineering controls or the use of personal protective equipment, this poses a significant <u>worker safety concern</u>.

7. The APVMA considers all relevant studies on a chemical under review, with each study assessed on its scientific merits. The human study used as the basis of the Australian dietary health standard and worker exposure limit for fenthion is the most scientifically valid study, and is supported by studies in laboratory animals. The use of this study is consistent with its use by European Union member states and the World Health Organisation in their assessments of fenthion.

Considerations

1. What harmful effects does fenthion cause?

1.1 Fenthion is an organophosphorus insecticide or 'OP', and like all chemicals belonging to this group, it kills insects by interfering with the nervous system. It also has the potential to kill humans (and other mammals) by the same mechanism of interference with the brain, spinal cord and peripheral nerves.

1.2 The types of adverse effects that can occur in humans depend entirely on the level of exposure, with a spectrum of increasingly-more severe effects occurring as the level of exposure increases. This spectrum ranges from effects on biochemical parameters in the blood and brain, to clinical signs (nausea, vomiting, diarrhoea, dizziness, confusion, salivation, muscle twitching, laboured breathing, lethargy and coma) to death. These same adverse effects also occur in laboratory animal species exposed to fenthion and on this basis, studies conducted using laboratory animals provide information relevant to effects on humans.

1.3 The inhibition of an enzyme critical for transmitting nerve signals is accepted by toxicologists, chemical regulators and the World Health Organisation (WHO) as the most sensitive adverse effect resulting from exposure to OPs, including fenthion. This enzyme, called acetylcholinesterase, is found in both the brain and blood and is specifically involved in maintaining normal nerve function. The statistically significant inhibition of this enzyme by greater than 20% above baseline is considered adverse and forms the basis of the health standards set for most OPs around the world. If the level of inhibition of acetylcholinesterase gets too high people will begin displaying overt signs of poisoning.

2.1 For Australian workers using OPs, Safe Work Australia[1] and WorkSafe WA[2] recommend that health monitoring be undertaken before starting, during and after working with OPs. This analysis includes the measurement of acetylcholinesterase in blood in addition to urine for the presence of metabolites (breakdown products). If the level of acetylcholinesterase activity drops too low then workers should not continue using these types of pesticides until their blood acetylcholinesterase level has normalised.

1.5 For the general public that may be exposed to fenthion residues in food, dietary health standards are set based on the same adverse effect on acetylcholinesterase in blood used to protect workers. Two health standards can be set: the dose that is safe to consume in a single meal (the so-called Acute Reference Dose) and the dose that is safe to consume on a daily basis over a lifetime (the so-called Acceptable Daily Intake).

1.6 One of the significant concerns arising from the APVMA's review of fenthion is that dietary exposure of Australians to residues in food significantly exceeds the acute reference dose for fenthion in children and adults. This health standard is set by the Office of Chemical Safety using a well-established methodology that has been developed and applied by chemical regulators and promulgated internationally by the World Health Organisation. Health standards are

[1] http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/801/Organophosphate-Pesticides.pdf
[2] https://www.commerce.wa.gov.au/publications/organophosphate-health-surveillance-notification-form

intended to protect all Australians (from the most sensitive to the least sensitive) from exposure to unsafe levels of chemicals – the exceedance by up to 10-fold of the acute reference dose in children is a serious public health concern.

2. What is the evidence that fenthion causes these effects?

2.1 There is a compelling weight-of-evidence across many studies by different investigators involving multiple species (including humans) that fenthion causes adverse effects.

2.2 Independent reviews of this evidence have been conducted by the US Environmental Protection Agency (US EPA) in 2001, Health Canada in 2003 and European Union in 1998. Fenthion has been reviewed on multiple occasions by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) from 1971 to 2000. The JMPR is an expert scientific advisory panel that provides advice on the effects of pesticides on health and sets international food standards important for trade. All of these reviews identified the adverse effects that fenthion has on the nervous system and established health standards to protect people against unsafe exposure to residues in food and from the use of fenthion products.

2.3 Around 160 studies were evaluated by the Office of Chemical Safety as part of its 2012 Toxicological Assessment and 2014 Occupational Health and Safety Assessment of fenthion. Specifically in humans, the following adverse effects have been reported:

- chills, headache, vomiting, diarrhoea and irregular pulse (Jung 1963)
- multiple shooting pains, muscle weakness, back pain, numbness, tingling of the hands and feet, eye weakness and paralysis (Metcalf et al 1985)
- intermediate syndrome[3], weakness of the cranial nerves, respiratory weakness, muscle twitching and the inhibition of acetylcholinesterase activity (De Wilde et al 1991; De Bleecker 1995)
- headache, sweating, eye problems (pain, watery eyes, impaired vision), muscle cramps, salivation and sweating (Jeyaratanam and Ponnambalam 1980)
- inhibition of acetylcholinesterase activity, headache, giddiness, adverse effects on the eyes and paraesthesia (Misra et al 1985)
- reduced cognitive function (Misra et al 1994)
- convulsions, muscle twitching, unusual tiredness, asthma, burning sensation in eyes and headache (Ames et al 1989)
- adverse effects on the eyes (Misra et al 1985).

[3] The intermediate syndrome is a delayed-onset of muscular weakness and paralysis following an episode of acute poisoning by an OP, such as fenthion.

3. The APVMA considers all relevant data on a chemical under review

3.1 When a chemical review is commenced by the APVMA, approval holders and product registrants are required to submit all of their data holdings on that chemical. These data holdings include unpublished company studies (often conducted by contract laboratories) in addition to studies published in scientific journals.

3.2 The APVMA and its risk assessment partners in the Office of Chemical Safety and the Department of the Environment, undertake their own literature searches to identify additional information available in the public domain. This additional information includes:

- studies published in peer-reviewed scientific journals;
- assessment reports prepared by overseas regulators; and
- assessment reports prepared by independent expert bodies such as the World Health Organisation (WHO) and the Food and Agricultural Organisation of United Nations (FAO).

3.3 The APVMA also invites interested stakeholders to submit any information that they consider relevant to the review. This occurs at the start of a review and also during any period of public consultation.

4. All studies are assessed on their scientific merits

4.1 Irrespective of the age of a study, whether it is an unpublished company study or one published in a scientific journal, all studies are assessed on their scientific merits. This includes a consideration of the design and conduct of a study, in addition to the results of the study.

4.2 All studies are benchmarked against international standards of experimental design and analysis, such those published by the Organisation for Economic Cooperation and Development as part of their Test Guideline Program (see: http://www.oecd.org/env/ehs/testing/oecdguidelinesforthetestingofchemicals.htm).

4.3 These standards guide anyone intending to examine the potential adverse effect of a chemical by specifying how particular studies should be conducted, including the types of parameters that need to be analysed to generate scientifically-valid data.

4.4 Additionally, all studies are assessed for compliance with principles of Good Laboratory Practice (GLP) and Good Clinical Practice (GCP), which ensure a high standard of record keeping, reporting detail and accountability. Principles of GLP and GCP also cover the ethical treatment of laboratory animals and human volunteers.

4.5 If a study complies with a particular national or international test guideline, and principles of GLP or GCP, then this provides confidence in the scientific integrity of that study. Studies that predate these contemporary standards in addition to peer-reviewed published studies that would generally not comply with these standards anyway, would still be assessed on their scientific merits and be included in an assessment if considered acceptable.

4.6 All regulators of food additives, pesticides, veterinary medicines and drugs rely on unpublished company studies to support their respective registration processes. These studies are specifically designed for regulatory purposes and because all the raw data is provided, the studies are amenable to an independent scientific assessment. Most unpublished company studies that are submitted for regulatory purposes are test-guideline and GLP-compliant, and have been through a quality assurance process.

4.7 Such studies are not published in journals as at the time of data generation, the chemical would be under patent protection.

5. The APVMA examines studies conducted in laboratory animals and humans

5.1 There are a range of studies that the APVMA and its risk assessment partners consider during a review including those conducted in both laboratory animals and humans. In general, studies conducted in humans are weighted higher than those conducted in laboratory animals.

5.2 Any adverse effects observed in laboratory animals are always assessed for their relevance to humans. For most pesticides, the number of studies conducted in laboratory animals is larger than those conducted in humans, which reflects the general ethical concern with conducting human studies on pesticides. Some registrants are reluctant to invest in the conduct of these studies, particularly when US and Canadian regulators have a policy of excluding human studies from regulatory decision-making on ethical grounds.

5.3 Studies that are evaluated during a review cover a number of areas including how a chemical is broken down in the body, whether it can cause adverse effects after a single exposure and what the adverse effects may be over long periods of exposure (such as the potential to cause cancer, birth defects or affect the brain and nervous system).

5.4 An evaluation of all studies included in a review aims to:

- determine the harmful effects that a chemical can cause;
- identify the most sensitive harmful effect; and
- establish safety limits for human exposure to that chemical (both public exposure to residues in food and exposure of workers using a chemical product).

5.5 The evaluation of all of the toxicological studies on fenthion is contained in the toxicological report that was published by the APVMA in 2012. (http://www.apvma.gov.au/products/review/docs/fenthion_part_2_toxicology_report.pdf).

6. Why was the 1979 study by Coulson et al chosen as the basis of the Australian health standard for fenthion?

6.1 The study by Coulston et al (1979)[4] was determined to be the most suitable for establishing the Australian acute reference dose because it was:

- designed appropriately
- conducted in a relevant target species (humans)
- measured the most sensitive harmful effect relevant to humans
- is supported by the monkey study by Rosenblum (1980)[5].

6.2 The use of the Coulston study to set the Australian Acute Reference Dose for fenthion was endorsed by Australia's Advisory Committee on Pesticides and Health in 2000.

6.3 The Coulston study was independently chosen by the European Union in 1998 and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR)[6] in 1997 when setting the health standards for fenthion.

6.4 The Coulston study was considered by the US and Canada during their assessments of fenthion but was not included as the basis of any regulatory decision because of government policy that specifically excludes human studies on pesticides because of ethical concerns over the conduct of such studies. Consequently, both the US and Canada have used the monkey study by Rosenblum (1980) as the basis of their health standards. The OCS evaluated the same monkey study as part of its assessment of the toxicity of fenthion.

6.5 It should be noted that the Coulston study was not used to restrict the use of fenthion. It was used to support the Acute Reference Dose, which allows the limited use of fenthion on tropical and subtropical fruit. Without this study, the Office of Chemical Safety would have used the next most suitable study, which is a laboratory animal study resulting in a conservative Acute Reference Dose.

6.6 As the Coulston study was a volunteer study, it was not ethical or suitable to dose the volunteers with amounts of fenthion that were likely to cause them any lasting harm. Therefore any human study is unlikely to establish the level at which harm occurs, as that is the role of animal studies. Human studies, where available, are used to test the safety of doses lower than those known to harm animals, and to confirm that the levels achieved in the body and the enzyme changes used to measure the effects of fenthion are consistent with those seen in animal studies.

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[4] Coulston F, Griffin T & Rosenblum I (1979) Safety evaluation of fenthion in human volunteers. Unpublished Mobay report No. 68790 from the Institute of Comparative and Human Toxicology, International Center of Environment Safety, Albany Medical College, New York, USA.

[5] Rosenblum I (1980) A Safety Evaluation of Fenthion (S1752) in Rhesus Monkeys (Macaca mulata): Final Report: Report No. 68789. Unpublished study prepared by The Albany Medical College of Union University. 117 p

[6] The JMPR provides expert scientific advice to the Codex Alimentarius Commission and its specialist committee on pesticide residues, the Codex Committee on Pesticide Residues. The Codex Alimentarius Commission develops international food standards and guidelines, with the aim of protecting consumer health, ensuring fair trade practices and promoting coordination of all food standards work undertaken by government and non-government organisations.

7. Regulatory status of fenthion in other countries

7.1 Fenthion is no longer registered for use on food producing plants in Canada, the European Union (EU), New Zealand or the USA.

7.2 There are currently no products containing fenthion registered for use on food producing plants in the US. The US EPA issued an Interim Reregistration Eligibility Decision (IRED) for fenthion in January 2001, which stated that dietary exposures from fenthion use on livestock were above the level of concern for the entire U.S. population and that the livestock products were being voluntarily cancelled by the registrant. Mosquito control products were voluntarily cancelled in 2003.

7.3 Fenthion is not currently approved as a plant protection or biocidal product in the EU. In 1998 the Scientific Committee on Plants recommended that the use of fenthion on all crops (other than olives and citrus as bait applications) be phased out within three years[7]. In February 2004, the European Commission announced that all the remaining uses of fenthion (bait uses in citrus and olives) were to be withdrawn by 30 June 2007.

[7] Opinion of the Scientific Committee on Plants concerning the non-inclusion of Fenthion in annex I of Directive 91/414/EEC (Opinion expressed by the SCP on 2 October 1998), http://ec.europa.eu/food/fs/sc/scp/out22_en.html

References

Ames RG, Brown SK, Rosenberg J, Jackson RJ, Stratton JW, Quenon SG (1989) Health Symptoms and Occupational Exposure to Flea Control Products among California Pet Handlers. Am Ind Hyg Assoc J. 50(9): 466-472.

Bryant DH (1985) Asthma due to insecticide sensitivity. Aust NZ J Med. 15:(1), 66-68.

Coulston F, Griffin T, Rosenblum I (1979) Safety Evaluation of Fenthion in Human Volunteers, Unpublished study prepared by the Institute of Comparative and Human Toxicology, Albany Medical College, New York and International Center of Environmental Safety, Albany Medical College, New York.

De Bleecker JL (1995) The Intermediate Syndrome in Organophosphate Poisoning: an Overview of Experimental and Clinical Observations. Clinical Toxicology. 33(6): 683-686.

De Wilde V, Vogelaers D, Colardyn F, Vanderstraeten G, Van den Neucker K, De Bleecker J, De Reuck J & Van den Heede M (1991) Postsynaptic neuromuscular dysfunction in organophosphate induced intermediate syndrome. Klin Wochenschr. 69(4):177-83

Jeyaratnam J, Ponnamblam N (1980) Monitoring of Public Health Workers Exposed to Fenthion, Field Worker Exposure during Pesticide Application, Studies in Environmental Science No. 7, Tordoir, W.F., and Van Heemstra-Lequin, Editors; Elsevier Scientific Publishing Company, New York.

Jung HF (1963) Poisoning cases caused from aerial application of Baytex dust. NTHS Letter (15/10/63).

Metcalf RL, Swift TR, Sikes RK (1985) Neurologic Findings among Workers Exposed to Fenthion in a Veterinary Hospital. MMWR Morbidity Mortality Weekly Report (USA), July 5, 34(26): 402-403.

Misra UK, Prasad M, Pandey CM (1994) A study of cognitive functions and event related potentials following organophosphate exposure. Electromyography and Clinical Neurophysiology. 34:(4), 197-203.

Misra UK, Nag D, Bhushan V, Ray PK (1985) Clinical and Biochemical Changes in Chronically Exposed Organophosphate Workers: Toxicology Letters. 24:187-193.

Misra UK, Nag D, Misra NK, Mehra MK, Ray PK (1985) Some observations on the Macula of Pesticide Workers. Human Toxicology. 4:135-145.

Rosenblum I (1980) A Safety Evaluation of Fenthion (S1752) in Rhesus Monkeys (*Macaca mulata*): Final Report: Report No. 68789. Unpublished study prepared by The Albany Medical College, New York. 117 p