US EPA ARCHIVE DOCUMENT

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Addendum to the S.F. Biscardi review of
EPA Nos. 3215-EUP-146, 147, 148 (3/20/79)

TO: Program Manager #16

SUBJECT: PP# 8F2090

FROM: Toxicology Branch - C. Frick C. Frick 11/5/81

ACTION: Review of two-year feeding study in the dog from the above petition (8F2090) employing oftanol (technical) as the test compound.

RESULTS: On the basis of this two year feeding study a NEL of 2 PPM and a safety factor of 10X can be used to determined the ADI and MPI (see enclosed computer printout).

It will be noted that based on the above calculations the percent of ADI used in the implementation of EPA Nos. 3125-EUP-146, 147, 148 is 10.55% as opposed to the calculated 421.86% found in the Biscardi review which was based on a 90-day dog feeding study; NEL of 1 PPM and safety factor of 200X.

PP# 8F2090

Chronic Toxicity - two Year Feeding Study in the Dog

Study performed at Bayer AG Institut Für Toxikologie, October 25, 1977 by K. Hoffmann and G. Kaliner - Report No. 7072, SRA 12-869 Submitted by Chemagro Agricultural Division Mobay Chemical Corporation.

Material Tested

SRA 12-869, common name is isofenphos, tradename is oftanol. Chemical name is O-ethyl-O-(2-isopropoxy-carbonyl)phenyl isopropyl phosphoramidothioate. Technical grade compound is 89.3% and it was necessary to prepare a 50% premix with Wessalon S in order to administ er the test compound with the animal food.

Animals Tested

Thirty-two pure-bred Beagle dogs which at the start of the study were 22 to 29 weeks old and weighed between 5.9 and 11.0 kg. All animals were housed individually. Food consumption was controlled and actual consumption measured.

Protocol

8 Animals Per Test Group (4 male and 4 female)

Control group	0 PPM	
Group I:	Male dogs:	3 PPM from week 1-83
		2 PPM from week 84-104
	Female dogs:	3 PPM from week 1-104
Group II:	15 PPM	
Group III:	75 PPM from week	1-53
	150 PPM from week	54-99
	300 PPM from week	100-104

The following parameters were investigated:

1. General examination
2. Ophthalmoscopic examination
3. Hematology
4. Clinical chemistry
5. Cholinesterase activity (Plasma, RBC, Brain)
6. Urinalysis
7. Food and test compound intake
8. Body and organ weights
9. Gross and histopathology

Results

Clinical findings - The dietary levels of up to and including 75 PPM were well tolerated. The dogs receiving these dose levels showed no differences from the controls in physical appearance and behavioral patterns. It was not until after the dietary concentration had been raised from 75 to 150 PPM that symptoms associated with the test compound's cholinesterase-inhibitory effect were noted toward the end of the second treatment year. When the concentration was raised from 150 to 300 PPM as from Week 100, the symptoms became intensified especially among the males; one dog in this group died in Week 104 and another had to be sacrificed in a moribund condition.

Food consumption and food intake times were not affected by administration of test compound at concentrations of up to and including 150 PPM.

There were no noteworthy differences in body weight gains between the dogs fed test compound at levels of up to and including 150 PPM and the controls. It was not until the level was raised to 300 PPM that body weight depressions were noted in all males and in 3 of the 4 females of Group III.

Ophthalmoscopic examination of the eyes provided no indication of any treatment-related variations from the physiological norm in either the transparent media or on the Fundus oculi.

Hematological tests were performed before the start of the feeding experiment and in Treatment Weeks 14, 27, 39, 53, 66, 79, 92 and 104. The following were measured: hematocrit level, hemoglobin, medium cell hemoglobin, erythrocyte count, reticulocyte count, thrombocyte count, sedimentation rate and thromboplastin time. Nothing extraordinary noted with the possible exception noted in Dog C537/Group III just before the dog died; it had a marked increased in the number of stab leucocytes, accompanied by a reduction in the number of segmented cells. The 7% "other" cells were made up of 4% myelocytes and 3% immature. At the same time, a substantially accelerated sedimentation rate was noted in this animal. The explanation given was that these alterations are considered to have been due to an accelerated decomposition of the blood and a reactively increased formation of new blood cells from the bone marrow.

Clinical chemistry was performed in the same intervals as hematology. The following were measured: glucose, urea, creatinine, total protein, GOT, GPT, Alkaline phosphatase and cholesterol. Nothing extraordinary noted with the following exceptions: alkaline phosphatase activity level in the Group III control level, or increased still further as the treatment progressed. This effect is attributed to the increase of the test compound in the diet from 75 to 150 PPM as from treatment Week 54.

Plasma cholinesterase activity depression was observed in animals with dietary concentrations of 15 PPM and above. The dietary concentration of 3 PPM of test compound did not cause any marked depression of plasma cholinesterase activity in female animals. In the male dogs the 3 PPM level showed some depression. The reduction of plasma cholinesterase in the male dogs in Group I were seen to have slightly exceeded the 20% tolerance at some of the testing intervals. For this reason, the dietary concentration of test compound administered to the male animals in Group I was reduced from 3 PPM to 2 PPM in the 84th week. The results were such that in the last 20 weeks of treatment the plasma cholinesterase levels in the male dogs returned to normal and did not differ substantially from the control group in Weeks 92 and 103.

Erythrocyte cholinesterase activity was not reduced in either male or female dogs at dietary levels of up to and including 15 PPM.

Brain cholinestersase activity measured in week 104 was not depressed by the test compound in dietary concentrations of up to and including 15 PPM. The level of 300 PPM depressed this enzyme by an average of approximately 65% as compared to the controls.

Urinalyses

Nothing extraordinary noted.

Gross Pathology

No consistent pathology or dose relationship was noted. The following tissues were weighed and examined: brain, lung, liver, spleen, kidneys, pituitary, thyroid, adrenals, testes, heart, ovaries, prostate gland and pancreas.

Absolute and relative organ weights

Nothing extraordinary noted.

Histopathology

The following tissues were taken from all animals and fixed in Bouin's solution, embedded in Paraplast, stained with hemalum and eosin:

small and large intestine
heart
testes
pituitary
liver
lung
stomach
spleen
epididymides
adrenal
kidneys
esophagus
ovaries
prostate gland
thyroid and uterus

In addition the following tissues from the control dogs and the dogs of the highest dose group (300 PPM) were similarly processed and examined: eyes, aorta, fasciculi optici, gall bladder, brain, urinary bladder, bone and bone marrow, mesenteric lymph nodes, Nervus ischiadicus, pancreas, parotis, skeletal muscle and thymus.

In three of the four male dogs in the 300 PPM dose group the esophagus showed erosions of variable microscopic distension and the propria mucosae showed cell infiltration and proliferation. Some alterations seen in the brain stems in two dogs at the high dose level (300 PPM) were interpreted to be foci of softening (degenerative processes) the intensity of this finding in the high dose group might be treatment related. No other consistent or dose related pathology was noted.

Conclusion

Because of the wide dosage difference between systemic effects compared to cholinergic effects, a safety factor of 10X reflecting cholinergic toxicity is employed.

Based on this study the NEL = 2 PPM
Study classification - Core Guideline