Australian Government
Australian Pesticides and
Veterinary Medicines Authority

21 July 2014

Tim Watling
Secretary
Senate Standing Committee on Rural and Regional Affairs and Transport
Department of the Senate
SG.62 Parliament House Canberra, ACT 2600

Dear Mr Watling

Senate Rural, Roads and Transport Committee - Inquiry into the Implications of the use of Fenthion on Australia's horticultural industry: request for further advice following the hearing of Monday 07 July 2014

Thank you for your email of Wednesday 16 July 2014, requesting further advice from the APVMA regarding the human study of fenthion provided to the Committee and also requesting advice regarding transition periods following removal of a product.

SUMMARY OF FINDINGS OF THE 1979 HUMAN VOLUNTEER STUDY

The human report provided to the Committee on Monday 14 July 2014 presents the results of a study of fenthion in human volunteers conducted in 1979. This study was designed to confirm that levels of fenthion that were already understood to be safe from previous animal studies (monkeys) were also safe for humans.

Toxicologists from the Office of Chemical Safety within the Department of Health independently assessed this report and its conclusions and provided a summary of their assessment of this report in pages 131 to 135 of the *Review of the Mammalian Toxicology and Metabolism/Toxicokinetics of Fenthion* (2008 published 2012 on the APVMA website). The findings of the human study were used in conjunction with other studies across a range of animal species to determine safe levels for short-term and long-term exposure to fenthion.

The study was conducted on healthy, adult male volunteers with four people in each group. Each group received a daily dose of either no fenthion, 0.02 mg/kg body weight of fenthion or 0.07 mg/kg bodyweight of fenthion for up to 28 days. As noted in the report summary (on Page 1), the doses used in this human study were chosen because they had been found to cause no effects in rhesus monkeys dosed over one year.

The volunteers were given physical examinations once a week and blood samples were collected for testing. The tests included activity of the enzyme cholinesterase in either the red blood cells or the plasma (liquid) component of the blood.

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In the APVMA additional submission to the Committee (July 2014 paragraph 1.3), it is noted that the inhibition of the cholinesterase enzyme which is 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 organophosphates (OPs) including fenthion. This enzyme 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 by regulators for most OPs around the world. Therefore studies, such as this human volunteer study include statistical analysis of the cholinesterase measurements to allow regulators to determine whether any observed changes are significant.

Changes in the cholinesterase activity in the red blood cells are used to detect short-term effects of organophosphate pesticides. Whereas, changes to cholinesterase activity in the plasma alone are used to detect long-term effects of organophosphate pesticides.

Paragraphs 1 to 3 of the conclusions section of the report, state that there were no symptoms or signs (including changes in body weight, temperature, pulse rate, blood pressure, clinical chemistry, haematology or urine tests) observed at either dose of fenthion. This is to be expected, as the doses used in this study were specifically selected to be below those likely to cause health effects.

Paragraph 4 of the report discusses the measurement of cholinesterase in the red blood cells and states that: "no statistically significant depression of erythrocyte cholinesterase activity was detected at daily oral doses of 0.07 or 0.02 mg fenthion/kg in human volunteers for up to 25 days".

This indicated that even the higher of the two doses (0.07 mg/kg bodyweight) did not affect the cholinesterase in red blood cells and therefore confirmed that this dose level was safe for short-term exposure of humans. This dose level was used to set the public health standard for short-term exposure to fenthion (The Acute Reference Dose). This is used to assess short-term dietary exposures in children and the general population.

Paragraphs 5, 6 and 7 of the report discuss the results for plasma cholinesterase, which is the endpoint used by regulators when setting the standard for long-term exposure to fenthion. Overall, fenthion had a significant effect on plasma cholinesterase at 0.07 mg/kg bw but not a clearly significant effect at the lower dose of 0.02 mg/kg bw, when comparing the treated and untreated groups.

This dose level (0.02 mg/kg) was selected to set the Acceptable Daily Intake for fenthion for both long-term dietary and worker exposure assessments.

TRANSITION PERIODS FOR CANCELLED CHEMICALS AND PRODUCTS

When a decision is made to cancel a chemical (active ingredient), chemical products or product labels, there are transition periods that may apply. This is often informally referred to as 'phase out periods'.

Section 45 of the *Agricultural and Veterinary Chemicals Code Act 1994* (Agvet Code) allows a maximum period of 12 months for a holder or person to possess, have custody of, supply or use a product after it has been cancelled. These sections of the Agvet Code do not allow any manufacture or importation of products after the date of cancellation.
The APVMA may also impose a shorter phase-out period of less than 12 months, depending on the risk posed by continued use of the product, or due to the likelihood of adverse events occurring from continued access to the chemical or product.

As part of the phase-out process, the APVMA may issue specific instructions for the use, supply of and possession of the cancelled products and active constituents. The instructions can range from immediate cessation of all uses of a product with no further supply permitted (in the case of identified risks to people or the environment), restrictions on specific use patterns through to no restrictions on existing uses of a product during its phase out period where there are no identified risks arising from its continued use.

The matters taken into account include: whether any uses remain as an outcome of the review, likely adverse effects from the continued use of the products, information from the state and territory regulators about control of use difficulties, any potential impacts on trade and produce sold for export, availability and stocks of product in the marketplace or with individual users and issues associated with recall of products.

As part of developing new instructions for use, conditions of use may be imposed that could include restricted access and use of products, record-keeping requirements, monitoring requirements and any other matter that the APVMA thinks is needed to manage identified risks during such a phase-out period.

When products, actives or labels are cancelled the APVMA will publish this decision in an APVMA Gazette Notice. This Notice will specify which active ingredients, products or product labels have been cancelled, the reasons for the cancellation, the date of effect of the cancellation, and will specify the instructions for their continued possession, supply or use, through an APVMA permit.

In addition to the Gazette Notice and the notice to holders the APVMA may also issue permits that clearly identify the use instructions for any cancelled products (or products with cancelled labels). All current permits are available from the APVMA website from the permits database and should be referred to individual users or retailers for their guidance during the phase out periods after cancellation.

The instructions for supply of products and possession with intent to supply are enforced by the APVMA. Manufacturers, wholesalers and retailers must follow these instructions. Instructions for use during phase out periods are enforced by the States and Territories.

The APVMA may also use its website, direct emails to stakeholders and direct communications with specific stakeholders or user groups to advise them of the cancellation and referring them to the Gazette Notice and any permits for the official advice of the conditions of use, possession or supply and the duration of the phase out period.

Yours sincerely

KAREENA ARTHY
Chief Executive Officer