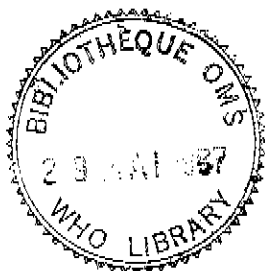


11381

DATA SHEET ON PESTICIDES

No. 74

PHOSPHAMIDON



CLASSIFICATION:

Primary Use: Insecticide

Secondary Use: Acaricide

Chemical Group: Organophosphorus compound

1.0 GENERAL INFORMATION

1.1 COMMON NAME: Phosphamidon (ISO, BSI and ANSI)

1.1.1 Identity:

IUPAC: 2-chloro-2-diethylcarbamoyl-1-methylvinyl dimethyl phosphate

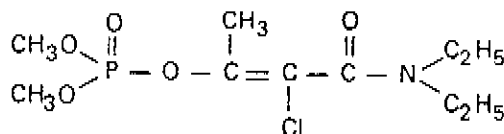
CAS: 2-chloro-3-(diethylamino)-1-methyl-3-oxo-1-propenyl dimethyl phosphate

CAS Reg. No.: 297-99-4 (trans-isomer), 23783-98-4 (cis-isomer), 13171-21-6 (mixture)

Molecular formula: C<sub>10</sub>H<sub>19</sub>ClNO<sub>5</sub>P

Molecular weight: 299.70

Structural formula:



- 1.1.2 Synonyms: Phosphamidone; Famfos; Dimecron<sup>R</sup>; Dixon<sup>R</sup>; C-570; Ciba-570; ENT 25,515; ML-97; Or-1,911
- 1.2 SYNOPSIS: Phosphamidon is a noncumulative systemic organophosphorous pesticide with a broad spectrum of activity: It is a cholinesterase inhibitor with rapid contact and stomach action. The technical product is very highly toxic to mammals and is listed in WHO Hazard Class Ia.
- 1.3 SELECTED PROPERTIES
- 1.3.1 Physical characteristics - Phosphamidon is a pale yellow to colorless oily liquid with a faint odour. It has a boiling point of 162°C at 1.5 mmHg; a density (d)<sub>4</sub><sup>25</sup> of 1.2132 and a refractive index (n)<sub>D</sub><sup>20</sup> of 1.4721. Phosphamidon exists as a mixture of 70% cis-isomer and 30% trans-isomer and is corrosive to iron, tinplate and aluminium.
- 1.3.2 Solubility - Phosphamidon is miscible with water. It is soluble in aromatic hydrocarbons but insoluble in non-polar aliphatic hydrocarbons.
- 1.3.3 Stability - It is stable in neutral and acid media but is hydrolyzed by alkali; half-life at 23°C is 13.8 days at pH 7 and 2.2 days at pH 10. Phosphamidon decomposes above 160°C.
- 1.3.4 Vapour pressure -  $2.5 \times 10^{-5}$  mmHg.
- 1.4 AGRICULTURE, HORTICULTURE AND FORESTRY
- 1.4.1 Common formulations - Available as 20-100% soluble concentrates (from 200 to 1000 g a.i./l in 2-propanol), as 0.5g/kg granules and in U.L.V. formulations. The granules are in WHO Hazard Class II (moderately hazardous).
- 1.4.2 Pests controlled - These include sap-feeding insects, sugar cane and rice stemborers and rice leaf beetles.
- 1.4.3 Use pattern - Phosphamidon is used on citrus and cotton crops, deciduous fruit and nut crops at rates of 300-600 g a.i./ha for sap-feeding insects and 500-1000 g a.i./ha for other pests.
- 1.4.4 Unintended effects - Phosphamidon is highly toxic to bees. It is non-phytotoxic except to some cherry and sorghum varieties.
- 1.5 PUBLIC HEALTH USE - No recommended use.
- 1.6 HOUSEHOLD USE - No recommended use.
- 2.0 TOXICOLOGY AND RISKS
- 2.1 TOXICOLOGY - MAMMALS
- 2.1.1 Absorption route - Phosphamidon may be readily absorbed from the gastrointestinal tract, through the intact skin and by inhalation of spray mists and dusts.
- 2.1.2 Mode of action - Phosphamidon is a cholinesterase inhibitor. An impurity in the technical product, gamma-chlorphosphamidon, inhibits mammalian cholinesterases 10 to 20 times more than pure phosphamidon.
- 2.1.3 Excretion products - Metabolism and excretion is rapid in mammals. After ip injection of <sup>32</sup>P-labeled phosphamidon to rats, 60% of the dose was recovered in 24 hours. In rats and goats, oxidative metabolism yielded mostly desethyl phosphamidon, phosphamidon amide and deschloro-phosphamidon. However over 90% of radioactivity in the urine was in the form of nontoxic unextractable polar metabolites.

2.1.4 Toxicity, single dose -Oral LD50:

Rat	17 mg/kg b.w.
Mouse	10 mg/kg b.w.
	6.5 mg/kg b.w. ( <u>cis</u> -isomer)
	220 mg/kg b.w. ( <u>trans</u> -isomer)
Dog	50 mg/kg b.w.
Rabbit	32 mg/kg b.w.

Onset of poisoning is extremely rapid. Clinical signs include hypersalivation, lacrimation, miosis, dyspnea, vomiting, ataxia, convulsions, tetany and opisthotonos.

Dermal LD50:

Rat	374 mg/kg b.w.
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Inhalation LC50:

Rat	102 mg/m <sup>3</sup> /4h (head only exposure)
Rat	135 mg/m <sup>3</sup> /4h (whole body exposure)
Rat	160 mg/m <sup>3</sup> /4h
Mouse	33 mg/m <sup>3</sup> /4h
Guinea pig	1300 mg/m <sup>3</sup> /4h

I.P. LD50:

Rat	9.2 mg/kg b.w.
Mouse	5.8 mg/kg b.w.

I. V. LD50:

Mouse	6 mg/kg b.w.
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Most susceptible species - No appreciable species variability has been found among the animals tested.

2.1.5 Toxicity, repeated doses -

Oral: Male rats (5/group) were administered 2.5, 5.0 or 10 mg/kg b.w./day of 83% phosphamidon by stomach tube. All rats at 5 and 10 mg/kg b.w./day died after 1-33 days. Similarly all rats given daily oral doses of 5 and 10 mg/kg b.w. of 20% phosphamidon in isopropanol died within 41 days. One of five rats at 2.5 mg/kg b.w./day died during a ten-week period.

Rats were dosed daily by stomach tube with 0.3 or 3.0 mg/kg b.w. phosphamidon in propylene glycol. At 3 mg/kg b.w. serum cholinesterase activity was reduced by 14% and

brain cholinesterase was reduced by 12.5% after one dose. After seven and 14 days treatment, the inhibition was 42.5 and 37% in serum and 55 and 67.5% in brain respectively. In rats left undosed for a further seven days, brain cholinesterase activity remained inhibited at 47.5%. The no-effect level was reported to be 0.3 mg/kg b.w./day.

Daily oral doses of phosphamidon of 1.08 mg (approximately 68 mg/kg b.w.) in adult female rabbits for 30 days did not reveal any significant clinical symptoms of toxicity. Higher levels of 2.16 mg of phosphamidon (approximately 1.35 mg/kg b.w.) resulted in overt toxicity in a 15 day treatment period. Treated animals showed morphological changes in liver, kidney, adrenal and brain, and haemoglobin and erythrocyte levels increased. Cholinesterase activity was inhibited in erythrocytes and brain by 72.05 and 84.15% respectively.

Daily oral doses of phosphamidon in rabbits resulted in one of three animals dying at 3.5 mg/kg b.w. (in 21 days), two of three animals dying at 7 mg/kg b.w. (in eight days), and total mortality of five animals at 15 mg/kg b.w. within seven days.

Dermal: Rabbits dosed with 0.1, 0.25 or 0.5 ml/kg b.w. of a 12% solution of phosphamidon for six weeks showed erythema and oedema in increasing incidence, thought to be solvent related. Other toxic signs included hyperpnoea, hypersalivation, tremor and ataxia at the two highest dose levels. Inhibition of blood and brain cholinesterases was significant in males and females at 0.25 ml/kg level with the exception of brain cholinesterase activity in females which appeared unaffected at 0.25 ml/kg level. No effect level: 0.1 ml/kg (0.012 mg a.i./kg b.w.).

Inhalation: Wistar rats exposed to a continuous flow of air containing 0.05 or 0.5 mg/m<sup>3</sup> of phosphamidon for four hours daily, five times a week, for 42 days suffered a temporary inhibition of erythrocyte cholinesterase. No effect on mortality, behaviour, haematology, clinical chemistry or pathology was observed.

Intravenous: In a 14 day experiment, rabbits survived daily injections of 3 mg/kg b.w. phosphamidon whereas 2/3 mortality was observed at 7.5 mg/kg b.w.

#### 2.1.6 Dietary studies -

Short term: Dogs fed phosphamidon at 0, 0.05, 0.1, or 2.5 mg/kg b.w./day in capsule form for three months did not show any ill effects except in the highest dose group. Decreases in body weight gain, in food consumption in females, in haematology parameters, as well as an increase in GTP in males and inhibitions of blood and brain cholinesterases for both sexes occurred at the highest dose level. No other findings were noted.

No effect level: 0.1 mg/kg/b.w./day.

Long term: Two year feeding studies: No effect levels:

Rat 1.25 mg/kg b.w./day

Dog 0.1 mg/kg b.w./day

A 5 mg/kg b.w./day dose in rats caused significant weight depression while moderate clinical symptoms, attributable to cholinesterase inhibition, occurred at a dose level of 2.5 mg/kg b.w./day in dogs.

2.1.7 Supplementary studies of toxicity -

Carcinogenicity: When Osborne-Mendel rats were fed dietary levels of 80 or 160 mg/kg diet phosphamidon was found to give equivocal results. In B6C3F1 mice fed similar dietary levels of phosphamidon, no evidence of carcinogenicity was indicated.

Teratogenicity: No information available.

Reproduction: No information available.

Mutagenicity: Phosphamidon has been shown to demonstrate clastogenic effects in in vivo tests with bone marrow cells of rats and mice. It has also been shown to be capable of inducing genetic damage in in vitro human lymphocyte studies and in vivo host mediated assays and micronuclei tests. Phosphamidon was not mutagenic in metabolically activated or non-activated systems of mouse lymphoma cells (L5178Y/TK+/-), or Salmonella typhimurium. Phosphamidon was mutagenic only in metabolically activated systems of Saccharomyces cerevisiae D7, exerted slight clastogenic activity in a Chinese hamster-nucleus anomaly test at levels over 5 mg/kg but was not mutagenic in sister chromatid exchange assays using Chinese hamster bone marrow cells (10 mg/kg). No DNA damage was induced in systems utilizing rat hepatocytes and human fibroblasts.

Neurotoxicity: No published information available.

- 2.1.8 Modifications of toxicity - The cis-isomers of phosphamidon and its desethyl metabolite were found to be approximately 40 times more toxic than the trans-isomers. N-deethylation of phosphamidon increases its toxicity.

In acute studies, no potentiation occurred between equal quantities of phosphamidon and other organophosphorus insecticides (dimethoate, endosulfan, ethion, malathion, mevinphos, oxydemeton-methyl, and parathion).

2.2 TOXICOLOGY - MAN

- 2.2.1 Absorption - Phosphamidon may be absorbed from the gastrointestinal tract, through the intact skin and by inhalation of spray mists and dusts.

2.2.2 Dangerous doses -

Single: Phosphamidon has been given a toxicity rating of 5 (Gosselin), the probable oral lethal dose is 5-50 mg/kg b.w. Temporary acceptable daily intake for man: 0-0.001 mg/kg b.w.

Repeated: No information available.

- 2.2.3 Observations on occupationally exposed workers - Two operators were completely drenched with 50% phosphamidon and six others were splashed. Following a thorough wash, symptoms of gastric pains, headache and burning sensation in the eyes were reported with uneventful recovery.

- 2.2.4 Observations on exposure of the general public - No information available.

- 2.2.5 Observations on volunteers - Thirty two people (10-70 years old) remained in paddy fields during and one hour after ULV phosphamidon aerially sprayed at 550 g/ha. The unprotected volunteers, exposed to twice the recommended rate of compound, experienced conjunctival irritation. Plasma cholinesterase levels were depressed 0-25% in 19 people, 26-50% in 19 other people and over 50% in two people with complete recovery in nine days. Erythrocyte cholinesterase was not affected.

[Editors note: Inhibition of plasma cholinesterase is an accepted sign of exposure as in this case intoxication is related to inhibition of erythrocyte cholinesterase.]

- 2.2.6 Mishaps - In one suicidal poisoning, an apneic and cyanotic 18-year-old girl survived six days before severe bilateral bronchopneumonia caused her death. Autopsy revealed brain and liver injury but investigators concluded that anoxia may have been a factor in tissue injury.

A 10 year-old boy ingested between 60 and 120 mg/kg b.w. of 20% phosphamidon. Recovery was rapid following the use of an emetic.

### 2.3 TOXICOLOGY - NON-MAMMALIAN SPECIES

#### 2.3.1 Fish - Low toxicity to fish.

LC <sub>50</sub> : (24 hr)	Fathead minnows	4.8 mg/l
	Rainbow trout	4.4 mg/l
LC <sub>50</sub> : (96 hr) (technical product)	Rainbow trout	3.2-20 mg/l
	Crucian carp	600 mg/l
	Channel catfish	360 mg/l
	Bluegill	150 mg/l
	Guppy	54 mg/l

#### 2.3.2 Birds -

##### Acute Oral LD<sub>50</sub>:

Mallard duck (F)	3.81 mg/kg b.w. 80% in water
Mallard duck (F)	3.05 mg/kg b.w. 80% in isopropanol
Chukar partridge (M,F)	9.07 mg/kg b.w. 80% in isopropanol
Pigeon (M,F)	2-3 mg/kg b.w. 80% in isopropanol
Mourning dove (M,F)	2-4 mg/kg b.w. 80% in isopropanoglycol
Whitewing dove (M,F)	26 mg/kg b.w. 85% in isopropanol

##### Acute Dermal LD<sub>50</sub>:

Mallard duck (F)	26 mg/kg b.w. 85% in propylene
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##### Eight Day Feeding Study LD<sub>50</sub>:

##### Technical Product:

Wildbirds (five species)	3.16-5.62 mg/kg
Other species	2.1-14.0 mg/kg
Pheasant	0.8 mg/kg

Eight Day Feeding Study LC50:

Peking Ducks	918.0 mg/1
Japanese Quails	1612.0 mg/1

Dietary Studies:

In a 100 day study, 50% mortality in young and adult birds was observed at dietary levels of 1-100 and 10-200 mg/kg respectively. Treatment of chick embryos with phosphamidon (1 mg per egg) resulted in growth retardation and malformations in the head, and neck regions. Limb buds and eyes were also adversely affected. Complete agenesis was seen in some organs such as eyes at higher doses (2 and 20 mg per egg).

2.3.3 Other species - Phosphamidon is highly toxic to bees.

3.0 FOR REGULATORY AUTHORITIES - RECOMMENDATIONS ON REGULATION OF COMPOUND

3.1 RECOMMENDED RESTRICTIONS ON AVAILABILITY

(For definitions of categories, see the Introduction to Data Sheets)

All formulations 85% and over are placed in Category 1

All other available formulations are placed in Category 2

3.2 TRANSPORTATION AND STORAGE -

Formulations in category 1 and 2: Should be transported or stored in clearly labelled rigid and leakproof containers and away from containers of food and drink. Storage should be under lock and secure from access by unauthorized persons and children.

3.3 HANDLING

Formulations in category 1 and 2: Full protective clothing (see part 4) should be used by all those handling the compound. Adequate washing facilities should be available close at hand. Eating, drinking and smoking should be prohibited during handling and before washing after handling.

3.4 DISPOSAL AND/OR DECONTAMINATION OF CONTAINER - Container must be either burned or crushed and buried below topsoil. Care must be taken to avoid subsequent contamination of water sources. Container may be decontaminated (for method see paragraph 4.3 of Part 4) but should not be used for food or drink.

3.5 SELECTION, TRAINING AND MEDICAL SUPERVISION OF WORKERS -

Formulations in category 1 and 2: Pre-employment and periodic medical examination for workers desirable. Workers suffering from active hepatic or renal diseases should be excluded from contact. Pre-employment and cholinesterase tests for workers are desirable except for those handling only 0.5g/kg granules. Special account should be taken of workers' ability to comprehend and follow instructions. Training of workers in techniques to avoid contact is essential.

## 3.6 ADDITIONAL REGULATIONS RECOMMENDED IF DISTRIBUTED BY AIRCRAFT -

All formulations: Pilot and loaders should have special training in application methods and early symptoms of poisoning. Flagmen, if used, should wear overalls and a broad brimmed hat and, be located well away from the dropping zone.

## 3.7 LABELLING -

All formulations, minimum cautionary statement:

"DANGER - POISON"

(skull and cross bones insignia)

Phosphamidon is an organophosphorous compound which inhibits cholinesterase. It is of very high toxicity. Contact with the skin, inhalation of dust or spray, or swallowing may cause illness or be fatal. Wear protective gloves, and clean protective clothing, when handling this material. Bathe immediately after work. Ensure that containers are stored under lock and key. Empty containers must be disposed of in such a way as to prevent all possibility of accidental contact with them. Keep the material out of reach of children and well away from foodstuffs, animal feed and their containers.

In case of contact, immediately remove contaminated clothing and wash the skin thoroughly with soap and water, for eyes, flush with water for 15 minutes. If poisoning occurs, call a physician. Atropine and oximes are accepted antidotes; repeated doses may be necessary. Artificial respiration also may be needed.

3.8 RESIDUES IN FOOD - Maximum residue levels have been recommended by the Joint FAO/WHO Meeting on Pesticide Residues.

## 4.0 PREVENTION OF POISONING IN MAN AND EMERGENCY AID

## 4.1 PRECAUTIONS IN USE

4.1.1 General - Phosphamidon is an organophosphorous pesticide of extremely high mammalian toxicity. It is readily absorbed through the intact skin, from the gastrointestinal tract and by inhalation of dust or spray mist. Repeated exposure may have a cumulative effect on cholinesterase levels. Most formulations should be handled by trained personnel wearing protective clothing.

4.1.2 Manufacture and formulation - TLV - No information. Closed systems and forced ventilation may be required to reduce, as much as possible, the exposure of workers to the chemical.

4.1.3 Mixers and applicators - When opening the container and when mixing, protective impermeable boots, clean overalls, and gloves should be worn. Mixing, if not mechanical, should always be carried out with a paddle of appropriate length. When spraying tall crops or during aerial application, a face mask should be worn, as well as an impermeable hat, clothing, boots and gloves. The applicator should avoid working in spray mist and avoid contact with the mouth. Particular care is needed when equipment is being washed after use. All protective clothing should be washed immediately after use, including the insides of gloves. Splashes must be washed immediately from the skin, or eyes, with large quantities of water. Before eating, drinking, or smoking, hands and other exposed skin should be washed.

4.1.4 Other associated workers (including flagmen in aerial operations) - Persons exposed to phosphamidon and associated with its application should wear protective clothing and observe the precautions described above in 4.1.3 under "Mixers and applicators".

- 4.1.5 Other populations likely to be affected - With good application practice, subject to 4.2 below, other persons are not likely to be exposed to hazardous amounts of phosphamidon.
- 4.2 ENTRY OF PERSONS INTO TREATED AREA - Unprotected persons should be kept out of tall crops for four days and out of other crops for at least 24 hours.
- 4.3 DECONTAMINATION OF SPILLAGE AND CONTAINERS - Residues in containers should be emptied in a diluted form into a deep pit, taking care to avoid ground waters. The empty container may be decontaminated by rinsing two or three times with water and scrubbing the sides. An additional rinse should be carried out with 5% sodium hydroxide solution which should remain in the container overnight. Impermeable gauntlets should be worn during this work, and a soakage pit should be provided for the rinsings. The container should then be filled with water and allowed to stand 24 hours. Empty and repeat three times. Decontaminated containers should not be used for food, feed or drinking water. Spillage of phosphamidon and its formulations should be removed by rinsing with large quantities of water.
- 4.4 EMERGENCY AID
- 4.4.1 Early symptoms of poisoning - Early symptoms of poisoning may include excessive sweating, headache, weakness, giddiness, nausea, vomiting, hypersalivation, stomach pains, blurred vision, slurred speech and muscle twitching. Later there may be convulsions and coma.
- 4.4.2 Treatment before person is seen by a physician, if these symptoms appear following exposure - The person should stop work immediately, remove contaminated clothing and wash the affected skin with soap and water, if available, and flush the area with large quantities of water. If swallowed, and if the person is conscious, vomiting should be induced. In the event of collapse, artificial resuscitation should be given, bearing in mind that if mouth-to-mouth resuscitation is used, vomit may contain toxic amounts of phosphamidon.
- 5.0 FOR MEDICAL AND LABORATORY PERSONNEL
- 5.1 MEDICAL DIAGNOSIS AND TREATMENT IN CASES OF POISONING
- 5.1.1 General information - Phosphamidon is an organophosphorous pesticide of extremely high mammalian toxicity which is active against a variety of agricultural pests. It is readily absorbed from the gastrointestinal tract; through the intact skin; and, by inhalation of dust or spray mist. It is converted in vivo to the oxygen analogues of phosphamidon which also inhibits cholinesterase. It does not accumulate in body tissues.
- 5.1.2 Symptoms and signs - Initial symptoms of poisoning may include excessive sweating, headache, weakness, giddiness, nausea, hypersalivation, vomiting, stomach pains, blurred vision, slurred speech and muscle twitching. More advanced symptoms of poisoning may be convulsions, coma, loss of reflexes and loss of sphincter control.
- 5.1.3 Laboratory - The most important finding is reduction of activity of whole blood or erythrocyte cholinesterase. Urinary levels of organic phosphorus containing metabolites may also be used as a measure of exposure. Neither method is specific for phosphamidon.

5.1.4 Treatment - If the pesticide has been ingested, unless the patient is vomiting, rapid gastric lavage should be performed using 5% sodium bicarbonate if available. For skin contact, the skin should be washed with soap and water. If the compound has entered the eyes, they should be washed with large quantities of isotonic saline or water. Persons without signs of respiratory inefficiency but with manifest peripheral symptoms should be treated with 2-4 mg of atropine sulfate by intravenous injection and 1000 mg pralidoxime chloride or 250 mg of toxogonin (adult dose) by slow intravenous injection. More atropine may be given as needed. Persons with severe intoxication, with respiratory difficulties, convulsions and unconsciousness should immediately be given atropine and a reactivator. In such severe cases 4-6 mg of atropine sulfate should be given initially followed by repeated doses of 2 mg at 5-10 minute intervals. Diazepam may be given to control convulsions. The patient's condition including respiration, blood pressure, pulse frequency, salivation, and convulsions should be carefully observed as a guide to further administration of atropine. If the patient is cyanotic, oxygen should be given at the same time as atropine sulfate. The airways should be kept free and artificial resuscitation should be applied if required, preferably by mechanical means. If necessary, intubation should be performed. Contraindications are morphine, barbiturates, phenothiazine, tranquilizers (except Diazepam) and central stimulants of all kinds. Pralidoxime and toxogonin alone are not regarded as effective antidotes in phosphamidon poisoning.

5.1.5 Prognosis - If the acute toxic effect is survived and adequate artificial resuscitation has been given if needed, the chances of complete recovery are good. However, in very severe cases, particularly if artificial resuscitation has been inadequate, prolonged anoxia may give rise to permanent brain damage.

5.1.6 References of previously reported cases - Phosphamidon has been implicated in several cases of pesticide poisoning, see Gitelson, S. et al., (1965) Br. J. Ind. Med., 22 236-239.

## 5.2 SURVEILLANCE TESTS

<u>Test</u>	<u>Normal level*</u>	<u>Action level*</u>	<u>Symptomatic level*</u>
Plasma cholinesterase	100%	50%	variable
Whole blood or erythrocyte cholinesterase	100%	70%	usually 40%

## 5.3 LABORATORY METHODS

5.3.1 Detection and assay of compound - Thin-layer chromatography and gas-liquid chromatography methods have been used to analyse phosphamidon in technical products and in its formulations. Analysis of residues in plant and animal tissues - gas chromatography and flame photometry methods.

5.3.2 Other tests in case of poisoning - Levels of cholinesterase in the blood, particularly plasma, provide the most useful diagnosis of poisoning.

Michel, N. O. (1949), J. Lab. Clin. Med., 34, 1564-1568

Ellman, G. L. et al. (1961), Biochem. Pharmacol., 7, 88-95.

Measurement of urine metabolites may also be determined in order to given indication of exposure for methods. See section 5.3.1, Detection and Assay.

\* Expressed as percentage of pre-exposure values