EDIFENPHOS

Explanation

Edifenphos was evaluated by the 1976 and 1979 Joint Meetings.* A temporary ADI was allocated in 1976 and extended in 1979. Temporary MRLs recommended by the 1976 Meeting were increased in 1979.

Further studies were required on hepatic involvement observed in several animal species and the results of a carcinogenicity study was also required. Information was also desired on humans relative to occupational exposure and on residues of edifenphos and its p-hydroxy metabolite in food animals arising from the use of rice straw and bran in animal feeds.

Data were received on the carcinogenicity study in mice, as well as additional data on residue levels in rice and in animal products, and are evaluated in this monograph addendum.

DATA FOR THE ESTIMATION OF ACCEPTABLE DAILY INTAKE

BIOCHEMICAL ASPECTS

Rat and mouse - distribution and excretion

Comparative studies on the metabolic fate of ^{35}S-labelled edifenphos in rats and mice have been reported (Ueyama *et al* 1978). Dose levels were 10 mg/kg in female rats and 20 mg/kg in mice and male rats. Edifenphos was rapidly absorbed and metabolized by both species following oral administration. The major metabolic pathway was the cleavage of the P-S bond, accompanied by the release of benzene thiol (Fukami *et al* 1969: Ueyama and Takase 1976, Ueyama *et al* 1978). Only 15 to 30% of the administered radioactivity was detected in digestive organs 6 h after administration. At 72 h, only a trace amount of radioactivity was found over the whole body of the animals. The major part of the radioactivity was excreted in urine (75-90%) and faeces (5-20%). The main metabolite in the rat was ethyl hydrogen-S-phenyl phosphorothiolate (54-59%) and that in mice was dihydrogen-S-phenyl. Diphenyl disulphide was found in faeces in both species, but metabolites such methyl phenyl sulphide and its derivatives were absent.

Poultry - distribution and excretion

Five groups of 4 chickens each were fed Hinosan at levels of 0, 1.5, 4.5, 15 and 45 ppm in the diet for 28 days. Only slight weight losses were noted in the two highest feeding levels. Only two giblet samples from the highest feeding level (45.0 ppm) showed any measurable residues (0.08 mg/kg). All other tissue samples had gross residues <0.01 mg/kg; 26-and 28-day egg samples from all the feeding studies indicated less than 0.001 mg/kg residue levels. No adverse effects could be detected on egg production for any of the treated groups compared to the control birds (Morris 1976).

In vitro hepatic subcellular metabolism

The metabolism of ^{35}S-edifenphos by hepatic subcellular fractions of five mammalian species was studied in *vitro* in order to investigate the effect of inhibitors against drug metabolism enzymes and to observe metabolism and degradation in hepatic microsomes that were induced by administration with phenobarbital. Additionally, animal speciesrelated differences of metabolic patterns, degradation and metabolism of edifenphos in five different species of mammalian hepatic subcellular fractions, including humans. was

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See Annex II for FAO and WHO documentation.

examined by the comparative method (Ueyama *et al* 1976).

The salient results were as follows: (a) enzymatic degradation of edifenphos occurred in both microsomal and soluble (105,000 g-supernatant) fractions; (b) degradation of edifenphos by microsomes was accelerated by addition of NADPH and inhibited by SKF 525-A or piperonyl butoxide; (c) ^{35}S-edifenphos was more rapidly metabolized by rat hepatic microsomes that were previously induced by administration with phenobarbital; (d) the above mentioned results suggested that a part of enzymatic degradation of edifenphos was accomplished by drug metabolizing enzymes; (e) the degradation of 35S-edifenphos by the soluble fraction was not increased by addition of glutathion; (f) the difference of metabolic patterns of edifenphos by hepatic microsomes of five mammalian species implied that the metabolic activity for edifenphos was as follows: guinea pig >rabbit >mouse >human >rat; (g) in the water soluble fractions of these mammalian microsomes, ethyl hydrogen S-phenyl phosphorothiolate was found for human and mouse, and dihydrogen S-phenyl phospihorothiolate was also found for mouse and rabbit.

Antiesterase activity in vitro and in vivo

The *in vitro* anticholinesterase action of Hinosan was measured by addition of the compound at several concentrations to homogenized rat brain in the cholinesterase system. Hinosan was a potent direct inhibitor of cholinesterase *in vitro* producing 50% inhibition of cholinesterase at a concentration of 1.05 X 10^{-6}M (Chen *et al* 1972).

The effect of Hinosan on cholinesterase activity in *vivo* was studied by giving 5/8 of the acute i.p. LD_{50} to male and female rats. Because of the sex difference in susceptibility, equitoxic doses amount to 16 mg/kg for females and 41 mg/kg for males. Hinosan is a very effective inhibitor *in vivo,* which gains access to and inhibits the cholinesterase activity of both the central nervous system and peripheral tissues and hence produces a generalized cholinergic action. The rapid onset of action and the extremely slow reversal of its inhibitory action on cholinesterase are two distinguishing features of this compound (Chen *et al* 1972).

Aliesterase inhibition

Data obtained by feeding Holtzman rats various levels of Hinosan in the diet (0.75, 5, 12.5, 25, 50, 75 and 100 ppm) for 1 week demonstrated that Hinosan was a strong inhibitor of aliesterases. The inhibitory effect of Hinosan on the enzymes that were examined was in the order of tributyrinase (the most susceptible), diethylsuccinase (the next most sensitive) and cholinesterase (the most resistant) (Chen *et al* 1972). (A similar order of susceptibility was obtained with several insecticidal organophosphorus compounds, Su et al 1971)

The dietary levels producing 50% inhibition of enzyme activity were obtained by plotting percent inhibition of the enzyme against the logarithm of the dietary levels. From this plot of data, 50% inhibition of hydrolysis of diethylsuccinate by liver and serum were found to occur at the levels of 11.5 and 7.4 ppm respectively for female rats, and 18.4 and 10.2 ppm respectively for male rats. The levels that produced 50% inhibition of tributyrin hydrolysis by liver and serum were found to be 5.4 and 9.5 ppm respectively for female rats, and 4.9 and 8.4 ppm respectively for male rats.

In a few experiments, Hinosan was fed at a dietary level of 5 ppm to young rats (28 days old) for 1 week. There was 60% inhibition of diethylsuccinate hydrolysis and 70% inhibition of the liver tributyrinase in young rats as compared with 3O% and 50% of the diethylsuccinase and tributyrinase, respectively, of adult rat liver at this same dietary level. However, the greater enzyme induction in the livers of young rats might be due to higher dietary intake, relative to body weight, than in adults (Chen *et al* 1972).

Effects of pre-treatment with microsomal enzyme inducers

Pre-treatment of animals with microsomal enzyme inducers has been shown to protect against the toxicity of various organophosphorus compounds. Pre-treatment of rats with phenobarbital, DDT, 3-methylcholanthrene or testosterone markedly reduced the anticholinesterase action of Hinosan (Chen *et al* 1972). The amount of inhibition of cholinesterase of brain and submaxillary gland of female rats was somewhat less than in male rats after treatment with the inducing agents. Phenobarbital and DDT were more effective in protecting against Hinosan toxicity than 3-methylcholanthrene and testosterone.

Pesticide potentiation

To ascertain the degree of potentiation of malathion toxicity by Hinosan, groups each containing 4 Holtzman rats were given a sublethal dose of malathion (400 mg/kg)i.p. after they had been fed for 1 week with various dietary levels of Hinosan. After feeding dietary levels of 0, 5 and 25 ppm, the mortality resulting from 400 mg/kg of malathion was 0, 25 and 100% respectively. Thus, Hinosan was shown to increase markedly the susceptibility of rats to malathion (Chen *et al* 1972).

TOXICOLOGICAL STUDIES

Acute toxicity

Edifenphos is intermediate in toxicity among the organophosphorus insecticides. A sex difference in the acute toxicity (oral and i.p.) to rats was observed, with male rats exhibiting greater resistance than females (see Table 1).

TABLE 1. Acute toxicity of edifenphos in four animal species

Species	Sex	Route	LD_{50}(mg/kg)	Reference
Rat	M	oral	340	Martin 1972
	M	oral	212	Bayer 1916
	F	oral	150	Martin 1972
	F	oral	100	Bayer 1976
	M	i.p.	66.5 ± 7.7	Chen *et al* 1972
	F	i.p.	25.5± 0.8	ibid.
		i.p.	26	Melnikov 1971
Mouse	M	oral	214	Bayer 1976
	F	oral	218	Martin 1972
Guinea pig		oral	350[1/]	Bayer 1976; Wisswesser 1976
Rabbit		oral	350[2/]	ibid; ibid.

1/ Technical product in ethanol/propylene glycol

2/ Technical product in Lutrol (polyethylene glycol 400).

In acute toxicity studies of orally administered edifenphos conducted on buffalo calves, it was shown that doses of 30, 45 and 60 mg/kg resulted in maximal inhibition of blood cholinesterase to the extent of 59.3, 71.4 and 73.9% respectively after 12 to 24h of edifenphos administration (Malik *et al* 1978a). The onset of severe toxic symptoms with higher doses (45 and 60 mg/kg) correlated well with the maximum inhibition of cholinesterase activity. The inhibited enzyme recovered slowly after 4 weeks, returning to 86.5 and 81.6% of the pre-treatment level with 30 and 45 mg/kg of edifenphos respectively. Doses of 45 and 60 mg/kg increased the serum glutamic-pyruvic transaminase levels (SGPT) while elevation in levels of serum glutamic-oxalacetic transaminase (SGOT) was found with all the doses, suggesting that edifenphos can induce internal tissue damage. Doses of 30 and 45 mg/kg resulted in a gradual rise of the SGOT level, which approached its peak at the second week and began recovering afterwards, but remained elevated 4 weeks after administration of edifenphos. No change in serum alkaline phosphatase activity was observed (Malik *et al* 1978a).

Short-term studies

Buffalo

Edifenphos was administered orally in daily doses of 4 and 8 mg/kg bw for 28 days to male buffalo calves *(Bubalus bubalis).* The lower dose did not produce any apparent toxic manifestation**.** With the higher dose all the animals died within 13 to 17 days. A gradual and significant inhibition of blood cholinesterase was noted with both the doses (p -0.01). The extent of inhibition of blood cholinesterase was not related to the severity of toxicosis. No significant change in levels of blood glucose, blood lactic acid, serum total cholesterol and serum creatinine was observed after the administration of the drug (Malik *et al* 1978a, b).

Edifenphos given at 4 mg/kg/day did not produce toxic symptoms until 28 days had passed, while doses of 8 mg/kg brought on toxic symptoms between days 11 and 14. The toxic symptoms included anorexia, depression, increased salivation, lachrymation and diarrhoea. Diarrhoea was more pronounced in the later stages and was followed by weakness of the hind legs and paralysis. Animals receiving 8 mg/kg of edifenphos showed maximum increases in SGOT levels of 141.73 and 167.77% on day 28 and 12 after the start of the study. The SGOT elevation was both dose and time dependent. SGPT levels were increased, but not significantly. No significant changes were noted in the serum alkaline phosphatase activity throughout the period (Malik *et al* 1978c).

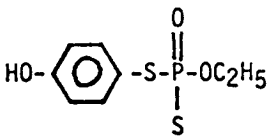
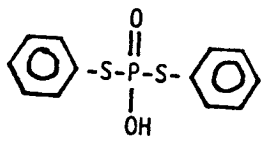
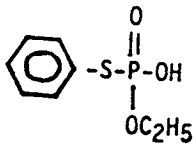
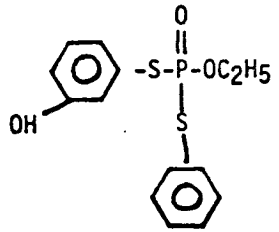
Rat

Groups of male and female rats were treated daily for 28 days with the following dosage regimens: (a) Hinosan, 20 mg/kg; (b) Hinosan/thiophenol (20:1), 5 and 20 mg/kg and (c) thiophenol, 1 and 10 mg/kg.

Hinosan 20 mg/kg bw as well as Hinosan/thiophenol (20:1), 5 and 20 mg/kg caused a reduction in cholinesterase activity. Doses of 5 mg of Hinosan/thiophenol 20:1 should be considered a no-effect dosage for both plasma cholinesterease as well as erythrocyte cholinesterase.

The liver metabolized all three of the above samples similarly, with no apparent differences. The effects found were: (a) increases in liver enzymes and liver weight (the effect was more pronounced in male than in female rats); (b) in the investigated dose levels no liver damage could be observed. All 3 samples induced definite kidney damage. In male rats, no minimal safe dose could be established for Hinosan or Hinosan/ thiophenol (20:1 mixture) and thiophenol. A borderline dose for male rats with thiopheriol is 1 mg/kg bw. Female rats tolerated 1 mg/kg bw thiophenol during the 28-day treatment without any damage. As a borderline dose for female rats, the following were considered: Hinosan/thiophenol (20:1 mixture)-5 mg/kg bw; thiophenol-10 mg/kg bw. The results indicate that the 3 test samples using the above mentioned dosages could induce kidney damage and somatic changes in the liver (Thyssen and Schilde 1978).

TABLE 2. Acute oral toxicity of Hinosan metabolites to rats [1/]

	Sample	Weight (g)	Sex	Dose (mg/kg)	Observations Deaths/ Symptoms/No. Exposed	Symptoms Begin within (h)	Symptoms End within (h)	Time of Death within (h)	LD_{50} (mg Samples/kg)
S36:	O-ethyl-S-phenyl-S-(4-hydroxyphenyl)-phosphorodithioate	270-320	M	500	0/0/5	---	---	---	> 500
		178-240	F	500	0/0/5	---	---	---	
				1000	0/0/5	---	---	---	>1000
S37:	S,S-diphenyl.phosphorodithioate	222-377	M	500	0/0/5	---	---	---	
				1000	0/5/5	1.5	24	---	>1000; <2000
				2000	4/5/5	0.5	48	16	
		180-253	F	500	0/0/5	---	---	---	
				1000	1/5/5	1	24	1.5	>1000; <2000
				2000	5/5/5	0.5	---	2	
S39:	O-ethyl-S-phenyl-phosphorothioate	230-364	M	500	0/5/5	1.5	24	---	
				1000	1/5/5	1.5	24	2	>1000; <2000
				2000	4/5/5	0.5	48	2.5	
		180-242	F	250	0/0/5	---	---	---	
				500	2/5/5	1.5	24	2.5	616 (397 to 954) [2/]
				1000	4/5/5	1	24	3	
				2000	5/5/5	0.5	---	1	
S64:	O-ethyl-S-phenyl-S-(3-hydroxyphenyl)-phosphorodithioate	156-266	M	500	0/5/5	2	24	---	
				1000	2/5/5	1	72	16	~1000
		168-198	F	250	0/0/5	---	---	---	
				500	2/5/5	2	48	3	~ 500
				1000	4/5/5	2	/ days	24	

1/ From Lamb and Matzkanin 1976; 2/ 95% confidence limits.

Long-term studies

Groups of 40 male and 40 female NMRI mice were maintained for 108 weeks on a diet containing SRA 7847 (supplied as a 50% premix) at dietary concentrations of 2, 15 and 100 ppm, respectively. The control group also consisted of 40 males and 40 females. Subgroups consisting of 20 male and 20 female mice each were additionally formed for haematological and clinical chemical tests. Physical appearance, behavioural patterns and survival rate of both males and females were not affected by administration of SRA 7847 even at the highest dietary level. No differences were seen between treated mice and controls with respect to growth rate and food consumption. The haematological and urinalysis data recorded for the treated groups and the controls were within the physiological range.

Glutamate-pyruvate transaminase (GPT) and alkaline phosphatase (AP) activities did not show any variations from normal in any of the groups. Blood plasma and erythrocyte cholinesterase activities in mice of the 15 and 100 ppm groups showed nonphysiological depression (more than 20%).

Statistically significantly increased thyroid weights (100 ppm group) and statistically significantly increased brain weights (15 and 100 ppm groups) were recorded, but only in male mice. A statistically significantly lower heart weight was additionally noted in the 100 ppm group.

The number of tumours noted in all groups corresponded to the known spontaneous tumour rate for the animal strain used in the study. There was no indication of a dose/ incidence relationship. Under the described experimental conditions SRA 7847 was not carcinogenic. Although benign pituitary tumours were observed in males of the 2 ppm group, the incidence was comparable to that in the control group.

Taking account of the cholinesterase activities, the no-effect dose in the chosen experimental design was stated to be 2 ppm SRA 7847 (Mohr 1980).

Special studies on acute oral toxicity of Hinosan metabolites

Four metabolites, e.g., S-36 [0-ethyl-S-phenyl-S-(4-hydroxyphenyl)-phosphorodithioate]; S-37 [S,S-diphenyl phosphorodithioate]; S-39[0-ethyl-S-phenyl-phosphorothioate] and S-64 [0-ethyl-S-phenyl-S-(3-hydroxyphenyl)-phosphorodithioate]were administered in a diluent of Lutrol (polyethylene glycol 400) to Sprague-Dawley rats fasted for 18 to 20 h. Dose volumes were given at 0.5% body weight. Lethargy, diarrhoea and ataxia were symptoms for S-39 treated animals. S-64 treated animals showed symptoms of lethargy, diarrhoea, muscular fasciculations, salivation and lachrymation. Occurrence and severity of symptoms were dose related. Although minor lung lesions occurred in a few animals on each compound, these lesions did not appear to be compound-induced. No other lesions were noted (Lamb and Matzkanin 1976). Table 2 illustrates the acute toxicity of the 4 metabolites in terms of the structures of S-36, S-37, S-39 and S-64; doses administered to rats of both sexes; observations (deaths) symptoms/number of animals exposed; time of beginning and end of symptoms, time and death and LD_{50}'s.

Special studies on mutagenicity

Edifenphos, tested at a concentration of 1 mg/ml in DMSO with screening methods consisting of the rec-assay procedure (a sensitivity test utilizing $H17Rec^{+}$ and $M45Rec^{-}$ strains of *Bacillus subtilis)* as well as the reversion assays on plates utilizing auxotrophic strains of *Escherichia* coli(WP 2) and *Salmonella typhimupium* strains TA1535 (reversible by base change type mutagens) and TA 1536, 1537 and 1538 (reversible by frameshift mutagens), was found to be nonmutagenic (Shirasu *et al* 1976).

In the dominant lethal test, no mutagenic effects were noted when edifenphos was administered to male mice in an acute oral dose of 100 mg/kg bw (Herbold 1980a).

A micronucleus test was performed with edifenphos according to the procedure of Schmid. The doses of edifenphos were 2 x 40 mg/kg and 2 x 80 mg/kg bw and for the positive control (Endoxan) 2 x 660 mg/kg orally administered to mice. No mutagenic effects were noted for edifenphos at the doses tested (Herbold 1980b).

RESIDUES IN FOOD

RESIDUES RESULTING FROM SUPERVISED TRIALS

Rice

Supervised trials were carried out at 3 locations in the USA in 1976. Hinosan 4.5 EC was applied one to four times at rates of 0.63 and 1.26 kg a.i./ha, which are in the recommended dose rate interval (0.3 to 0.8 kg a.i./ha) or somewhat higher (Mobay 1976). Hinosan DP and EC formulations were used at supervised trials in Japan. In 7 experiments edifenphos was applied three to four times at rates of 0.45 to 1 kg/ha (Nihon 1979).

Samples were taken 21 to 30 days after the last treatment, with two exceptions when samples were taken 60 days after the last application. Rice in husk, hulled rice, polished rice, rice bran, straw and hulls were analysed separately in most of the experiments. The limits of determination of analytical methods applied were 0.005 mg/kg in the Japanese experiments and 0.02 mg/kg in the USA ones.

The intact edifenphos was detected alone in all of the experiments. The results of these experiments, summarized in Table 3, showed no difference in the distribution of residues in samples taken 21 to 31 days after the last treatment, independently of the number of applications or dose rates. Measurable residue (0.005 to 0.16 mg/kg) was detected in polished rice and the residues in rice in husk were significantly higher than those found in previous experiments evaluated by the 1976 Joint Meeting.

Soil samples, taken from depths of 0 to 15 and 15 to 30 cm in the rice field at the same time as the rice samples, contained no detectable residue (<0.01 mg/kg) in all cases.

FATE OF RESIDUES

In animals

Lactating dairy cows were fed, via bolus, with technical edifenphos twice daily in equal portions for 28 consecutive days. Dosages administered to animals were 0.9 mg/kg and 5.7 mg/kg on a dry feed basis, which were approximately equivalent to 0.03 and 0.17 mg/kg bw/day respectively.

Residues in milk samples taken 26 to 28 days after the first treatment were below the limit of determination (<.001 mg/kg) in all cases.

In another experiment, edifenphos was mixed in alfalfa meal and pressed into pellets to provide 5, 15 and 50 mg/kg concentrations in the feed. The pellets were fed to lactating cows for 28 days (Mobay 1976b). The animals were sacrificed 28 days after first application and brain, heart, liver, kidney, muscle and fat samples were analysed for edifenphos. No residue (<0.01 mg/kg) was detectable in any of the samples with the exception of liver, in which 0.02, 0.07 and 0.13 mg/kg edifenphos was found at the 50 mg/kg feeding level.

Laying hens kept on a diet containing 1.5, 4.5, 15 and 45 mg/kg technical edifenphos were sacrificed 28 days after consecutive feeding. Eggs were collected on the 26th and 28th days. Giblet, muscle, fat, skin and eggs were sampled and analysed for edifenphos.

TABLE 3. Residues of edifenphos in rice

Sample	Dosage (a.i. kg/ha)	Number of samples in residue ranges (mg/kg)								
		≤0.02	≤0.05	≤0.1	≤0.2	≤0.5	≤1	≤2	≤5	≤10
Rice in husk	0.45-0.63	1	1	1		1	1	1		
	1-1.26	2						2		
Rice(hulled)	0.45-0.63	2	1	3						
	1-1.26	7	1	1	1					
Rice(polished)	0.45-0.63	9								
	1-1.26	10								
Rice bran	0.45-0.63	4		1		4	1			
	1-1.26	3		1	2	2	1			
Straw	0.45-0,63	2							3	
	1-1.26	1		2			2	1	1	
Hulls	0.45-0.63			1	2	2		2	1	
	1-1.26			2	1	1		2	2	1

Two of the three giblet samples contained 0.08 mg/kg residue, but none was detected in an tissues or in eggs above the limit of determination, i.e. 0.01 mg/kg in tissues and 0.001 mg/kg in eggs.

EVALUATION

COMMENTS AND APPRAISAL

Satisfactory data were received detailing the results, required by the 1979 JMPR, of the carcinogenicity study in mice. These alleviated concern with respect to this aspect of toxicology.

The concerns regarding effects on the liver in experimental animals previously reported were reconsidered. They were deemed to be of doubtful significance since they appeared to result from liver microsomal enzyme induction. Hence an ADI was allocated.

Results of supervised trials, carried out in the USA and Japan, indicated no difference in the distribution or levels of residues in samples taken 21 to 31 days post- treatment, independently of the number of applications or dose rates. These results support the changes proposed by the 1979 JMPR for rice, in husk, rice, hulled and rice, polished.

The residue of edifenphos was below the limit of determination in various tissues (<0.01 mg/kg), milk or eggs (<0.001 mg/kg) of lactating dairy cows and laying hens fed with feed containing edifenphos up to 15 mg/kg.

The liver of cattle and poultry giblets were the only samples containing detectable residues up to 0.13 and 0.08 mg/kg at a diet of 50 and 45 mg edifenphos per kg, respectively, for 28 days. The results of feeding studies indicate that no detectable residue can be expected in animal products deriving from animals fed withstraw and bran of rice treated with edifenphos according to good agriculture practice.

Level causing no toxicological effect

Mouse	:	10 ppm in the diet equivalent to 1.53 mg/kg bw/day
Rat	:	5 ppm in the diet equivalent to 0.25 mg/kg bw/day
Dog	:	20 ppm in the diet equivalent to 0.58 mg/kg bw/day

Estimate of acceptable daily intake for man

0 - 0.003 mg/kg bw

RECOMMENDATIONS OF RESIDUE LIMITS

On the basis of the new data the Meeting recommends the following additional temporary maximum residue limits. The levels refer to the parent compound only.

Commodity	MRL (mg/kg)
Rice bran	1
Milk	0.01 *
Carcass meat of cattle	0.02 *
Cattle meat by-product	0.02 *
Meat of chicken	0.02 *
Chicken by-products	0.02 *
Eggs	0.01 *

* Limit of determination.

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