

DIETARY RISK ASSESSMENT

Long term intake

The evaluation of dimethomorph has resulted in recommendations for MRLs and STMRs for raw and processed commodities. Consumption data was available for 31 food commodities and was used in the dietary intake calculation. The results are shown in Annex 3.

The International Estimated Daily Intakes in the 13 GEMS/Food cluster diets, based on the estimated STMRs were in the range 0–1% of the maximum ADI of 0.2 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of dimethomorph from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The international estimated short-term intake (IESTI) for dimethomorph was calculated for the food commodities (and their processing fractions) for which maximum residue levels and HRs were estimated and for which consumption data was available. The results are shown in Annex 4.

The IESTI varied from 0–10% of the ARfD (0.6 mg/kg bw) for the general population. The IESTI varied from 0–20% of the ARfD for children 6 years and below. The Meeting concluded that the short-term intake of residues of dimethomorph from uses considered by the Meeting was unlikely to present a public health concern.

5.12 FENITROTHION (037)

TOXICOLOGY

Fenitrothion is the ISO approved name for O,O-dimethyl O-4-nitro-m-tolyl phosphorothioate (IUPAC) (CAS No. 122-14-5), a broad-spectrum organophosphorus pesticide. Its toxicity was first evaluated by the JMPR in 1969, and re-evaluated in 1974, 1977, 1982, 1984, 1986, and 1988. The 2000 JMPR confirmed the ADI of 0–0.005 mg/kg bw based on a NOAEL of 0.5 mg/kg bw per day in a 2-year study of toxicity in rats, that had been established by the 1988 JMPR. Also at the 2000 JMPR, an ARfD of 0.04 mg/kg bw was established based on a NOAEL of 0.36 mg/kg bw per day for inhibition of erythrocyte acetylcholinesterase activity in a study in human volunteers.

The 2004 JMPR noted that some estimations of long-term and short-term intake exceeded the ADI or ARfD that had been established by the 2000 JMPR. The 2004 JMPR concluded that a review of the toxicological database of fenitrothion might enable a refinement of the ADI or ARfD, particularly when concepts such as setting of an overall NOAEL or deriving compound-specific adjustment factors, were taken into account. Owing to the intake concerns identified, the CCPR at its 38th Session in 2006²⁸ asked JMPR to consider possible refinement of the ADI and ARfD for fenitrothion. Since no relevant new toxicological data had been submitted for evaluation, the data from previous evaluations conducted by the JMPR were reconsidered by the present Meeting.

For technical fenitrothion, specifications have been published as *WHO specification and evaluation for public health pesticides: technical fenitrothion* (1999).²⁹ Specifications have also been established for other formulations of fenitrothion.

Toxicological evaluation

²⁸ Codex Alimentarius Commission. *Report of the 38th Session of the Codex Committee on Pesticide Residues, 3–8 April 2006, Fortaleza, Brazil* (ALINORM06/29/24).

²⁹ Available from: <http://www.who.int/whopes/quality/en/Fenitrothion.pdf>

The Meeting reviewed the toxicological database for fenitrothion with regard to establishing an overall NOAEL as a basis for the ADI. Inhibition of brain cholinesterase activity was identified as the critical effect after administration of repeated doses to rats. Based on a NOAEL of 0.5 mg/kg bw per day in a 2-year study of toxicity in rats, a NOAEL of 0.6 mg/kg bw per day in a 6-month study of toxicity in rats and a NOAEL of 0.57 mg/kg bw per day in a 3-month study of ocular toxicity in rats, an overall NOAEL of 0.6 mg/kg bw per day was established. The LOAELs for these studies were 1.5, 2.0 and 1.7 mg/kg bw per day, respectively. The NOAEL of 1.3 mg/kg bw per day in a 3-month study of neurotoxicity in rats was considered to be unsuitable as an overall NOAEL, since it was only slightly lower than the lowest LOAEL of 1.5 mg/kg bw per day and was associated with statistically significant inhibition of brain cholinesterase activity by 15%.

The Meeting also reviewed the toxicological database for fenitrothion with regard to deriving a chemical-specific assessment factor (CSAF). The available information was considered to be insufficient for the assessment of toxicokinetic and toxicodynamic differences between rodents and humans. Neither reliable data on concentrations in the general circulation (such as clearance or AUC) nor data on the concentration–effect relationship in target tissues were available for rats. Also, the Meeting considered that the use of a CSAF for human variability was inappropriate. The available data on plasma toxicokinetics were derived from 12 individuals only, which is an adequate sample to define the central tendency, but inadequate to define the potential variability in the human population. With regard to the acute toxicity of fenitrothion, the Meeting concluded that critical effects (inhibition of brain and/or erythrocyte cholinesterase activity) may not be related to the C_{max} but to AUC, on the basis of the slow recovery of the inhibition of cholinesterase activity and the evidence of slow clearance. Consequently, no modification of the standard safety factor for establishing the ARfD was considered to be justified.

The Meeting refined the ADI to 0–0.006 mg/kg bw based on the overall NOAEL of 0.6 mg/kg bw per day for inhibition of brain cholinesterase activity in repeat-dose studies of toxicity in rats and a safety factor of 100. The 4-day study in human volunteers was not considered suitable for establishing an ADI because of its short duration and the associated absence of steady-state kinetics.

The Meeting identified the 4-day study in human volunteers to be the most suitable basis for setting the ARfD. The Meeting confirmed the ARfD of 0.04 mg/kg bw that was established by the 2000 JMPR, based on a NOAEL of 0.36 mg/kg bw for inhibition of erythrocyte cholinesterase activity in humans and a safety factor of 10.

A toxicological monograph was not prepared.

Levels relevant to risk assessment

Species	Study	Effect	NOAEL	LOAEL
Rat	Six-month study of toxicity ^a	Toxicity (inhibition of brain acetylcholinesterase activity)	10 ppm, equal to 0.6 mg/kg bw per day	30 ppm, equal to 2.0 mg/kg bw per day
	Two-year study of toxicity and carcinogenicity ^a	Toxicity (inhibition of brain acetylcholinesterase activity)	10 ppm, equal to 0.5 mg/kg bw per day	30 ppm, equal to 1.5 mg/kg bw per day
	Thirteen-week study of neurotoxicity ^a	Toxicity (inhibition of brain acetylcholinesterase activity)	20 ppm, equal to 1.3 mg/kg bw per day	60 ppm, equal to 4.0 mg/kg bw per day
	Thirteen-week study of ocular toxicity ^a	Toxicity (inhibition of brain acetylcholinesterase activity)	10 ppm, equal to 0.57 mg/kg bw per day	30 ppm, equal to 1.7 mg/kg bw per day

Human	Four-day study of toxicity ^c	Toxicity (inhibition of erythrocyte acetylcholinesterase activity)	0.36 mg/kg bw per day ^b	—
-------	-----------------------------------------	--------------------------------------------------------------------	------------------------------------	---

^a Dietary administration.

^b Highest dose tested.

^c Capsule administration.

Estimate of acceptable daily intake for humans

0–0.006 mg/kg bw

Estimate of acute reference dose

0.04 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Additional toxicokinetic data in rats

Results from epidemiological, occupational health and other such observational studies of human exposures.

RESIDUE AND ANALYTICAL ASPECTS

Fenitrothion was evaluated for residues by the 2003 JMPR in the Periodic Re-evaluation Programme of the CCPR. The 2003 Meeting recommended an MRL of 10 mg/kg for cereals (post-harvest use only) and identified some data gaps. Additional data were provided to the 2004 JMPR, together with results of supervised trials on apples, pears, beans, peas, and soya beans. The 2004 JMPR confirmed the cereal MRL also for pre-harvest uses and recommended MRLs for apple and for animal commodities. Due to an insufficient number of trials corresponding to GAP, MRLs could not be recommended for pears, beans, peas, and soya beans.

The present Meeting received new labels covering uses on soya bean and cereals, a method of analysis, and additional residue trials on soya beans. Dietary intakes calculated by the 2004 JMPR exceeded the ADI and ARfD. As a consequence CCPR has returned the MRL for cereals to Step 6 several times. To resolve the issue the submission of alternative GAP data for cereals was requested.

Methods of analysis

The Meeting received descriptions and validation data for an analytical method for the determination of residues of fenitrothion in soya bean. The analytical method used in the Brazilian trials involves extraction of fenitrothion with ethyl acetate in the presence of sodium sulphate, partitioning by a mixture of cyclohexane and ethyl acetate, and cleaning by gel permeation chromatography. The analyte is determined quantitatively by pulsing flame photometric detection (FPD).

Although the method performed satisfactorily, it was only validated in the range of 0.1–1.0 mg/kg.

Results of supervised trials on crops

Pulses

The Meeting received information on supervised trials on soya beans from Brazil, and considered this information together with Japanese trials previously found to be matching GAP in 2004. In 2004, four trials were found to comply with Japanese GAP (foliar application, 4 times 0.025–0.050 kg ai/hL, PHI 21 days). Residues found were 0.004 (2), < 0.01 (2) mg/kg. The 2004 Meeting decided that four trials (of which two showed finite residues) were not sufficient to estimate a MRL for soya bean, dry.

The present Meeting received six additional soya bean trials from Brazil. The analytical method used in these trials was not validated below 0.1 mg/kg, but the chromatograms showed well-defined peaks below that level. Two of the six trials were decline trials, in which fenitrothion peaks could be observed at day 0 indicating that the use of fenitrothion on soya beans does not result in a nil-residue situation. However, in both of the decline trials (one at GAP rate, one at double rate) no peaks were observed later than 3 days after treatment. One of the trials was according to Brazilian GAP (foliar spray treatment together with esfenvalerate, 2 treatments at 0.1–0.2 kg/hL, interval 7–10 days, PHI 7 days). Residues were < 0.1 mg/kg. At the double rate, residues found were < 0.1 mg/kg. In the remaining four trials residues were only measured 14 days after the final treatment, residues < 0.1 mg/kg.

Based on the Japanese trials (residues in rank order: 0.004 (2), ≤ 0.01 (2)) and using the Brazilian trials to support on the basis that current uses would not lead to detectable residues at harvest, the Meeting estimated a maximum residue level of 0.01 mg/kg, and an STMR of 0.01 mg/kg to replace the previous recommendations for soya bean.

Cereal grains

Five trials on stored wheat were performed in Australia and Argentina and reported by the 2003 JMPR. The Argentinean trials complied with the GAP of Argentina for post-harvest use on cereals: 6 g ai/t with a waiting period of 1 day. The residues found were: 3.1, 3.5, 5.0, 5.6 mg/kg. The Australian trial complied with the GAP of Australia for post-harvest use on wheat: 12 g ai/t with a waiting period of 3 months. The residue found was 7.6 mg/kg. The previous recommendation of the JMPR of 10 mg/kg (Po) was based upon the Australian trial result. In response to a request examine alternative GAP, the Meeting evaluated the available trials against Argentinean GAP.

The Meeting decided to estimate a maximum residue level for cereals based on the post-harvest use at 6 g ai/t. Residues were 3.1, 3.5, 5.0, 5.6 mg/kg. The Meeting decided to withdraw the previous recommendation for cereal grain of 10 mg/kg (Po). Taking into account the results of the dietary risk assessment (see below) the Meeting recommended a new maximum residue level of 6 mg/kg (Po) for cereal grain, excluding maize and estimated an HR of 5.6 mg/kg and a STMR of 4.25 mg/kg.

Fate of residues during processing

In the table below (taken from the 2004 JMPR evaluation), processing factors for wheat, barley and rice commodities are summarized. STMR-P and HR-P values were updated as the cereal grain MRL recommendation had changed.

commodity	Processing factor, range (no. of trials)	Processing factor (mean or best estimate)	STMR-P	HR-P/highest residue
Wheat bran	3.9-4.0 (2)	3.95	16.79	22.12
Wheat flour	0.21-0.26 (2)	0.235	1.00	
White bread	0.089-0.11 (2)	0.10	0.425	
Wholemeal bread	0.33-0.43 (2)	0.38	1.615	
Barley malt	0.16-0.24 (2)	0.20	0.85	
Husked rice	0.031-0.64 (22)	0.64	2.72	
Polished rice	< 0.002-0.15 (26)	0.15	0.638	
Rice hulls	0.12-10 (21)	10	42.5	56
Rice bran	0.018-7.2 (23)	7.2	30.6	40.3
Cooked husked rice	0.11 (1)	0.11	0.468	
Cooked polished rice	0.04 (1)	0.04	0.17	
Washed polished rice	0.041-0.049 (4)	0.046	0.196	
Cooked washed polished rice	0.0060-0.033 (13)	0.020	0.085	

Using the HR for cereal grains (5.6 mg/kg) and the processing factors as indicated above, the Meeting estimated a maximum residue level of 25 mg/kg in wheat bran, and 40 mg/kg in rice bran. The Meeting maintained its decision to withdraw the current recommendations for polished rice,

wheat flour, white bread and wholemeal bread of 1, 2, 1 and 3 mg/kg (PoP) respectively, as the MRLs would be lower than that of the raw agricultural commodity.

Using the HR for cereal grains (5.6 mg/kg) the Meeting estimated HR-P/highest residues for wheat bran, rice hulls, rice bran, as shown in the table above.

Furthermore, using the STMR for cereal grains (4.25 mg/kg) the Meeting estimated STMR-Ps for wheat bran, wheat flour, white bread, wholemeal bread, barley malt, husked rice, polished rice, rice hulls, rice bran, cooked husked rice, cooked polished rice, washed polished rice and cooked washed polished rice, as shown in the table above.

For the purpose of undertaking a dietary risk assessment, the Meeting decided to extrapolate the processing factor for wheat flour to all other cereal flours (except maize flour as processing was considered to be different) and estimated STMR-Ps of 1 for all cereal flours except maize flour. The Meeting extrapolated the processing factor for wheat bran to buckwheat bran estimating an STMR-P of 16.79 for buckwheat bran. Since fenitrothion is used post-harvest, and the residue is a surface residue, the Meeting considered that removal of the hull and further polishing would reduce the residue in a similar way for all cereals. The Meeting therefore decided to extrapolate the processing factor for husked rice to pot barley³⁰, estimating an STMR-P of 2.72 for pot barley, and the processing factor for polished rice to pearled barley, estimating an STMR-P of 0.638 for pearled barley. Furthermore the processing factor from wholemeal bread was extrapolated to wheat bulgur³¹ wholemeal, yielding an STMR-P of 1.615 and the processing factor from white bread was extrapolated to wheat macaroni and wheat pastry, yielding STMR-Ps of 0.425.

The Meeting decided to use the STMR-Ps for cooked husked rice and cooked polished rice in the dietary intake calculations for rice.

Data were only available for the transfer of fenitrothion residues into malt rather than beer (see JMPR 2004 Evaluation). The Meeting received, at a very late stage, two new studies on the processing of barley to malt. However, upon consideration of these studies the Meeting decided to maintain the existing processing factor as the results of the new studies would not have resulted in an amended estimate. As a consequence the Meeting decided not to include the new data and to extrapolate the existing processing factor for malt to barley beer, millet beer, and sorghum beer yielding a STMR-P of 0.85 for barley beer, millet beer, and sorghum beer.

Farm animal dietary burden

The Meeting estimated the dietary burden of fenitrothion in farm animals on the basis of the diets listed in Annex 6 of the 2006 JMPR Report (OECD Feedstuffs Derived from Field Crops). Calculation from highest residue, STMR (some bulk commodities) and STMR-P values provides the levels in feed suitable for estimating MRLs, while calculation from STMR and STMR-P values for feed is suitable for estimating STMR values for animal commodities. The percentage dry matter is taken as 100% when the highest residue levels and STMRs are already expressed as dry weight.

Estimated maximum and mean dietary burdens of farm animals

Dietary burden calculations for beef cattle, dairy cattle, broilers and laying poultry are provided in Annex 6. The calculations were made according to the animal diets from US-Canada, EU and Australia in the OECD Table (Annex 6 of the 2006 JMPR Report).

		Animal dietary burden, fenitrothion, ppm of dry matter diet		
		US-Canada	EU	Australia
Beef cattle	max	14.9	7.0	24.5 ¹
	mean	14.3	6.7	22.2 ²

³⁰ Pot barley = hulled or husked barley; pearled barley = hulled barley with the ends of the kernel removed forming a round shape.

³¹ Bulgur (wheat) = wheat that has been cooked, dried, and coarsely ground.

Dairy cattle	max	14.0	15.0	22.5
	mean	13.7	14.5	22.2 ³
Poultry - broiler	max	19.6	11.6	14.4
	mean	19.2	10.6	13.5
Poultry - layer	max	19.6 ⁴	9.9	14.1
	mean	19.2 ⁵	8.9	13.2

¹ Highest maximum beef or dairy cattle dietary burden suitable for MRL estimates for mammalian meat and milk.

² Highest mean beef or dairy cattle dietary burden suitable for STMR estimates for mammalian meat.

³ Highest mean dairy cattle dietary burden suitable for STMR estimates for milk.

⁴ Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs.

⁵ Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs.

Animal commodity maximum residue levels

The calculated maximum dietary burden for dairy and beef cattle is 24 ppm. In the cattle feeding study described in 2004, no residues were found above the LOQ (0.05 mg/kg) in muscle, fat, liver or kidney at feeding levels of 10, 30 and 100 ppm. Therefore, no residues above the LOQ are to be expected at the calculated dietary burden. Residues of fenitrothion in milk were below the LOQ of 0.01 mg/kg for all dose groups.

The calculated dietary burden for poultry is 20 ppm. In the poultry feeding study no residues were detected in muscle, liver, fat and eggs (< 0.05 mg/kg) at feeding levels of 10, 30 and 100 ppm.

The Meeting confirmed its previous recommendation of maximum residue levels of 0.05* mg/kg in meat (from mammals other than marine mammals), in edible offal (mammalian), in poultry meat, and eggs. Further the Meeting recommended a maximum residue level of 0.01 mg/kg in milks. The HRs for muscle, fat, liver, kidney, poultry meat and fat are estimated to be 0 mg/kg, and the STMRs are all estimated to be 0 mg/kg.

DIETARY RISK ASSESSMENT

In previous evaluations (JMPR 2003, 2004) the Meeting identified both long-term and short-term intake exceedances of the ADI and ARfD. The Meeting noted at the time that the intake calculations were conservative, as they did not take into account any reduction in residue obtained by processing of cereal grains, except the processing of wheat, barley and rice. Processing information on maize was identified as necessary allow a refinement of intake calculations. The present Meeting did not receive processing information on maize, as a result intake problems arising for clusters B, C and M (long-term intake) as well as for the short-term intake remain. The Meeting considered that the group MRL for cereal grains would not go forward as processing data on one of the members of that group, with significant consumption, was lacking. The Meeting therefore decided to recommend a maximum residue level for cereal grains, *excluding maize*.

Long term intake

The evaluation of fenitrothion has resulted in recommendations for MRLs and STMRs for raw and processed commodities. Consumption data were available for 37 food commodities and was used in the dietary intake calculation. The results are shown in Annex 3.

The International Estimated Daily Intakes in the 13 GEMS/Food cluster diets, based on the estimated STMRs were in the range 30–80% of the maximum ADI of 0.006 mg/kg bw (Annex 3). The Meeting concluded that the long-term intake of residues of fenitrothion from uses that have been considered by the JMPR is unlikely to present a public health concern.

Short-term intake

The international estimated short-term intake (IESTI) for fenitrothion was calculated for the food commodities (and their processing fractions) for which maximum residue levels, STMRs and HRs were estimated and for which consumption data was available. The results are shown in Annex 4. The IESTI varied from 0–80 % of the ARfD (0.04 mg/kg bw) for the general population. The IESTI varied from 0–110% of the ARfD for children 6 years and below. The intake of 110% was for unprocessed wheat bran. Since this is not the edible commodity and further processing is likely to reduce the level of residues, the Meeting assumed that the intake of fenitrothion from processed wheat bran would be below the ARfD. The Meeting concluded that the short-term intake of residues of fenitrothion from uses considered by the Meeting was unlikely to present a public health concern.

5.13 FENPYROXIMATE (193)

TOXICOLOGY

Evaluation for an acute reference dose

Fenpyroximate is the ISO approved name for the phenoxy-pyrazole acaricide, *tert*-butyl (*E*)- α -(1,3-dimethyl-5-phenoxy-pyrazol-4-ylmethylene aminoxy)-*p*-toluate (International Union of Pure and Applied Chemistry, IUPAC), also known as 1,1-dimethylethyl 4-[[[(*E*)-[(1,3-dimethyl-5-phenoxy-1*H*-pyrazol-4-yl)methylene]amino]oxy]methyl] benzoate (CAS; CAS No. 134098-61-6). Fenpyroximate is a contact acaricide with a mode of action involving the inhibition of mitochondrial proton-translocating NADH-quinone oxidoreductase (complex I).³²

Fenpyroximate was evaluated by the JMPR in 1995, when an ADI of 0–0.01 mg/kg bw was established based on the NOAEL for reduced body-weight gain in a 2-year study in rats. In 2004, the JMPR established an ARfD of 0.01 mg/kg bw based on the LOAEL of 2 mg/kg bw per day for the induction of diarrhoea at the beginning of a 13-week study of toxicity in dogs. It was unclear whether the diarrhoea was the result of a direct irritant or pharmacological effect of fenpyroximate. Since a NOAEL for diarrhoea was not identified, an additional safety factor of 2 was applied to the usual 100 to establish the ARfD. The Meeting concluded that the ARfD was conservative and could be refined if a suitable study became available.

The present Meeting reconsidered the ARfD following submission of a new study of acute toxicity in dogs. The Meeting also reconsidered the existing database on fenpyroximate, as previously evaluated. The submitted study in dogs complied with GLP requirements.

Toxicological data

Previously evaluated study in dogs

In a 13-week study, groups of four male and four female dogs received capsules containing fenpyroximate (purity, 98.4–98.6%) at a dose of 2, 10 or 50 mg/kg bw per day. Controls (four dogs of each sex per group) received the empty gelatin capsules. Dogs were inspected throughout the working day and daily observation of each animal was carried out. A more detailed weekly examination was also carried out. A detailed veterinary examination was carried out before the start of the study and after 4, 8 and 12 weeks of treatment. Ophthalmoscopic examination of the eyes was undertaken after 4, 8 and 12 weeks of treatment. Debilitated animals were carefully observed and those in extremis were killed, blood samples having been taken ante-mortem. Body weight was measured at the start of the study, and then weekly and before death. Food consumption was measured daily. Water consumption was measured during 3 days in week 6. Electrocardiography was performed before the start of treatment and at weeks 6 and 12; at weeks 6 and 12, electrocardiography was performed 2 h

³²Nakamaru-Ogiso, E., Sakamoto, K., Matsuno-Yagi, A., Miyoshi, H. & Yagi, T. (2003) The ND5 subunit was labelled by a photoaffinity analogue of fenpyroximate in bovine mitochondrial complex I. *Biochemistry*, **42**, 7.