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Study Requirement

[Methylene-^{14}C-]Omethoate:
General Metabolism Study in the Rat

Data Requirement

EPA Pesticide Assessment Guidelines, Subdivision F,
40 CFR 158, 85-1, October 1982

Author

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Study Completion Date

Dec. 18th, 1989

Performing Laboratory

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Laboratory Project ID

M 01810019

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Good Laboratory Practice Certification

STATEMENT OF COMPLIANCE

To the best of our knowledge and belief we declare that this study was conducted in compliance with GLP-standards (USA, EPA, 40 CFR Part 160, November 29, 1983; OECD, C (81) 30 (Final), May 12, 1981).

T. Hoshino 31.7.1990

T.Hoshino, Date

Study Director

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Liquid Scintillation Counting Techniques

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1. Abstract

Absorption, distribution, excretion and metabolism of the insecticide omethoate (Folimat™) were studied in the rat. ^{14}C-Omethoate was administered to male and female Wistar rats at dose levels of 0.5 or 10 mg/kg bw (body weight) by the intravenous or oral route. In addition, rats of both sexes were pretreated for 14 days with a daily oral dose of 0.5 mg/kg bw using the non-radiolabelled omethoate followed by a single radiolabelled dose of the same rate after 24 hours. Radioactivity was measured in the excreta and plasma at different sampling times, and in the organs and tissues at 48 h (sacrifice) after administration. The results of the study concerning absorption, distribution, and excretion (pharmacokinetic study) refer to the sum of the parent compound and its radiolabelled metabolites. For the purpose of balance and comparison between the dose groups, all radioactivity values are expressed as percent of totally recovered radioactivity per animal or dose group, respectively. The recovery factors are reported in the raw data, copies of which are attached to this report.

Following oral administration of ^{14}C-omethoate at 10 mg/kg to male rats, only little radioactivity (ca. 0.14 % of the administered radioactivity) was detected in the expired air during 48 h.

The absorption rate after oral administration of 0.5 or 10 mg/kg, respectively, was evaluated by the results of excretion rate in urine and residue amounts in the body excluding gastrointestinal tract. More than 98 % of the administered radioactivity was absorbed in the rat.

Following administration of ^{14}C-omethoate intravenously or orally to male and female rats at 0.5 mg/kg or 10 mg/kg, the radioactivity was rapidly excreted; about 88-98 % of the administered radioactivity was eliminated into the excreta within 48 h after administration and total recovery was 89-98 %. The radioactivity was excreted mainly with the urine: 85-96 % of the administered radioactivity being found in urine and only 2-4 % in feces. The rate of renal excretion was very high, about 83-95 % of the administered radioactivity was renally eliminated within 24 h after administration.

Very little radioactivity remained in the body at sacrifice. The radioactivity in the gastrointestinal tract of rats sacrificed 48 h after administration was 0.03-0.04 % of the administered radioactivity and the residual radioactivity in the body excluding gastrointestinal tract was 0.24-0.42 %.

The pharmacokinetic parameters were estimated from the time course of the concentration of radioactivity in the plasma. Some of the pharmacokinetic parameters concerning the rate and the ratio of excretion showed statistically significant dependence on sex, route of administration and dose level. The area under the blood concentration vs. time curve (AUC) values of oral dose groups were close to AUC of intravenous dose groups, since omethoate was absorbed completely and rapidly in the rat after oral administration. The concentration of radioactivity reached the maximum at 40-60 min after oral administration of 0.5 or 10 mg/kg. In the case of elimination half-lives, significant differences were detected between low dose and high dose groups, but half-life values itself were in the similar order, 1.6-2.8 h [$T_{½\alpha}$] and 13-28 h [$T_{½z}$] for the initial and terminal elimination phases, respectively, in all test groups.

In organs and tissues, the relative concentration P in the thyroid was highest in all test groups, 0.34-0.59 in low dose groups and 0.16-0.19 in high dose groups. Compared with the plasma-concentration in each test, the concentration of thyroid was 112-197 times (low dose groups) and 65-70 times (high dose groups) higher than that of plasma.

Relative concentrations in liver, kidney, testes, spleen and lung were also higher than that of plasma, P values were 0.05-0.1 in liver and kidney, and 0.004-0.01 in testes, spleen and lung, and these were 1.5-4 times higher than the P values of plasma.

The metabolic pattern in urine and extracts of feces was studied. In the case of urine, samples collected from 0-24 h were combined (representative native urine) and investigated by TLC and HPLC. The metabolic pattern of omethoate was very similar in all test groups, the main radioactive compound was the parent omethoate and 26-62 % of the administered radioactivity was detected as omethoate. Two major metabolites were detected and these were identified as N-methyl-2-(methylsulphinyl)acetamide (16-36 %) and O-desmethyl metabolite of omethoate (free form, 4-9 %). Much more Omethoate was detected in females than in males, on the other hand more N-methyl-2-(methylsulphinyl)acetamide was observed in males. In comparison between low dose and high dose groups, more omethoate was found in high dose groups than in low dose groups. Some minor metabolites were observed and these were less than 10 % each. The structures of these minor metabolites could not be identified.

Feces (high dose groups only) was extracted with 70 % aqueous acetonitrile yielding ca. 63-77 % of the radioactivity in the extracts. They were concentrated and the metabolic pattern of feces extracts was investigated by TLC. The metabolic pattern of omethoate in feces extracts was very different from that of native urine and the main radioactive compound was the O-desmethyl metabolite (0.7-2.6 % of the administered radioactivity). Omethoate and N-methyl-2-(methylsulphinyl)acetamide were also identified in feces extracts, but these were very minor in amount: 0.1-0.3 % of the administered radioactivity was observed, respectively.

Omethoate itself is water soluble, excreted mainly with urine and was not metabolized excessively. The main metabolic pathway of omethoate was hydrolysis of the phosphoric acid structure and desmethylation; N-methyl-2-(methylsulphinyl)-acetamide was produced as the main metabolite in the rat.

To summarize, 72-85 % of the administered radioactivity was identified as omethoate and its metabolites in excreta of Test group 7 and 8 (high dose group) and 46-62 % thereof was the parent compound omethoate.

2. Introduction

Omethoate (Folimat(R), *O,O*-dimethyl *S*-[2-(methylamino)-2-oxoethyl] phosphorothioate is an insecticide and acaricide for control of spider mites, aphids, beetles, etc. on pome fruit, stone fruit, citrus fruit and crops.

Metabolism of omethoate has been studied in animal[1),2)], plant[3)] and soil[4)].

In the animal studies, the biokinetic and metabolic behaviour was investigated[1),2)]. H.Weber *et al.*[1)] reported on the time-dependent fate of radioactivity in excreta. The distribution and elimination of carbonyl-^{14}C-omethoate was investigated in the male rat with single dose. After oral administration of omethoate at 0.3, 5 or 10 mg/kg bw, 96-97 % of the administered radioactivity was eliminated within 48 h in urine and 1-2 % in feces. The radioactivity was rapidly excreted after intravenous injection of 0.3 mg/kg bw. The maximum concentration of radioactivity in plasma was reached not later than 1 h after oral administration of 5 mg/kg. From the quantitative investigation and whole body autoradiography, the radioactivity was homogeneously distributed in the rat body with the exception of the thyroid, in which a 10-20 fold higher concentration was found.
W.Ecker *et al.*[2)] studied the biotransformation of omethoate in the excreta of rat. Ca. 88 % of the administered radioactivity was excreted with the urine within 8 h after oral administration of 5 mg/kg of carbonyl-^{14}C omethoate to male rats, 30-50 % was the unchanged parent compound, 11 % was *O*-desmethylated omethoate and a further 15-22 % was identified as N-methyl-2-(methylsulphinyl)acetamide.

The purpose of the experiments reported herewith was to obtain information on biokinetic behaviour (absorption, distribution and excretion) of the total radioactivity and to identify and quantify the radioactive metabolites of omethoate in the excreta with relation to sex, dose, non-radioactive pretreatment, and to the route of administration according to the EPA Pesticide Assessment Guidelines.

In order to gather information on the biokinetic and metabolic behaviour of methylene-^{14}C-omethoate after oral or intravenous administration of low doses in comparison to oral high dose treatment and to non-radioactive pretreatment, the following study, fulfilling the requirements of the EPA Pesticide Assessment Guidelines, Subdivision F, 40 CFR Part 158, 85-1, October 1982, was performed according to GLP.

The compound was administered to male and female Wistar rats at two dose levels intravenously or orally. The following dose groups were used:

(group A)	0.5 mg/kg bw, single intravenous low dose (Test 1:male, Test 2:female)
(group B)	0.5 mg/kg bw, single oral low dose (Test 3:male, Test 4:female)
(group C)	14 x 0.5 mg/kg bw, one oral low dose of the non-radioactive compound per day in time intervals of 24 h for 14 consecutive days, followed by a single oral dose of the radiolabelled compound of the same dose level on 15th day (pretreatment, Test 5:male, Test 6:female)
(group D)	10 mg/kg bw, single oral high dose (Test 7:male, Test 8:female)

The excretion of radioactivity with the expired air was studied at the high dose level (10 mg/kg bw) using male rats (Test 9).
The dose levels used in this study were selected under consideration of the specific radioactivity, the high toxicity of the compound, and with respect to the corresponding recommendations in the EPA Pesticide Assessment Guidelines.

This report presents:

1) The results of experiments describing absorption, distribution and excretion of the total radioactivity,

2) The identification and quantification of the metabolites in the excreta.

The experiments pertaining to this report (Study-No. : M 01810019) were conducted from July 18th to December 8th, 1989 in the laboratories of the

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The raw data and the original issue of the report are stored in the archives of the above mentioned Institute for Metabolism Research.

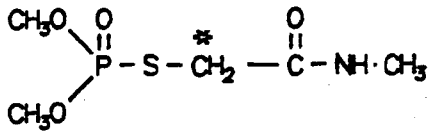
3. Materials and methods

3.1 Non-radiolabelled compounds

The non-radiolabelled parent compound was provided by Dr. Krohn, Bayer AG, PF-F/PBF FEA2 (reference-code No.890602ELB01) with a chemical purity of 99.2%.
The chemical purity and physical properties are shown in Appendix 1.
The reference compounds are listed in Table I with their reference No. (notebook code); they were synthesized by Dres. Reiner (code abbreviation:RNH); Wagner (WAK, Bayer AG, PF-F). All reference compounds were assayed for authenticity by MS and/or NMR spectroscopy.

3.2 Radioactively labelled compound

The methylene-1-^{14}C-labelled compound was provided by Dr. Thomas, Bayer AG, PH-FE, Pharmakokinetik Isotopenlabor Chemie (Protocol THS 3802, 22.6.89). It had been synthesized in the Radiosynthesis Laboratory of Mobay Corporation, Kansas City, MO in U.S.A.
The specific radioactivity was 3.59 MBq/mg (97.04 μCi/mg) with a radiochemical purity of 99.4% (Appendix 2).



*: Labelled Position

3.3 Animal characteristics

Animals were obtained from Winkelmann,Versuchstierzucht GmbH & Co KG at least one week before the start of the experiment and the body weight and health were checked every other day prior to administration.
Animal characteristics (species, age, breeder, food, etc) are summarized in Table II.

3.4 Experimental details

Animal groups were designed according to EPA Pesticide Assessment Guidelines as mentioned before.
Experimental details (body weight, dose group, dose level, route, etc.) are described in Table III.

3.5 Administration solution and dose level

The radiolabelled compound was liquid in form. In order to prepare a stock solution, the compound was dissolved in acetonitrile (concentration: 0.429 mg/ml). From this stock solution, the volume necessary for the preparation of the administration solutions was transferred by calibrated pipettes to an Erlenmeyer flask and evaporated in a nitrogen gas stream at room temperature to dryness and dissolved in physiological saline solution using an ultrasonic water bath at about 70°C to the final concentration of ca. 0.1 mg/ml (i.v.), ca. 0.05 mg/ml (p.o., low dose), ca. 1 mg/ml (p.o., high dose), respectively. The administered volume was 1 ml for a rat of a body weight of ca. 200 g (administration of the radioactive compound in group A), 2 ml (administration of the radioactive compound in groups B, C and D), or 10 ml/kg bw (administration of the non-radioactive compound in group C). The low dose level was 0.5 mg/kg bw, the high dose level was 10 mg/kg bw.

For the pretreatment trials, the rats were dosed orally for 14 consecutive days with the non-radioactive compound at the low dose level (0.5 mg/kg bw; one dose per day) followed at 24 hours after the last non-radioactive dose by one dose of the radioactively labelled compound.

The oral administration was carried out by stomach tube. For the intravenous injection, the dissolved compound was administered into a femoral vein immediately after the preparation of the administration solution. The dissolved compound was stable for at least 72 h as tested by means of thin layer chromatography (TLC) (silica gel; $CHCl_3$:isopropanol=1:1, v/v).

The radioactivity in the administration solution of each test was assayed in order to determine the amount actually administered. The values obtained from these measurements were the exclusive basis for the calculation of the recovery and for the determination of the radioactivity concentrations.

3.6 Check of volatility

Since feces, organs and tissues were lyophilized and the radioactivity was measured after combustion, loss of radioactivity during lyophilization was checked by *in vitro* and *in vivo* experiments. In an *in vitro* experiment, ^{14}C-omethoate was applied to carboxymethylcellulose sodium salt solution (0.75 g/H_2O) and the volatility was checked by determination of radioactivity of the trapped water after 24 h of lyophilization. In an *in vivo* experiment, ^{14}C-omethoate was orally administered once at 10 mg/kg to a male rat, the rat was sacrificed at 4 h after administration and the liver was collected. The radioactivity in trapped volatiles was measured after 24 h of lyophilization of the liver. Additionally, urine was frequently lyophilized prior to analysis in the metabolism part, therefore the volatility from urine was also investigated after 10 ml of urine was lyophilized.

3.7 Sampling and treatment of biological samples for determination of radioactivity

The sampling schedule is summarized in Table IV.

3.7.1 Urine

Urine was collected separately for each animal under cooling with dry-ice in the intervals 0-2, 2-4, 4-6, 6-8, 8-24, 24-48 h after administration. (In Test group 9, urine was collected in the intervals 0-4, 4-8, 8-24, 24-32, 32-48 h.) The funnels for urine collection were rinsed with demineralized water at the end of each sampling period; the rinsing solutions were drained into the same vial as the corresponding urine fraction.

3.7.2 Feces

Feces were collected separately for each animal in the intervals 0-24, 24-48 h after administration. They were lyophilized, weighed and homogenized for determination of radioactivity.

3.7.3 Plasma collection from tail vein

A small cut was made with a scalpel in the middle of the tail and a small amount (ca. 20-80 µl) of blood was collected in a heparin-coated capillary tube (Hirschmann™, Hirschmann E.M., West Germany). The capillary tube was centrifuged for 10 min at 10000 rpm in a hematocrit centrifuge (Biofuge A, HERAEUS CHRIST) and then the plasma part was collected.

3.7.4 Expired air

Volatile compounds and carbon dioxide were collected for each animal in test group 9 in the intervals 0-8, 8-24, 24-48 h after administration. Air was sucked by the pump at ca. 120 l/h and the outcoming air was passed through a trapping system of two gas-washing bottles containing each 147 ml of a mixture of ethanolamine/ethanol (1:1,v/v) on average. The trapping system was changed at the end of each sampling period.

3.7.5 Organs and tissues

The animals were anaesthetized using carbon dioxide gas. They were sacrificed and exsanguinated by transsection of the cervical blood vessels. The collected blood was separated into plasma and erythrocytes by centrifugation. The organs and tissues listed in the tables were prepared directly after sacrifice and they were weighed immediately after the dissection. Fatty tissue, thyroid, ovaries and uterus were solubilized with tissue solubilizer. Organs and tissues except fatty tissue, thyroid, ovaries and uterus were lyophilized, dried samples were weighed and then homogenized for determination of radioactivity.

3.8 Measurement of radioactivity

3.8.1 Measurement of liquid samples

Radioactivity of liquid samples as urine and plasma was measured directly by liquid scintillation counting (LSC, Table V) after liquid scintillation cocktail (scintillator) was added. Details (volume of liquid sample, scintillator, etc.) are described in Table VI.

3.8.2 Measurement of solid samples

Solid samples of feces, organs and tissues were combusted by an oxidizer and $^{14}CO_2$ was trapped with absorbent. The radioactivity of absorbent was measured by LSC after scintillator was added. Details are shown in Table VII.

3.8.3 Measurement of samples of fatty tissue, thyroid, ovaries and uterus

Fatty tissue was solubilized by means of a tissue solubilizer (BTS 450, Beckman Co.). Tissue solubilizer was added in a ratio of 5 ml/g sample to ca. 100 mg of fatty tissue and dissolved by heating at 50°C for 2 days. Ca. 0.05 - 0.5 ml of the dissolved solution was measured by LSC after 0.1 ml of glacial acetic acid and scintillator were added (Table VI).

3.9 Quantitative evaluation

3.9.1 Absorption

The absorbed amount was deducted from the percentages excreted in urine and residues in the body at 48 h after administration, and calculated as:

$$\text{Absorption (\%)} = \frac{\text{\% of the recovered radioactivity in urine after p.o. administration}}{\text{\% of the recovered radioactivity in urine after i.v. administration} + \text{\% of the recovered radioactivity in the body excluding GIT}}$$

3.9.2 Relative concentration P and equivalent concentration C

P stands for relative concentration and is defined as:

$$P = \frac{\text{Radioactivity measured/grams of plasma or tissue}}{\text{Radioactivity administered/grams of body weight}}$$

Using this relative value, it is easy to compare the concentrations obtained from experiments, in which the administered dose, based on the body weight, varies.

A value of P = 1 is equivalent to the so-called equidistribution concentration; its calculation is based upon the assumption that the amount administered is distributed evenly throughout the body volume. The body weight of the animals at the time of sampling is used as a measure of the body volume.
The equivalent concentrations based upon the amount of the parent compound administered are calculated from the relative concentration P (see above) by multiplying with the dose in [mg/kg]:

$$C = P * D \quad [\mu g/g] \text{ or } [\mu g/ml]$$

The term "equivalent" stands for the sum of radiolabelled metabolites and parent compound, as determined by total radioactivity measurement, expressed as parent equivalents in µg/g or µg/ml, respectively.

3.9.3 Amounts of radioactivity

The amounts of radioactivity present in the excreta and still present at sacrifice in the animals' body (organs and tissues) were calculated from previously measured concentrations of radioactivity and were related to the administered radioactivity. The amounts in the organs were obtained from the multiplication of the relative concentration P and the Gamma-values. The Gamma-value of an organ is defined as its percentage weight contribution to the total body weight of the animal. These values were determined by weighing where possible; those values which were not accessible by direct weighing were estimated according to Altman and Dittmer[5].

Plasma	: 3.2%;	Erythrocytes	: 3.2%
Dissectable fat	: 5.0%;	Muscle	: 40.0%

For the comparison of the amounts or concentrations of radioactivity present in the organism, the terms "total body", "body excluding the gastrointestinal tract" and "gastrointestinal tract" were used. The contents of radioactivity in the "total body" is an inappropriate standard for the radioactivity present in the tissues, especially if the compound is only partly absorbed following administration or is subject to partial elimination into the gastrointestinal tract after absorption. Therefore, in all tests the gastrointestinal tract (including its contents) was prepared and radioassayed separately from other tissues and organs including the residual carcass which was designated as "body excluding the gastrointestinal tract". This expression reflects the sum of all tissues and organs which are relevant for the consideration of the residues. The radioactivity concentrations in the tissues and organs were calculated in terms of the relative concentrations P. The radioactivity amounts were expressed in terms of the administered radioactivity or in terms of the recovered radioactivity. The latter was used to mutually compare the results of the different tests.

3.9.4 Limits of quantification

The limits of quantification of the individual tissues and organs under consideration were calculated in accordance to the following equation:

$$P_{Limit} = \frac{NE * G * D_f}{V * A_0}$$

NE = Minimum net disintegrations per minute above background = 20 DPM
(Background of the liquid scintillation counters: about 20 DPM)

G = Body weight of the rats (= 200 g)
D_f = Freeze-drying factor; for samples which were not freeze-dried this factor equals 1.
V = Amount of sample in g or ml used for measurement
A_0 = Administered radioactivity per animal in DPM

For the calculation of the limit of quantification in terms of the equivalent concentration C in [µg/g] or [µg/ml] the following equation is used :

$$C_{Limit} = P_{Limit} * D \text{ [mg/kg]}$$

3.9.5 Evaluations

The Appendices 3 to 53 were produced by computer-assistance (HP-3000) using a dedicated software package for generating tables. Prior to the listing, the values were checked for outliers by the program in accordance to the outlier test by GRAF and HENNING, if appropriate. Values identified as outliers were marked and were not taken into account in calculations of arithmetic means and standard deviations.
Characteristic values for the evaluation of the biokinetic behaviour based on the excretion or residue data from the different animal groups were checked for statistically significant differences using the non-parametric MANN-WHITNEY-U-test. The following levels of significance were specified:

< 95% = not significant (-)
> 95% = probably significant (o)
> 99% = significant (+)

3.10 Exponential analysis of pharmacokinetic parameters

If the processes are unknown that govern the pharmacokinetic behaviour of a xenobiotic in the body, the so-called Model-Free calculation is the simplest and safest method to obtain pharmacokinetic parameters which describe and characterize its behaviour.
The basis of this calculation is laid by the Area Under the Curve of the concentration of radioactivity in plasma (plasma curve).

$$AUC\ (t_1\text{-}t_N) = \sum_{i=1}^{N-1} \frac{1}{2}[(c(t_i)+c(t_{i+1}))*(t_{i+1}-t_i)]$$

$c(t_i)$: Concentration in the plasma at t_i

t_i : Sampling time

N : Number of experimental points

In some cases it is useful to determine a terminal elimination half life from the last data of the concentration time series by a nonlinear regression. The equation

$$c(t) = A_z * e^{-b_z t} \quad , t > t_N$$

$$T_{\frac{1}{2}\ lambda\ z} = \frac{\ln 2}{b_z}$$

gives the extrapolated time course and the corresponding area under this part of the curve is calculated using

$$AUC(t>t_N) = A_z/b_z * e^{-b_z t_N}$$

For monotonously decreasing concentrations (intravenous administrations) an extrapolation to t=0 can be made using a nonlinear regression for some part of the first data

$$c(t) = A_1 * e^{-b_1 t} \quad , t < t_1$$

$$AUC_{(t<t1)} = A_1/b_1 * (1 - e^{-b_1 t_1})$$

Otherwise (e.g. oral administration):

$$c_{(t=0)} = 0$$

and the corresponding part of the area under the curve is calculated using the equation:

$$AUC_{(0-t1)} = \tfrac{1}{2} * c_{(t1)} * t_1$$

The total area under the curve (AUC-fit) is:

$$AUC = AUC_{(0-t1)} + AUC_{(t1-tN)} + AUC_{(t>tN)}$$

In a similar manner the Mean residence time can be calculated:

$$MRT = \frac{AUMC}{AUC}$$

with $AUMC = AUMC_1 + AUMC_2 + AUMC_3$

and

$$AUMC_1 = \tfrac{1}{2} * c_{(1)} * t_1^2$$

$$AUMC_2 = \sum_{i=1}^{N-1} [\tfrac{1}{2} * (t_{(ti+1)} * c_{(ti+1)} + t_{(ti)} * c_{(ti)}) * (t_{i+1} - t_i)]$$

$$AUMC_3 = AUC_{(t>tN)} * (1/b_z + t_N)$$

The time for a rise in concentration from 25 % to 75 % of C-max (t-50) is determined in cases with extravascular administration by a linear interpolation of the concentration course in the absorption phase.

Clearance

$$CL = \frac{f * D}{AUC}$$ with f : Fraction of dose absorbed

Renal Clearance

$$CL\text{-}R = \frac{f_n}{AUC_{(0-t1)} + AUC_{(t1-tN)}}$$

with f_n : Fraction of dose renally excreted for $t < t_N$

Apparent initial volume of distribution

(for intravenous administrations, measured in the central compartment)

$$V_c = \frac{D}{A_1}$$

Apparent volume of distribution in the steady state

$$V_{ss} = MRT * CL$$

These equations are used in an interactive programme called Model Free which is available on an HP 3000 computer[6].

3.11 Metabolism (Extraction and metabolic pattern)

3.11.1 Urine (Fig.1)

Urine samples from 0-24 h, equivalent to more than 90 % of the recovered radioactivity in urine, were combined to one portion per dose group and sex and the combined urine (representative native urine) was subjected to further investigations on metabolism. Since UV absorption of omethoate and its metabolites was very low, the metabolism study was carried out mostly by TLC (Table VIII). For isolation of unknown metabolites, urine of the high dose groups was used. The representative native urine was applied to TLC and HPLC (Table IX) for characterization of radioactive compounds. For identification, the representative native urine was cochromatographed with reference substances by two dimensional TLC.

For the structure elucidation of unknown metabolites, they were isolated by column chromatography and HPLC. The representative native urine (about 250 ml) was lyophilized and the dried residue was dissolved in a small amount of water. The concentrated urine sample was subjected to reversed phase column chromatography (Nucleosil™, C_{18}, 15-25 μm, 10 g previously packed) with a step-wise elution system : tetrabutylammonium bromide solution (40 ml), H_2O (40 ml) and then acetonitrile (40 ml) in order to remove biological matrix of urine. The major radioactive fractions after column chromatography were concentrated and applied to reversed phase HPLC (preparative and analytical HPLC) to isolate unknown metabolites by repeated chromatography. Unknown metabolites were isolated and measured by NMR.

3.11.2 Feces (Fig.2)

Feces of the high dose groups (test groups 7-8) from time interval of 0-24 h, which contained more than 90 % of the recovered radioactivity of feces, were combined to one portion per sex. The combined lyophilized feces samples were mixed with 70 % acetonitrile/water (ratio: ca. 7 ml/g sample) and kept at room temperature overnight. Then the feces were extracted by means of an Ultra-Turrax (IKA-WERK). After filtration, the residue cake was mixed with 70 % aqueous acetonitrile again and reextracted twice by the same method.
Extraction balances were established after radioactivity measurement of extracts and residue material. The extracts were concentrated and subjected to TLC analysis. For identification of metabolites, feces extracts were cochromatographed with reference compounds by two-dimensional TLC with solvent systems A and B.

3.11.3 TLC and HPLC

TLC and HPLC methods are described in Tables VIII and IX.
In the case of isolation of metabolites by TLC, radioactive bands on TLC plates were detected by TLC linear analyser (Table X) and/or autoradiography (Table XI), scraped off and then the radioactive material was extracted with MeOH from the silica gel.

For identification, two-dimensional TLC was used, radioactive spots were detected by autoradiography and TLC linear analyser, and non-radioactive spots (reference compounds) were visible after staining (see 3.11.4).

In the case of purification by HPLC, radioactive peaks were monitored by a radioactivity detector and radioactive peaks were collected manually. The fractions collected were concentrated by evaporation and/or lyophilized.

HPLC was used for identification of omethoate and its metabolites, radioactive compounds were detected as described above and reference compounds were monitored by UV detection.

3.11.4 Detection reagents for TLC

Bromine-congo red reagents were used to visualize omethoate and its metabolites. The TLC plate was dried and exposed to bromine vapour generated from 10 % bromine solution in carbon tetrachloride for 20 sec. The TLC plate was aerated to remove bromine vapour and then sprayed with 0.4 % congo red solution in 50 % aqueous ethanol. Omethoate and reference compounds were detected as blue spots on dark orange background (the background colour depended on the solvent system used in TLC).

3.11.5 Spectrometry

The nuclear magnetic resonance (NMR) method is shown in Table XII.

3.11.6 Quantification of metabolites

For quantification of metabolites, the radioactivity was measured by TLC linear analyser and the amounts of metabolites were determined using the dedicated software (Table X).

4. Results

4.1 Toxicologic symptoms after administration of omethoate at 10 mg/kg

In a preliminary test omethoate was orally administered to male and female rats at 10 mg/kg as the high Dose. The rats showed symptoms such as trembling, flow of saliva, high breath frequency and congestion of eyes from about 30 min to 4 h after administration.

4.2 Loss of radioactivity during experimental procedure

The loss of radioactivity during lyophilization was checked by *in vitro* and *in vivo* experiments. In an *in vitro* experiment (carboxymethylcellulose), the loss of radioactivity was 0.15 % in 24 h of lyophilization, and in an *in vivo* experiment (liver), 0.02 % of radioactivity was removed from the liver. On the other hand, the representative native urine was lyophilized, but the loss of radioactivity was less than 0.01 % during lyophilization. Therefore no loss of radioactivity during lyophilization of biological materials such as urine, feces and organs after administration of ^{14}C-omethoate was assumed.

4.3 Absorption, distribution, excretion and residue of radioactivity

Excretion and distribution rate of the administered radioactivity is shown in Table XIII and those of the recovered radioactivity is described in Table XIV. For the comparison between the different dose groups, the recovered radioactivity is a much more reliable figure as far as balance, excretion, etc. are concerned. Therefore, values of the recovered radioactivity are generally used in this report for comparison purposes.

4.3.1 Excretion with expired air (Test group 9)

In the first test of the study, ^{14}C-omethoate was administered as a single oral dose of 10 mg/kg to male rats, in order to determine the quantity of radioactivity in the expired air, excreta, organs and tissues at sacrifice within a period of 48 h. The total recovery was ca. 94 % of the administered radioactivity. From the expired air ca. 0.14 % was recovered in the 1:1 mixture of triethanolamine/ethanol solution. This figure indicated that only negligible amounts of volatile radioactivity were expired (Tables XIII and XIV). Therefore test groups 1-8 were carried out using open metabolism cages and as a second result the test period was fixed to 48 h for the consecutive tests with the dose groups A through D.

4.3.2 Absorption rate

The extent of absorption after oral administration of ^{14}C-omethoate to male and female rats was calculated (see section 3.9.1) and found to be above 98 % (Table XV).

4.3.3 Excretion with urine and feces (Test groups 1-8)

Excretion rate in urine and feces is described in Tables XIII-XIV, XVI-XVII and Fig. 3-6. The radioactivity was rapidly excreted and more than 99 % of the recovered radioactivity (ca. 88-98 % of the administered radioactivity) was found in excreta 48 h after administration. About 95-98 % of the recovered radioactivity was excreted with urine and ca. 2-5 % was eliminated with the feces. Most of the radioactivity was eliminated during 24 h after administration, i.e. more than 97 % of the radioactivity in urine was excreted within 24 h.

The excretion ratio was basically similar with males and females, low and high doses, i.v. and p.o. administration with a few exceptions with significant differences depending on sex and dose level.

The significant difference on sex was detected between test group 7 (male) and test group 8 (female), the urinary excretion rate being lower in the male group than in the corresponding female group. Another significant difference was found concerning the dose level between the renal and fecal excretion of test group 3 (low dose group, male) and test group 7 (high dose group, male); the low dose animals exhibited a higher renal and a correspondingly lower fecal excretion than the high dose animals. A possible explanation is presented in the discussion (see 5.1).

No statistically significant differences were found for any dependence on route of administration and pretreatment with either sex.

4.3.4 Residues in organs and tissues

The relative concentration P is shown in Table XIX, the equivalent concentration C in Table XX and the recoveries in percent of the administered radioactivity in Table XXI.

Residues of radioactivity in gastrointestinal tract (GIT) amounted to 0.03-0.04 % of the recovered radioactivity in test groups 1-8 at 48 h after administration (Table XIII-XIV). Residues in body excluding GIT were found to be 0.3-0.4 % in test groups 1-8 (Table XIII-XIV).

In terms of the relative concentration P in organs and tissues, P values in thyroid were highest in each test group. The values were 0.34-0.59 in test groups 1-6 and 0.16-0.19 in test groups 7-8.

P values in liver, kidney and testes were higher in the second place: i.e. in liver, P values were 0.008-0.01 in test groups 1-6 and ca. 0.005 in test groups 7-8, in kidney, 0.006-0.008 in test groups 1-6 and about 0.005 in test groups 7-8, in testes 0.009-0.01 in test groups 1, 3, 5 and 7.

The relative concentration P in thyroid, liver, kidney was statistically lower in the high dose groups (test groups 7-8) than in the low dose groups (test groups 3-4) by the Mann-Whitney U test.

Comparing liver and kidney in each test group, the relative concentration was higher in liver than in kidney (statistically significant).
The relative concentration in spleen and lung was higher in the third rank, ranging from 0.005 to 0.006 in test groups 1-6 and ca. 0.004 in test groups 7-8.

P values in other organs and tissues ranged from 0.001 to 0.008 (erythrocyte, plasma, fat, ovaries, uterus, muscle, bone, heart, brain, skin, GIT and body excluding GIT) (Table XIX).
In Table XXII, the ratio of relative concentration P in organs and tissues vs. relative concentration P in the plasma (organs vs. plasma) are shown. This value is highest in the thyroid (112-197 in test groups 1-6 and 65-70 in test groups 7-8).
On the other hand, the ratio of organs vs. plasma in liver, kidney and testes is about 2-4 and 1.5-2 in spleen and lung.

Some tissue concentrations in µg parent equivalent/g tissue (ppm) are as follows (Table XX) :

thyroid;	0.16-0.28	(test group 1-6),	1.53-1.97	(test group 7-8)
liver ;	0.004-0.005	(test group 1-6),	0.05-0.06	(test group 7-8)
kidney ;	0.003-0.004	(test group 1-6),	0.04-0.05	(test group 7-8)
testes ;	0.004-0.005	(test group 1,3,5),	ca. 0.09	(test group 7)
ovaries;	ca. 0.002	(test group 2,4,6),	ca. 0.03	(test group 8)
uterus ;	0.002-0.004	(test group 2,4,6),	ca. 0.04	(test group 8)
spleen ;	ca. 0.003	(test group 1-6),	ca. 0.04	(test group 7-8)
lung ;	0.002-0.003	(test group 1-6),	ca. 0.04	(test group 7-8)

Residues in organs and tissues except skin and carcass were less than 0.05 % of the administered radioactivity at 48 h after administration (Table XXI).

4.4 Pharmacokinetic parameters

Pharmacokinetic parameters were calculated from the time course of the concentration in the plasma based on the relative concentration P (Table XVIII, Fig. 7-14) using the computer software "Model Free", and the obtained pharmacokinetic parameters are shown in Table XXIII.

4.4.1 Area under the blood concentration vs. time curve (AUC)

The AUC values (AUC-fit, see 3.10) of the intravenous low dose test groups 1-2 were higher (5.4 to 6.4 h) than the oral single dose test groups 3-4 and 7-8 which ranged from 4.9 to 5.5 h and the pretreated test groups 5-6 showed the lowest values (4.4 to 4.7 h).

4.4.2 Half-life

Both the initial ($T_{\frac{1}{2}\alpha}$) and the terminal ($T_{\frac{1}{2}z}$) half-lives were derived from linear regressions of the corresponding plasma curves, $T_{\frac{1}{2}z}$ being calculated by the Model-Free program and $T_{\frac{1}{2}\alpha}$ by the Peeling off method using semi-logarithm figures of plasma curves. The initial half-lives calculated for test groups 1-6 were comparable (1.6-2.2 h) and those for test groups 7-8 showed only marginally higher values (2.4-2.8 h). On the other hand the terminal half-life was estimated to 22-28 h in test groups 1-6 and 13-15 h in test groups 7-8.

4.4.3 Time of the maximum level of the plasma concentration (T-max)

T-max after oral administration ranged from 40 min to 1 h.

4.4.4 Maximum level of the plasma concentration (P-max)

P-max was in a narrow range throughout the dose groups, reaching 1.18-1.28 in test groups 3-4 (low dose), ca. 1.1 in test groups 5-6 (pretreated group) and 7-8 (high dose). These values are close to the equidistribution concentration.

4.4.5 Mean residence time (MRT)

MRT in all test groups was short, the values ranged from 6.2 to 7.8 h.

4.4.6 Distribution volume in the steady state (V-ss)

V-ss in test groups 1-8 was in the range of ca. 0.97 to 1.651 l/kg; this corresponds to 100-165 % of the total body volume.

4.4.7 Total plasma clearance (CL) and renal clearance (CL-R)

The CL values were in the range of 2.6-3.8 ml/min and the CL-R values (2.6-3.5 ml/min) were very close to the CL values due to the high renal excretion.

4.5 Metabolism

4.5.1 Urine

The representative native urine (see 3.11.1) of each test group was subjected to one-dimensional TLC for investigation of the metabolic patterns, and applied to two-dimensional TLC and/or HPLC for identification of omethoate and its metabolites. The radioactive bands on TLC were detected by autoradiography and/or TLC linear analyser and non-radioactive bands were visualised with staining reagents.

The chromatographic patterns of the representative native urine of each test group were identical (Fig. 15); the thin layer chromatograms as detected by the TLC linear analyser are shown in Fig. 16. Three major radioactive metabolites were detected in the autoradiograms and TLC linear analyser scans. These metabolites were identified by two-dimensional TLC cochromatography (Fig. 17-19) with reference compounds [solvent system : (A and B) or (A and C)], i.e. radioactive spots of the metabolites on TLC autoradiograms matched with the stained spots of the reference compounds.

The predominant radioactive metabolite was the parent compound omethoate followed by the sulphinyl metabolite and the O-desmethyl metabolite. These radioactive bands were quantified using the linear analyser software. Omethoate amounted to 26-62 % of the administered radioactivity, the sulphinyl metabolite showed 16-36 % and the O-desmethyl metabolite 4-9 % (Table XXIV). Female animals excreted higher amounts of unchanged parent compound and less of the sulphinyl metabolite than males in all dose groups.

Some unknown metabolites with amounts of less than 10 % of the administered radioactivity were detected in urine (see Fig. 15). The structures of these unknown metabolites were not elucidated. The unknown metabolite I (uk.I in Fig. 20 and 21) was characterized by TLC and HPLC, i.e. TLC R_f value was 0.72 (Fig. 20), HPLC retention time (R_t) with non-ionic solvent system (H_2O and acetonitrile) was ca. 5.4 min [see Fig. 21 (a)], and ca. 3.3 min with ionic solvent system [tetrabutylammonium bromide, see Fig. 21 (b)]. In HPLC uk.I showed identical retention behavior with the sulphinyl metabolite (metabolite III in Fig. 20 and 21).

To summarize, 68-84 % of the administered radioactivity was identified as omethoate and its metabolites in the urine. (69-84 % in the urine of the high dose test groups 7 and 8.)

4.5.2 Feces

The feces of the test groups 7 and 8 (high dose group) were selected for investigating the metabolic pattern, since these feces samples contained the highest radioactivity.

After lyophilisation the feces samples of test groups 7 and 8 were extracted with 70 % aqueous acetonitrile. The extraction efficiency was evaluated by determination of the radioactivity in the extracts and residues and found to be 77 % in test group 7 and 63 % in test group 8.

The extracts were concentrated and subjected to one- and two-dimensional TLC (solvent system A and B) and radioactive spots were detected by autoradiography. According to TLC autoradiograms and TLC linear analyser scans of feces extracts (Fig. 22 and 23), the chromatographic patterns were identical in test groups 7 and 8. Omethoate and its metabolites, sulphinyl and O-desmethyl metabolites, were identified by two-dimensional TLC cochromatography (Fig. 24-26) with each reference compound, respectively. The amounts of these compounds were evaluated by the TLC linear analyser program. Ca.0.3 % of the administered radioactivity was estimated as omethoate, 0.1-0.3 % as the sulphinyl metabolite and 1.1-2.6 % as the O-desmethyl metabolite (Table XXV).

The metabolic pattern of feces extracts was different from that of the representative native urine. In urine, the predominant radioactive compound was the parent compound followed by sulphinyl and O-desmethyl metabolites, whereas in feces extracts the major radioactive compound was the O-desmethyl metabolite and others were negligible.

In extracts of feces, totally about 1.5-3.1 % of the administered radioactivity was identified as omethoate and its metabolites.

4.5.3 Total amounts of omethoate and its metabolites in excreta after oral administration of 10 mg/kg to male and female rats

After oral administration of 10 mg/kg to male and female rats, omethoate and its metabolites were identified in excreta as follows :

test 7 (male) ; omethoate 45.8 %, O-desmethyl 8.8 %, sulphinyl 17.7 %
test 8 (female) ; omethoate 62.4 %, O-desmethyl 7.5 %, sulphinyl 15.6 %

Totally ca. 72 % of the administered radioactivity was identified in the excreta of test group 7 (male) and 85 % in test group 8 (female).
The proposed metabolic pathway resulting from these investigations is shown in Fig.27.

5. Discussion and Conclusion

5.1 Pharmacokinetic study

After administration of ^{14}C-omethoate to male and female rats, omethoate was absorbed completely (see 4.3.2), ca. 88-98 % of the administered radioactivity was excreted with urine and feces, 95-98 % of the recovered radioactivity was eliminated via urine within 48 h and ca. 93-97 % within 24 h. This indicates that omethoate was absorbed quickly and completely, and omethoate and its metabolites were rapidly excreted via urine and feces. Especially the renal excretion rate was very high.

In excretion ratio, significant differences were found only between test group 3 (low dose) and test group 7 (high dose)(i.e. renal excretion: test 3 > test 7), and between test group 7 (male) and test group 8 (female)(i.e. renal excretion: test 7 < test 8) (4.3.3).

Concerning the distribution of radioactivity in organs and tissues 48 h after administration, elevated concentrations of radioactivity were found in the thyroid glands as already reported[1]. The radioactivity concentration in the testes was in the range of that in liver, whereas the concentration in the ovarium and uterus samples was only half this concentration except in the low dose orally treated females, where it was slightly elevated. In comparing low dose and high dose groups, relatively higher concentrations were detected in liver, kidney, thyroid, lung and spleen of low dose groups, but these differences were low in absolute terms. It can therefore be concluded that the pharmacokinetic behaviour (i.e. absorption, distribution and excretion) of omethoate - in the range studied - is proportional to the dose, irrespective of the route of administration or pretreatment, and is independent of sex. This conclusion can also be drawn concerning the metabolism of omethoate, where only quantitative but no qualitative differences in the metabolite patterns were observed.

The pharmacokinetic parameter AUC which was nearly identical in the i.v., p.o., low dose and high dose groups, confirmed the absorption rate of about 100 % in all test groups.

The distribution volume in the steady state (V-ss) was calculated to 0.97 to 1.65 l/kg, which corresponds to 100-165 % of the total body volume. This indicated that the radioactivity was readily distributed from the plasma to peripheral compartments.

After oral administration, the maximum relative concentration in the plasma (T-max) was reached between 40 min to 1 h and the maximum plasma concentration (P-max) was in the range of 1.1-1.3, which is equivalent to the equidistribution concentration (P=1). These results again showed that omethoate was rapidly absorbed and distributed in the rat body as described above.

The half-lives in test groups 1-8 were of the same order. But $T_{½\beta}$ of the high dose groups was somewhat longer than that of the low dose groups, and $T_{½z}$ of the high dose groups was shorter than that of the low dose groups. This difference can be attributed to toxic effects caused by the high dose. The toxicological symptoms lasted from 30 min to 4 h, therefore biological functions like elimination and metabolism of omethoate were depressed during that period and the initial elimination half-life was slower. On the other hand, the elimination of the radioactivity of the high dose group was not complete after 24 h, and therefore the terminal elimination half-life appeared to be increased.

The differences between CL and CL-R were very small and CL-R was in the range of about 85-98 % of the CL values. This result confirms that the main excretion way was via urine after administration of omethoate.

The pharmacokinetic parameters derived from the plasma curves on the basis of AUC, like half-life, total clearance (CL), renal clearance (CL-R), mean residence time (MRT), apparent distribution volume (V-ss), maximum plasma concentration (P-max) and the time to reach P-max (T-max) were in the same range throughout the dose groups. This again confirms the conclusion that the behaviour of omethoate in the rat is dose-proportional irrespective of sex, dose level - in the range studied - and of the route of administration.

5.2 Metabolism study

After administration of omethoate to male and female rats, omethoate itself was excreted mainly into urine, and major metabolites were N-methyl-2-(methylsulphinyl)acetamide and O-desmethylated omethoate. Some minor unknown metabolites were found in the excreta, the structures of which were not elucidated. However, two types of metabolites were characterized, i.e. ionic and non-ionic metabolites.

In the case of the ionic and water-soluble metabolites such as the O-desmethyl metabolite, the TLC R_f value was about 0.18 with solvent system A ($CHCl_3$:MeOH:AcOH:H_2O=66:26:4:4), the R_t values of HPLC were ca. 2.2 min with a non-ionic solvent system (H_2O and acetonitrile) and ca.17.0 min with a ionic solvent system (tetrabutylammonium bromide) (see Fig. 21). On the other hand the non-ionic and water-soluble metabolites such as the sulphinyl metabolite showed a high TLC R_f value (0.60) with solvent system A and short R_t values (ca. 3-5 min) with both ionic and non-ionic solvent systems (see Fig. 21). Unknown metabolite I showed TLC and HPLC profiles similar to the sulphinyl metabolite. Therefore metabolites with high TLC R_f values (>ca. 0.5) such as the sulphinyl metabolite and the unknown metabolite I, can be characterized as non-ionic, water-soluble and of relatively small size. Those metabolites with low TLC R_f values are to be regarded as polar, ionic and water-soluble compounds.

In animals, xenobiotics with a high rate of absorption are generally metabolized to polar, water-soluble compounds which are excreted with urine and, via bile, into the feces. Omethoate, being water-soluble, after administration to rats was excreted unchanged into urine to a considerable amount. Only little changes of the molecule took place prior to elimination so that the metabolites were apparently not conjugated but excreted as readily water-soluble compounds via urine.

In the extracts of feces, omethoate, sulphinyl and desmethyl metabolites were identified, the major metabolite being the O-desmethyl compound whereas omethoate and the sulphinyl metabolite were minor constituents.

The metabolic pattern of omethoate found in this study confirmed the results of the previously reported study[2]; the metabolic pathway established on the basis of the results of this study includes hydrolysis of the thiophosphoric acid structure either to yield the desmethylated metabolite or the sulphur containing side chain which is then methylated at the sulphur atom followed by sulphoxidation to the "sulphinyl" metabolite. Apparently no volatile metabolites (including $^{14}CO_2$) were observed indicating that the organic side chain of omethoate was not subjected to further degradation to C_1-fragments; the unidentified minor metabolites can proposedly be sulphide or sulphone homologues of the "sulphinyl" metabolite, further N- or O-desmethylated products or their conjugates which are not supposed to be of toxicological concern.

6. References

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Signatures

J. Hoshino 31.7.1990 (Study Director)
T.Hoshino Date

Eckel 31.7.1990 (Group Leader)
Dr. W. Ecker Date

Kaufmann 1.8.1990 (Head of Institute)
Dr. E. Kaußmann Date

List of Tables

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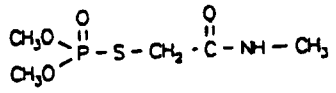
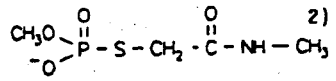
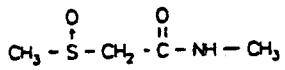
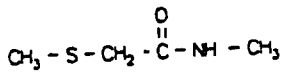
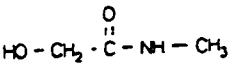
Table I Structures and thin layer chromatographic properties of omethoate and its related compounds

Structure	Abbr.	Mw.	TLC Rf value[1)]		
			A	B	C
I. 		213	0.86	0.57	0.71
II.  [2)]	O-desmethyl	198	0.18	0	0.14
III. 	sulfinyl	135	0.60	0.24	0.39
IV. 	sulfide	119	0.89	0.72	0.83
V. 	alcohol	89	0.61	0	0.07

1) Solvent system
   A) $CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4, v/v
   B) $CHCl_3$:isopropanol=85:15, v/v
   C) isopropanol:toluene:CH_3COOH:H_2O=65:25:5:5, v/v
2) Sodium salt of O-desmethyl was prepared.

Table II Animal characteristics

Species	Rat, male and female Strain : Wistar BOR: WISW (SPF Cpb)
Breeder	Winkelmann,Versuchstierzucht GmbH & Co. KG, 4799 Borchen, West Germany
Number	45 in total; 25 males, 20 females
Age	about 8 weeks old(male) or about 12 weeks old(female)
Weight	Approximately 200 g (see Table III) at the date of the administration of the radiolabelled compound
Diet	-Pelleted Altromin 1324 standard feed for rats supplied by Altrogge Lage/Lippe, West Germany -18 g per animal per day The day before treatment, the animals received 8 g of food. -Food was analysed and checked for contaminations according to current standards, certifications are archived at the producer and/or the internal supplier (Zentralstelle für Versuchstierfragen; Bayer AG, Wuppertal).
Water	Tap water ad libitum; water specification in accordance to current drinking water standards
Acclimation	Groups of 5 animals were kept in Type II Makrolon cages for at least one week before the start of the experiment.
Housing	Animals were held under conventional hygienic conditions in air-conditioned room at 21-24°C, 50-85 % relative humidity, 12 h photocycle and 10-15 air changes/h.
Randomization	was carried out by lot.
Identification	Cage cards and coloured spots on the tail

Table III Experimental details

Test group	1	2	3	4	5	6	7	8	9
Sex[1]	M	F	M	F	M	F	M	F	M
Body weight (g) at administration	216	199	200	182	197	182	211	199	201
Body weight (g) at sacrifice	205	187	199	189	193	178	204	186	200
Dose level (mg/kg)	low dose 0.5						high dose 10		
Specific activity (MBq/mg)	3.59						0.56	0.54	0.56
Route	i.v.	p.o.							
Frequency	1				14 + 1[2]		1		
Vehicle	Physiological saline								
Volume administered (ml/rat)	1	2							
Animal No.	5								
Sacrifice	48 h								
Date administered[3]	08/30	07/26	08/01	08/09	08/21	08/22	08/16	09/13	07/18
Date sacrificed[3]	09/01	07/28	08/03	08/11	08/23	08/24	08/18	09/15	07/20
Cages	After administration of the radiolabelled compound, the rats were kept individually in special metabolism cages which allowed for separate and quantitative collection of urine and feces.								

1) M: male, F: female
2) The rats were dosed orally for 14 consecutive days with the non-radiolabelled compound followed by one dose of the radiolabelled compound at 24 h after the administration of the last non-radiolabelled compound.
3) Year: 1989, month/day

Table IV Schedule of sample collections

Sample	Time after administration	Test group
Urine	2, 4, 6, 8, 24, 48 h	1-8, 9[1)]
Feces	24, 48 h	1-9
Plasma from tail vein	5, 10, 20, 40 min 1, 1.5, 2, 3, 4, 6, 8, 24, 32, 48 h	1-8
Organs and tissues	48 h	1-9
Expired air	8, 24, 48 h	9

1) Test 9 : Urine was collected at 4, 8, 24, 32, 48 h after administration.

Table V Liquid scintillation counter

Model	Method of quench correction
Beckman LS 7800	H-number[1]
Philips PW 4700	ESCR-number[2]
LKB Rack Beta 1219 Spectral	SQPE -number[3]

1) H-number: The inflection point of the external-standard-spectrum is used to correct for the quench.
2) ESCR : External standard channels ratio
3) SQPE : The end point of the external-standard-spectrum is used to correct for the quench.

Table VI Measurement of the radioactivity of liquid samples

1. Instrument: Liquid scintillation counter
2. Vials for measurement: Liquid scintillation glass vials or poli-vials

Material		Scintillator	
Sample	Volume (ml)	Type	Volume(ml)
Urine	0.2, 0.5	Instant Scint.Gel[1)]	7
Plasma	0.1	Instant Scint.Gel	7
$^{14}CO_2$-expired in ethanolamine/ethanol	1	8 g/l butyl-PBD[2)] in toluene:dioxane:methanol = 1:1:1	10
Fatty tissue and small organs[3)] solubilized with BTS 450[4)]	0.1-0.5	Quickszint 401[5)]	7
Administration solution diluted with dimethylsulphoxide	0.1	Instant Scint.Gel	7

1) Packard Co., U.S.A.
2) 2-(4-biphenylyl)-5-(4-tert.-buthylphenyl)-1,3,4-oxadiazole, Zinsser Co.
3) Thyroid, ovaries and uterus
4) Beckman™, Measured after 0.02-0.1 ml of glacial acetic acid was added.
5) Zinsser Co., West Germany

Table VII Measurement of the radioactivity of solid samples

1. The samples such as feces and organs except fatty tissue and small organs were weighed and combusted in an oxygen atmosphere using the following equipment.
2. Instrument for combustion : -Oxidizer 306 (Packard) brain, heart, muscle, testes, kidney, liver, skin, residual carcass and feces containing high radioactivity
   -OX 300 (Harvey) gastrointestinal tract, erythrocytes, lung, bone, spleen and feces containing low radioactivity
3. Instrument for counting : Liquid scintillation counter (see Table V)
4. Vials for measurement: Liquid scintillation glass vial or poli-vial

Material		CO_2 absorbent		Scintillator	
Sample	Amount (mg)	Type	Volume (ml)	Type	Volume (ml)
Feces Organs Tissues	10-500	Carbosorb[1)]	8	Permafluor V[1)]	10

1) Packard Co., U.S.A.

Table VIII Thin layer chromatography

TLC plate	-Silica Gel 60 F_{254} precoated glass plate 20 x 20 cm, 0.25 mm thickness (Merck) -Silica Gel 60 precoated glass plate 20 x 20 cm, 0.25 mm thickness (Merck) -Silica Gel 60 precoated glass plate 20 x 20 cm, 0.5 mm thickness (Merck)
Solvent system	A) $CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4; v/v [1] B) $CHCl_3$:isopropanol=85:15, v/v [1] C) isopropanol:toluene:CH_3COOH:H_2O=65:25:5:5; v/v [1] D) $CHCl_3$:Isopropanol=4:1,v/v [2]
Detection	1) TLC linear analyzer model IM 3016 (see Table X) 2) Autoradiography (see Table XI)

1) Solvent system A-C : For metabolism study
2) D : For determination of the purity

Table IX High performance liquid chromatography (HPLC)

Equipment	1) Analysis : -HP 1090 Liquid Chromatograph with diode array detector (HP 1040) -Flow through radioactivity detector with solid scintillator cell ; Ramona-5 (Raytest, Isotopenmeßgeräte) 2) Preparative : -Pump ; LATEK-P402 (LATEK) -UV detector ; LC-55 (PERKIN-ELMER) -Injector ; model 7161 (RHEODYNE) -Flow-through radioactivity detector with solid scintillator cell ; Ramona-D (Raytest, Isotopenmeßgeräte)
Columns	1) Analytical: -LiChrosorb RP 18, 5 µm, 4 mm x 250 mm (Merck) -LiChrospher RP-select B, 5 µm, 4 mm x 250 mm (Merck) 2) Preparative: -LiChrosorb RP 18, 10 µm, 10 mm x 250 mm (Merck)
Mobile phase	Given in the legends of the corresponding figures
Flow rate	1) Analytical: 1 ml/min 2) Preparative: 5 ml/min
Detection	-UV; 210 nm -Radioactivity (^{14}C)

Table X TLC linear analyzer

Equipment	IM 3016 with computer system RITA 68000 (Raytest, Isotopenmeßgeräte, West Germany)
Detector	Geiger-Müller type tube counter
Counting gas	1) 90 % argon + 10 % methane, saturated with isopropanol 2) Flow ; 0.5 l/min
Window	Mylar foil covered
Sensitivity	100 dpm for ^{14}C

Table XI Autoradiography

X-ray film	CURIX RP 1 (AGFA GEVAERT)
Exposure	-Room temperature (about 21-24°C) -In freezer (for isolation of metabolites)
Equipment for development	-CURIX 60 processor (AGFA GEVAERT) -Developer ; G 153 A & B (AGFA GEVAERT) -Fixer ; G 353 (AGFA GEVAERT)

Table XII Nuclear magnetic resonance spectroscopy

Equipment	AC-300 (Bruker)
Mode	Fourier transform
Magnet	Superconducting magnet
Frequency	^1H : 300 MHz
Solvent	-Methanol-d_4
Internal reference	Me_4Si

Table XIII Excretion of total radioactivity and residues of radioactivity in the body at 48 h after administration to male and female rats[1] (% of the administered radioactivity)

B A Y E R A G	Test Compound : omethoate	Study No. : M01810019	Date: 01-Dec-89
SECTOR 5	Rat : male, female	Study Dir. : T.Hoshino	
PF-F/CE-ME	Low Dose : 0.5 mg/kg	Test No. : 1-9	
ANIMAL-METAB.	High Dose : 10 mg/kg	Sacrif. : 48 h	
BIOKINETICS			

EXCRETION AND RESIDUES [% of the administered dose]

BIOLOGICAL MATERIAL	i. v. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 10 mg/kg		p.o. 10 mg/kg
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male pretreatment	Test 6 female pretreatment	Test 7 male	Test 8 female	Test 9 male CO_2 Test
CO_2									0.14
URINE	95.67	84.45	94.37	92.55	89.40	87.26	84.69	95.85	90.42
FAECES	2.07	3.30	2.26	2.85	2.70	3.71	4.20	2.27	3.35
GASTROINT. TR.[2]	0.03	0.04	0.03	0.03	0.03	0.04	0.03	0.03	0.04
BODY EXCL. GIT[3]	0.42	0.37	0.29	0.30	0.32	0.28	0.27	0.26	0.24
RECOVERY [%]	98.19	88.16	96.95	95.73	92.44	91.30	89.19	98.41	94.19

1) This data shows mean values from the data of 5 rats.
2) Gastrointestinal tract
3) Body excluding gastrointestinal tract

Table XIV Excretion of total radioactivity and residues of radioactivity in the body at 48 h after administration to male and female rats[1] (% of the recovered radioactivity)

B A Y E R A G	Test Compound	: omethoate	Study No. : M01810019	Date: 01-Dec-89
SECTOR 5	Rat	: male, female	Study Dir. : T.Hoshino	
PF-F/CE-ME	Low Dose	: 0.5 mg/kg	Test No. : 1-9	
ANIMAL-METAB.	High Dose	: 10 mg/kg	Sacrif. : 48 h	
BIOKINETICS				

EXCRETION AND RESIDUES [% of the recovered radioactivity]

BIOLOGICAL MATERIAL	i. v. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 10 mg/kg		p.o. 10 mg/kg
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male pretreatment	Test 6 female pretreatment	Test 7 male	Test 8 female	Test 9 male CO_2 Test
CO_2									0.15
URINE	97.43	95.79	97.34	96.68	96.71	95.58	94.96	97.40	96.00
FAECES	2.11	3.74	2.33	2.98	2.92	4.07	4.70	2.31	3.55
GASTROINT. TR.[2]	0.03	0.05	0.03	0.03	0.03	0.04	0.03	0.03	0.04
BODY EXCL. GIT[3]	0.42	0.42	0.30	0.32	0.34	0.31	0.30	0.27	0.26
TOTAL [%]	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
FACTOR OF BALANCE	1.018	1.134	1.031	1.045	1.082	1.095	1.121	1.016	1.062

1) This data shows mean values from the data of 5 rats.
2) Gastrointestinal tract
3) Body excluding gastrointestinal tract

Table XV Absorption rate after oral administration[1)]

B A Y E R A G	Test Compound : omethoate	Study No. : M01810019	Date: 01-Dec-89
SECTOR 5	Rat : male, female	Study Dir. : T.Hoshino	
PF-F/CE-ME	Low Dose : 0.5 mg/kg	Test No. : 1-9	
ANIMAL-METAB.	High Dose : 10 mg/kg	Sacrif. : 48 h	
BIOKINETICS			

	i. v. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 10 mg/kg		p.o. 10 mg/kg
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male pretreatment	Test 6 female pretreatment	Test 7 male	Test 8 female	Test 9 male CO_2 Test
EXCRETION IN URINE [% of the recovered administration][2)]									
URINE	97.50	95.83	97.34	96.68	96.71	95.58	94.96	97.40	96.00
BODY EXCL. GIT[3)]	0.42	0.41	0.30	0.32	0.34	0.31	0.30	0.27	0.26
ABSORPTION RATE (%)[4)]			100	101	100	100	98	102	99

1) This table shows mean values from the data of 5 rats.
2) % of the recovered radioactivity are shown in Table XIV.
3) Body excluding gastrointestinal tract
4) Absorbed amount (%) was calculated as :

$$\frac{\text{excretion \% in urine after p.o. administration}}{\text{excretion \% in urine after i.v. administration}} + \text{residue \% in body excluding GIT ("BODY EXCL.GIT" in Table XIV)}$$

Table XVI Time course of the excretion of the total radioactivity with urine after administration to male and female rats[1)]

B A Y E R A G	Test Compound : omethoate	Study No. : M01810019	Date: 01-Dec-89
SECTOR 5	Rat : male, female	Study Dir. : T.Hoshino	
PF-F/CE-ME	Low Dose : 0.5 mg/kg	Test No. : 1-9	
ANIMAL-METAB.	High Dose : 10 mg/kg	Sacrif. : 48 h	
BIOKINETICS			

EXCRETION [% of the administered radioactivity]

TIME (hours)	i. v. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 10 mg/kg		p.o. 10 mg/kg
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male pretreatment	Test 6 female pretreatment	Test 7 male	Test 8 female	Test 9 male CO2 Test
2	26.22	25.95	24.35	24.89	26.64	27.63	20.16	35.60	---[2)]
4	27.92	30.27	33.77	33.45	29.25	24.82	16.38	21.42	51.89
6	20.98	13.30	18.81	15.89	18.85	15.65	18.84	14.91	---[2)]
8	8.10	5.32	8.69	8.18	6.47	7.93	11.18	8.40	22.79
24	11.61	8.66	8.17	9.19	7.59	10.10	16.16	14.29	13.15
48	0.85	0.96	0.58	0.95	0.59	1.14	1.97	1.24	2.59[3)]
RECOVERY [%]	95.67	84.45	94.37	92.55	89.40	87.26	84.69	95.85	90.42

1) This table shows mean values from the data of 5 rats.
2) Not collected.
3) Urine was collected at 32 hr after administration, 2.59 % was the sum of excretion data at 32 and 48 hr after administration.

Table XVII Time course of the excretion of the total radioactivity with feces after administration to male and female rats[1)]

B A Y E R A G SECTOR 5 PF-F/CE-ME ANIMAL-METAB. BIOKINETICS	Test Compound : omethoate Rat : male, female Low Dose : 0.5 mg/kg High Dose : 10 mg/kg		Study No. : M01810019 Study Dir. : T.Hoshino Test No. : 1-9 Sacrif. : 48 h	Date: 01-Dec-89

EXCRETION [% of the administered radioactivity]

TIME (hours)	i. v. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 10 mg/kg		p.o. 10 mg/kg
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male pretreatment	Test 6 female pretreatment	Test 7 male	Test 8 female	Test 9 male CO_2 Test
24	1.82	3.02	2.07	1.82	2.46	2.77	3.71	2.05	2.82
48	0.24	0.28	0.19	1.03	0.24	0.94	0.48	0.22	0.52
RECOVERY [%]	2.07	3.30	2.26	2.85	2.70	3.71	4.20	2.27	3.35

1) This table shows mean values from the data of 5 rats.

Table XVIII Time course of the relative concentration P of radioactivity in the plasma after administration to male and female rats[1)]

B A Y E R A G SECTOR 5 PF-F/CE-ME ANIMAL-METAB. BIOKINETICS	Test Compound : omethoate Rat : male, female Low Dose : 0.5 mg/kg High Dose : 10 mg/kg	Study No. : M01810019 Study Dir. : T.Hoshino Test No. : 1-9 Sacrif. : 48 h	Date: 01-Dec-89

RELATIVE CONCENTRATION [P] OF RADIOACTIVITY IN THE PLASMA

TIME (hours)	i. v. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 10 mg/kg	
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male pretreatment	Test 6 female pretreatment	Test 7 male	Test 8 female
0.083	1.6762	1.4865	0.1488	0.2089	0.1371	0.1712	0.1173	0.1310
0.170	1.5100	1.3838	0.5808	0.5746	*0.3281	0.4480	0.3068	0.3500
0.333	1.3950	1.3828	0.9277	0.9339	0.7467	0.8350	0.6534	0.7506
0.667	1.3735	1.3317	1.1832	1.1671	1.1418	1.0515	1.0007	1.0512
1.000	1.3159	1.1973	1.1721	1.2760	1.1395	1.0292	1.1114	1.0488
1.500	1.1746	1.0309	1.0495	1.0810	1.0218	0.9486	0.9465	0.8905
2.000	1.0285	0.8882	0.8866	0.9553	0.8580	0.7951	0.7875	0.7213
3.000	0.7525	0.6365	0.6423	0.6840	0.5844	0.5853	0.6221	0.5796
4.000	0.5213	0.3840	0.4681	0.4615	0.3746	0.4543	0.5095	0.4242
6.000	0.2651	0.1726	0.1985	0.2132	*0.1314	*0.1842	0.3614	0.2578
8.000	0.1680	0.0951	0.0981	0.1116	0.0834	0.1037	0.1990	0.1610
24.000	0.0076	0.0095	0.0060	0.0084	0.0062	0.0085	0.0088	0.0112
32.000	0.0057	0.0071	0.0050	0.0063	0.0057	0.0061	*0.0052	0.0073
48.000	0.0039	0.0052	0.0031	0.0039	0.0034	0.0044	0.0028	*0.0030

1) This table shows mean values from the data of 5 rats, outliers were determined according to the method of Nalimov and taken into consideration. Mean values derived from less than 5 rats are marked with an asterisk (*).

Table XIX Omethoate : The relative concentration P of organs and tissues at 48 h after administration to male and female rats[1)]

B A Y E R A G SECTOR 5 PF-F/CE-ME ANIMAL-METAB. BIOKINETICS	Test Compound : omethoate Rat : male, female Low Dose : 0.5 mg/kg High Dose : 10 mg/kg		Study No. : M01810019 Study Dir. : T.Hoshino Test No. : 1-9 Sacrif. : 48 h	Date: 01-Dec-89

RELATIVE CONCENTRATION [P] OF RADIOACTIVITY

ORGANS AND TISSUES	i. v. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 10 mg/kg	
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male pretreatment	Test 6 female	Test 7 male	Test 8 female
Erythrocyte	0.0025	0.0029	0.0030	0.0025	0.0022	0.0026	0.0020	*0.0022
Plasma	0.0030	0.0029	0.0026	0.0033	0.0027	0.0032	0.0022	0.0029
Spleen	0.0057	0.0054	0.0053	0.0063	0.0054	0.0052	0.0044	0.0042
Liver	0.0097	0.0092	0.0099	0.0096	0.0086	0.0082	0.0054	0.0052
Kidney	0.0078	0.0075	0.0077	0.0083	0.0060	0.0072	0.0045	0.0046
Fat	0.0020	0.0009	0.0022	0.0017	*0.0019	*0.0015	0.0016	0.0006
Testis	0.0103		0.0088		0.0097		0.0091	
Ovaries		0.0028		0.0034		0.0033		0.0026
Uterus		0.0033		0.0081		0.0032		0.0040
Muscle	0.0018	0.0032	0.0019	0.0023	0.0024	0.0021	0.0020	0.0015
Bone	0.0021	0.0030	0.0037	0.0035	0.0028	0.0026	0.0017	0.0031
Heart	0.0033	0.0045	0.0034	0.0038	0.0036	0.0034	0.0026	0.0029
Lung	0.0051	0.0048	0.0058	0.0059	0.0052	0.0054	0.0037	0.0038
Brain	0.0013	0.0020	0.0018	0.0020	0.0014	0.0013	0.0009	0.0011
Thyroid	0.5924	0.3845	*0.3219	0.5184	0.3390	0.3605	0.1558	0.1879
Skin	0.0062	0.0050	0.0034	0.0037	0.0033	0.0028	0.0030	0.0045
GIT[2)]	0.0033	0.0037	0.0030	0.0023	0.0026	0.0037	0.0029	0.0035
Carcass	0.0026	0.0035	0.0025	0.0029	0.0032	0.0029	0.0029	0.0023

1) This table shows mean values from the data of 5 rats, outliers were determined according to the method of Nalimov and taken into consideration. Mean values derived from less than 5 rats are marked with an asterisk (*).

2) Gastrointestinal tract

Table XX The equivalent concentration C of organs and tissues at 48 h after administration to male and female rats[1)]

B A Y E R A G SECTOR 5 PF-F/CE-ME ANIMAL-METAB. BIOKINETICS	Test Compound : omethoate Rat : male, female Low Dose : 0.5 mg/kg High Dose : 10 mg/kg	Study No. : M01810019 Study Dir. : T.Hoshino Test No. : 1-9 Sacrif. : 48 h	Date: 01-Dec-89

EQUIVALENT CONCENTRATION C (ppm)

ORGANS AND TISSUES	i. v. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 10 mg/kg	
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male pretreatment	Test 6 female	Test 7 male	Test 8 female
Erythrocyte	0.0012	0.0016	0.0015	0.0013	0.0011	0.0015	0.0198	0.0231
Plasma	0.0014	0.0016	0.0013	0.0017	0.0014	0.0018	0.0220	0.0307
Spleen	0.0027	0.0030	0.0026	0.0033	0.0028	0.0029	0.0433	0.0445
Liver	0.0046	0.0051	0.0049	0.0050	0.0044	0.0046	0.0531	0.0553
Kidney	0.0037	0.0042	0.0038	0.0044	0.0031	0.0040	0.0445	0.0489
Fat	0.0009	0.0005	0.0011	0.0009	0.0010	0.0008	0.0161	0.0068
Testis	0.0049		0.0044		0.0050		0.0890	
Ovaries		0.0016		0.0018		0.0018		0.0279
Uterus		0.0019		0.0042		0.0018		0.0426
Muscle	0.0009	0.0018	0.0009	0.0012	0.0012	0.0012	0.0193	0.0159
Bone	0.0010	0.0017	0.0018	0.0018	0.0015	0.0014	0.0163	0.0325
Heart	0.0016	0.0025	0.0017	0.0020	0.0019	0.0019	0.0252	0.0306
Lung	0.0024	0.0027	0.0029	0.0031	0.0027	0.0030	0.0358	0.0403
Brain	0.0006	0.0011	0.0009	0.0010	0.0007	0.0007	0.0084	0.0113
Thyroid	0.2815	0.2135	0.1624	0.2718	0.1743	0.2045	1.5289	1.9705
Skin	0.0029	0.0028	0.0017	0.0019	0.0017	0.0016	0.0293	0.0470
GIT[2)]	0.0016	0.0020	0.0015	0.0012	0.0013	0.0021	0.0286	0.0368
Carcass	0.0013	0.0020	0.0012	0.0015	0.0017	0.0016	0.0287	0.0245

1) This table shows mean values from the data of 5 rats.
2) Gastrointestinal tract

Table XXI The recovery of the administered radioactivity in organs and tissues after administration to male and female rats[1)]

B A Y E R A G	Test Compound : omethoate	Study No. : M01810019	Date: 01-Dec-89
SECTOR 5	Rat : male, female	Study Dir. : T.Hoshino	
PF-F/CE-ME	Low Dose : 0.5 mg/kg	Test No. : 1-9	
ANIMAL-METAB.	High Dose : 10 mg/kg	Sacrif. : 48 h	
BIOKINETICS			

% OF THE ADMINISTERED RADIOACTIVITY

ORGANS AND TISSUES	i. v. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 10 mg/kg	
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male pretreatment	Test 6 female pretreatment	Test 7 male	Test 8 female
Erythrocyte	0.003	0.005	0.004	0.004	0.003	0.003	0.003	0.003
Plasma	0.002	0.002	0.003	0.003	0.002	0.003	0.002	0.003
Spleen	0.001	0.001	0.001	0.001	0.001	0.001	0.000	0.000
Liver	0.038	0.038	0.045	0.041	0.042	0.038	0.024	0.021
Kidney	0.005	0.005	0.006	0.006	0.005	0.005	0.003	0.003
Fat	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
Testis	0.015		0.013		0.014		0.014	
Ovaries		0.000		0.000		0.000		0.000
Uterus		0.001		0.002		0.001		0.000
Muscle	0.001	0.002	0.001	0.002	0.002	0.002	0.002	0.001
Bone	0.000	0.001	0.001	0.001	0.000	0.000	0.000	0.001
Heart	0.001	0.002	0.001	0.001	0.001	0.001	0.000	0.001
Lung	0.003	0.004	0.004	0.004	0.003	0.004	0.002	0.002
Brain	0.001	0.002	0.002	0.002	0.001	0.001	0.000	0.001
Thyroid	0.003	0.002	0.001	0.003	0.001	0.002	0.000	0.002
Skin	0.137	0.106	0.075	0.075	0.065	0.059	0.062	0.092
GIT[2)]	0.031	0.035	0.031	0.028	0.028	0.040	0.030	0.029
Carcass	0.144	0.199	0.131	0.157	0.175	0.161	0.159	0.133

1) This table shows mean values from the data of 5 rats.
2) Gastrointestinal tract

Table XXII The ratio of organs vs. plasma concentration at 48 h after administration to male and female rats[1)]

B A Y E R A G	Test Compound : omethoate	Study No. : M01810019	Date: 01-Dec-89
SECTOR 5	Rat : male, female	Study Dir. : T.Hoshino	
PF-F/CE-ME	Low Dose : 0.5 mg/kg	Test No. : 1-9	
ANIMAL-METAB.	High Dose : 10 mg/kg	Sacrif. : 48 h	
BIOKINETICS			

ORGANS VS: PLASMA RATIO

ORGANS AND TISSUES	i. v. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 10 mg/kg	
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male pretreatment	Test 6 female pretreatment	Test 7 male	Test 8 female
Erythrocyte	0.821	1.003	1.134	0.761	0.819	0.808	0.897	0.763
Plasma	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Spleen	1.894	1.849	2.027	1.903	1.978	1.601	1.973	1.460
Liver	3.219	3.154	3.793	2.906	3.159	2.542	2.411	1.819
Kidney	2.591	2.568	2.939	2.524	2.225	2.223	2.027	1.606
Fat	0.648	0.315	0.843	0.503	0.712	0.449	0.728	0.223
Testis	3.429		3.368		3.561		4.049	
Ovaries		0.969		1.030		1.019		0.916
Uterus		1.140		2.455		0.994		1.408
Muscle	0.611	1.099	0.724	0.691	0.886	0.644	0.875	0.519
Bone	0.684	1.041	1.398	1.048	1.037	0.796	0.741	1.073
Heart	1.096	1.534	1.284	1.148	1.325	1.046	1.147	1.003
Lung	1.688	1.651	2.226	1.794	1.908	1.678	1.629	1.324
Brain	0.442	0.682	0.693	0.609	0.513	0.393	0.384	0.373
Thyroid	196.8	131.7	123.3	157.1	125.1	111.6	69.6	65.5
Skin	2.066	1.702	1.303	1.127	1.221	0.876	1.339	1.551
GIT[2)]	1.083	1.260	1.165	0.709	0.959	1.149	1.304	1.209
Carcass	0.877	1.202	0.950	0.867	1.188	0.901	1.308	0.801

1) This table shows mean values from the data of 5 rats.
2) Gastrointestinal tract

Table XXIII Pharmacokinetic parameters from plasma curve analysis after administration to male and female rats[1)]

B A Y E R A G	Test Compound : omethoate	Study No. : M01810019	Date: 01-Dec-89
SECTOR 5	Rat : male, female	Study Dir. : T.Hoshino	
PF-F/CE-ME	Low Dose : 0.5 mg/kg	Test No. : 1-9	
ANIMAL-METAB.	High Dose : 10 mg/kg	Sacrif. : 48 h	
BIOKINETICS			

	i. v. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 0.5 mg/kg		p. o. 10 mg/kg	
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male pretreatment	Test 6 female	Test 7 male	Test 8 female
Absorption [%]			100	101	100	100	98	102
AUC-exp[h][2)]	6.116	5.064	4.795	5.123	4.268	4.552	5.436	4.920
AUC-fit[h][3)]	6.395	5.395	4.911	5.251	4.409	4.720	5.500	4.981
T-a (25-75 %) [h][4)]			0.2	0.3	0.3	0.2	0.4	0.2
T-a [h]	2.2	1.7	1.8	1.8	1.6	1.9	2.8	2.4
$T_{\frac{1}{2}}B$ [h]	25.0	28.4	24.6	21.6	26.6	26.2	15.2	12.8
CL [ml/min][5)]	2.61	3.09	3.39	3.17	3.78	3.53	3.03	3.34
CL-R [ml/min][6)]	2.55	2.71	3.28	3.01	3.49	3.15	2.59	3.24
MRT [h][7)]	6.2	7.8	6.2	6.5	7.1	7.8	6.2	6.3
V-ss [l/kg][8)]	0.97	1.45	1.26	1.23	1.60	1.65	1.12	1.27
P-max[9)]			1.183	1.276	1.142	1.051	1.111	1.051
T-max [h][10)]			0.67	1.00	0.67	0.67	1.00	0.67

1) Each value is calculated from the plasma curve of the average relative concentration.
2) AUC-exp : area under the blood concentration vs. time curve of experimental values calculated by data from the measured first time point to the last time point
3) AUC-fit : sum of AUC-exp and AUC integrated from time point 0 to 5 min and from 48 h to infinity by extrapolation.
4) T-a (25-75 %) : time for a rise in concentration from 25 % to 75% of C-max
5) CL : total plasma clearance
6) CL-R : renal clearance
7) MRT : mean residence time
8) V-ss : distribution volume in the steady state
9) P-max : maximum level of the plasma concentration
10) T-max : time of the maximum level of the plasma concentration after oral administration. T-max was evaluated from experimental time points.

Table XXIV Distribution of omethoate and its metabolites in urine after administration to male and female rats

B A Y E R A G	Test Compound : omethoate	Study No. : M01810019	Date: 01-Dec-89
SECTOR 5	Rat : male, female	Study Dir. : T.Hoshino	
PF-F/CE-ME	Low Dose : 0.5 mg/kg	Test No. : 1-9	
ANIMAL-METAB.	High Dose : 10 mg/kg	Sacrif. : 48 h	
BIOKINETICS			

% OF THE ADMINISTERED RADIOACTIVITY

METABOLITES	i.v. 0.5 mg/kg		p.o. 0.5 mg/kg		p.o. 0.5 mg/kg		p.o. 10 mg/kg		p.o. 10 mg/kg
	Test 1 male	Test 2 female	Test 3 male	Test 4 female	Test 5 male	Test 6 female	Test 7 male	Test 8 female	Test 9 male
					pretreatment				CO_2 Test
I. omethoate	30.90	43.59	25.86	42.48	32.54	39.01	45.56	62.01	55.52
II. O-desmethyl[1]	8.51	5.10	6.04	5.55	4.38	4.89	6.18	6.42	6.60
III. sulphinyl[2]	35.11	22.86	35.86	26.75	31.11	24.26	17.45	15.53	16.37
TOTAL IN URINE	74.53	71.55	67.76	74.78	68.03	68.15	69.19	83.96	78.49

1) O-desmethylated metabolite
2) N-methyl-2-(methylsulphinyl)acetamide

Table XXV Distribution of omethoate and its metabolites in excreta after oral administration of 10 mg/kg to male and female rats (Test 7 and 8)

B A Y E R A G	Test Compound : omethoate	Study No. : M01810019	Date: 01-Dec-89
SECTOR 5	Rat : male, female	Study Dir. : T.Hoshino	
PF-F/CE-ME	Low Dose : 0.5 mg/kg	Test No. : 1-9	
ANIMAL-METAB.	High Dose : 10 mg/kg	Sacrif. : 48 h	
BIOKINETICS			

% OF THE ADMINISTERED RADIOACTIVITY

METABOLITES	TEST 7 p.o. male			TEST 8 p.o. female		
	URINE	FECES	SUBTOTAL	URINE	FECES	SUBTOTAL
I. omethoate	45.56	0.21	45.77	62.01	0.21	62.22
II. O- desmethyl[1)]	6.18	2.00	8.18	6.42	0.68	7.10
III. sulphinyl[2)]	17.45	0.20	17.65	15.53	0.07	15.60
TOTAL IN EXCRETA			71.60			84.92

1) O-desmethylated metabolite

2) N-methyl-2-(methylsulphinyl)acetamide

List of Figures

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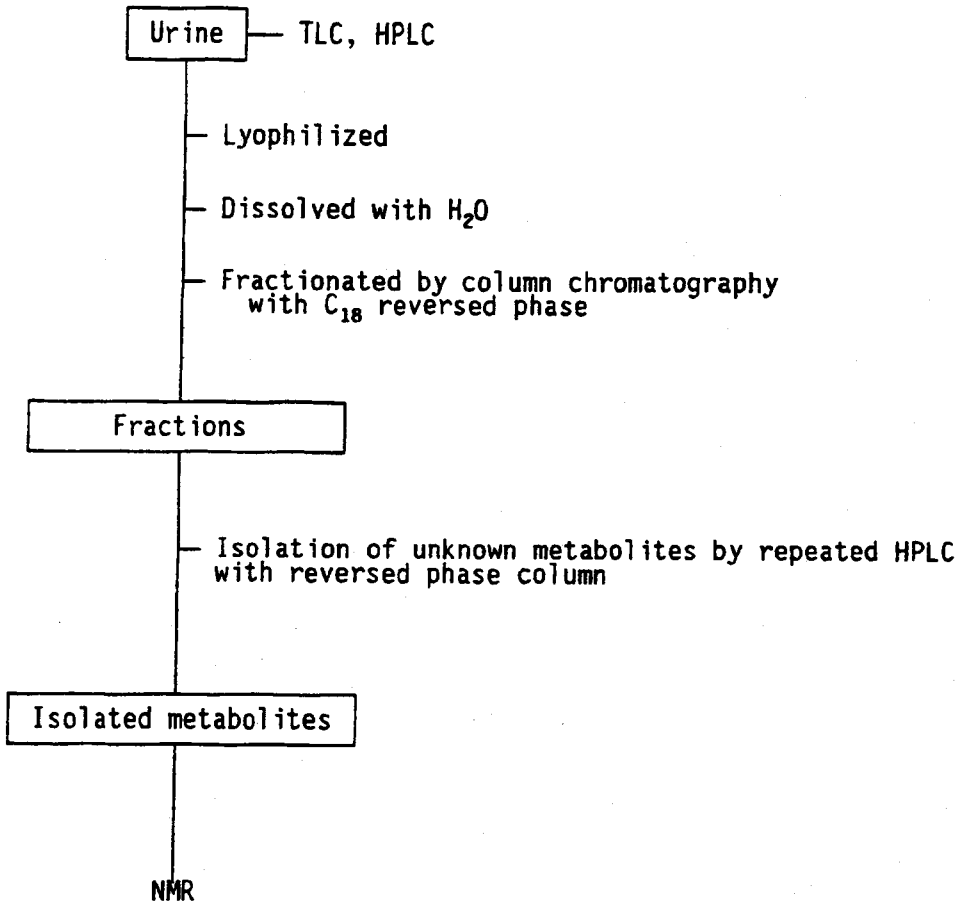


Fig. 1 Scheme for investigation and isolation of omethoate and its metabolites from urine after oral administration

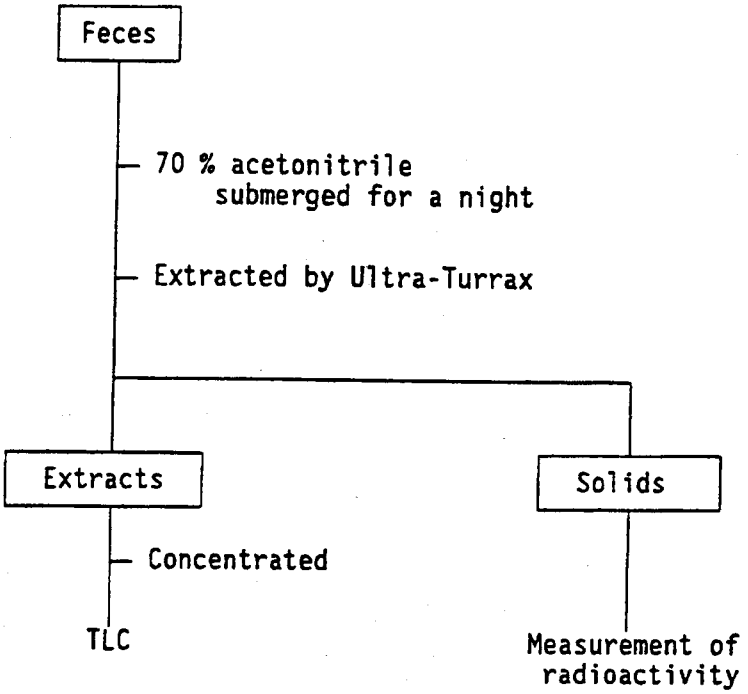


Fig.2 Scheme for extraction of omethoate and its metabolites

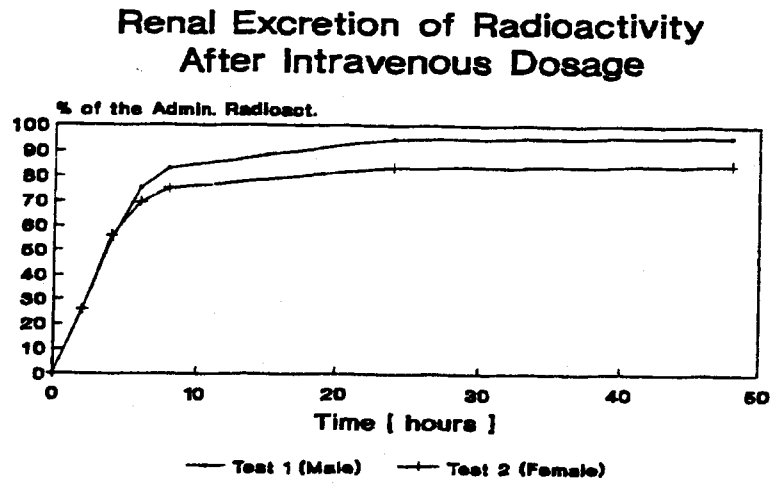


Fig. 3 Cumulative excretion of the total radioactivity with urine after single intravenous administration of 0.5 mg/kg (Test group 1: male, Test group 2: female)

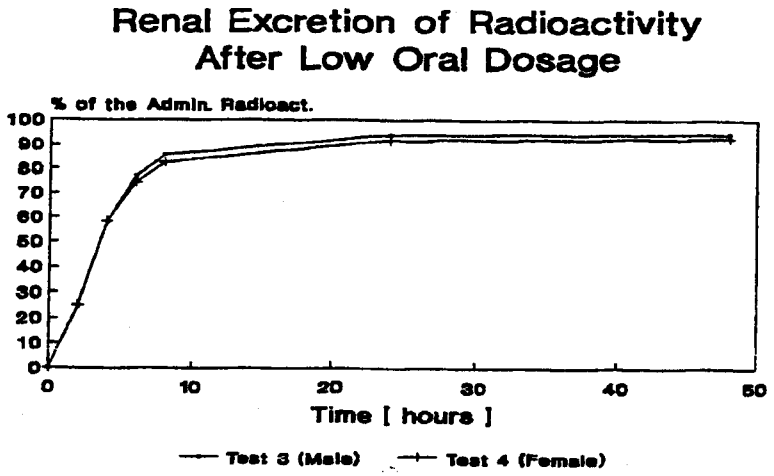


Fig. 4 Cumulative excretion of the total radioactivity with urine after single oral administration of 0.5 mg/kg (Test group 3: male, Test group 4: female)

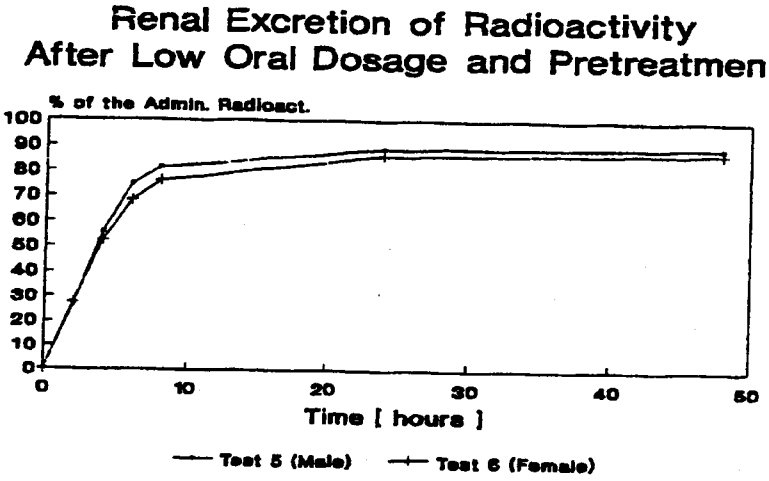


Fig. 5 Cumulative excretion of the total radioactivity with urine after consecutive oral administration of 0.5 mg/kg (Test group 5: male, Test group 6: female)

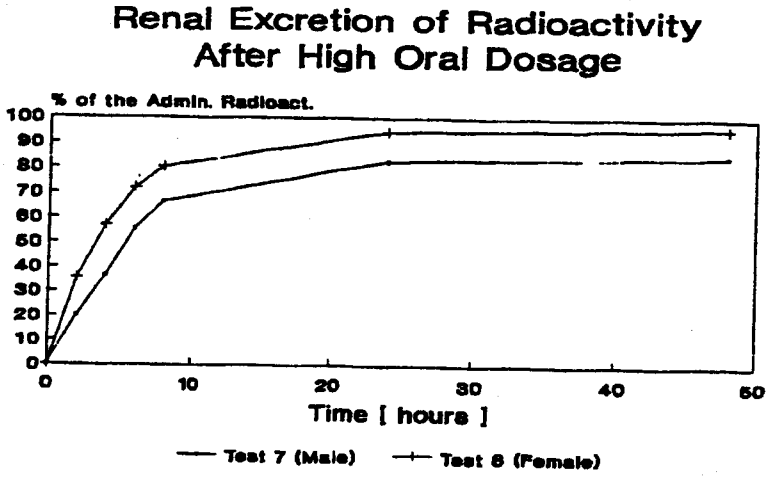


Fig. 6 Cumulative excretion of the total radioactivity with urine after single oral administration of 10 mg/kg (Test group 7: male, Test group 8: female)

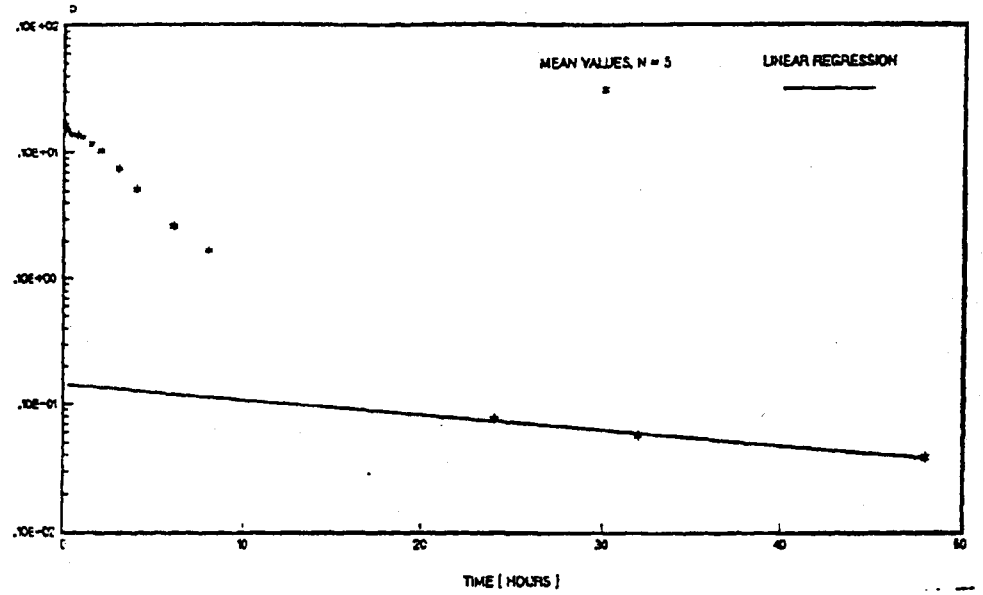


Fig.7 Time course of the relative concentration P of total radioactivity in the plasma after single intravenous administration of 0.5 mg/kg to male rats (Test group 1)

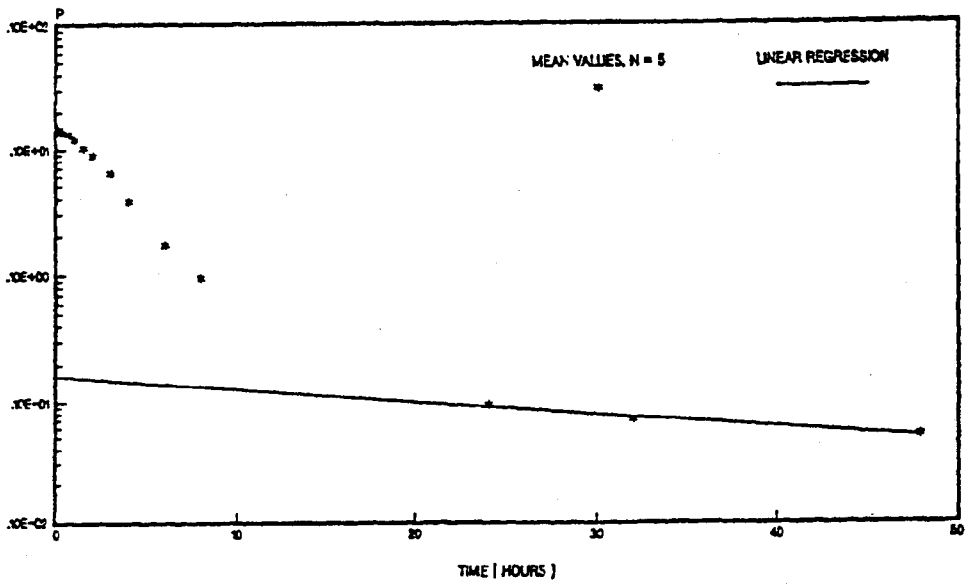


Fig.8 Time course of the relative concentration P of total radioactivity in the plasma after single intravenous administration of 0.5 mg/kg to female rats (Test group 2)

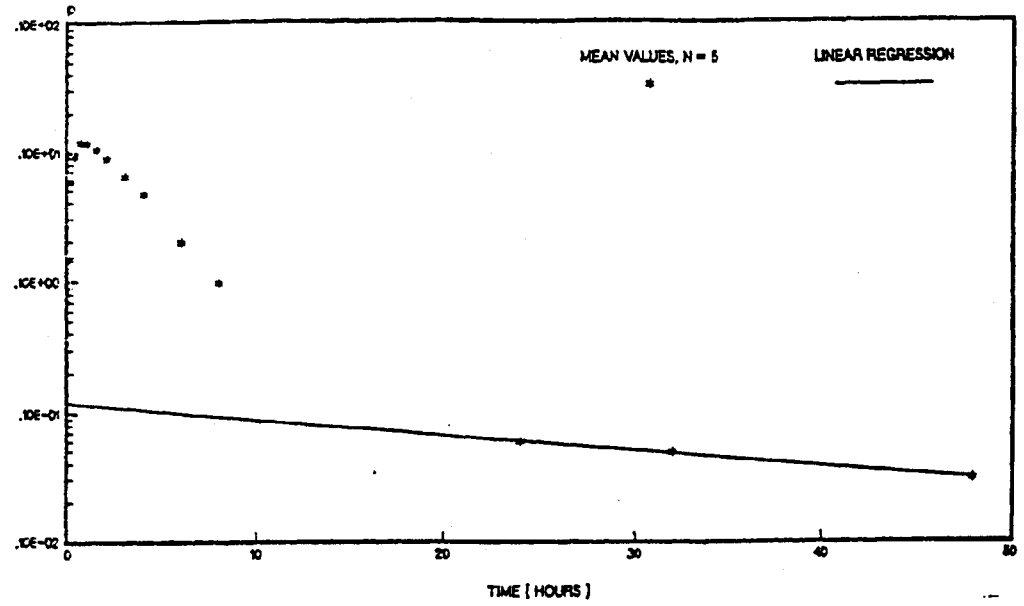


Fig.9 Time course of the relative concentration P of total radioactivity in the plasma after single oral administration of 0.5 mg/kg to male rats (Test group 3)

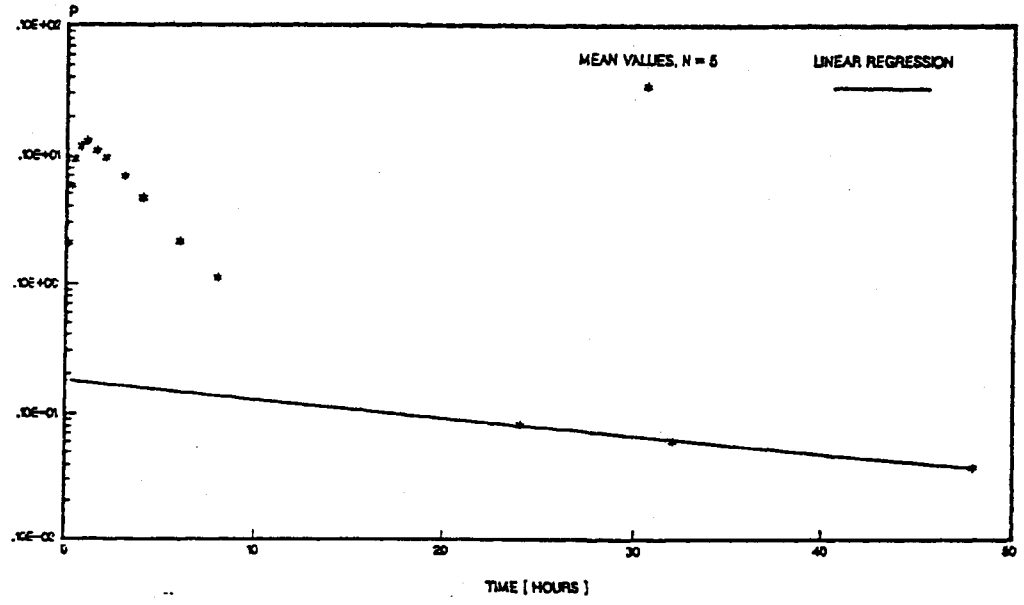


Fig.10 Time course of the relative concentration P of total radioactivity in the plasma after single oral administration of 0.5 mg/kg to female rats (Test group 4)

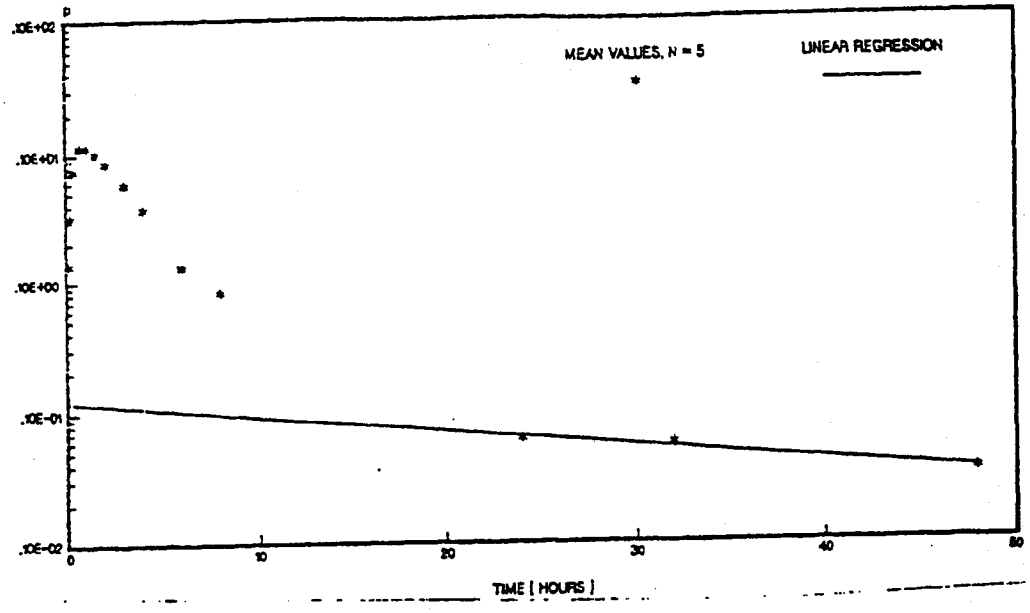


Fig.11 Time course of the relative concentration P of total radioactivity in the plasma after consecutive oral administration of 0.5 mg/kg to male rats (Test group 5)

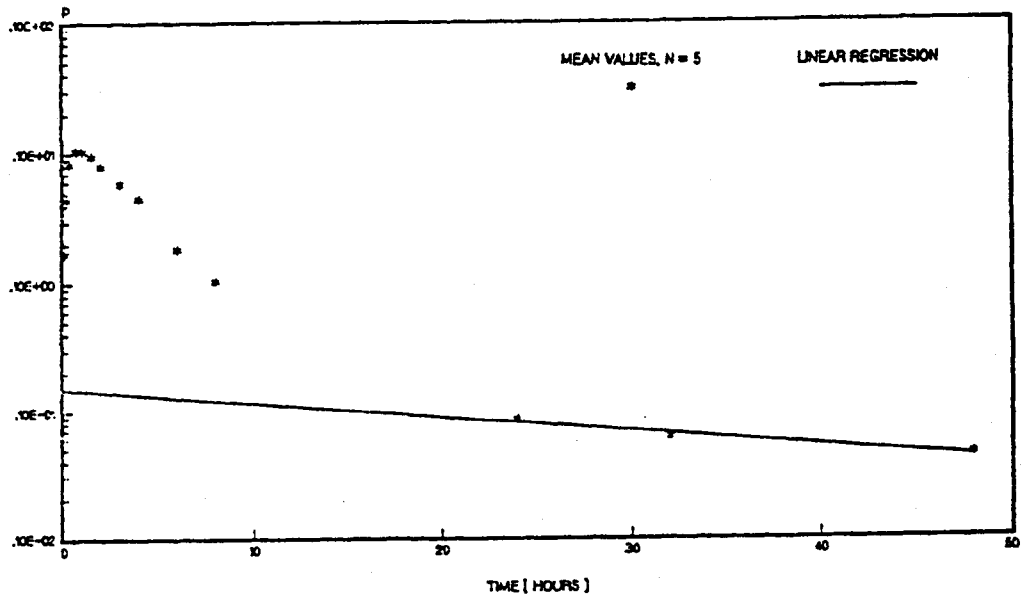


Fig.12 Time course of the relative concentration P of total radioactivity in the plasma after consecutive oral administration of 0.5 mg/kg to female rats (Test group 6)

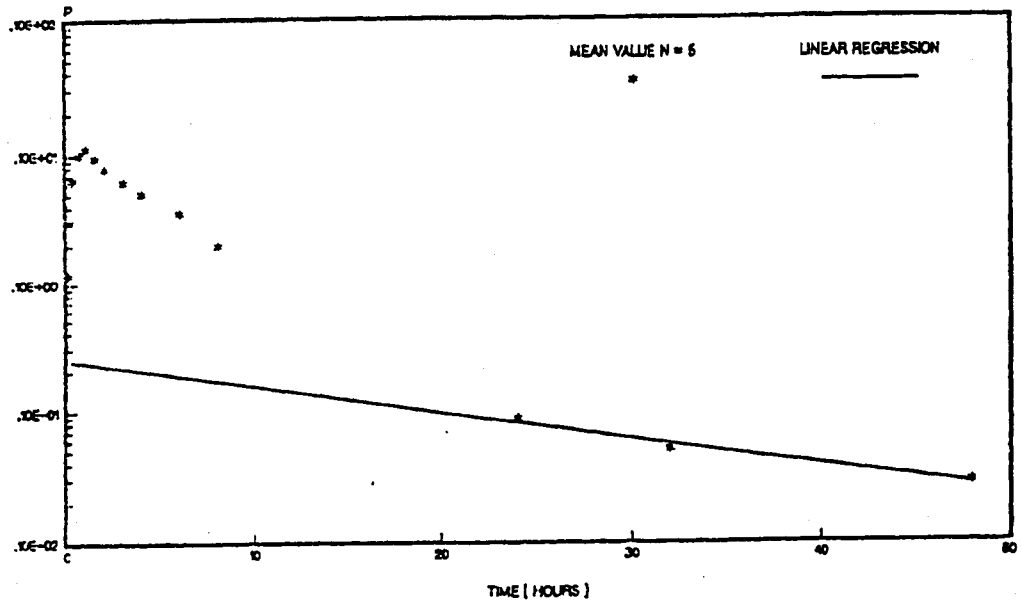


Fig.13 Time course of the relative concentration P of total radioactivity in the plasma after single oral administration of 10 mg/kg to male rats (Test group 7)

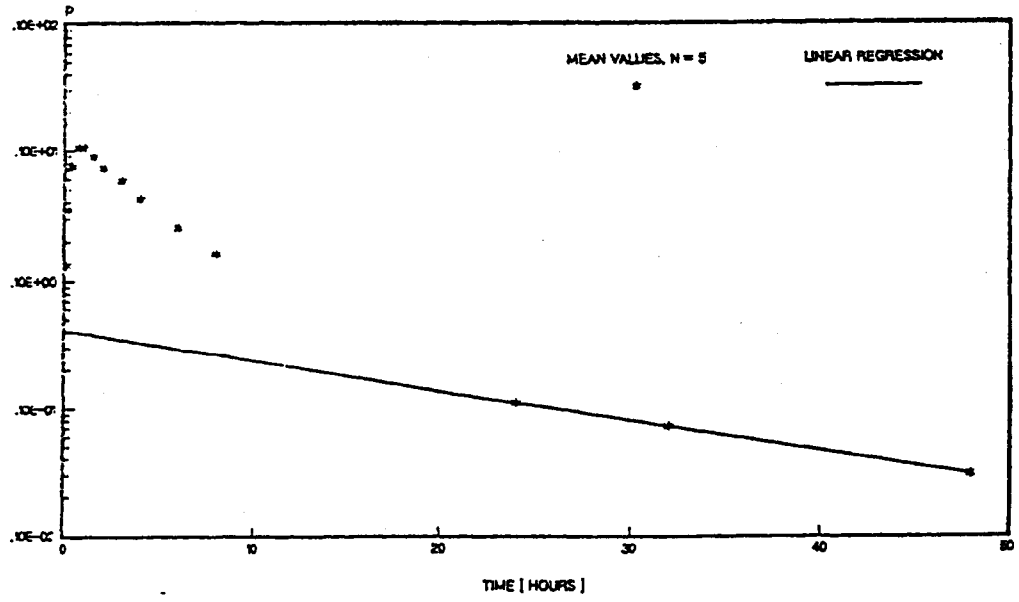


Fig.14 Time course of the relative concentration P of total radioactivity in the plasma after single oral administration of 10 mg/kg to female rats (Test group 8)

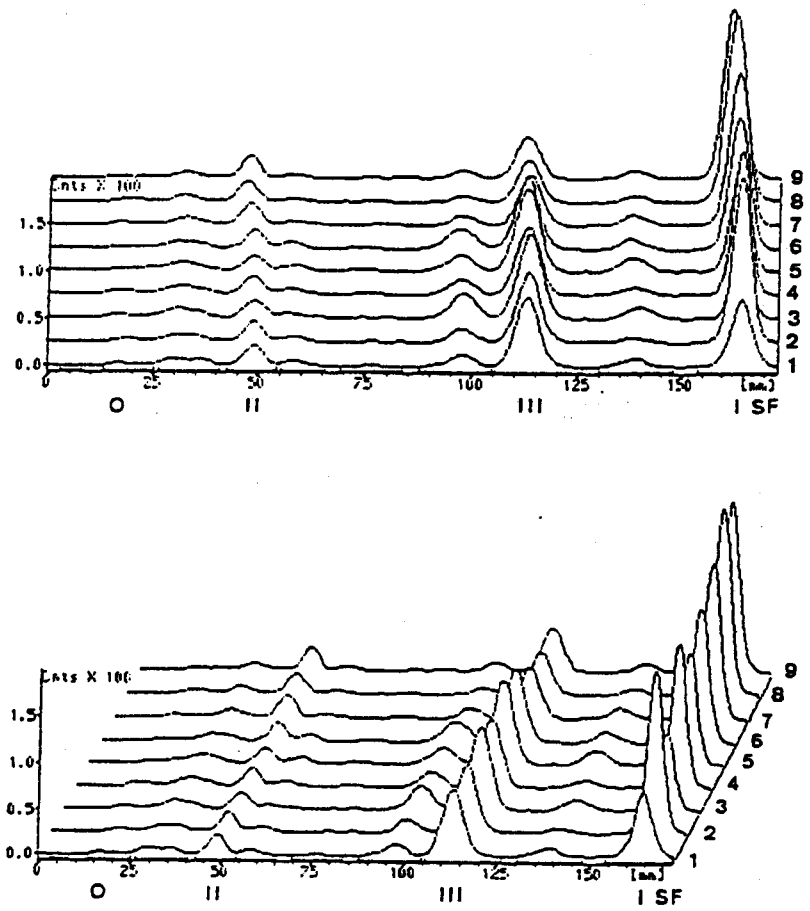


Fig.15 Linear Analyser scans of one-dimensional TLC of the representative native urines in test groups 1-9;
3-dimensional plot with two angles

TLC solvent system : A) $CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4,v/v
I. omethoate
II. O-desmethylated omethoate
III. N-methyl-2-(methylsulphinyl)acetamide

O = origine; SF = solvent front

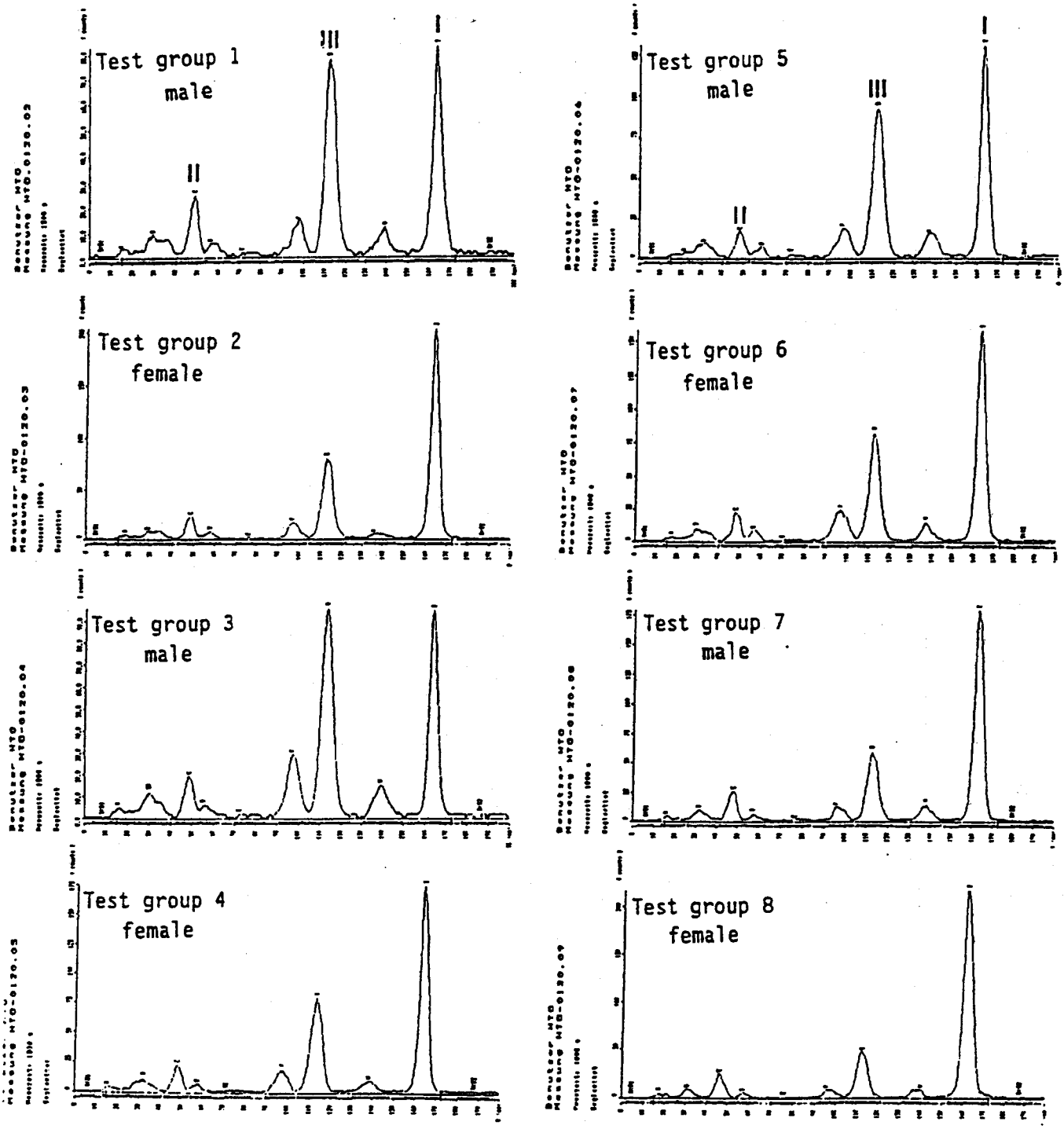


Fig.16 TLC scans of the representative native urine of test groups 1-8

These TLC chromatograms correspond to the 3-D plot in Fig.15.
TLC solvent system : A) $CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4,v/v

I. omethoate
II. O-desmethylated omethoate
III. N-methyl-2-(methylsulphinyl)acetamide

O = origine; SF = solvent front

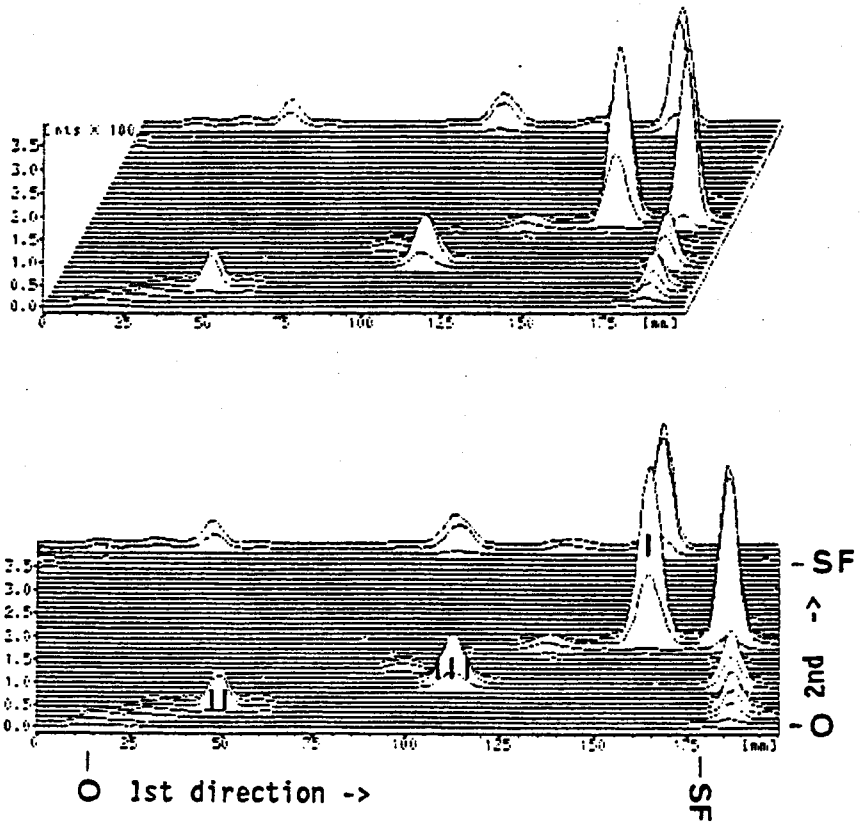


Fig.17 Identification of omethoate in urine by two-dimensional thin layer cochromatography; 3-D plot.

Sample: representative native urine of test 9 (10 mg/kg,p.o.,male)
TLC solvent system:1st;A)$CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4,v/v
2nd;C)isopropanol:toluene:CH_3COOH:H_2O=65:25:5:5,v/v
Reference compounds were detected with staining reagents.
I. omethoate
II. O-desmethylated omethoate
III. N-methyl-2-(methylsulphinyl)acetamide

O = origine; SF = solvent front

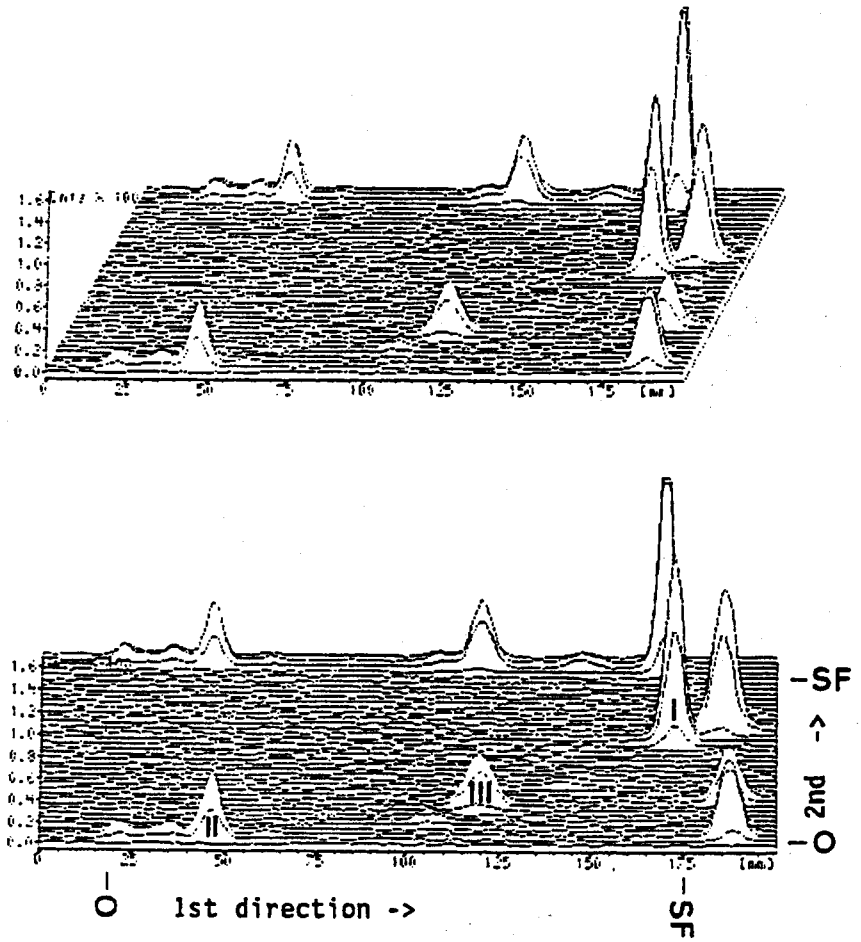


Fig.18 Identification of N-methyl-2-(methylsulphinyl)acetamide in urine by two-dimensional thin layer cochromatography; 3-D plot.

Sample : representative native urine of test 9 (10 mg/kg,p.o.,male)
TLC solvent system:1st;A)$CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4,v/v
2nd;B)$CHCl_3$:isopropanol=85:15,v/v
Reference compounds were detected with staining reagents.
I. omethoate
II. O-desmethylated omethoate
III. N-methyl-2-(methylsulphinyl)acetamide

O = origine; SF = solvent front

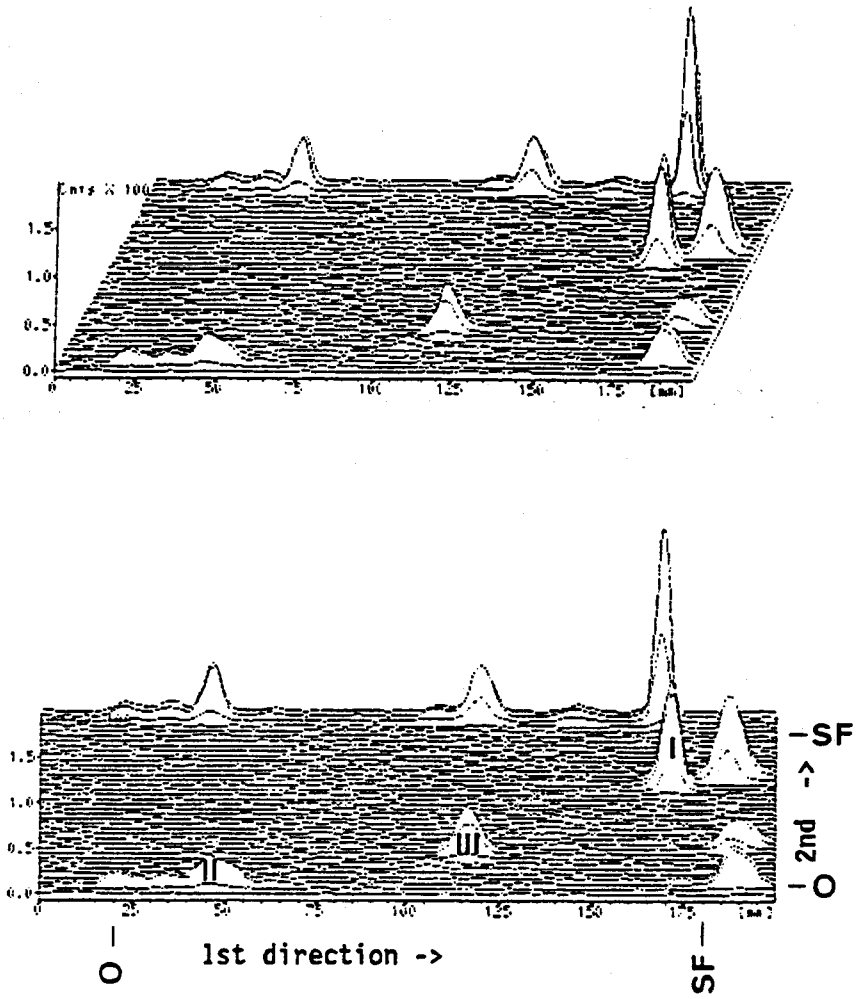


Fig.19 Identification of O-desmethyl metabolite in urine by two-dimensional thin layer cochromatography; 3-D plot.

Sample : representative native urine of test 9 (10 mg/kg,p.o.,male)
TLC solvent system:1st;A)$CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4,v/v
2nd;B)$CHCl_3$:isopropanol=85:15,v/v
Reference compounds were detected with staining reagents.
I. omethoate
II. O-desmethylated omethoate
III. N-methyl-2-(methylsulphinyl)acetamide

O = origine; SF = solvent front

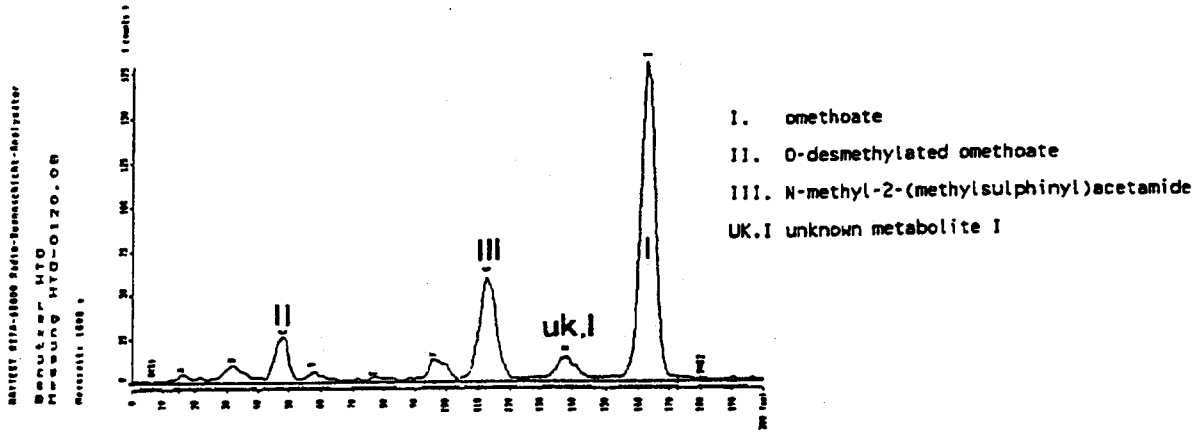
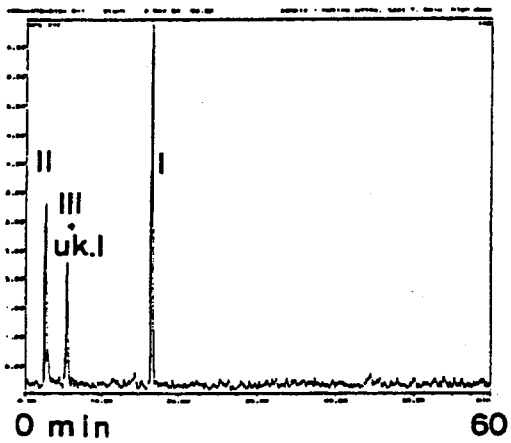


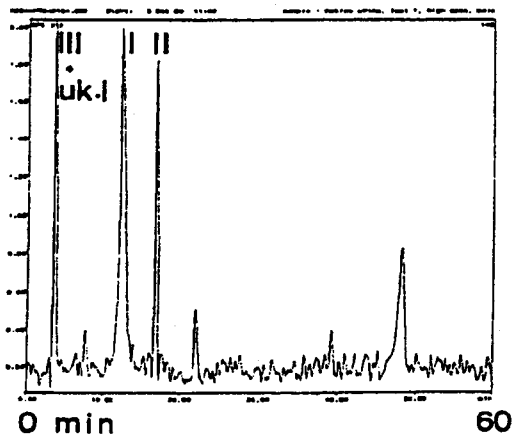
Fig. 20 TLC scan of a chromatogram of native urine of test group 7 (10 mg/kg, male)



a)

Mobile phase A: H_2O; B: acetonitrile
Detection: radioactivity detector

Gradient : T=0 min, A=100%, B= 0%
T=30 min, A= 75%, B= 25%
T=45 min, A= 0%, B=100%
T=55 min, A= 0%, B=100%
T=60 min, A=100%, B= 0%



b)

Mobile phase
A: 0.005 M TBAB in 100 ml 0.003 M phosphate buffer (pH7) and 900 ml H_2O;
B: 0.005 M TBAB in 100 ml 0.003 M phosphate buffer (pH7), 300 ml H_2O and 600 ml acetonitrile
Detection: radioactivity detector

Gradient : T=0 min, A=100%, B= 0%
T=30 min, A= 75%, B= 25%
T=45 min, A= 0%, B=100%
T=55 min, A= 0%, B=100%
T=60 min, A=100%, B= 0%

Fig. 21 HPLC chromatograms of the representative native urine of test group 7 (10 mg/kg, male)

HPLC conditions: see Table IX; column: LiChrosorb RP 18

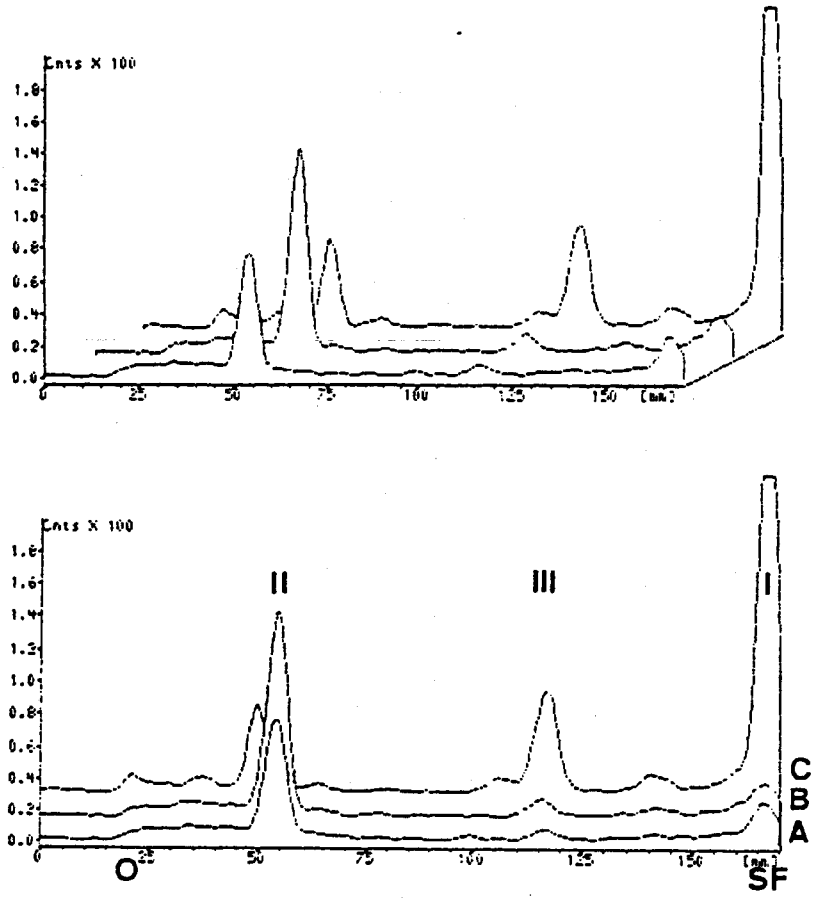


Fig.22 Linear Analyser scans of one-dimensional TLC of the extracts of feces (test groups 7 and 9);
3-dimensional plot with two angles

Sample : A ; feces extracts of test group 7
B ; feces extracts of test group 8
C ; representative urine of test group 9
TLC solvent system : A) $CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4,v/v
I. omethoate
II. O-desmethylated omethoate
III. N-methyl-2-(methylsulphinyl)acetamide
(Since feces extracts contained much matrix, the chromatograms of feces did not correspond properly with that of urine.)

O = origine; SF = solvent front

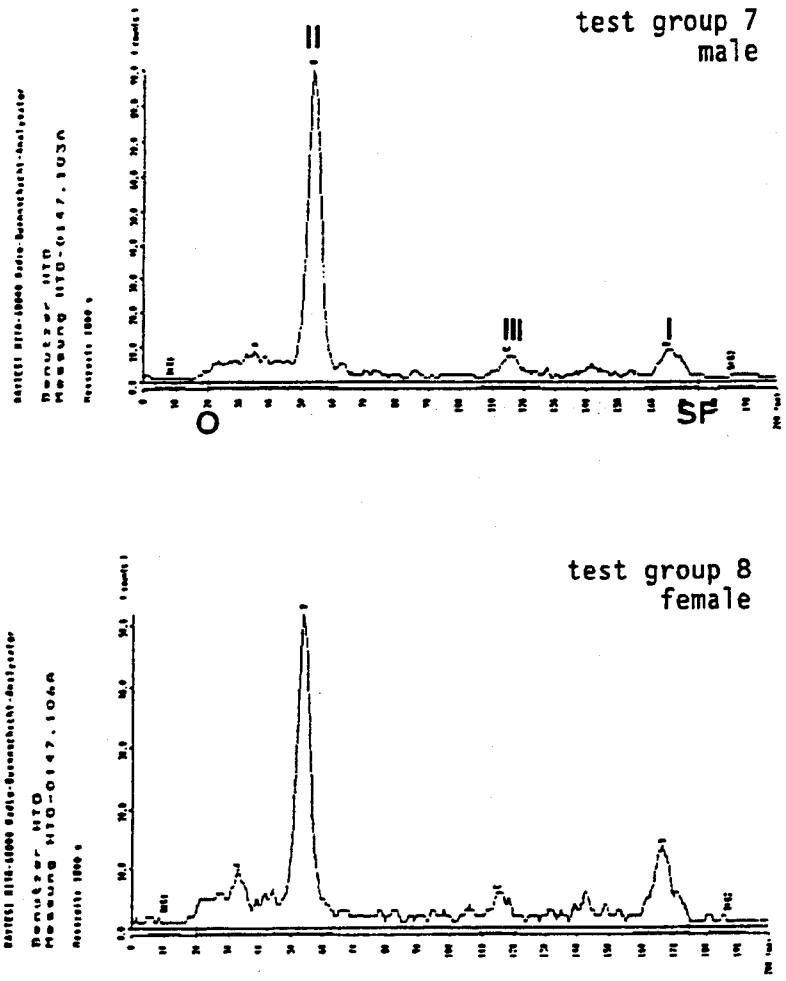


Fig.23 TLC chromatograms of the extracts of feces
(Test groups 7 and 8, 10 mg/kg)

These TLC chromatograms correspond to the 3-D plot in Fig.22.
TLC solvent system : A) $CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4,v/v
I. omethoate
II. O-desmethylated omethoate
III. N-methyl-2-(methylsulphinyl)acetamide

O = origine; SF = solvent front

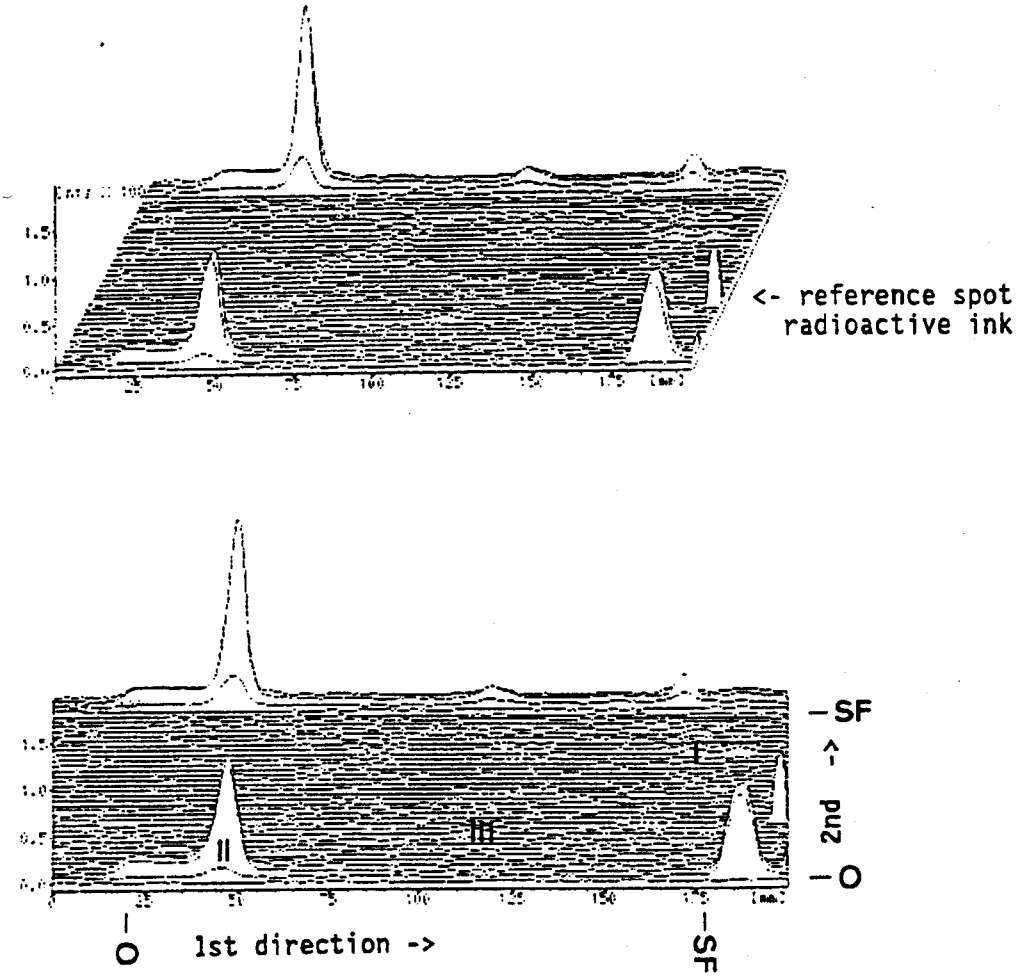


Fig.24 Identification of omethoate in extracts of feces by two-dimensional thin layer cochromatography

Sample: extract of feces of test 9 (10 mg/kg,p.o.,male)
TLC solvent system:1st;A)$CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4,v/v
2nd;B)$CHCl_3$:isopropanol=85:15,v/v
Reference compounds were detected with staining reagents.
I. omethoate
II. O-desmethylated omethoate
III. N-methyl-2-(methylsulphinyl)acetamide

O = origine; SF = solvent front

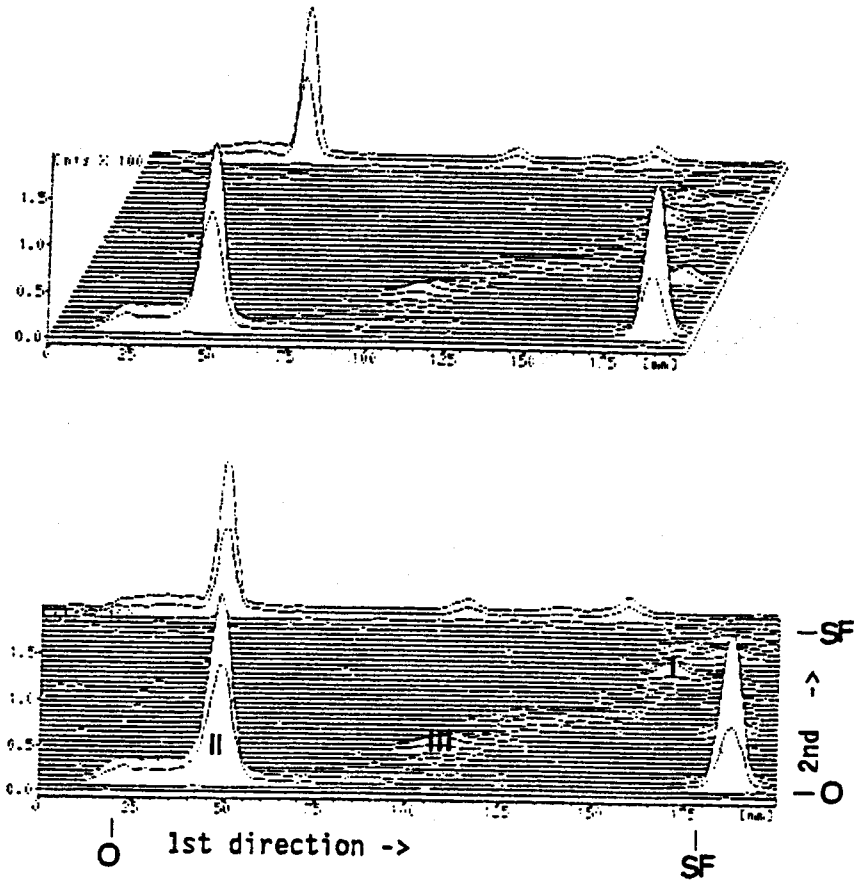


Fig.25 Identification of N-methyl-2-(methylsulphinyl)acetamide in extracts of feces by two-dimensional thin layer cochromatography

Sample: extract of feces of test 9 (10 mg/kg,p.o.,male)
TLC solvent system:1st;A)$CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4,v/v
2nd;C)$CHCl_3$:isopropanol=85:15,v/v
Reference compounds were detected with staining reagents.

I. omethoate
II. O-desmethylated omethoate
III. N-methyl-2-(methylsulphinyl)acetamide

O = origine; SF = solvent front

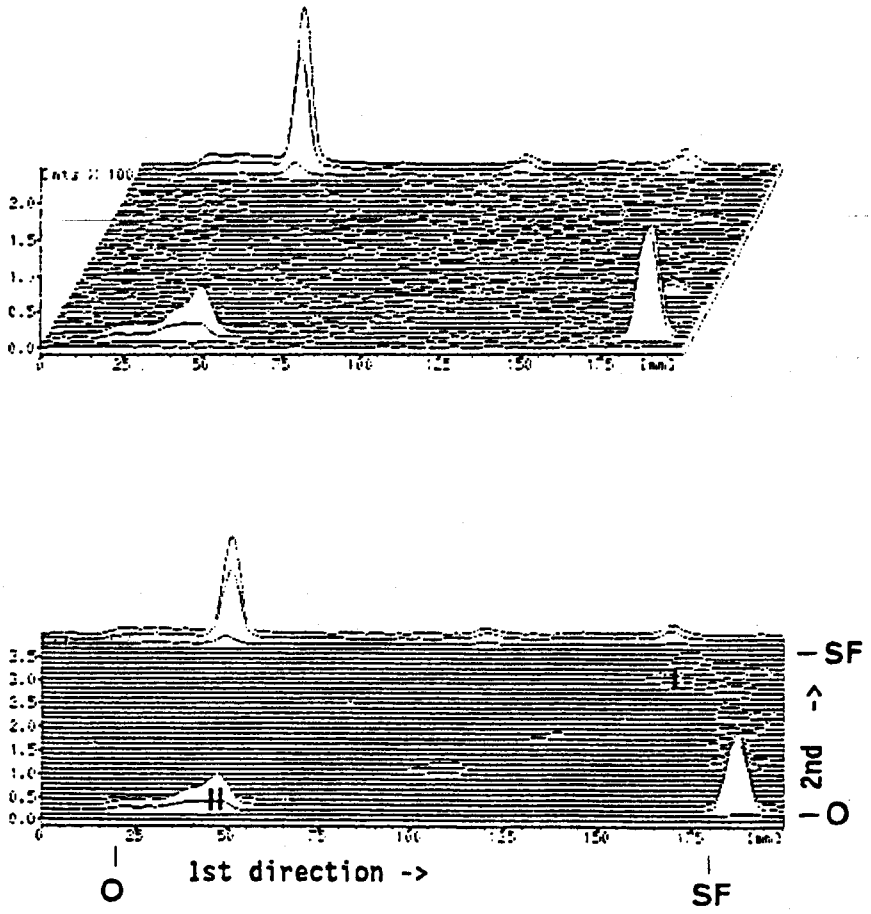


Fig.26 Identification of O-desmethyl metabolite in extracts of feces by two-dimensional thin layer cochromatography

Sample: extract of feces of test 9 (10 mg/kg,p.o.,male)
TLC solvent system:1st;A)$CHCl_3$:MeOH:CH_3COOH:H_2O=66:26:4:4,v/v
2nd;C)$CHCl_3$:isopropanol=85:15,v/v
Reference compounds were detected with staining reagents.
I. omethoate
II. O-desmethylated omethoate
III. N-methyl-2-(methylsulphinyl)acetamide

O = origine; SF = solvent front

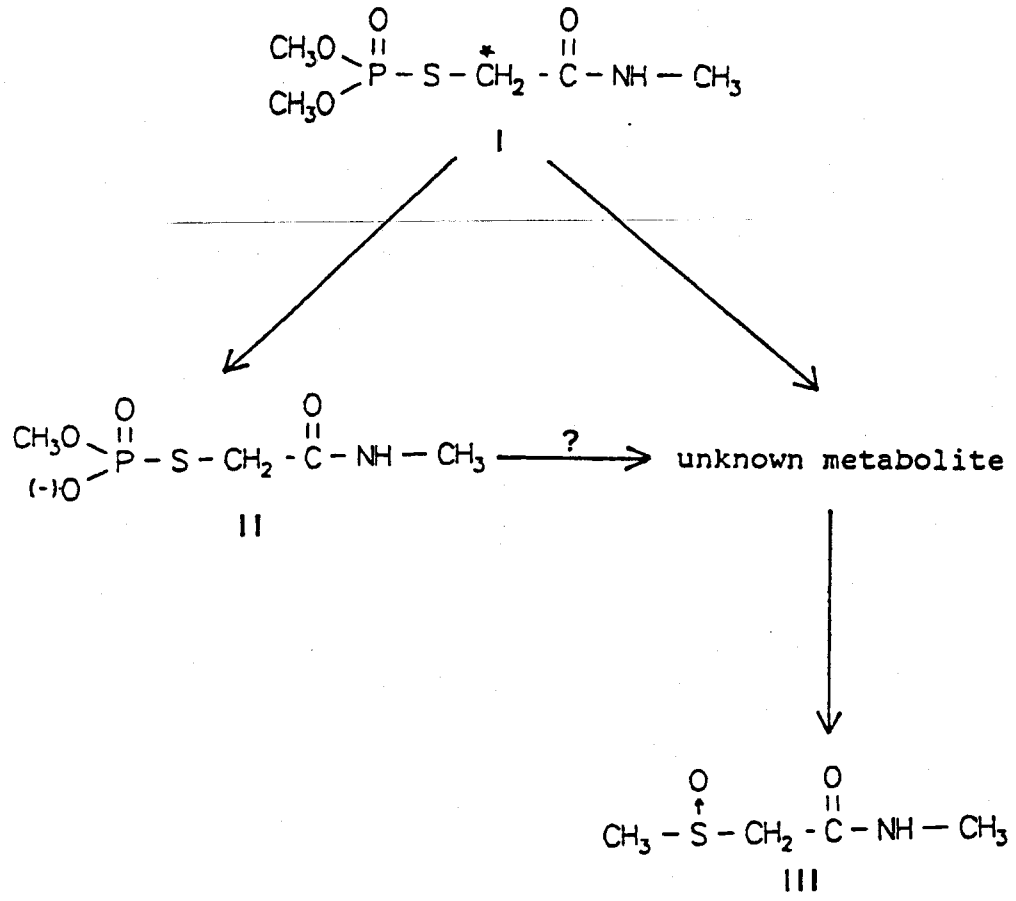


Fig. 27 Proposed Metabolic Pathway of Omethoate in the Rat
*: radiolabelled position

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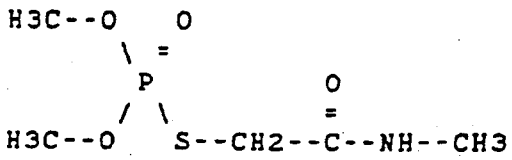
Appendix 1 Certification of the purity of non-radiolabelled parent compound

BAYER AG
PF-F/PBF-FEA 2

REFERENCE SUBSTANCE 890602ELB01

Common Name: Omethoate
Trade Mark: Folimat
Code Name: E 6876



Empirical formula: C5 H12 N O4 P S

Molar mass: 213.2 g/mole

Appearance: faint yellowish liquid

Identity: mass spectrum and elemental analysis complies

Characteristic:

Sum of impurities from HPLC (RP): 0.2 %, not ident.: 1x 0.2 %;
Sum of impurities from GLC: 0.8 %, not ident.: 1x 0.2 %, 1x 0.1 %;
Solvent from GLC head space analysis:
methanol: 0.01 %, traces of MTB and THF
TLC (phoshoric acid ester specific detection):
by-products not detectable;

CERTIFIED ASSAY: 99.2 %

Storage : Preserve in a refrigerator or at - 20 C.

Expiry date of the reference substance: June 1990

Wuppertal, Jun. 26, 1989

i.V.

- Dr. J. Krohn -
Head of Laboratory

Appendix 2 Certification of the purity and of the specific radioactivity of [methylene-^{14}C]omethoate

Labor Dr. Ecker
PF-F/CE-ME

12. Juli 1989

Certification of Purity

Compound: [methylene-^{14}C]Omethoate

Method: HPLC; column RP18, 7 µm; 250 mm length; 4 mm iD
flow 1ml/min; water-acetonitrile: 30-70

Radiochemical purity: 99.6%

Chemical purity: 99.4%

Specific radioactivity: 97.04 µCi/mg

Dr. W. Ecker

Appendix 3 The recovered radioactivity from the excreta and body at 48 h after single intravenous administration of 0.5 mg/kg to male rats (Test group 1)

Test Compound : omethoate
Rat : male
Test-No. : 1
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.450 [μCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

EXCRETION AND RESIDUES [% OF THE ADMINISTERED RADIOACTIVITY]

Animal-number	962	963	964	965	966	Mean value	SDEV	VC [%]	Number
Admin.-wght. [g]	216	217	218	212	218	216	2	1	5
Sacri.-wght. [g]	210	187	214	207	208	205	11	5	5
GIT	0.029	0.035	0.026	0.032	0.034	0.031	0.004	12	5
Body excl. GIT	0.520	0.278	0.671	0.341	0.274	0.417	0.174	42	5
Animal	0.549	0.313	0.697	0.373	0.308	0.448	0.170	38	5
Feces	2.408	1.437	1.374	3.173	1.934	2.065	0.747	36	5
Urine	97.452	87.379	100.197	95.450	97.882	95.672	4.933	5	5
Total (%)	100.409	89.129	102.268	98.996	100.124	98.185	5.197	5	5

Appendix 4 Time course of the recovered radioactivity in the urine after single intravenous administration of 0.5 mg/kg to male rats (Test group 1)

Test Compound : omethoate
Rat : male
Test-No. : 1
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.450 [μCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RENAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Numbers 962	963	964	965	966	Mean value	VC [%]
2	25.574	22.059	25.508	23.808	34.132	26.216	17.75
4	29.092	18.308	38.952	24.221	29.013	27.917	27.18
6	16.571	28.416	20.210	26.808	12.871	20.975	31.54
8	10.844	8.725	6.171	6.280	8.494	8.103	23.99
24	14.367	9.118	8.702	13.357	12.493	11.608	22.01
48	1.004	0.753	0.653	0.977	0.879	0.853	17.46
Total (%)	97.452	87.379	100.197	95.450	97.882	95.672	5.16

Appendix 5 Time course of the recovered radioactivity in the feces after single intravenous administration of 0.5 mg/kg to male rats (Test group 1)

Test Compound : omethoate
Rat : male
Test-No. : 1
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.450 [μCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

FECAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Numbers 962	963	964	965	966	Mean value	VC [%]
24	2.266	1.272	1.267	2.973	1.336	1.823	42.21
48	0.142	0.166	0.107	0.201	0.598	0.243	83.11
Total (%)	2.408	1.437	1.374	3.173	1.934	2.065	36.19

Appendix 6 Relative concentration P of the total radioactivity in organs and tissues at 48 h after single intravenous administration of 0.5 mg/kg to male rats (Test group 1)

Test Compound : omethoate
Rat : male
Test-No. : 1
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.450 [μCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY

ORGANS AND TISSUES	Animal numbers 962	963	964	965	966	Mean value	VC [%]
ERYTHROCYTE	0.00272	0.00234	0.00226	0.00267	0.00236	0.00247	8.47
PLASMA	0.00332	0.00291	0.00275	0.00308	0.00299	0.00301	7.01
SPLEEN	0.00634	0.00545	0.00520	0.00627	0.00523	0.00570	9.91
GIT	0.00309	0.00510	0.00242	0.00272	0.00296	0.00326	32.53
LIVER	0.01032	0.00971	0.00976	0.00952	0.00911	0.00969	4.52
KIDNEY	0.00912	0.00707	0.00746	0.00757	0.00777	0.00780	10.02
FAT	0.00233	0.00125	0.00340	0.00144	0.00132	0.00195	47.21
TESTES	0.01115	0.01124	0.00948	0.00995	0.00977	0.01032	7.93
MUSCLE	0.00221	0.00133	0.00201	0.00185	0.00181	0.00184	17.58
BONE	0.00260	0.00207	0.00189	0.00189	0.00182	0.00206	15.54
HEART	0.00396	0.00304	0.00314	0.00319	0.00319	0.00330	11.23
LUNG	0.00615	0.00474	0.00436	0.00476	0.00538	0.00508	13.79
BRAIN	0.00166	0.00123	0.00121	0.00139	0.00114	0.00133	15.87
THYROID	0.64954	0.59289	0.57163	0.56757	0.58029	0.59239	5.64
SKIN	0.01292	0.00286	0.00608	0.00575	0.00349	0.00622	64.28
CARCASS	0.00282	0.00248	0.00270	0.00273	0.00247	0.00264	5.88

Appendix 7 Time course of the total radioactivity in the plasma after single intravenous administration of 0.5 mg/kg to male rats (Test group 1)

Test Compound : omethoate
Rat : male
Test-No. : 1
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.450 [μCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY IN THE PLASMA

Time [h:min]	Animal Numbers 962	963	964	965	966	Mean value	VC [%]
0:05		1.36077			1.99153		
0:10	1.42412	1.42500	1.50466	1.50485	1.69134	1.50999	7.22
0:20	1.31000	1.37407	1.41112	1.44830	1.43148	1.39499	3.94
0:40	1.33956	1.38385	1.36398	1.38296	1.39689	1.37345	1.62
1	1.33219	1.31788	1.27484	1.32547	1.32891	1.31586	1.79
1:30	1.24262	1.18722	1.11029	1.14758	1.18507	1.17456	4.21
2	1.11442	1.01664	0.94579	1.01441	1.05136	1.02852	5.97
3	0.87778	0.72753	0.66859	0.72433	0.76419	0.75248	10.36
4	0.60252	0.48183	0.46498	0.51299	0.54431	0.52133	10.47
6	0.34437	0.23300	0.22248	0.25659	0.26898	0.26508	18.11
8	0.21754	0.12335	0.13537	0.21531	0.14855	0.16802	26.83
24	0.00879	0.00713	0.00722	0.00769	0.00720	0.00761	9.21
32	0.00747	0.00536	0.00506	0.00580	0.00494	0.00572	18.01
48	0.00370	0.00566	0.00299	0.00309	0.00388	0.00387	27.79

Appendix 8 Pharmacokinetic parameters from plasma curve analysis after single intravenous administration of 0.5 mg/kg to male rats (Test group 1)

Test Compound : omethoate
Rat : male
Test-No. : 1
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.450 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

PHARMACOKINETIC PARAMETERS

	Animal Number					Mean	VC
	962	963	964	965	966	value	[%]
AUC-Exp [h]	6.732	5.720	5.428	6.125	6.132	6.027	8
AUC-Fit [h]	7.087	6.527	5.774	6.468	6.452	6.462	29
T-a (25-75 %) [h]							
$T_{\frac{1}{2}}$ (B) [h]	18.6	89.3	19.2	18.2	28.6	34.8	89
CL [ml/min]	2.35	2.55	2.89	2.58	2.58	2.590	7
CL-R [ml/min]	2.33	2.50	2.92	2.49	2.59	2.57	9
MRT [h]	5.9	22.8	5.3	5.6	6.3	9.17	83
V-ss [l/kg]	0.83	3.49	0.92	0.86	0.98	1.42	82

Each value is calculated from plasma curve of average relative concentration.
AUC-exp : area under the blood concentration vs. time curve of experimental values calculated by data from the measured first time point to the last time point
AUC-fit : sum of AUC-exp and AUC integrated from time point 0 to 5 min and from 48 h to infinity by extrapolation.
T-a (25-75 %) : time for a rise in concentration from 25 % to 75% of C-max
CL : total plasma clearance
CL-R : renal clearance
MRT : mean residence time
V-ss : distribution volume in the steady state

Appendix 9 The recovered radioactivity from the excreta and body at 48 h after single intravenous administration of 0.5 mg/kg to female rats (Test group 2)

Test Compound : omethoate
Rat : female
Test-No. : 2
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 10.087 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

EXCRETION AND RESIDUES [% OF THE ADMINISTERED RADIOACTIVITY]

Animal-number	967	968	969	970	971	Mean value	SDEV	VC [%]	Number
Admin.-wght. [g]	195	200	200	198	200	199	2	1	5
Sacri.-wght. [g]	185	190	189	185	185	187	2	1	5
GIT	0.046	0.033	0.034	0.031	0.033	0.035	0.006	17	5
Body excl. GIT	0.354	0.396	0.371	0.339	0.397	0.372	0.026	7	5
Animal	0.400	0.429	0.405	0.370	0.430	0.407	0.025	6	5
Feces	5.922	3.173	2.995	1.96	2.438	3.298	1.543	47	5
Urine	83.552	79.483	90.238	83.481	88.104	84.972	4.240	5	5
Total (%)	89.874	83.085	93.638	85.811	90.972	88.676	4.207	5	5

Appendix 10 Time course of the recovered radioactivity in the urine after single intravenous administration of 0.5 mg/kg to female rats (Test group 2)

Test Compound : omethoate
Rat : female
Test-No. : 2
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 10.087 [μCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RENAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 967	968	969	970	971	Mean value	VC [%]
2	36.679	24.227	19.762	19.046	30.011	25.945	28.62
4	23.566	35.185	33.527	34.745	24.345	30.274	19.18
6	7.342	8.201	19.772	16.584	14.605	13.301	40.46
8	4.427	3.300	7.262	5.076	6.509	5.315	29.93
24	8.054	7.670	9.029	7.255	11.307	8.663	18.67
48	0.894	0.899	0.887	0.775	1.327	0.956	22.31
Total (%)	80.962	79.483	90.238	83.481	88.104	84.454	5.45

Appendix 11 Time course of the recovered radioactivity in the feces after single intravenous administration of 0.5 mg/kg to female rats (Test group 2)

Test Compound : omethoate
Rat : female
Test-No. : 2
Sacrifice: 48 h

Study-No.: MD1810019
Dose : 0.5 [mg/kg]
Admin.-RA: 10.087 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

FECAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 967	968	969	970	971	Mean value	VC [%]
24	5.601	2.622	2.824	1.848	2.206	3.020	49.37
48	0.321	0.551	0.171	0.111	0.232	0.277	61.91
Total (%)	5.922	3.173	2.995	1.960	2.438	3.298	46.79

Appendix 12 The recovered radioactivity from the excreta and body at 48 h after single intravenous administration of 0.5 mg/kg to female rats (Test group 2)

Test Compound : omethoate
Rat : female
Test-No. : 2
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 10.087 [μCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY

ORGANS AND TISSUES	Animal Number 967	968	969	970	971	Mean value	VC [%]
ERYTHROCYTE	0.00302	0.00292	0.00303	0.00256	0.00315	0.00293	7.66
PLASMA	0.00313	0.00260	0.00323	0.00250	0.00315	0.00292	11.78
SPLEEN	0.00567	0.00538	0.00562	0.00484	0.00549	0.00540	6.15
GIT	0.00465	0.00367	0.00356	0.00315	0.00339	0.00368	15.54
LIVER	0.00891	0.00892	0.00907	0.00869	0.01047	0.00921	7.78
KIDNEY	0.00770	0.00747	0.00799	0.00682	0.00752	0.00750	5.74
FAT	0.00121	0.00064	0.00115	0.00060	0.00100	0.00092	30.70
OVARIES	0.00226	0.00161	0.00354	0.00265	0.00411	0.00283	35.19
UTERUS	0.00476	0.00454	0.00226	0.00276	0.00234	0.00333	36.65
MUSCLE	0.00334	0.00343	0.00332	0.00284	0.00312	0.00321	7.36
BONE	0.00363	0.00291	0.00324	0.00235	0.00307	0.00304	15.41
HEART	0.00537	0.00437	0.00448	0.00417	0.00402	0.00448	11.74
LUNG	0.00477	0.00471	0.00503	0.00448	0.00509	0.00482	5.14
BRAIN	0.00211	0.00192	0.00200	0.00188	0.00203	0.00199	4.62
THYROID	0.47433	0.44791	0.42314	0.23895	0.33794	0.38445	25.00
SKIN	0.00488	0.00537	0.00430	0.00362	0.00666	0.00497	23.15
CARCASS	0.00333	0.00379	0.00366	0.00354	0.00327	0.00351	6.23

Appendix 13 Time course of the total radioactivity in the plasma after single intravenous administration of 0.5 mg/kg to female rats (Test group 2)

Test Compound : omethoate
Rat : female
Test-No. : 2
Sacrifice: 48 h
Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 10.087 [µCi/Anim]
Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY IN THE PLASMA

Time [h:min]	Animal Number 967	968	969	970	971	Mean value	VC [%]
0:05	1.51349	1.39615		1.46498	1.57121	1.48646	4.99
0:10	1.32395	1.32738	1.39482		1.48887	1.38376	5.59
0:20	1.34984	1.38607	1.46022	1.33525		1.38284	4.04
0:40	1.30554	1.37491	1.36212	1.27154	1.34412	1.33165	3.20
1		1.24347	1.16009	1.14283	1.24296	1.19734	4.46
1:30	0.92364	1.12714	1.08649	0.96510	1.05206	1.03088	8.21
2	0.78937	0.93702	0.90996	0.89736	0.90729	0.88820	6.44
3		0.67223	0.71555	0.56882	0.58925	0.63646	10.86
4	0.27045	0.45285	0.43338	0.37466	0.38885	0.38404	18.50
6	0.13360	0.17320	0.20705	0.15703	0.19216	0.17261	16.73
8	0.07692	0.08305	0.10057	0.09781	0.11718	0.09511	16.63
24	0.00957	0.00765	0.01405	0.00751	0.00851	0.00946	28.49
32	0.00772	0.00611	0.00770	0.00758	0.00528	0.00708	11.43
48	0.00569	0.00374	0.00537	0.00425	0.00680	0.00517	23.39

Appendix 14 Pharmacokinetic parameters from plasma curve analysis after single intravenous administration of 0.5 mg/kg to female rats (Test group 2)

Test Compound : omethoate
Rat : female
Test-No. : 2
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 10.087 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

PHARMACOKINETIC PARAMETERS

	Animal Number					Mean	VC
	967	968	969	970	971	value	[%]
AUC-Exp [h]	4.391	5.165	5.353	4.834	5.240	4.997	8
AUC-Fit [h]	4.776	5.401	5.719	5.127	6.255	5.456	10
T-a (25-75 %) [h]							
T½ (β) [h]	32.6	23.2	18.5	27.2	94.9	39.3	80
CL [ml/min]	3.49	3.09	2.91	3.25	2.66	3.08	10
CL-R [ml/min]	2.99	2.51	2.69	2.81	2.74	2.75	6
MRT [h]	9.7	5.9	6.5	7.3	30.2	11.9	87
V-ss [l/kg]	2.03	1.10	1.14	1.42	4.83	2.10	75

Each value is calculated from plasma curve of average relative concentration.
AUC-exp : area under the blood concentration vs. time curve of experimental values calculated by data from the measured first time point to the last time point
AUC-fit : sum of AUC-exp and AUC integrated from time point 0 to 5 min and from 48 h to infinity by extrapolation.
T-a (25-75 %) : time for a rise in concentration from 25 % to 75% of C-max
CL : total plasma clearance
CL-R : renal clearance
MRT : mean residence time
V-ss : distribution volume in the steady state

Appendix 15 The recovered radioactivity from the excreta and body at 48 h after single oral administration of 0.5 mg/kg to male rats (Test group 3)

Test Compound : omethoate
Rat : male
Test-No. : 3
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.622 [μCi/Anim]

Study-Dir.: T.Hoshino

Date: Dec-15-89

EXCRETION AND RESIDUES [% OF THE ADMINISTERED RADIOACTIVITY]

Animal-number	972	973	974	975	976	Mean value	SDEV	VC [%]	Number
Admin.-wght. [g]	208	202	192	204	192	200	7	4	5
Sacri.-wght. [g]	206	198	189	207	193	199	8	4	5
GIT	0.031	0.031	0.030	0.030	0.032	0.031	0.001	3	5
Body excl. GIT	0.294	0.282	0.281	0.285	0.295	0.287	0.007	2	5
Animal	0.325	0.313	0.311	0.315	0.327	0.318	0.007	2	5
Feces	2.607	1.732	1.549	1.797	3.613	2.260	0.859	38	5
Urine	95.065	94.543	94.170	96.153	91.933	94.373	1.555	2	5
Total (%)	97.997	96.588	96.030	98.265	95.873	96.951	1.114	1	5

Appendix 16 Time course of the recovered radioactivity in the urine after single oral administration of 0.5 mg/kg to male rats (Test group 3)

Test Compound : omethoate
Rat : male
Test-No. : 3
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.622 [μCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RENAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Numbers 972	973	974	975	976	Mean value	VC [%]
2	27.066	32.313	37.501	0.000	24.854	24.347	59
4	24.273	23.477	33.665	55.786	31.637	33.768	39
6	24.456	16.435	10.689	25.084	17.382	18.809	32
8	9.628	13.838	5.947	5.803	8.252	8.694	38
24	9.018	7.921	5.902	8.876	9.146	8.173	17
48	0.624	0.558	0.466	0.605	0.662	0.583	13
Total (%)	95.065	94.543	94.170	96.153	91.933	94.373	2

Appendix 17 Time course of the recovered radioactivity in the feces after single oral administration of 0.5 mg/kg to male rats (Test group 3)

Test Compound : omethoate
Rat : male
Test-No. : 3
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.622 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

FECAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 972	973	974	975	976	Mean value	VC [%]
24	2.438	1.632	1.453	1.693	3.147	2.072	34
48	0.170	0.099	0.097	0.104	0.466	0.187	85
Total (%)	2.607	1.732	1.549	1.797	3.613	2.260	38

Appendix 18 Relative concentration P of the total radioactivity in organs and tissues at 48 h after single oral administration of 0.5 mg/kg to male rats (Test group 3)

Test Compound : omethoate
Rat : male
Test-No. : 3
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.622 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY

ORGANS AND TISSUES	Animal Number 972	973	974	975	976	Mean value	VC [%]
ERYTHROCYTE	0.00294	0.00285	0.00292	0.00297	0.00311	0.00296	3
PLASMA	0.00253	0.00261	0.00243	0.00291	0.00258	0.00261	7
SPLEEN	0.00536	0.00513	0.00511	0.00534	0.00553	0.00529	3
GIT	0.00353	0.00292	0.00282	0.00285	0.00307	0.00304	10
LIVER	0.01093	0.00867	0.00936	0.01087	0.00967	0.00990	10
KIDNEY	0.00838	0.00699	0.00790	0.00769	0.00741	0.00767	7
FAT	0.00189	0.00233	0.00228	0.00246	0.00203	0.00220	11
TESTES	0.00900	0.00948	0.00695	0.00892	0.00961	0.00879	12
MUSCLE	0.00221	0.00175	0.00204	0.00179	0.00168	0.00189	12
BONE	0.00367	0.00382	0.00362	0.00398	0.00319	0.00365	8
HEART	0.00342	0.00332	0.00338	0.00328	0.00334	0.00335	2
LUNG	0.00606	0.00600	0.00527	0.00605	0.00569	0.00581	6
BRAIN	0.00201	0.00186	0.00177	0.00174	0.00169	0.00181	7
THYROID	0.60646	0.32463	0.32334	0.31439	0.32529	0.37882	34
SKIN	0.00335	0.00326	0.00313	0.00318	0.00405	0.00340	11
CARCASS	0.00248	0.00250	0.00242	0.00248	0.00250	0.00248	1

Appendix 19 Time course of the total radioactivity in the plasma after single oral administration of 0.5 mg/kg to male rats (Test group 3)

Test Compound : omethoate
Rat : male
Test-No. : 3
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.622 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY IN THE PLASMA

Time [h:min]	Animal Number 972	973	974	975	976	MEAN value	VC [%]
0:05	0.11700	0.12586	0.21293	0.16601	0.12237	0.14883	27
0:10	0.52077	0.51419	0.67746	0.66707	0.52471	0.58084	14
0:20	0.84361	0.82988	1.06537	1.01194	0.88775	0.92771	11
0:40	1.16198		1.23514	1.19500	1.14080	1.18323	3
1	1.19289	1.14737		1.18428	1.16390	1.17211	2
1:30	1.09373	1.06007	0.95794	1.06263	1.07311	1.04950	5
2	0.96401	0.89170	0.76797	0.87345	0.93584	0.88659	8
3	0.72272	0.68785	0.50540	0.59688	0.69883	0.64234	14
4	0.73455	0.44649	0.30889	0.38409	0.46629	0.46806	34
6	0.22863	0.20411	0.14842	0.17021	0.24105	0.19848	20
8	0.12242	0.10646	0.06138	0.08482	0.11521	0.09806	25
24	0.00619	0.00639	0.00597	0.00593	0.00559	0.00602	5
32	0.00520	0.00518	0.00457	0.00553	0.00439	0.00497	10
48	0.00313	0.00291	0.00292	0.00336	0.00308	0.00308	6

Appendix 20 Pharmacokinetic parameters from plasma curve analysis after single oral administration of 0.5 mg/kg to male rats (Test group 3)

Test Compound : omethoate
Rat : male
Test-No. : 3
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.622 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

PHARMACOKINETIC PARAMETERS

	Animal Number					Mean	VC
	972	973	974	975	976	value	[%]
AUC-Exp [h]	5.152	4.779	4.049	4.575	5.016	4.714	9
AUC-Fit [h]	5.266	4.872	4.155	4.721	5.146	4.832	9
T-a (25-75 %) [h]	0.3	0.8	0.2	0.2	0.2	0.3	84
$T_{1/2}$ (B) [h]	24.0	20.9	23.5	28.0	28.3	24.9	13
CL [ml/min]	3.17	3.42	4.01	3.53	3.24	3.47	10
CL-R [ml/min]	3.07	3.29	3.87	3.50	3.05	3.36	10
MRT [h]	6.2	5.9	6.0	6.9	6.5	6.3	6
V-ss [l/kg]	1.18	1.22	1.44	1.45	1.27	1.3	10
P-Max	1.193	1.147	1.235	1.195	1.164	1.187	3
T-Max [h]	1.00	1.00	0.67	0.67	1.00	0.87	21

Each value is calculated from plasma curve of average relative concentration.
AUC-exp : area under the blood concentration vs. time curve of experimental values calculated by data from the measured first time point to the last time point
AUC-fit : sum of AUC-exp and AUC integrated from time point 0 to 5 min and from 48 h to infinity by extrapolation.
T-a (25-75 %) : time for a rise in concentration from 25 % to 75% of C-max
CL : total plasma clearance
CL-R : renal clearance
MRT : mean residence time
V-ss : distribution volume in the steady state
P-max : maximum level of the plasma concentration
T-max : time of the maximum level of the plasma concentration after oral administration. T-max was evaluated from experimental time points.

Appendix 21 The recovered radioactivity from the excreta and body at 48 h after single oral administration of 0.5 mg/kg to female rats (Test group 4)

Test Compound : omethoate
Rat : female
Test-No. : 4
Sacrifice: 48 h
Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.639 [µCi/Anim]
Study-Dir.: T.Hoshino
Date: Dec-15-89

EXCRETION AND RESIDUES [% OF THE ADMINISTERED RADIOACTIVITY]

Animal-number	977	978	979	980	981	Mean value	SDEV	VC [%]	Number
Admin.-wght. [g]	180	184	187	180	180	182	3	2	5
Sacri.-wght. [g]	186	190	200	187	184	189	6	3	5
GIT	0.027	0.028	0.035	0.026	0.025	0.028	0.004	14	5
Body excl. GIT	0.271	0.315	0.349	0.348	0.277	0.312	0.037	12	5
Animal	0.298	0.343	0.384	0.374	0.302	0.340	0.040	12	5
Feces	3.008	1.888	4.921	2.558	1.875	2.850	1.253	44	5
Urine	89.472	95.249	83.442	96.853	97.706	92.544	6.017	7	5
Total (%)	92.778	97.480	88.747	99.785	99.883	95.735	4.854	5	5

Appendix 22 Time course of the recovered radioactivity in the urine after single oral administration of 0.5 mg/kg to female rats (Test group 4)

Test Compound : omethoate
Rat : female
Test-No. : 4
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.639 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RENAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 977	978	979	980	981	Mean value	VC [%]
2	25.392	20.483	16.972	32.223	29.359	24.886	25
4	32.478	34.050	33.384	29.970	37.374	33.451	8
6	15.757	19.878	13.464	15.694	14.645	15.888	15
8	6.814	8.861	8.862	8.532	7.806	8.175	11
24	7.843	10.704	9.920	9.626	7.877	9.194	14
48	1.188	1.274	0.839	0.808	0.645	0.951	28
Total (%)	89.472	95.249	83.442	96.853	97.706	92.545	7

Appendix 23 Time course of the recovered radioactivity in the feces after single oral administration of 0.5 mg/kg to female rats (Test group 4)

Test Compound : omethoate
Rat : female
Test-No. : 4
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.639 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

FECAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 977	978	979	980	981	Mean value	VC [%]
24	2.699	1.723	0.843	2.072	1.779	1.824	37
48	0.308	0.165	4.078	0.485	0.096	1.026	167
Total (%)	3.008	1.888	4.921	2.558	1.875	2.850	44

Appendix 24 The recovered radioactivity from the excreta and body at 48 h after single oral administration of 0.5 mg/kg to female rats (Test group 4)

Test Compound : omethoate
Rat : female
Test-No. : 4
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.639 [μCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY

ORGANS AND TISSUES	Animal Number 977	978	979	980	981	Mean value	VC [%]
ERYTHROCYTE	0.00240	0.00297	0.00329	0.00230	0.00161	0.00251	26
PLASMA	0.00276	0.00379	0.00400	0.00296	0.00298	0.00330	17
SPLEEN	0.00589	0.00716	0.00647	0.00692	0.00496	0.00628	14
GIT	0.00217	0.00242	0.00270	0.00208	0.00233	0.00234	10
LIVER	0.00841	0.00977	0.01015	0.00993	0.00968	0.00959	7
KIDNEY	0.00681	0.00849	0.01079	0.00821	0.00737	0.00833	18
FAT	0.00130	0.00196	0.00210	0.00176	0.00120	0.00166	24
OVARIES	0.00337	0.00359	0.00371	0.00319	0.00317	0.00340	7
UTERUS	0.00688	0.00945	0.00939	0.00458	0.01019	0.00810	29
MUSCLE	0.00178	0.00256	0.00283	0.00246	0.00179	0.00228	21
BONE	0.00174	0.00749	0.00397	0.00262	0.00147	0.00346	71
HEART	0.00347	0.00422	0.00422	0.00370	0.00334	0.00379	11
LUNG	0.00558	0.00669	0.00655	0.00611	0.00466	0.00592	14
BRAIN	0.00154	0.00273	0.00232	0.00186	0.00159	0.00201	25
THYROID	0.42082	0.69115	0.46895	0.51215	0.49898	0.51841	20
SKIN	0.00348	0.00366	0.00490	0.00355	0.00300	0.00372	19
CARCASS	0.00251	0.00295	0.00331	0.00284	0.00269	0.00286	11

Appendix 25 Time course of the total radioactivity in the plasma after single oral administration of 0.5 mg/kg to female rats (Test group 4)

Test Compound : omethoate
Rat : female
Test-No. : 4
Sacrifice: 48 h
Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.639 [µCi/Anim]
Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY IN THE PLASMA

Time [h:min]	Animal Number 977	978	979	980	981	Mean value	VC [%]
0:05	0.38534		0.15894		0.08235	0.20888	75
0:10	0.82986	0.53581	0.55674	0.65470	0.29571	0.57456	34
0:20	1.12737	0.82974	0.97049	1.06308	0.67890	0.93392	19
0:40	1.27210		1.15117	1.22044	1.02458	1.16707	9
1		1.17636	1.18051	1.55322	1.19406	1.27604	14
1:30	1.04101	1.10254	1.07828	1.09557	1.08768	1.08102	2
2	0.85730	1.03569	0.95496		0.97315	0.95528	8
3	0.59934	0.79705	0.70507	0.70164	0.61687	0.68399	12
4	0.39243	0.52853	0.48091	0.48695	0.41860	0.46148	12
6	0.21160		0.21286	0.25150	0.17698	0.21324	14
8	0.08730	0.11805	0.12133	0.12852	0.10267	0.11157	15
24	0.00683	0.01025	0.01115	0.00736	0.00642	0.00840	26
32	0.00550	0.00714	0.00759	0.00611	0.00496	0.00626	18
48	0.00337	0.00436	0.00442	0.00353	0.00363	0.00386	13

Appendix 26 Pharmacokinetic parameters from plasma curve analysis after single oral administration of 0.5 mg/kg to female rats (Test group 4)

Test Compound : omethoate
Rat : female
Test-No. : 4
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.639 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

PHARMACOKINETIC PARAMETERS

	Animal Number					Mean	VC
	977	978	979	980	981	value	[%]
AUC-Exp. [h]	4.749	5.410	5.271	5.438	4.631	5.100	7
AUC-Fit [h]	4.878	5.533	5.392	5.553	4.789	5.229	7
T-a (25-75 %) [h]	0.2	0.8	0.2	0.4	0.4	0.4	64
$T_{\frac{1}{2}}$ (B) [h]	23.4	19.8	18.3	22.3	29.9	22.8	20
CL [ml/min]	3.42	3.01	3.09	3.00	3.48	3.2	7
CL-R [ml/min]	3.13	2.93	2.64	2.97	3.51	3.04	11
MRT [h]	6.2	6.7	6.6	6.2	7.4	6.6	7
V-ss [l/kg]	1.28	1.20	1.22	1.12	1.55	1.274	13
P-Max	1.272	1.176	1.181	1.553	1.194	1.275	13
T-Max [h]	0.67	1.00	1.00	1.00	1.00	0.93	16

Each value is calculated from plasma curve of average relative concentration.
AUC-exp : area under the blood concentration vs. time curve of experimental values calculated by data from the measured first time point to the last time point
AUC-fit : sum of AUC-exp and AUC integrated from time point 0 to 5 min and from 48 h to infinity by extrapolation.
T-a (25-75 %) : time for a rise in concentration from 25 % to 75% of C-max
CL : total plasma clearance
CL-R : renal clearance
MRT : mean residence time
V-ss : distribution volume in the steady state
P-max : maximum level of the plasma concentration
T-max : time of the maximum level of the plasma concentration after oral administration. T-max was evaluated from experimental time points.

Appendix 27 The recovered radioactivity from the excreta and body at 48 h after consecutive oral administration of 0.5 mg/kg to male rats (Test group 5)

Test Compound : omethoate
Rat : male
Test-No. : 5
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.697 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

EXCRETION AND RESIDUES [% OF THE ADMINISTERED RADIOACTIVITY]

Animal-number	982	983	984	985	986	Mean value	SDEV	VC [%]	Number
Admin.-wght. [g]	199	202	201	193	192	197	5	2	5
Sacri.-wght. [g]	196	195	196	194	186	193	4	2	5
GIT	0.025	0.030	0.029	0.028	0.028	0.028	0.002	7	5
Body excl. GIT	0.309	0.304	0.316	0.320	0.323	0.314	0.008	2	5
Animal	0.334	0.334	0.345	0.348	0.351	0.342	0.008	2	5
Feces	2.318	3.365	2.830	1.977	3.016	2.701	0.554	21	5
Urine	88.642	87.204	92.525	89.096	89.530	89.399	1.954	2	5
Total (%)	91.294	90.903	95.700	91.421	92.897	92.443	1.972	2	5

Appendix 28 Time course of the recovered radioactivity in the urine after consecutive oral administration of 0.5 mg/kg to male rats (Test group 5)

Test Compound : omethoate
Rat : male
Test-No. : 5
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.697 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RENAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 982	983	984	985	986	Mean value	VC [%]
2	31.892	24.816	15.197	28.697	32.614	26.643	27
4	32.371	24.971	41.801	16.704	30.425	29.254	32
6	12.641	24.408	16.536	26.407	14.259	18.850	33
8	5.297	5.004	8.451	7.440	6.178	6.474	22
24	5.878	7.399	9.855	9.207	5.618	7.591	25
48	0.564	0.606	0.685	0.640	0.436	0.586	16
Total (%)	88.642	87.204	92.525	89.096	89.530	89.399	2

Appendix 29 Time course of the recovered radioactivity in the feces after consecutive oral administration of 0.5 mg/kg to male rats (Test group 5)

Test Compound : omethoate
Rat : male
Test-No. : 5
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.697 [μCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

FECAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 982	983	984	985	986	Mean value	VC [%]
24	2.187	2.977	2.532	1.775	2.841	2.463	20
48	0.131	0.388	0.298	0.202	0.175	0.239	43
Total (%)	2.318	3.365	2.830	1.977	3.016	2.701	21

Appendix 30 Relative concentration P of the total radioactivity in organs and tissues at 48 h after consecutive oral administration of 0.5 mg/kg to male rats (Test group 5)

Test Compound : omethoate
Rat : male
Test-No. : 5
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.697 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY

ORGANS AND TISSUES	Animal Number 982	983	984	985	986	Mean value	VC [%]
ERYTHROCYTE	0.00195	0.00205	0.00246	0.00250	0.00213	0.00222	11
PLASMA	0.00237	0.00254	0.00243	0.00269	0.00354	0.00271	18
SPLEEN	0.00532	0.00478	0.00535	0.00638	0.00499	0.00536	11
GIT	0.00232	0.00292	0.00279	0.00236	0.00259	0.00260	10
LIVER	0.00901	0.00788	0.00873	0.00879	0.00839	0.00856	5
KIDNEY	0.00538	0.00563	0.00659	0.00709	0.00546	0.00603	13
FAT	0.00372	0.00186	0.00214	0.00177	0.00194	0.00229	36
TESTES	0.00964	0.00910	0.01061	0.01057	0.00832	0.00965	10
MUSCLE	0.00219	0.00238	0.00234	0.00240	0.00270	0.00240	8
BONE	0.00236	0.00207	0.00283	0.00266	0.00412	0.00281	28
HEART	0.00337	0.00361	0.00414	0.00336	0.00347	0.00359	9
LUNG	0.00458	0.00501	0.00586	0.00556	0.00483	0.00517	10
BRAIN	0.00127	0.00126	0.00149	0.00150	0.00144	0.00139	8
THYROID	0.39820	0.23646	0.46875	0.39218	0.19922	0.33896	34
SKIN	0.00352	0.00334	0.00340	0.00289	0.00339	0.00331	7
CARCASS	0.00304	0.00301	0.00305	0.00358	0.00344	0.00322	8

Appendix 31 Time course of the total radioactivity in the plasma after consecutive oral administration of 0.5 mg/kg to male rats (Test group 5)

Test Compound : omethoate
Rat : male
Test-No. : 5
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.697 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY IN THE PLASMA

Time [h:min]	Animal Number 982	983	984	985	986	Mean value	VC [%]
0:05	0.08317	0.07019	0.19469	0.19355	0.14374	0.13707	43
0:10	0.45961	0.26180	0.28821	0.30261	0.77566	0.41758	51
0:20	0.83957		0.76055	0.77268	0.61414	0.74673	13
0:40	1.13283	1.14460	1.13675	1.21220	1.08262	1.14180	4
1	1.12411	1.15542	1.14647	1.17534	1.09622	1.13951	3
1:30	0.96932	1.01312	1.07390	1.07358	0.97908	1.02180	5
2	0.79501	0.82925	0.94929	0.91605	0.80018	0.85795	8
3	0.50668	0.52314	0.67159	0.66350	0.55724	0.58443	13
4	0.30858	0.32834	0.48698			0.37463	26
6	0.13282	0.12972	0.23128		0.13179	0.15640	32
8	0.06471	0.07934	0.10767	0.10808	0.05697	0.08335	29
24	0.00566	0.00757	0.00691	0.00646	0.00462	0.00624	18
32	0.00449	0.00638	0.00532	0.00801	0.00449	0.00574	26
48	0.00348	0.00352	0.00346	0.00366	0.00302	0.00343	7

Appendix 32 Pharmacokinetic parameters from plasma curve analysis after consecutive oral administration of 0.5 mg/kg to male rats (Test group 5)

Test Compound : omethoate
Rat : male
Test-No. : 5
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.697 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

PHARMACOKINETIC PARAMETERS

	Animal Number					Mean	VC
	982	983	984	985	986	value	[%]
AUC-Exp. [h]	3.936	4.083	4.952	4.935	3.869	4.355	12
AUC-Fit [h]	4.411	4.196	5.080	5.089	4.040	4.563	11
T-a (25-75 %) [h]	0.2	0.2	0.3	0.3	0.3	0.2	25
$T_{\frac{1}{2}}$ (B) [h]	35.3	21.2	24.3	25.4	37.0	28.6	25
CL [ml/min]	4.05	3.97	3.28	3.27	4.13	3.74	11
CL-R [ml/min]	3.75	3.56	3.11	3.00	3.85	3.45	11
MRT [h]	8.3	6.7	6.5	7.1	8.1	7.4	11
V-ss [l/kg]	2.02	1.60	1.28	1.40	2.02	1.66	21
P-Max	1.133	1.155	1.146	1.212	1.096	1.148	4
T-Max [h]	0.67	1.00	1.00	0.67	1.00	0.87	21

1) Each value is calculated from plasma curve of average relative concentration.
2) AUC-exp : area under the blood concentration vs. time curve of experimental values calculated by data from the measured first time point to the last time point
3) AUC-fit : sum of AUC-exp and AUC integrated from time point 0 to 5 min and from 48 h to infinity by extrapolation.
4) T-a (25-75 %) : time for a rise in concentration from 25 % to 75% of C-max
5) CL : total plasma clearance
6) CL-R : renal clearance
7) MRT : mean residence time
8) V-ss : distribution volume in the steady state
9) P-max : maximum level of the plasma concentration
10) T-max : time of the maximum level of the plasma concentration after oral administration. T-max was evaluated from experimental time points.

Appendix 33 The recovered radioactivity from the excreta and body at 48 h after consecutive oral administration of 0.5 mg/kg to female rats (Test group 6)

Test Compound : omethoate Study-No.: M01810019 Study-Dir.: T.Hoshino
Rat : female Dose : 0.5 [mg/kg]
Test-No. : 6 Admin.-RA: 9.685 [µCi/Anim]
Sacrifice: 48 h Date: Dec-15-89

EXCRETION AND RESIDUES [% OF THE ADMINISTERED RADIOACTIVITY]

Animal-number	987	988	989	990	991	Mean value	SDEV	VC [%]	Number
Admin.-wght. [g]	174	191	185	182	176	182	7	4	5
Sacri.-wght. [g]	170	194	179	180	169	178	10	6	5
GIT	0.034	0.058	0.028	0.043	0.037	0.040	0.011	29	5
Body excl. GIT	0.282	0.315	0.271	0.283	0.248	0.280	0.024	9	5
Animal	0.316	0.373	0.299	0.326	0.285	0.320	0.034	11	5
Feces	1.755	4.066	5.772	3.726	3.248	3.713	1.450	39	5
Urine	93.374	89.890	90.234	82.875	79.942	87.263	5.611	6	5
Total (%)	95.445	94.329	96.305	86.927	83.475	91.296	5.739	6	5

Appendix 34 Time course of the recovered radioactivity in the urine after consecutive oral administration of 0.5 mg/kg to female rats (Test group 6)

Test Compound : omethoate
Rat : female
Test-No. : 6
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.685 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RENAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 987	988	989	990	991	Mean value	VC [%]
2	30.373	27.085	40.235	19.468	20.964	27.625	30
4	29.559	25.472	25.314	17.445	26.316	24.821	18
6	14.783	16.020	11.280	21.724	14.424	15.646	24
8	7.814	6.966	5.924	11.168	7.761	7.927	25
24	10.013	12.869	6.583	11.713	9.322	10.100	24
48	0.832	1.478	0.898	1.356	1.155	1.144	25
Total (%)	93.374	89.890	90.234	82.875	79.942	87.263	6

Appendix 35 Time course of the recovered radioactivity in the feces after consecutive oral administration of 0.5 mg/kg to female rats (Test group 6)

Test Compound : omethoate Study-No.: M01810019 Study-Dir.: T.Hoshino
Rat : female Dose : 0.5 [mg/kg]
Test-No. : 6 Admin.-RA: 9.685 [μCi/Anim]
Sacrifice: 48 h Date: Dec-15-89

FECAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 987	988	989	990	991	Mean value	VC [%]
24	1.644	3.844	2.450	3.558	2.360	2.771	332
48	0.111	0.223	3.322	0.168	0.888	0.942	145
Total (%)	1.755	4.066	5.772	3.726	3.248	3.713	39

Appendix 36 The recovered radioactivity from the excreta and body at 48 h after consecutive oral administration of 0.5 mg/kg to female rats (Test group 6)

Test Compound : omethoate
Rat : female
Test-No. : 6
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.685 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY

ORGANS AND TISSUES	Animal Number 987	988	989	990	991	Mean value	VC [%]
ERYTHROCYTE	0.00267	0.00292	0.00236	0.00281	0.00229	0.00261	11
PLASMA	0.00343	0.00346	0.00308	0.00333	0.00283	0.00323	8
SPLEEN	0.00506	0.00579	0.00519	0.00535	0.00449	0.00517	9
GIT	0.00299	0.00611	0.00233	0.00340	0.00370	0.00371	39
LIVER	0.00777	0.00761	0.00920	0.00872	0.00776	0.00821	9
KIDNEY	0.00654	0.00783	0.00777	0.00729	0.00647	0.00718	9
FAT	0.00144	0.00396	0.00149	0.00178	0.00110	0.00195	59
OVARIES	0.00369	0.00388	0.00280	0.00397	0.00211	0.00329	25
UTERUS	0.00304	0.00259	0.00146	0.00406	0.00487	0.00321	41
MUSCLE	0.00205	0.00272	0.00181	0.00220	0.00164	0.00208	20
BONE	0.00296	0.00285	0.00224	0.00277	0.00204	0.00257	16
HEART	0.00334	0.00377	0.00320	0.00354	0.00307	0.00338	8
LUNG	0.00536	0.00590	0.00471	0.00588	0.00524	0.00542	9
BRAIN	0.00109	0.00145	0.00120	0.00148	0.00112	0.00127	15
THYROID	0.48665	0.22411	0.29528	0.34986	0.44661	0.36050	30
SKIN	0.00254	0.00279	0.00319	0.00305	0.00257	0.00283	10
CARCASS	0.00313	0.00346	0.00262	0.00285	0.00249	0.00291	14

Appendix 37 Time course of the total radioactivity in the plasma after consecutive oral administration of 0.5 mg/kg to female rats (Test group 6)

Test Compound : omethoate
Rat : female
Test-No. : 6
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.685 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY IN THE PLASMA

Time [h:min]	Animal Number 987	988	989	990	991	Mean value	VC [%]
0:05	0.13262	0.20289	0.13977	0.19254	0.18794	0.17115	19
0:10	0.34857	0.41770	0.59383	0.37975	0.50033	0.44803	22
0:20	0.87773	0.84386	0.92223	0.75761	0.77361	0.83501	8
0:40	1.09451	1.07880	1.09703	1.02499	0.96205	1.05148	6
1	0.97327	1.06898	1.05117	1.08237	0.97035	1.02923	5
1:30	0.95397	1.07201	0.88872	0.96026	0.86779	0.94855	8
2	0.82893	0.84103	0.72751	0.82950	0.74849	0.79509	7
3	0.61210	0.61551	0.51178	0.64980	0.53729	0.58530	10
4	0.41027	0.40435	0.44674	0.61242	0.39768	0.45429	20
6	0.20167	0.21258	0.13225	0.37179	0.19039	0.22174	40
8	0.09203	0.12055	0.07413	0.13719	0.09441	0.10366	24
24	0.00862	0.00883	0.00680	0.00993	0.00813	0.00846	13
32	0.00681	0.00669	0.00478	0.00580	0.00614	0.00605	14
48	0.00414	0.00431	0.00384	0.00413	0.00546	0.00438	14

Appendix 38 Pharmacokinetic parameters from plasma curve analysis after consecutive oral administration of 0.5 mg/kg to female rats (Test group 6)

Test Compound : omethoate
Rat : female
Test-No. : 6
Sacrifice: 48 h

Study-No.: M01810019
Dose : 0.5 [mg/kg]
Admin.-RA: 9.685 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

PHARMACOKINETIC PARAMETERS

	Animal Number					Mean	VC
	987	988	989	990	991	value	[%]
AUC-Exp [h]	4.520	4.799	4.113	5.277	4.259	4.594	10
AUC-Fit [h]	4.661	4.952	4.285	5.399	4.613	4.782	9
T-a (25-75 %) [h]	0.2	0.2	0.2	0.3	0.2	0.2	22
$T_{½}$ (B) [h]	22.6	23.5	31.0	20.2	45.4	28.5	36
CL [ml/min]	3.58	3.37	3.89	3.09	3.61	3.51	9
CL-R [ml/min]	3.44	3.12	3.65	2.61	3.12	3.13	10
MRT [h]	7.2	7.4	8.0	6.8	13.3	8.5	32
V-ss [l/kg]	1.55	1.49	1.86	1.25	2.89	1.81	36
P-Max	1.095	1.079	1.097	1.082	0.970	1.065	5
T-Max [h]	0.67	0.67	0.67	1.00	1.00	0.80	23

Each value is calculated from plasma curve of average relative concentration.
AUC-exp : area under the blood concentration vs. time curve of experimental values calculated by data from the measured first time point to the last time point
AUC-fit : sum of AUC-exp and AUC integrated from time point 0 to 5 min and from 48 h to infinity by extrapolation.
T-a (25-75 %) : time for a rise in concentration from 25 % to 75% of C-max
CL : total plasma clearance
CL-R : renal clearance
MRT : mean residence time
V-ss : distribution volume in the steady state
P-max : maximum level of the plasma concentration
T-max : time of the maximum level of the plasma concentration after oral administration. T-max was evaluated from experimental time points.

Appendix 39 The recovered radioactivity from the excreta and body at 48 h after single oral administration of 10 mg/kg to male rats (Test group 7)

Test Compound : omethoate
Rat : male
Test-No. : 7
Sacrifice: 48 h

Study-No.: M01810019
Dose : 10.0 [mg/kg]
Admin.-RA: 30.275 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

EXCRETION AND RESIDUES [% OF THE ADMINISTERED RADIOACTIVITY]

Animal-number	992	993	994	995	996	Mean value	SDEV	VC [%]	Number
Admin.-wght. [g]	210	216	213	216	198	211	7	4	5
Sacri.-wght. [g]	206	203	211	206	193	204	7	3	5
GIT	0.022	0.024	0.040	0.031	0.032	0.030	0.007	24	5
Body excl. GIT	0.281	0.255	0.339	0.251	0.232	0.272	0.042	15	5
Animal	0.303	0.279	0.379	0.282	0.264	0.301	0.046	15	5
Feces	4.555	4.3	3.210	5.775	3.136	4.195	1.087	26	5
Urine	84.145	80.918	81.099	84.790	92.508	84.692	4.705	6	5
Total (%)	89.003	85.497	84.688	90.847	95.908	89.189	4.523	5	5

Appendix 40 Time course of the recovered radioactivity in the urine after single oral administration of 10 mg/kg to male rats (Test group 7)

Test Compound : omethoate
Rat : male
Test-No. : 7
Sacrifice: 48 h
Study-No.: M01810019
Dose : 10.0 [mg/kg]
Admin.-RA: 30.275 [µCi/Anim]
Study-Dir.: T.Hoshino
Date: Dec-15-89

RENAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 992	993	994	995	996	Mean value	VC [%]
2	22.290	21.170	16.639	22.330	18.364	20.159	13
4	17.386	9.173	13.584	13.495	28.243	16.376	44
6	16.190	19.294	18.282	23.223	17.226	18.843	14
8	7.619	14.849	12.738	11.238	9.446	11.178	25
24	19.235	15.349	18.158	13.154	14.912	16.162	15
48	1.424	1.084	1.699	1.349	4.317	1.974	67
Total (%)	84.145	80.918	81.099	84.790	92.508	84.692	6

Appendix 41 Time course of the recovered radioactivity in the feces after single oral administration of 10 mg/kg to male rats (Test group 7)

Test Compound : omethoate Study-No.: M01810019 Study-Dir.: T.Hoshino
Rat : male Dose : 10.0 [mg/kg]
Test-No. : 7 Admin.-RA: 30.275 [µCi/Anim]
Sacrifice: 48 h Date: Dec-15-89

FECAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 992	993	994	995	996	Mean value	VC [%]
24	3.696	3.671	3.045	5.285	2.858	3.711	26
48	0.859	0.629	0.165	0.490	0.279	0.484	57
Total (%)	4.555	4.300	3.210	5.775	3.136	4.195	26

Appendix 42 Relative concentration P of the total radioactivity in organs and tissues at 48 h after single oral administration of 10 mg/kg to male rats (Test group 7)

Test Compound : omethoate | Study-No.: M01810019 | Study-Dir.: T.Hoshino
Rat : male | Dose : 10.0 [mg/kg]
Test-No. : 7 | Admin.-RA: 30.275 [µCi/Anim]
Sacrifice: 48 h | Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY

ORGANS AND TISSUE	Animal Number 992	993	994	995	996	Mean value	VC [%]
ERYTHROCYTE	0.00186	0.00206	0.00199	0.00216	0.00201	0.00201	5
PLASMA	0.00222	0.00241	0.00222	0.00213	0.00222	0.00224	5
SPLEEN	0.00497	0.00280	0.00500	0.00466	0.00467	0.00442	21
GIT	0.00202	0.00247	0.00395	0.00322	0.00293	0.00292	25
LIVER	0.00511	0.00560	0.00527	0.00488	0.00615	0.00540	9
KIDNEY	0.00426	0.00421	0.00553	0.00405	0.00465	0.00454	13
FAT	0.00213	0.00112	0.00163	0.00125	0.00204	0.00163	28
TESTES	0.00845	0.00941	0.00931	0.00891	0.00927	0.00907	4
MUSCLE	0.00185	0.00192	0.00158	0.00261	0.00186	0.00196	20
BONE	0.00147	0.00172	0.00199	0.00139	0.00173	0.00166	14
HEART	0.00264	0.00248	0.00256	0.00259	0.00258	0.00257	2
LUNG	0.00293	0.00386	0.00354	0.00390	0.00401	0.00365	12
BRAIN	0.00083	0.00085	0.00090	0.00081	0.00090	0.00086	5
THYROID	0.11692	0.17256	0.16247	0.16505	0.16203	0.15581	14
SKIN	0.00393	0.00223	0.00418	0.00201	0.00264	0.00300	33
CARCASS	0.00289	0.00281	0.00366	0.00296	0.00235	0.00293	16

Appendix 43 Time course of the total radioactivity in the plasma after single oral administration of 10 mg/kg to male rats (Test group 7)

Test Compound : omethoate Study-No.: M01810019 Study-Dir.: T.Hoshino
Rat : male Dose : 10.0 [mg/kg]
Test-No. : 7 Admin.-RA: 30.275 [μCi/Anim]
Sacrifice: 48 h Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY IN THE PLASMA

Time [h:min]	Animal Number 992	993	994	995	996	Mean value	VC [%]
0:05	0.06335	0.11613	0.14935	0.17760	0.07985	0.11726	40
0:10	0.22569	0.29648	0.39729	0.36008	0.25428	0.30676	23
0:20	0.54570	0.56427	0.84536	0.70463	0.60691	0.65337	19
0:40	0.91742	0.88259	1.22772	1.03857	0.93740	1.00074	14
1	1.11559	1.06852	1.21142	1.11791	1.04362	1.11141	6
1:30	1.00296	0.93441	0.98158	0.94249	0.87086	0.94646	5
2	0.85628	0.79523	0.79546	0.76055	0.72983	0.78747	6
3	0.64289	0.68741	0.56615	0.62991	0.58425	0.62212	8
4	0.52979	0.57737	0.41033	0.54304	0.48719	0.50954	13
6	0.31176	0.37299	0.50048	0.32479	0.29716	0.36143	23
8	0.18784	0.19733	0.25879	0.16972	0.18132	0.19900	18
24	0.00878	0.00718	0.01124	0.00601	0.01072	0.00879	25
32	0.00566	0.00606	0.00481	0.00410	0.01570	0.00727	66
48	0.00291	0.00323	0.00268	0.00287	0.00250	0.00284	10

Appendix 44 Pharmacokinetic parameters from plasma curve analysis after single oral administration of 10 mg/kg to male rats (Test group 7)

Test Compound : omethoate Study-No.: M01810019 Study-Dir.: T.Hoshino
Rat : male Dose : 10.0 [mg/kg]
Test-No. : 7 Admin.-RA: 30.275 [µCi/Anim]
Sacrifice: 48 h Date: Dec-15-89

PHARMACOKINETIC PARAMETERS

	Animal Number					Mean	VC
	992	993	994	995	996	value	[%]
AUC-Exp [h]	5.351	5.488	6.052	5.184	5.077	5.430	7
AUC-Fit [h]	5.416	5.589	6.101	5.286	5.121	5.503	7
T-a (25-75 %) [h]	0.4	0.4	0.3	0.3	0.3	0.4	18
$T_{\frac{1}{2}}$ (B) [h]	15.3	20.3	12.3	23.4	11.4	16.5	31
CL [ml/min]	3.08	2.98	2.73	3.15	3.25	3.04	7
CL-R [ml/min]	2.62	2.46	2.23	2.72	3.04	2.63	10
MRT [h]	6.2	6.7	6.2	6.4	6.2	6.3	3
V-ss [l/kg]	1.14	1.19	1.01	1.20	1.21	1.15	7
P-Max	1.116	1.069	1.228	1.118	1.044	1.115	6
T-Max [h]	1.00	1.00	0.67	1.00	1.00	0.93	16

Each value is calculated from plasma curve of average relative concentration.
AUC-exp : area under the blood concentration vs. time curve of experimental values calculated by data from the measured first time point to the last time point
AUC-fit : sum of AUC-exp and AUC integrated from time point 0 to 5 min and from 48 h to infinity by extrapolation.
T-a (25-75 %) : time for a rise in concentration from 25 % to 75% of C-max
CL : total plasma clearance
CL-R : renal clearance
MRT : mean residence time
V-ss : distribution volume in the steady state
P-max : maximum level of the plasma concentration
T-max : time of the maximum level of the plasma concentration after oral administration. T-max was evaluated from experimental time points.

Appendix 45 The recovered radioactivity from the excreta and body at 48 h after single oral administration of 10 mg/kg to female rats (Test group 8)

Test Compound : omethoate
Rat : female
Test-No. : 8
Sacrifice: 48 h

Study-No.: M01810019
Dose : 10.0 [mg/kg]
Admin.-RA: 29.125 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

EXCRETION AND RESIDUES [% OF THE ADMINISTERED RADIOACTIVITY]

Animal-number	3	4	5	6	7	Mean value	SDEV	VC [%]	Number
Admin.-wght. [g]	203	201	195	195	201	199	4	2	5
Sacri.-wght. [g]	190	193	178	181	189	186	6	3	5
GIT	0.025	0.039	0.026	0.020	0.037	0.029	0.008	28	5
Body excl. GIT	0.308	0.300	0.224	0.240	0.237	0.262	0.039	15	5
Animal	0.333	0.339	0.250	0.260	0.274	0.291	0.042	14	5
Feces	2.000	2.442	2.070	2.219	2.624	2.271	0.260	11	5
Urine	97.980	93.750	92.912	97.926	96.684	95.850	2.376	2	5
Total (%)	100.313	96.531	95.232	100.405	99.582	98.413	2.377	2	5

Appendix 46 Time course of the recovered radioactivity in the urine after single oral administration of 10 mg/kg to female rats (Test group 8)

Test Compound : omethoate Study-No.: M018J0019 Study-Dir.: T.Hoshino
Rat : female Dose : 10.0 [mg/kg]
Test-No. : 8 Admin.-RA: 29.125 [μCi/Anim]
Sacrifice: 48 h Date: Dec-15-89

RENAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time	Animal Number					Mean	VC
[hour]	3	4	5	6	7	value	[%]
2	35.043	40.493	33.110	34.441	34.900	35.597	8
4	23.448	18.977	16.539	31.517	16.610	21.418	29
6	14.375	15.974	12.146	15.115	16.933	14.909	12
8	7.781	6.147	11.801	7.162	9.126	8.403	26
24	16.619	10.542	17.698	8.836	17.732	14.285	30
48	0.715	1.617	1.618	0.856	1.383	1.238	34
Total (%)	97.980	93.750	92.912	97.926	96.684	95.850	2

Appendix 47 Time course of the recovered radioactivity in the feces after single oral administration of 10 mg/kg to female rats (Test group 8)

Test Compound : omethoate Study-No.: M01810019 Study-Dir.: T.Hoshino
Rat : female Dose : 10.0 [mg/kg]
Test-No. : 8 Admin.-RA: 29.125 [μCi/Anim]
Sacrifice: 48 h Date: Dec-15-89

FECAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 3	4	5	6	7	Mean value	VC [%]
24	1.943	2.064	1.841	2.078	2.310	2.047	9
48	0.057	0.379	0.229	0.141	0.314	0.224	58
TOTAL (%)	2.000	2.442	2.070	2.219	2.624	2.271	11

Appendix 48 The recovered radioactivity from the excreta and body at 48 h after single oral administration of 10 mg/kg to female rats (Test group 8)

Test Compound : omethoate
Rat : female
Test-No. : 8
Sacrifice: 48 h

Study-No.: M01810019
Dose : 10.0 [mg/kg]
Admin.-RA: 29.125 [μCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY

ORGANS AND TISSUES	Animal Number 3	4	5	6	7	Mean value	VC [%]
ERYTHROCYTE	0.00210	0.00230	0.00350	0.00201	0.00236	0.00245	24
PLASMA	0.00228	0.00290	0.00411	0.00231	0.00277	0.00287	26
SPLEEN	0.00354	0.00463	0.00382	0.00438	0.00456	0.00419	11
GIT	0.00330	0.00446	0.00363	0.00253	0.00341	0.00347	20
LIVER	0.00489	0.00558	0.00463	0.00428	0.00671	0.00522	18
KIDNEY	0.00447	0.00514	0.00460	0.00395	0.00486	0.00461	10
FAT	0.00056	0.00054	0.00071	0.00080	0.00059	0.00064	17
OVARIES	0.00226	0.00291	0.00251	0.00272	0.00275	0.00263	10
UTERUS	0.00485	0.00383	0.00259	0.00162	0.00729	0.00404	54
MUSCLE	0.00137	0.00167	0.00161	0.00133	0.00148	0.00149	10
BONE	0.00569	0.00346	0.00216	0.00161	0.00251	0.00308	52
HEART	0.00273	0.00345	0.00268	0.00253	0.00302	0.00288	13
LUNG	0.00327	0.00441	0.00342	0.00338	0.00451	0.00380	16
BRAIN	0.00097	0.00127	0.00095	0.00100	0.00114	0.00107	13
THYROID	0.25630	0.30948	0.08393	0.08004	0.20981	0.18791	55
SKIN	0.00651	0.00576	0.00272	0.00401	0.00322	0.00445	37
CARCASS	0.00229	0.00243	0.00224	0.00223	0.00234	0.00230	4

Appendix 49 Time course of the total radioactivity in the plasma after single oral administration of 10 mg/kg to female rats (Test group 8)

Test Compound : omethoate
Rat : female
Test-No. : 8
Sacrifice: 48 h
Study-No.: M01810019
Dose : 10.0 [mg/kg]
Admin.-RA: 29.125 [µCi/Anim]
Study-Dir.: T.Hoshino
Date: Dec-15-89

RELATIVE CONCENTRATION OF RADIOACTIVITY IN THE PLASMA

Time [h:min]	Animal Number 3	4	5	6	7	Mean value	VC [%]
0:05	0.13129	0.11794	0.15659	0.11138	0.13796	0.13103	14
0:10	0.36651	0.34446	0.33048		0.35869	0.35004	5
0:20	0.73615	0.79560	0.63935	0.84873	0.73325	0.75062	10
0:40	0.95369	1.16965	1.02420	1.10756	1.00080	1.05118	8
1	0.91146	1.14348	1.01755	1.18748	0.98421	1.04884	11
1:30	0.72788	0.96814	0.84015	1.07412	0.84200	0.89046	15
2	0.60585	0.79105	0.67388	0.84991	0.68580	0.72130	14
3	0.48213	0.64142	0.49785	0.68158	0.59523	0.57964	15
4	0.32175	0.50304	0.36909	0.45350	0.47352	0.42418	18
6	0.23398	0.30073		0.23854		0.25775	14
8	0.14625	0.17570	0.18235	0.12574	0.17472	0.16095	15
24	0.00845	0.01852	0.00890	0.00716	0.01270	0.01115	41
32	0.00553	0.00879	0.00718	0.00519	0.00957	0.00725	27
48	0.00269	0.00914	0.00350	0.00266	0.00326	0.00425	65

Appendix 50 Pharmacokinetic parameters from plasma curve analysis after single oral administration of 10 mg/kg to female rats (Test group 8)

Test Compound : omethoate | Study-No.: M01810019 | Study-Dir.: T.Hoshino
Rat : female | Dose : 10.0 [mg/kg]
Test-No. : 8 | Admin.-RA: 29.125 [µCi/Anim]
Sacrifice: 48 h | Date: Dec-15-89

PHARMACOKINETIC PARAMETERS

	Animal Number 3	4	5	6	7	Mean value	VC [%]
AUC-Exp. [h]	4.200	5.550	4.695	4.991	5.110	4.909	10
AUC-Fit [h]	4.262	5.649	4.791	5.060	5.173	4.987	10
T-a (25-75 %) [h]	0.2	0.3	0.3	0.2	0.2	0.2	24
$T_{\frac{1}{2}}$ (B) [h]	14.7	7.4	17.4	16.8	11.9	13.6	30
CL [ml/min]	3.91	2.95	3.48	3.29	3.22	3.37	11
CL-R [ml/min]	3.88	2.81	3.29	3.27	3.15	3.28	12
MRT [h]	6.4	6.1	7.1	5.6	6.7	6.4	9
V-ss [l/kg]	1.50	1.08	1.47	1.11	1.29	1.29	15
P-Max	0.954	1.170	1.024	1.187	1.001	1.067	10
T-Max [h]	0.67	0.67	0.67	1.00	0.67	0.74	20

Each value is calculated from plasma curve of average relative concentration.
AUC-exp : area under the blood concentration vs. time curve of experimental values calculated by data from the measured first time point to the last time point
AUC-fit : sum of AUC-exp and AUC integrated from time point 0 to 5 min and from 48 h to infinity by extrapolation.
T-a (25-75 %) : time for a rise in concentration from 25 % to 75% of C-max
CL : total plasma clearance
CL-R : renal clearance
MRT : mean residence time
V-ss : distribution volume in the steady state
P-max : maximum level of the plasma concentration
T-max : time of the maximum level of the plasma concentration after oral administration. T-max was evaluated from experimental time points.

Appendix 51 The recovered radioactivity from the excreta and body at 48 h after single oral administration of 10 mg/kg to male rats (Test group 9, CO_2 study)

Test Compound : omethoate
Rat : male
Test-No. : 9
Sacrifice: 48 h

Study-No.: M01810019
Dose : 10.0 [mg/kg]
Admin.-RA: 30.632 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

EXCRETION AND RESIDUES [% OF THE ADMINISTERED RADIOACTIVITY]

Animal-number	997	998	999	1	2	Mean value	SDEV	VC [%]	Number
Admin.-wght. [g]	204	206	197	194	205	201	5	3	5
Sacri.-wght. [g]	202	207	193	194	203	200	6	3	5
Skin	0.053	0.075	0.044	0.092	0.102	0.073	0.025	34	5
Carcass	0.164	0.172	0.148	0.199	0.174	0.171	0.019	11	5
GIT	0.026	0.035	0.020	0.052	0.060	0.039	0.017	44	5
Body excl. GIT	0.217	0.247	0.192	0.291	0.276	0.245	0.041	17	5
Animal	0.243	0.282	0.212	0.343	0.336	0.283	0.057	20	5
Feces	2.506	3.390	2.153	2.887	5.791	3.345	1.442	43	5
Urine	87.466	90.555	95.043	90.884	88.165	90.423	2.976	3	5
CO_2	0.156	0.132	0.129	0.139	0.145	0.140	0.011	8	5
Total (%)	90.371	94.359	97.537	94.253	94.437	94.191	2.544	3	5

Appendix 52 Time course of the recovered radioactivity in the urine after single oral administration of 10 mg/kg to male rats (Test group 9, CO_2 study)

Test Compound : omethoate	Study-No.: M01810019	Study-Dir.: T.Hoshino
Rat : male	Dose : 10.0 [mg/kg]	
Test-No. : 9	Admin.-RA: 30.632 [µCi/Anim]	
Sacrifice: 48 h		Date: Dec-15-89

RENAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time	Animal Number					Mean	VC
[hour]	997	998	999	1	2	value	[%]
4	51.959	45.409	64.838	42.739	54.494	51.888	17
8	18.799	25.492	18.562	31.959	19.139	22.790	26
24	15.493	15.822	10.384	12.261	11.812	13.154	18
32	0.709	2.814	0.777	2.341	1.461	1.621	58
48	0.506	1.018	0.482	1.584	1.259	0.970	49
Total (%)	87.466	90.555	95.043	90.884	88.165	90.423	3

Appendix 53 Time course of the recovered radioactivity in the feces after single oral administration of 10 mg/kg to male rats (Test group 9, CO_2 study)

Test Compound : omethoate
Rat : male
Test-No. : 9
Sacrifice: 48 h

Study-No.: M01810019
Dose : 10.0 [mg/kg]
Admin.-RA: 30.632 [µCi/Anim]

Study-Dir.: T.Hoshino
Date: Dec-15-89

FECAL EXCRETION [% OF THE ADMINISTERED RADIOACTIVITY]

Time [hour]	Animal Number 997	998	999	1	2	Mean value	VC [%]
24	2.405	2.937	1.665	2.257	4.848	2.822	43
48	0.101	0.453	0.488	0.630	0.944	0.523	58
Total (%)	2.506	3.390	2.153	2.887	5.791	3.345	43

QUALITY ASSURANCE STATEMENT

REFERAT GLP	
Quality Assurance Statement	
Report No.: HTD	Study-No.: M 181 0019-0 (= M 018100019)
Title of Study:	[Methylene- ^{14}C-]Omethoate General Metabolism Study in the Rat.

The conduct of this study has been periodically inspected and this report has been audited by the Quality Assurance Unit. The dates of inspection are given below.

Date of Protocol Inspection:	Date of Report to Management:
July 7, 1989	July 7, 1989
Date of Inspection of Study in Progress:	**Date of Report to Management:**
July 18, 1989	July 21, 1989
August 9/11, 1989	August 11, 1989
Date of Final Report Audit:	**Date of Report to Management:**
July 5, 1990	August 8, 1990

The results reported in this study have been checked on the basis of our current SOPs and to the best of our knowledge accurately reflect the raw data.

(Dr. R. Rauchschwalbe)
Manager, Quality Assurance Unit, PF-Stab

Date: 08.08.90