Fenitrothion: Toxicokinetics and Toxicologic Evaluation in Human Volunteers

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An unblinded crossover study of fenitrothion 0.18 mg/kg/day [36 times the acceptable daily intake (ADI)] and 0.36 mg/kg/day (72 × ADI) administered as two daily divided doses for 4 days in 12 human volunteers was designed and undertaken after results from a pilot study. On days 1 and 4, blood and urine samples were collected for analysis of fenitrothion and its major metabolites, as well as plasma and red blood cell cholinesterase activities, and biochemistry and hematology examination. Pharmacokinetic parameters could only be determined at the higher dosage, as there were insufficient measurable fenitrothion blood levels at the lower dosage and the fenitrooxone metabolite could not be measured. There was a wide range of interindividual variability in blood levels, with peak levels achieved between 1 and 4 hr and a half-life for fenitrothion of 0.8–4.5 hr. Although based on the half-life, steady-state levels should have been achieved; the area under the curve $(AUC)_{0–12\ hr}$ to $AUC_{0–\infty}$ ratio of 1:3 suggested accumulation of fenitrothion. There was no significant change in plasma or red blood cell cholinesterase activity with repeated dosing at either dosage level of fenitrothion, and there were no significant abnormalities detected on biochemical or hematologic monitoring. *Key words:* **fenitrothion, pesticides, pharmacokinetics, toxicity.** *Environ Health Perspect* **111:305–308 (2003). doi:10.1289/ehp.5726 available via** *http://dx.doi.org/* **[Online 30 October 2002]**

Fenitrothion is a broad spectrum organic phosphorothiate (organophosphate) insecticide used to protect fruit, vegetables, and grain crops. In Australia it has been widely used to protect stored grain, whereas in many tropical countries it has found extensive use as a residual spray in homes for malaria control. Its popularity stems from the high potency and broad spectrum of its insecticide action, its chemical stability, and its low acute mammalian toxicity.

Because of its widespread use on stored grain, fenitrothion is the most common insecticide residue in Australian food. Surveys undertaken during the 1980s showed the daily intake of fenitrothion among individuals consuming reasonable quantities of cereals, bread, and other grain-based foods could come close to the upper end of the Food and Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) acceptable daily intake (ADI) of 0.0–0.005 mg/kg body weight/day (*1*). During the 1990s, however, residue levels have declined, and the 1996 Australian Market Basket survey suggested the average intake among young children was approximately 12% of the ADI, whereas that in adults was approximately 4% of the ADI (*2*).

The ADI for a chemical is the highest level of consumption believed to cause no adverse health effects over a lifetime of exposure. For fenitrothion, it is based on studies in rodents that have established a no-observed adverse effect level to which a safety margin is applied to account for possible interspecies differences in toxicity between humans and animals. Because of the widespread human exposure to fenitrothion, it is important to have more direct evidence of the agent's kinetic behavior and the relationship between plasma level and toxicity.

This study was established to examine the kinetics of fenitrothion in humans after single and repeated dosing and to relate the observed plasma levels to suppression of plasma and red blood cell cholinesterase levels. The subjects were selected from volunteers chosen because of their high level understanding of toxicology and selection was approved by the Ethics Committee at Monash University in Australia. All subjects underwent careful hematologic and biochemical monitoring.

Materials and Methods

Pilot study. In an initial pilot study, three adult males (mean age 45 years) ingested single doses of fenitrothion at dose levels of 0.06, 0.18, and 0.36 mg/kg (12, 36, and 72 × ADI, respectively). Doses were separated by at least 2 weeks. Blood samples were collected at intervals over the subsequent 4 days for the analysis of fenitrothion, fenitrooxon, and plasma cholinesterase levels. Urine was collected for 2 days, and biochemical and hematologic monitoring was also performed during the course of the study.

Main study design. Twelve adult volunteers received each of two dose levels of fenitrothion, formulated as capsules and taken with food over 4 days. Dose level 1 was 0.18 mg/kg/day (36 × ADI) administered as two divided doses given at 12-hr intervals (morning and evening). Dose level 2 was 0.36 mg/kg/day (72 × ADI). The two dosing periods were separated by at least 2 weeks, and up to 5 months with some participants. The study commenced in November 1994 and was completed by May 1995.

Participants. Twelve healthy adult volunteers were recruited from among the scientific and medical communities in Melbourne, Australia. Eight were male and four were female, with ages ranging from 23 to 50 years (mean 33 years). Before commencing the study, participants underwent a medical examination and biochemical screens (including plasma cholinesterase levels) to confirm suitability for inclusion. Volunteers were required to be otherwise healthy and have normal baseline blood tests for hematology, organ function, biochemistry profile, and cholinesterase activity.

Protocol. All clinical procedures were conducted in The Alfred Hospital, Department of Clinical Pharmacology in Melbourne. After an overnight fast, individuals received a single dose of fenitrothion (formulated as a capsule and given with food) equivalent to one-half the daily dose. Blood samples were drawn predose for measurement of fenitrothion and its metabolites and at 1, 2, 3, 4, 6, 8, 10, and 12 hr after the first dose on day 1 and at similar times after the morning dose on day 4. Blood was also drawn predose and at 4 and 8 hr after dosing for measurement of whole blood and plasma cholinesterase levels. Urine was collected over a 24-hr period on days 1 and 4.

Subjects were observed in the department for 12 hr on days 1 and 4, with regular blood pressure measurement and regular questioning about the presence of adverse effects. Biochemical and hematologic parameters

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were measured predose on day 1 and 3 days after the completion of each dosing period. On days 2 and 3 of each dosing period, the study coordinator or study nurse contacted participants daily to deliver capsules and to ensure compliance with the study protocol.

Formulation of fenitrothion capsules. Fenitrothion capsules were manufactured in Melbourne by The Institute of Drug Technology from technical-grade fenitrothion supplied by Sumitomo Chemical Company Ltd. (Osaka, Japan). Capsules were formulated in accordance with the Code of Good Manufacturing Practice (*3*) and kept refrigerated prior to dispensing.

Analysis. Fenitrothion was extracted from acidified whole blood with butyl chloride. After evaporation of the solvent, the reconstituted extract was chromatographed on a BP-5 capillary column (J&W Scientific, Melbourne, Australia) and the response measured with a nitrogenphosphorus detector (Agilent Technologies, Melbourne, Australia). Diazinon was used as an internal standard to correct for variation in recovery. Detection limits were 0.1–0.4 ng/mL, and assay precision was 17% at 0.3 ng/mL, 13% at 0.6 ng/mL, and 5.8% at 1.0 ng/mL. Accuracy at all concentrations was ± 20%, and reproducibility of fenitrothion at these concentrations (n = 17–20) was 16, 7.5, and 8.6%, respectively. Fenitrothion was stable when stored at –20°C over a 6-month period.

The levels of the metabolite 3-methyl-4-nitrophenol (MNP) in urine were measured after hydrolysis of the urine samples with 8 M HCl to convert conjugated MNP to free MNP. MNP was then extracted with butyl chloride and acetylated with acetic anhydride, and the derivative was extracted with butyl chloride. The reconstituted solvent was chromatographed on a 15-m BP-5 capillary column using splitless injection and a nitrogen-phosphorus detector. Pentobarbitone was used as an internal standard.

The detection limit of this method from 1 mL urine was 0.25 mg/L, although some specimens had a slightly higher limit because of sample volume and small background interferences. Intraassay precision and interassay reproducibility were 6% at a concentration of 8.0 mg/L.

Plasma and red blood cell cholinesterase levels were determined by the Michel method (*4*), which measures the change in pH of a blood mixture over time (units in ΔpH/hr).

Ethics. The research protocol was approved by the Monash University Ethics Committee. Participants were provided with a Plain Language Statement plus a complete study protocol. They were recruited from a group with sufficient scientific knowledge to evaluate the toxicologic issues and risks of the study and were provided with the option of discussing these with an independent physician. All participants gave written informed consent.

Pharmacokinetic analysis. The plasma concentration time data were entered into WinNonlin (Version 3.0; Pharsight Corporation, Mountain View, California, USA) to calculate the time to achieve maximum concentration (T_{max}), the maximum fenitrothion concentration (C_{max}), the half-life ($t_{1/2}$), and the area under the curve (AUC). To calculate $AUC_{0-\infty}$ when results for plasma samples were not detectable, half the not-detectable value was entered for the first value and zero for subsequent values.

Results

Pilot study. No significant symptoms or adverse effects were observed among the volunteer participants, and cholinesterase levels were not suppressed below 70% of predose levels in any subject. Only limited information was available on plasma fenitrothion or its oxon metabolite because of difficulties experienced with the assay development. The available data indicated the half-life of fenitrothion and its oxon metabolite were of the order of 3–6 hr, and the high urinary recovery of MNP suggested there were unlikely to be substantial levels of other metabolites present in humans. It was expected that steady-state levels of fenitrothion and its metabolites would be achieved after relatively brief exposure to these compounds.

Main study. **Fenitrothion levels.** Whole-blood concentrations of fenitrothion on days 1 and 4 after each of the two dosing schedules are shown in Tables 1 and 2. As there were insufficient measurable fenitrothion blood levels at the lower dose, the mean blood concentration–time data are presented only for the higher dose (Figure 1). Principal toxicokinetic parameters are summarized in Table 3.

Table 1. Fenitrothion plasma concentrations (ng/mL): dose 1 (0.18 mg/kg/day fenitrothion).

	Time (hours postdose)										
Subject	0	0.5	1	2	3	4	6	8	10	12	D/L
Day 1											
001	[a]	[b]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	0.10
002	[a]	0.59	1.08	0.55	0.44	[a]	[a]	[a]	[a]	[a]	0.10
003	[a]	[b]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	0.20
004	[a]	[b]	0.12	1.12	0.88	0.78	[b]	0.31	[a]	[a]	0.10
005	[a]	[b]	0.54	[a]	[a]	[a]	[a]	[a]	[a]	[a]	0.20
006	[a]	0.57	0.74	0.42	[a]	[a]	[a]	[a]	[a]	[a]	0.20
007	[a]	[b]	[a]	0.42	[a]	0.87	0.33	[a]	[a]	[a]	0.40
008	[a]	[b]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	0.10
009	[a]	[b]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	0.20
010	[a]	[b]	0.88	0.24	[a]	[a]	[a]	[a]	[a]	[a]	0.10
011	[a]	[b]	1.30	[a]	[a]	[a]	[a]	[a]	[a]	[a]	0.20
012	[a]	[b]	0.77	[a]	0.52	[a]	[a]	[a]	[a]	[a]	0.20
Day 4											
001	1.42	[b]	2.10	0.66	0.54	0.40	0.39	0.31	[a]	[a]	0.10
002	[a]	[b]	[a]	0.32	[a]	[a]	[a]	[a]	[a]	[a]	0.10
003	[a]	[b]	0.20	[a]	[a]	[a]	[a]	[a]	[a]	[a]	0.20
004	1.48	[b]	2.97	2.89	2.20	2.90	1.00	0.71	0.48	0.36	0.10
005	[a]	[b]	0.86	0.32	0.78	0.50	[a]	[a]	[a]	[a]	0.20
006	[a]	[b]	0.35	0.48	0.43	[a]	[a]	[a]	[a]	[a]	0.20
007	0.42	[b]	1.02	1.30	0.57	0.51	0.55	[a]	[a]	[a]	0.40
008	0.14	[b]	0.58	0.24	0.11	0.12	[a]	[a]	[a]	[a]	0.10
009	[a]	[b]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	0.20
010	[a]	[b]	0.48	1.16	0.33	0.24	[a]	[a]	[a]	[a]	0.10
011	[a]	[b]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	0.20
012	[a]	[b]	1.04	0.43	0.54	0.62	0.38	0.25	[a]	[a]	0.20

D/L, detection limit of assay.
[a]Not detected. [b]No sample was obtained.

Fenitrothion concentrations showed high interindividual variation, with four subjects having all levels below the limit of detection after the first day of the lower doses, and two others having no identifiable levels with the lower dose on day 4. All subjects had detectable levels with the higher dose on day 1 and day 4, though five subjects had only one to two detectable levels after the first dose. Fenitrothion was cleared and metabolized from the blood too fast to obtain valid concentrations in a sufficient number of volunteers at the lower dose; therefore, valid calculation of kinetic parameters was possible only at the highest dose.

The agent was absorbed rapidly, with peak blood levels generally achieved 1–4 hr after dosing. The half-life of the parent substance ranged from 0.8 to 4.5 hr. Although we could not accurately determine the $AUC_{0–12\ hr}$ on day 4 for the lower dose and hence the ratio of $AUC_{0–12\ hr}$ for the two dose levels, the concentration–time data indicate a dose-dependent increase in blood concentrations within this dose range. For the higher dose, the ratio of $AUC_{0–12\ hr}$ on day 4/$AUC_{0–\infty}$ on day 1 was approximately 1:3, suggesting accumulation of the parent substance; however, the high degree of interindividual variability makes these comparisons relatively imprecise.

The fenitrooxon metabolite appeared to co-elute with a large caffeine peak, which prevented determination of its blood concentrations.

Urine 3-methyl-4-nitrophenol. MNP was detected in all but one of the 24-hr urine specimens analyzed (Table 4). After adjusting for the molar equivalent of MNP to fenitrothion, the MNP excretion corresponded to 83 and 67% of the total fenitrothion dose consumed on days 1 and 4 of the lower dose, and 97 and 76% of that consumed on days 1 and 4 of the higher dose, respectively.

Cholinesterase level. Plasma and red cell cholinesterase activity recorded during the study were all within the normal range quoted for the healthy adult exposed population (i.e., 0.60–1.10 ΔpH/hr in red cells, 0.62–2.0 ΔpH/hr in plasma). No statistically significant trends were observed in mean plasma or red blood cholinesterase levels. There were no individual cases where cholinesterase activity

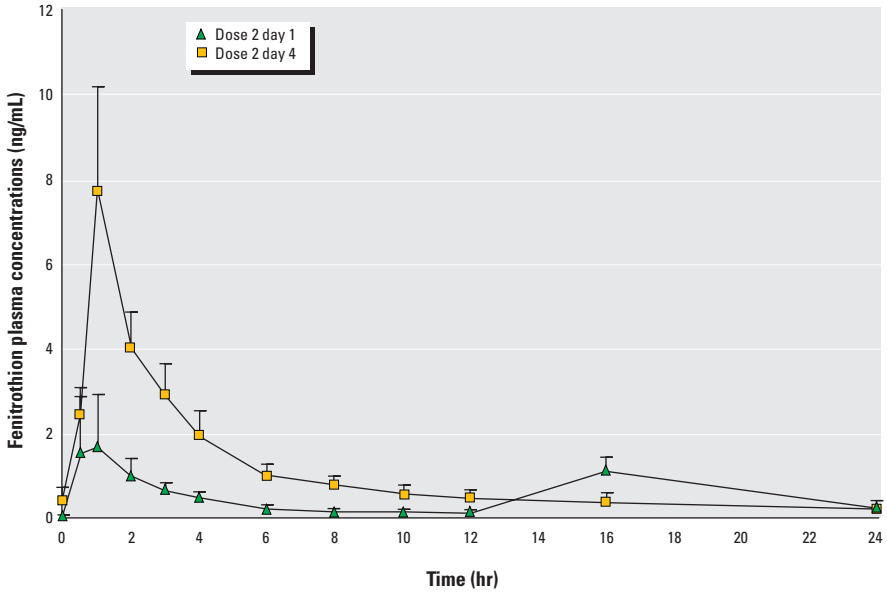

Figure 1. Fenitrothion plasma concentrations (mean, standard error) after 0.36 mg/kg/day (dose 2). The rise in fenitrothion concentration at 16 hr postdose on dose 2 day 1 is due to administration of the evening dose at 12 hr postdose; this measurement reflects fenitrothion levels 16 hr after the initial (morning) dose plus 4 hr after the evening dose.

Table 2. Fenitrothion plasma concentrations (ng/mL): dose 2 (0.36 mg/kg/day fenitrothion).

	Time (hours postdose)												
Subject	0	0.5	1	2	3	4	6	8	10	12	16	24	D/L
Day 1													
001	[a]	[a]	[a]	0.89	0.30	0.20	[a]	[a]	[a]	[a]	0.59	[a]	0.20
002	[a]	1.13	1.36	0.82	0.35	0.70	[a]	0.22	[a]	[a]	2.05	0.35	0.10
003	[a]	[a]	[a]	[a]	[a]	0.43	[a]	[a]	[a]	[a]	0.42	[a]	0.40
004	[a]	16.10	15.28	5.15	1.82	1.16	1.07	0.67	0.31	0.47	2.32	0.91	0.10
005	[a]	0.33	0.85	0.60	1.46	0.68	[a]	[a]	[a]	[a]	0.27	[a]	0.20
006	[a]	[a]	0.40	0.62	[a]	[a]	[a]	[a]	[a]	[a]	0.40	[a]	0.20
007	[a]	0.24	0.33	1.30	0.71	0.53	0.47	0.28	0.26	[a]	1.79	0.34	0.10
008	0.34	0.13	1.45	1.70	1.78	1.20	0.40	0.44	0.39	0.95	3.70	0.56	0.20
009	[a]	0.22	0.17	0.72	0.56	0.58	0.31	0.18	[a]	[a]	0.54	0.17	0.10
010	[a]	0.37	0.17	[a]	[a]	[a]	[a]	[a]	0.55	[a]	[a]	[a]	0.10
011	[a]	[a]	[a]	[a]	0.62	[a]	[a]	[a]	[a]	[a]	0.61	[a]	0.40
012	[a]	[a]	[a]	[a]	[a]	0.28	[a]	[a]	[a]	[a]	0.50	[a]	0.20
Day 4													
001	[a]	0.29	1.43	4.44	2.75	2.00	0.71	0.32	0.42	[a]	[a]	[a]	0.20
002	0.24	1.05	16.40	3.66	1.82	1.36	1.90	0.82	0.35	0.28	0.19	0.22	0.10
003	0.52	1.15	1.30	2.08	1.58	2.50	1.08	1.40	1.04	0.53	0.51	0.45	0.40
004	1.58	[b]	22.68	10.13	7.64	6.97	2.82	2.24	1.99	1.66	1.74	1.07	0.10
005	0.34	6.30	5.70	6.20	7.51	2.37	[a]	0.88	[a]	[a]	0.34	[a]	0.20
006	[a]	6.44	10.24	4.31	1.96	1.18	0.73	[a]	[a]	0.62	[a]	[a]	0.20
007	0.51	1.17	1.30	3.60	1.44	0.96	2.28	1.37	0.89	0.96	0.65	0.39	0.10
008	0.80	3.22	23.68	8.26	5.61	3.61	1.86	1.61	1.61	1.36	0.83	0.52	0.20
009	[a]	4.69	4.15	1.96	1.23	0.56	0.22	[a]	[a]	[a]	[a]	[a]	0.10
010	[a]	1.24	1.61	0.12	[a]	[a]	[a]	[a]	[a]	[a]	[a]	[a]	0.10
011	[a]	[a]	[a]	1.15	0.56	0.65	[a]	[a]	[a]	[a]	[a]	[a]	0.40
012	0.44	0.96	3.51	2.34	2.66	1.49	[a]	[a]	0.49	[a]	[a]	[a]	0.20

For calculating the means, half the D/L value was assigned for first value D/L level, then zero for subsequent values.
[a]Not detected. [b]No sample was obtained.

Table 3. Pharmacokinetic parameters of fenitrothion: dose 2 (0.36 mg/kg/day).

	C_{max} (ng/mL)[a]	T_{max} (hr)[a]	AUC (ng/hr/mL)[a]	$t_{1/2}$ (hr)[a]
Day 1	2.2 ± 4.4	2.5	10.2 ± 12.0	2.5 ± 1.3
Day 4	8.5 ± 8.1	1.0	30.9 ± 21.5	3.6 ± 4.0

[a]Values derived by averaging individual measurements of subjects with sufficient levels to enable calculation of the relevant parameters.

Table 4. Excretion of MNP metabolite related to fenitrothion dose.

	Dose 1		Dose 2	
	Day 1	Day 4	Day 1	Day 4
Mean MNP excretion (mg)	5.97	3.63	9.85	5.69
Fenitrothion equivalent (mg)	10.8	6.56[a]	17.8	10.3[a]
Mean oral fenitrothion dose (mg)	13	6.75	26.4	13.5
Percent excreted in 24 hr	83	97	67	76

[a]Only the morning fenitrothion dose was given to subjects on day 4.

was depressed in a clinically significant fashion (i.e., more than 25% depression from baseline). The largest decrease in red blood cell cholinesterase activity from baseline was 17% during dose 1 and 12% during dose 2. Most subjects showed less than a 10% decrease in red blood cell cholinesterase activity. Changes in plasma cholinesterase activity were variable, with subjects demonstrating an increase, decrease, or no effect after fenitrothion dosing.

Toxicity monitoring. No clinically significant changes were noticed in blood pressure or pulse rate. No abnormalities were observed among the individual hematologic and biochemical parameters monitored, and no trends were observed in mean values. Few symptoms were observed apart from one subject in whom specific questioning elicited a report of mild sweating and colic that did not affect normal physical functioning and were not accompanied by alterations in cholinesterase levels. Similar but even milder symptoms were present during the second dosage and resolved after completion of the study.

Discussion

Short-term studies in rats and dogs have shown that depression of plasma cholinesterase is the most sensitive indicator of fenitrothion toxicity. No-effect levels based on plasma cholinesterase depression have been established in rats (0.25 mg/kg body weight) and in dogs (0.3 mg/kg body weight) (*5*). Application of a 100-fold safety margin has led to a human ADI of 0.003 mg/kg body weight/day. Until the early 1990s, human exposure to fenitrothion among Australian eaters of cereals and cereal products came close to this value.

This study involved the administration of fenitrothion doses at 36 × and 72 × the FAO/WHO ADI value over 4-day periods. The previous pilot study suggested these doses were likely to be well tolerated. Measurement of the half-life of fenitrothion and its major metabolite suggested a relatively short half-life of 3 hr. Thus, a 4-day period of regular dosing was considered sufficient to produce steady-state blood concentrations close to those likely after a more prolonged period of dosing.

Results of the toxicokinetic study indicate fenitrothion is rapidly absorbed and extensively metabolized in humans. The majority of each dose was rapidly excreted in the form of MNP. However, the AUC observed after 3 days of dosing was approximately 3-fold greater than that seen after the initial dose, raising the possibility that excretion is less rapid after the initial dose. Further studies with a longer duration of kinetic monitoring would be needed to determine whether significant pharmacokinetic accumulation is occurring.

The findings of rapid absorption and extensive metabolism are in keeping with those observed in various animal species (*6,7*). The minimal suppression of plasma cholinesterase at the doses administered suggests the present ADI is likely to confer a substantial safety margin. Plasma cholinesterase is substantially more sensitive to anticholinergic agents than red cell cholinesterase, whereas the latter more closely reflects the activity of cholinesterase enzymes within the nervous system. Therefore, the safety margin between the current ADI and the levels exerting a toxic effect on nerve synapses is likely to be even greater. The lack of symptoms and the absence of abnormalities detected on biochemical and hematologic monitoring also support the likelihood that the present ADI confers a substantial safety margin.

The results are also in keeping with a previously published human study. Nosal and Hladka (*8*) reported results of a single-dose study in which 24 volunteers ingested fenitrothion in doses of 2.5–20 mg (equivalent to 0.04–0.33 mg/kg body weight) (*8*). Depression of plasma cholinesterase was observed in only one subject whose activity declined to 72% after a 20-mg dose. No symptoms were reported, and levels returned to normal within 24 hr.

Although the primary toxicity associated with fenitrothion exposure is related to acetylcholinesterase inhibition, there has also been some concern about the endocrine and reproductive toxicity, or more specifically, the inhibitory effects on the human androgen receptor (*9*). A recent study using HepG2 human hepatoma cells and male Sprague-Dawley rats has demonstrated that fenitrothion competitively antagonizes androgen receptor activity in transfected cells and causes regression of androgen-dependent tissue weights *in vivo* (*9*). Researchers reported that inhibition of androgen receptor function *in vivo* occurred at a dose of fenitrothion that did not significantly alter acetylcholinesterase activity. These findings have not resulted in a decrease in the ADI and were not considered in this study, where we based the safety of fenitrothion on its inhibition of cholinesterase.

In summary, these results suggest fenitrothion is rapidly absorbed and extensively metabolized after oral administration to humans. The lack of significant suppression of plasma or red cell cholinesterase (and the absence of symptoms or of abnormalities in laboratory testing) after 3 days of dosing at a level 72 × that of the ADI suggests the present ADI confers a substantial margin of safety, at least in relation to acute (first dose) and subacute effects of the agent. However, more prolonged repeat-dosing studies are required to resolve the issue of accumulation.

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