VI. Toxicity

A summary of toxicological studies conducted with isoxathion is outlined below.

1. Acute Toxicity

Animal		Route	LD_{50}(mg/kg)
Rat	(♂)[a]	Oral	112
Rat	(♂)[a]	Dermal	>450
Mouse	(♂)[a]	Oral	98.4
Mouse	(♂)[b]	Oral	79.1
Mouse	(♀)[b]	Oral	92.2
Mouse	(♂)[b]	Intraperitoneal	105.4
Mouse	(♀)[b]	Intraperitoneal	137.4
Mouse	(♂)[b]	Subcutaneous	719.5
Mouse	(♀)[b]	Subcutaneous	737.9
Chicken	(♂)[a]	Oral	21.6

[a) Central Research Laboratories, Sankyo, 1966-1968,

b) Laboratory Animal Science and Toxicology Lab., Sankyo, 1975].

2. Skin Irritation

Isoxathion caused no skin irritation responses in rabbits (Laboratory Animal Science and Toxicology Lab., Sankyo, 1974).

3. Ninety-Day Feeding Studies

Rat

Test groups, each consisting of 10 male and 10 female rats (Wistar), were fed at dietary levels of 0, 3.2, 6.3, 12.5, 25, 50 and 100 ppm of isoxathion for 90 days. No significant changes in behavioral reactions, growth rates, food consumption, blood counts and pathological findings in organs could be observed. Plasma cholinesterase depression, however, was noted at levels of 50 ppm and above (Tohoku University, 1970).

Test groups, each consisting of 10 male and 10 female rats (Wistar-Imamichi), were fed at dietary levels of 0, 12.5, 25, 50, 100 and 200 ppm of isoxathion for 90 days. Dosed groups were similar to the control group with regard to survival rates, food consumption, body weights, haematology, and gross and microscopic pathology. A dose-related cholinesterase inhibition, however, was found in plasma at higher levels, which made the no-effect levels of isoxathion 25 ppm to the male and 12.5 ppm to the female (Tokyo Dental College, 1969).

Mouse

Test groups, each consisting of 10 male and 10 female mice (DDY), were fed at dietary levels of 0, 3.2, 6.3, 12.5, 25, 50 and 100 ppm of isoxathion for 90 days.

No significant changes in behavioral reactions, growth rates, food consumption, blood counts and histopathological findings in organs could be observed. A plasma cholinesterase depression, however, was noted at levels of 6.3 ppm and above (Tohoku University, 1970).

Test groups, each consisting of 15 male and 15 female mice (ICR-JCL), were fed at dietary levels of 0, 6.25, 12.5, 25, 50 and 100 ppm of isoxathion for 90 days.

Dosed groups were similar to the control group with regard to survival rates, food consumption, body weights, haematology, and gross and microscopic pathology. Plasma cholinesterase inhibition occurred at levels of 12.5 ppm and above. Erythrocyte cholinesterase inhibition occurred at levels of 25 ppm and above. Brain cholinesterase was slightly depressed at the level of 100 ppm (Tokyo Dental Colledge, 1969).

4. Two-Year Feeding Studies

Dog

To test groups, each consisting of 3 male and 3 female beagle dogs, was administered isoxathion incorporated into a stock diet at dose levels of 0, 0.2, 0.6 and 1.2 mg/kg/day for 104 weeks.

During and after the consecutive administration period of 104 weeks, no changes were observed in behavioral reactions, growth rates, food consumption, haematological findings, blood-chemical findings, organ weights and macroscopic findings of various organs. Cholinesterase activity in red blood cells and plasma, however, was markedly reduced immediately after the first daily administration of isoxathion at dose levels of 0.6 and 1.2 mg/kg/day, and this reduction lasted until the end of the experiment. Vacuolation of liver cells was observed in one each of both sex in the group that received isoxathion at 1.2 mg/kg/day (Shizuoka Pharmaceutical College, 1974).

Rat

Isoxathion was incorporated into a stock diet and fed to test groups, each consisting of 30 male and 30 female rats (Wistar), at dose levels of 0, 0.6, 1.2, 2.4 and 35 mg/kg/day for 104 weeks.

Isoxathion caused no significant changes in the behavioral reactions, mortality, food consumption, haematological findings, organ weights, and gross and histopathological findings, except the followings.

After the consecutive administration period, cholinasterase activity in red blood cells at levels of 2.4 and 35 mg/kg/day and that in brain at the level of 35 mg/kg/day were considerably reduced in the male rats. In the female rats, cholinesterase activity in both red blood cells and brain was considerably reduced at 2.4 mg/kg/day and above.

Three weeks after the final daily administration, cholinesterase activity in both male and female rats was recovered to nomal at 2.4 mg/kg/day. Cholinesterase activity in both red blood cells and brain of the male and in the brain of the female, however, was found to be still slightly reduced at the level of 35 mg/kg/day.

Body weight gains in the dosed groups were not significantly different from that of the control, except in the group dosed at 35 mg/kg/day. The body weight gains in both male and female rats at the 35 mg/kg/day dose level had a tendency to be depressed at the terminal stage of the experiment.

There were no abnormal blood-chemical findings, except for an increase of the serum alkaline phosphatase activity found in the female 35 mg/kg/day-dose group.

Tumour incidence was comparably between groups (Shizuoka Pharmaceutical College, 1974).

5. Three-generation Reproduction Study Including Teratology Phase in Rats

In a three generation reproduction study, three groups, each consisting of 25 male and 40 female rats received diets containing 0, 2.5 and 12.5 ppm of isoxathion.

No treatment-related effects on behavioral reactions, survival rates, body weight gains and food consumption were observed in parental animals. Fertility, gestation, viability and lactation indices were comparable to control values. No foetal malformations could be attributed to isoxathion.

Offsprings from isoxathion-treated rats showed a normal postnatal growth, food consumption and general status. No macroscopical, histopathological, haematological and blood-chemical abnormalities were found in the offsprings (Shizuoka Pharmaceutical College, 1974).

6. Mutagenicity

Isoxathion have been examined for its mutagenic activity in 2 strains of *B. subtilis,* a strain of *E. coli* and 5 strains of *S. typhimurium* by using a direct exposure method in vitro and in 1 strain of *S. typhimurium* by using a host-mediated assay method (ICR strain mice).

Isoxathion did not affect the mutation rates by either of the methods (The Institute of Environmental Toxicology, 1977).

7. Delayed Neurotoxicity to Hens

Isoxathion and tri-*o*-cresyl phosphate (TOCP) dissolved in a vegetable oil were administered daily into hen's crops by using a pipette for 4 days at dose levels of 5.25 and 125 mg/kg/day, respectively. Each test group consisted of five 69-week old white Leghorn hens. The daily dosage of each chemical was 1/4 of its LD_{50} value. The vegetable oil was given to a control group. Clinical signs were recorded for 21 days after the final administration. The birds were sacrificed and pathologically examined, especially with the sciatic nerve, on 25th day after the first daily administration.

During the observation period the appetite and the laying rate were comparable between the isoxathion-treated group and the control group. From 10th day after the final administration every hen in the TOCP-treated group had an attack of leg paralysis and could not walk.

Histopathological studies showed that the demyelination and the degeneration of axon in sciatic nerve occurred definitly in the hens treated with TOCP. These abnormalities were not in the hens treated with isoxathion (Central Research Laboratories, Sankyo, 1977).

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