S-Methyl Isomer Content of Stored Malathion and Fenitrothion Water-Dispersible Powders and Its Relationship to Toxicity

James W. Miles,* Dwight L. Mount, Michael A. Staiger, and Winnie R. Teeters

A study was undertaken to determine the role of S-methyl isomer formation in the toxicity of malathion and fenitrothion water-dispersible powders held in tropical storage. The S-methyl isomers of malathion and fenitrothion were synthesized, high-pressure liquid chromatography and gas–liquid chromatography methods were developed for their determination in powder formulations. Samples of malathion water-dispersible powders returned from storage in tropical countries were found to have S-methyl isomer contents as high as 3.3% and rat oral LD_{50} values of 500 mg/kg compared to fresh powders containing less than 0.3% of the isomer and having rat oral LD_{50} values of above 2500 mg/kg. Increasing S-methyl isomer content and toxicity were also observed in malathion water-dispersible powders held at elevated temperatures in the laboratory. The rate of formation of S-methyl isomer of malathion was found to depend upon the type of "inert" ingredients in the formulation. No increase in toxicity was observed in fenitrothion powders stored at elevated temperatures although the S-methyl isomer was formed in concentrations up to 1%.

By 1975 some 24 species of anopheline mosquitoes were reported to be resistant to DDT (World Health Organization, 1976). This has forced many countries to seek alternate pesticides for use in their malaria control programs. The most promising alternate compounds are malathion, fenitrothion, and propoxur. The Government of Pakistan began to use malathion, water-dispersible powder, on a large scale for malaria control in 1976. Shortly after initiation of the spraying program, many spraymen became ill and five died from pesticide intoxication (Baker et al., 1978). Chemical and toxicological analyses of samples of powders returned from the field showed that powders furnished by two companies had high S-methyl isomer content (>2.0%) and high mammalian toxicity (rat oral LD_{50}'s <1000 mg/kg). Samples furnished by a third company had low S-methyl isomer content (<0.3%) and relatively low mammalian toxicity (rat oral LD_{50}'s >1500 mg/kg). The purpose of this study was to develop improved methods of analysis for the S-methyl isomer content of malathion and fenitrothion powders and to determine the relationship of toxicity to S-methyl isomer content.

EXPERIMENTAL SECTION

Reagents. The malathion, analytical standard (99.1%), technical grade, and 50% water-dispersible powder, as well as fenitrothion, analytical standard (97.5%) were obtained from the American Cyanamid Co., Princeton, NJ. Purified malathion was prepared by crystallizing the technical grade material three times from methanol at −50 °C. Fenitrothion, technical grade, and 40% water-dispersible powder were obtained from Sumitomo Chemical America, Inc., New York, NY. Purified fenitrothion was prepared from technical grade material according to the procedure described by Kovacicova et al. (1971). Di-*n*-butyl sebacate and *m*-diphenoxybenzene were obtained from the Eastman Kodak Co., Rochester, NY. Di-*n*-hexyl azelate obtained from ICN Pharmaceuticals, Plainview, NJ, was purified by vacuum distillation. The cyclohexane and isopropyl alcohol were distilled in glass by Burdick and Jackson Laboratories, Muskegon, MI.

Malathion, S-methyl isomer was prepared from malathion. One-half mole of malathion, technical in 600 mL of methanol was refluxed for 2 h with an equimolar amount of potassium ethyl xanthate. After evaporation of the solvent in a vacuum rotary evaporator, the residue was taken up in 400 mL of water and extracted three times with benzene. The aqueous phase was filtered through Celite and the water removed by lyophilization to yield 75 g of the crude potassium salt of desmethyl malathion. Three grams of the above salt was dissolved in 10 mL of acetonitrile and 1.5 g of CH_3I was added. After standing overnight the precipitated KI was removed by filtration and the solvent was evaporated in a vacuum rotary evaporator. The crude product was purified on a silica gel column as described by Umetsu et al. (1977).

Fenitrothion, S-methyl isomer was prepared from fenitrothion. One-tenth mole of technical grade fenitrothion was demethylated with potassium ethyl xanthate by the same procedure described above for malathion to yield 21.5 g of the crude desmethyl salt crystals. The above salt was dissolved in 75 mL of acetonitrile, 12.5 g of CH_3I was added, and the mixture was heated to reflux temperature and the solvent removed in a vacuum rotary evaporator. Fifty milliliters of water was added to the residue and the mixture extracted three times with 50-mL portions of ether. After drying over Na_2SO_4, the ether was evaporated. Three-gram portions of the crude S-methyl isomer were purified on a silica gel column as described by Umetsu et al. (1977) for the purification of the S-methyl isomer of malathion.

Tetraethyl thiodisuccinate (TEMS) was prepared by a modification of the synthesis of a related series of compounds (Chakrabarti, 1975). A mixture of 0.2 mol of sodium maleate and 0.2 mol of sodium mercaptosuccinate in 200 mL of water was heated on a water bath at 55 °C for 3 h. The mixture was then lyophilized and the resultant solid esterified using dry HCl in ethanol. After reaction workup, the 40 g of crude oil was vacuum distilled to yield 25 g of purified product, bp 160 °C (0.5 torr).

Malathion, S-methyl isomer standard solution for GLC was prepared by weighing accurately approximately 30 mg of the purified S-methyl isomer, 10 mg of TEMS, and 1.5 g of purified malathion into a 25-mL volumetric flask and adding by pipet 2.0 mL of internal standard

Vector Biology and Control Division, Bureau of Tropical Diseases, Center for Disease Control, Public Health Service, U.S. Department of Health, Education, and Welfare, Atlanta, Georgia 30333 (J.W.M., D.L.M., M.A.S.) and the Environmental Protection Agency, Beltsville, Maryland 20705 (W.R.T.).

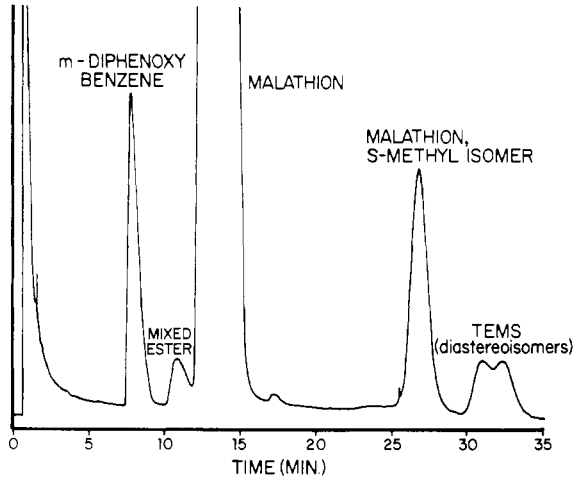

Figure 1. Gas chromatogram of malathion, S-methyl isomer standard solution (*m*-diphenoxybenzene used as internal standard).

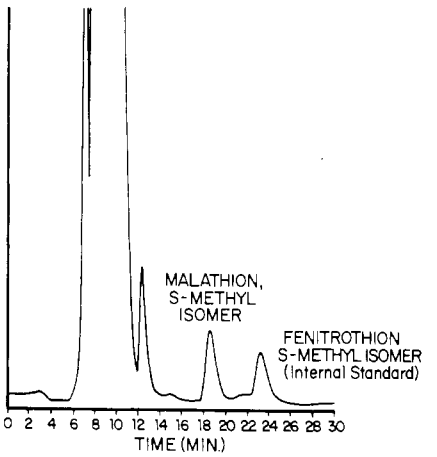

Figure 2. LC chromatogram of a sample analyzed for malathion, S-methyl isomer (fenitrothion, S-methyl isomer used as internal standard).

(0.4% *m*-diphenoxybenzene in chloroform) and making to volume with chloroform.

Malathion, *S*-methyl isomer standard solution for high-pressure liquid chromatography (LC) was prepared by weighing accurately approximately 30 mg of the purified *S*-methyl isomer and 1.5 g of purified malathion into a 25-mL volumetric flask and adding by pipet 2.0 mL of internal standard (0.2% isofenitrothion in chloroform) and making to volume with chloroform.

Fenitrothion, *S*-methyl isomer standard solution for GLC was prepared by weighing accurately approximately 30 mg of the purified *S*-methyl isomer and 1.2 g of purified fenitrothion into a 25-mL volumetric flask, adding by pipet 2.0 mL of internal standard (1.5% di-*n*-hexyl azelate in chloroform), and making to volume with chloroform.

Apparatus. A Varian Model 3700 gas chromatograph equipped with a Model CDS-111 chromatography data system, a Model 8000 automatic sample injector, a flame ionization detector, and a 183 cm × 2 mm i.d. glass column packed with 7.5% OV-210 on Chromosorb W HP was used for the gas chromatographic analysis. A Waters Model 6000A solvent delivery system equipped with a Waters Model U6K loop injector, a Varian Vari-chrom variable wavelength absorbance detector, a Varian Model CDS-111 chromatography data system, and a Whatman Partisil-10 PAC column (4.6 mm × 25 cm) was used for the LC analyses.

Analytical Methods. *Malathion Content.* The malathion powders were analyzed according to the procedure described by Wayne (1978), with the substitution of a column packed with 7.5% OV-210 on Chromosorb W HP in lieu of 5% SP-2401 on Gas-Chrom Q. With this column operated at 180 °C, the internal standard (*m*-diphenoxybenzene) eluted at 7.5 min and the malathion eluted at 12.5 min.

Malathion, S-Methyl Isomer Content. (a) *GLC Method.* Approximately 3.0 g of the unknown powders was accurately weighed into a 30-mL screw-cap bottle, and 2.0 mL of the internal standard solution (0.4% *m*-diphenoxybenzene in chloroform) was added by pipet. Approximately 25 mL of chloroform was added and the mixture shaken to dissolve the malathion. A portion of the supernatant liquid was filtered and held for GLC analysis. Duplicate 3-μL aliquots of the *S*-methyl isomer standard solution were injected into the gas chromatograph under the conditions described below and the response ratio of the *S*-methyl isomer to internal standard was determined. These injections were followed by duplicate injections of the unknown solution. The S-methyl isomer content was determined by comparison of the response ratio of the unknown to that of the standard. A typical chromatogram is shown in Figure 1.

Operating parameters of gas chromatograph were: oven, 175 °C; injection port, 190 °C; flame detector, 280 °C; hydrogen flow rate, 30 mL/min; air, 300 mL/min; carrier gas (nitrogen), 30 mL/min. Separation of the diasterioisomers of TEMS serves as a resolution check for the column. Conditions were considered to be satisfactory when the distance measured from the top of the TEMS peaks to the valley between the peaks was at least 10% of the height of the TEMS peaks.

Almost all malathion powders contain small quantities of the tetraethyl dithiodisuccinate (TEDS). The temperature of the column oven must be programmed to 240 °C after each unknown run in order to remove this compound prior to injection of the next sample.

(*b*) *LC Method.* Three-gram samples of powder were accurately weighed into 30-mL glass bottles, and 2.0 mL of internal standard (0.2% isofenitrothion in chloroform) was added by pipet. An additional 25 mL of chloroform was added by pipet and the mixture was shaken to dissolve the organic phase. A portion of the supernatant was filtered through a 0.45 μm filter and analyzed by LC.

Duplicate 5-μL volumes of the *S*-methyl isomer standard solution were injected into the chromatograph, and the average response ratio of the *S*-methyl isomer to internal standard was calculated. Immediately following, duplicate 5-μL injections of the unknown solutions were analyzed, and the *S*-methyl isomer content of each was determined by comparison of the response ratio of the unknown to that of the standard. A typical chromatogram of an unknown is shown in Figure 2.

Samples were eluted with cyclohexane/isopropyl alcohol (90:10) at a flow rate of 0.4 mL/min at 100 psi. UV absorbance was measured at 222 nm with an attenuation of 0.2 aufs.

Fenitrothion Content. The fenitrothion powders were analyzed by GLC according to the method of Takimoto et al. (1976) with slight modifications. Separations were made on the same column described above for malathion. The column temperature was 165 °C. Dibutyl sebacate was used as an internal standard. A typical chromatogram is shown in Figure 3.

Fenitrothion, S-Methyl Isomer Content. (*a*) *GLC Method.* Approximately 3.0 g of the unknown powders was accurately weighed into a 30-mL screw-cap bottle and 2.0

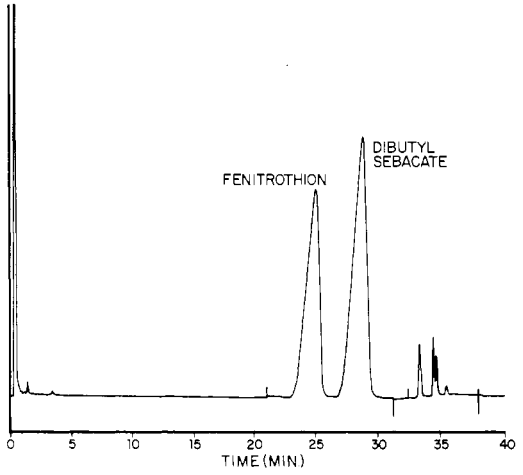

Figure 3. Gas chromatogram of an unknown fenitrothion powder analyzed for fenitrothion (dibutyl sebacate used as internal standard).

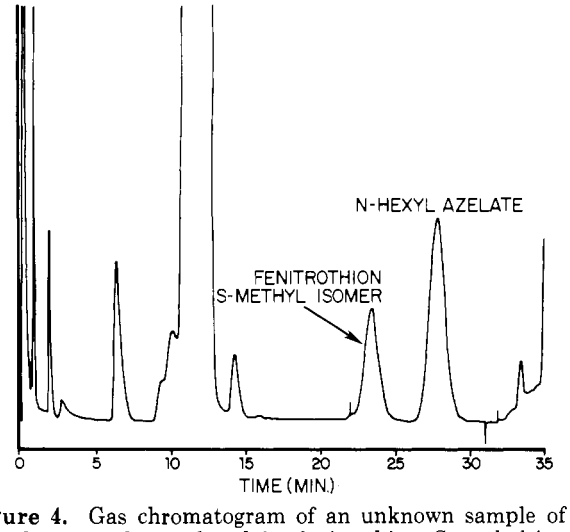

Figure 4. Gas chromatogram of an unknown sample of fenitrothion powder analyzed for fenitrothion, S-methyl isomer content (di-*n*-hexyl azelate used as internal standard).

mL of the internal standard (1.5% of di-*n*-hexyl azelate in chloroform) was added by pipet. Approximately 25 mL of chloroform was added and the mixture was shaken to dissolve the fenitrothion. A portion of the supernatant liquid was filtered and held for GLC analysis.

Duplicate 3-μL aliquots of the *S*-methyl isomer standard solution were injected into the gas chromatograph under the conditions described above for the analysis of the malathion *S*-methyl isomer. The response ratio of the *S*-methyl isomer to internal standard was determined. These injections were followed by duplicate injections of the unknown solution. The *S*-methyl isomer content was determined by comparison of the response ratio of the unknown to that of the standard. A typical chromatogram is shown in Figure 4.

(*b*) *LC Method.* Samples containing approximately 1.5 g of active ingredient were accurately weighed into 30-mL screw-cap bottles, and 25 mL of chloroform was added by pipet. After shaking to dissolve the organic phase, a portion of the supernatant was filtered through a 0.45 μm filter and held for analysis. A standard solution was prepared by weighing 1.5 g of purified fenitrothion and 30 mg of the *S*-methyl isomer into a 25-mL flask and adding 25 mL of chloroform by pipet.

Duplicate 5-μL samples of the standard and unknown solutions were injected into the liquid chromatograph. The samples were eluted with cyclohexane/isopropyl alcohol

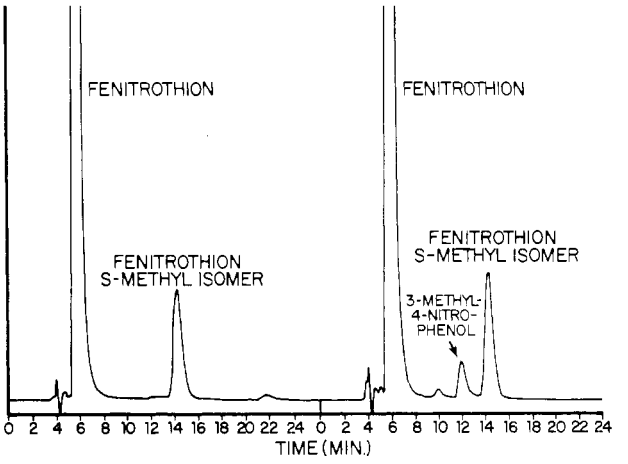

Figure 5. LC chromatograms of a standard and an unknown sample of fenitrothion powder analyzed for the S-methyl isomer.

(90:10) at a flow rate of 0.8 mL/min at 320 psi. Absorbance was measured at 280 nm with an attentuation of 1 aufs. Quantitation was made by comparison of the *S*-methyl isomer peak areas of the unknown with those of the standard. Typical chromatograms of the standard and a sample are shown in Figure 5.

Toxicity Test Methods. Acute oral toxicity was determined in young adult female rats of the Wistar strain. They received a single oral dose following an overnight fast. Suspensions of the powders at 200 mg/mL concentration were prepared in corn oil for the 184 series samples returned from Pakistan and in water with the aid of polysorbate 80 for all other samples. Cumulative mortality recorded at 48 h after dosing was used in estimating the LD_{50} for the 184 series while similar data recorded at 1 week after dosing were used for all other samples.

The method of Litchfield and Wilcoxon (1949) was used to estimate the LD_{50} and its 95% confidence limits. Values were determined on the basis of the total formulation, not malathion nor fenitrothion content.

Analysis of Samples. Samples of malathion, 50% water-dispersible powder, manufactured by three companies were collected in the field in Pakistan following the report of poisoning in 1976. The samples were analyzed for malathion and *S*-methyl isomer by gas chromatography. Subsamples were tested for toxicity.

Three types of malathion powders were subjected to accelerated storage tests to determine changes in composition and toxicity. A sample of malathion, 50% water-dispersible powder, manufactured by an American supplier for use in malaria programs was divided into subsamples and placed in ovens maintained at 38, 55, and 90 °C. A product containing malathion on Hi-Sil was prepared in a blender, and samples of this material were stored under the same conditions. A third formulation was prepared with high-quality malathion mixed with the same "inert" ingredients used in one of the products associated with the deaths in Pakistan. The composition of the experimental formulation was American Cyanamid malathion, technical, 54%; Ketjensil, 32%; Empilan, 5%; Empicol, 6%; and $CaCO_3$, 3%. Subsamples of this formulation were held at 38 °C for 3 months and at 55 °C for 6 and 13 days. After storage, the samples were analyzed for malathion and *S*-methyl isomer by GLC and tested for toxicity.

Samples of fenitrothion, 40% water-dispersible powder, manufactured by the Sumitomo Chemical Co. were placed in storage at 38 and 55 °C. Subsamples of the powder held at 38 °C were removed after 2, 4, and 6 months and

Table I. Chemical Composition and Toxicity of Malathion 50% Water-Dispersible Powders Returned from Pakistan

desig-nation	manu-fact.	mala-thion found, %	S-methyl isomer found, %	rat oral LD_{50}, mg/kg (95% confidence limits)
184A	A	44.8	0.2	2500 (2137-2925)
184H	A	42.1	0.2	1800 (1488-2178)
184M	B	34.4	2.9	850[a]
184N	B	36.9	3.3	500 (400-625)
184P	C	47.6	2.0	520 (456-593)
184R	C	46.1	2.2	760 (603-958)

[a] Approximation; slope too steep for dosage interval (> 792 < 1002).

Table II. Changes in Chemical Composition and Toxicity of an American-Made 50% Malathion Water-Dispersible Powder Stored at 38, 55, and 90 °C

time in stor-age	T, °C	mala-thion found, %	S-methyl isomer found, %	rat oral LD_{50}, mg/kg (95% confidence limits)
0		48.0	0.38	2800 (2545-3080)
1 mo	38	46.7	0.37	1790 (1421-2255)
2 mo	38	45.5	0.37	2230 (1756-2832)
3 mo	38	44.2	0.49	1740 (672-4507)
6 mo	38	39.8	0.45	1500 (1351-1665)
6 da	55	47.6	0.30	2520 (2049-3100)
13 da	55	46.4	0.37	1760 (1504-2059)
24 h	90	40.9	0.69	950 (704-1283)
48 h	90	26.2	2.89	560[a]
72 h	90	14.0	2.06	385 (338-439)

[a] Approximation; slope too steep for dosage interval (> 502 < 632).

Table III. Changes in Composition and Toxicity of a Mixture of Malathion and Hi-Sil Stored at 38, 55, and 90 °C

time in stor-age	T, °C	mala-thion found, %	S-methyl isomer found, %	rat oral LD_{50}, mg/kg (95% confidence limits)
0		48.8	0.18	2540 (2288-2819)
1 mo	38	48.3	0.71	1680 (1436-1966)
2 mo	38	47.2	0.79	1130 (974-1311)
3 mo	38	46.5	0.81	1330 (1127-1569)
6 da	55	45.2	0.67	1200 (1043-1380)
13 da	55	43.6	0.55	1170 (975-1404)
24 h	90	39.9	0.32	1900 (1624-2223)
48 h	90	38.0	0.34	1580 (1244-2007)
72 h	90	26.0	0.33	1080 (973-1199)

subsamples of that held at 55 °C were removed at 6, 13, and 21 days. All samples were analyzed for fenitrothion and S-methyl isomer by GLC and tested for toxicity.

Selected samples of malathion and fenitrothion powders having a wide range of S-methyl isomer content were analyzed for this isomer by both GLC and LC using the procedures described above.

RESULTS AND DISCUSSION

Analyses of samples of malathion water-dispersible powder returned from the field as well as those stored at elevated temperatures in the laboratory have shown that the S-methyl isomer forms in the powder stored under these conditions (Tables I–IV). Some formulations tend to isomerize more rapidly than others. The rate of isomerization at a given temperature appears to be a function of the carrier and surfactants used in the formulation. Although other minor components are present in malathion water-dispersible powders, Baker et al. (1978) showed that the toxicity to humans correlated best with

Table IV. Changes in Composition and Toxicity of a Malathion Water-Dispersible Powder Prepared with Ketjensil, Epilan, Empicol, and $CaCO_3$ Stored at 38 and 55 °C

time in stor-age	T, °C	mala-thion found, %	S-methyl isomer found, %	rat oral LD_{50}, mg/kg (95% confidence limits)
0		50.6	0.61	2660[a]
3 mo	38	44.9	3.7	590 (518-673)
6 da	55	46.2	3.4	535 (482-594)
13 da	55	43.7	3.5	555 (455-677)

[a] Approximation; slope too steep for dosage interval (> 2520 < 2820).

Table V. Chemical Composition and Toxicity of Fenitrothion 40% Water-Dispersible Powder Stored at 38 and 55 °C

time in stor-age	T, °C	fenitro-thion found, %	S-methyl isomer found, %	rat oral LD_{50}, mg/kg (95% confidence limits)
0		38.0	0.32	2370 (490-11471)
2 mo	38	36.8	0.78	2360 (2126-2620)
4 mo	38	36.1	0.82	2300 (2072-2553)
6 mo	38	36.0	0.85	2320 (2109-2522)
6 da	55	37.1	0.80	2360 (2017-2761)
13 da	55	36.6	0.94	2940 (2534-3410)
21 da	55	36.2	1.05	2550 (338-19227)

the S-methyl isomer content. The animal data obtained in the present study support this finding (Table I). Samples having high S-methyl isomer content (2.0% or more) exhibit high acute toxicity to rats (LD_{50} of 800 mg/kg or less). With one exception, all samples with less than 1% S-methyl isomer had rat oral LD_{50}'s greater than 1000. This is true of samples returned from tropical storage in the field and samples stored at elevated temperatures in the laboratory.

Data obtained on samples of mixtures of malathion and Hi-Sil (Table III) and malathion, Ketjensil, and surfactants (Table IV) show that the rate of formation of the S-methyl isomer is much higher in the latter mixture. The relatively high S-methyl isomer content of the zero-time samples containing Ketjensil shows that isomerization has occurred in the short time from preparation of the mixture to the actual time of analysis.

The S-methyl isomer content of fenitrothion water-dispersible powders also increased with time in storage at 38 and 55 °C but not to the same extent as noted for the corresponding isomer in some malathion powders (Tables I–V); moreover, no appreciable decrease in the rat oral LD_{50} values, that is, increase in toxicity, was observed for fenitrothion (Table V). Rosival et al. (1976) showed that the S-methyl isomer was more toxic to rats than purified fenitrothion. The present study shows that the rat oral LD_{50} values for fenitrothion 40% water-dispersible powders containing up to 1% S-methyl isomer were essentially the same as those obtained on powders containing 0.3% of the isomer. Thus it was concluded that up to 1% concentration, the S-methyl isomer of fenitrothion does not potentiate the toxicity of the parent compound in powder formulations.

Although both malathion and fenitrothion powders induced in rats signs typical of acetylcholinesterase depression, there were marked differences in the effects on the animals. Those receiving fenitrothion generally showed signs at a lower dosage and shorter onset than with malathion. Muscular weakness, tremors, fasciculation, and chromodacryorrhea were particularly marked and per-

Table VI. Comparison of S-Methyl Isomer Content of Malathion 50% Water-Dispersible Powders Obtained by LC and GLC

malathion, 50% wdp	S-methyl isomer found, % LC	GLC
as received	0.10	0.38
1 mo at 38 °C	0.18	0.37
2 mo at 38 °C	0.20	0.37
6 mo at 38 °C	0.23	0.45
6 da at 55 °C	0.12	0.30
13 da at 55 °C	0.23	0.37
24 h at 90 °C	0.85	0.65
48 h at 90 °C	2.96	2.89
72 h at 90 °C	2.92	2.06
>1 year field storage (Pakistan Sector B-12)	0.96	1.05
>1 year field storage (Pakistan Sector E-11)	1.41	1.38

Table VII. Comparison of S-Methyl Isomer Content of Fenitrothion 40% Water-Dispersible Powders Obtained by LC and GLC

fenitrothion, 40% wdp	S-methyl isomer found, % LC	GLC
as received	0.05	0.32
2 mo at 38 °C	0.50	0.78
4 mo at 38 °C	0.67	0.82
6 mo at 38 °C	0.68	0.85
6 da at 55 °C	0.45	0.80
13 da at 55 °C	0.62	0.94
21 da at 55 °C	0.99	1.05
Sumitomo product stored 7 years	1.65	1.44
Bayer product stored 7 years	1.29	1.16

sistent with fenitrothion and the rats would lie prostrate for several days before death or recovery. Only a few deaths occurred the first day; most deaths came on the second, third, and fourth days, with some coming as late as the sixth and seventh days. In contrast, most deaths with malathion occurred the first 24 h, and animals surviving beyond this period were usually free of signs after the second day. Additionally, most of the animals that were severely affected by malathion also succumbed. Differences between the two pesticides have been noted in their effects on humans as well; when water-dispersible powders were used for malaria control under identical operational conditions in the field in Pakistan in 1977, a higher incidence of cholinesterase depression and clinical symptoms of poisoning was found among spraymen exposed to 2.5% suspensions of fenitrothion than those exposed to 5% suspensions of malathion (Miller, 1978). The two formulations used in these field operations were similar to those described in Table I (manufacturer A) and Table V; it will be noted that the rat oral LD_{50} values for those two formulations are comparable.

The S-methyl isomer of both malathion and fenitrothion forms in the block or on the front of the column of a gas chromatograph whenever samples of the parent compound are injected. Isomer formation can be minimized by frequent cleaning of the block and replacement of column packing at the front of the column or by lowering the block temperature. The LC method has the advantage over the GLC method in that isomerization does not occur in the liquid chromatograph. Data presented in Table VI and VII show that higher values are usually obtained by GLC as compared to LC. This is particularly true for samples containing low S-methyl isomer content. The GLC method for determination of S-methyl isomer content of malathion powders described above is satisfactory for samples with S-methyl isomer content in the range of 1% and has been adopted by the Agency for International Development and the World Health Organization for use in specifications for malathion water-dispersible powders. These specifications require that a 50% powder contain not more than 0.9% of the S-methyl isomer after storage at 55 °C for 6 days.

ACKNOWLEDGMENT

The authors thank Fred Churchill for his assistance in the synthesis of the reagents used as standards.

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Received for review September 19, 1978. Accepted December 1, 1978. These studies were conducted as part of a contractual agreement between the Center for Disease Control and the World Health Organization. Presented (in part) at the IVth International Congress of Pesticide Chemistry (IUPAC), Zurich, Switzerland, 1978. Use of tradenames or commercial sources does not constitute endorsement by the Public Health Service or by the U.S. Department of Health, Education, and Welfare.