

US EPA ARCHIVE DOCUMENT

Memorandum

Date: 29 November 1983

Subject: EPA Reg. Nos. 3125-330; 3125-331 OFTANOL 5% GRANULAR, 1.5% GRANULAR
Caswell #447AB
In 11-16-83; record nos. 106839; 108760

From: B. T. Backus
IRB/TSS

To: Mr. William Miller
Product Manager 16

Registrant: Mobay Chemical Corp.
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Background:

According to the state of California, the active ingredient in this formulation has been found to be a delayed neurotoxin at a dosage level of approximately 100 mg/kg in atropinized hens.

Comments and Recommendations:

The acute oral toxicity study for Oftanol is in Acc. 096657. The study was carried out at the Institute for Toxicologie, Wuppertal-Elberfeld, and is dated March 20, 1972.

The report focuses on 3 groups of 5 or 6 hens, either dosed with 20 mg/kg active with no atropine pretreatment, dosed at 14 mg/kg with protective atropine pretreatment, or dosed with 350 mg/kg TOCP (positive controls). The first two groups were part of a much larger number of groups that had been used to determine the oral LD₅₀ of oftanol (reported as 20.9 (17.6-24.9) mg/L) with and without atropine. At these particular dosage levels, observation was for 3 weeks, followed by sacrifice with preservation of key nervous tissues (brain, spinal cord, sciatic nerve). Preserved tissues were subsequently examined at the Huntingdon Research Centre, ~~with Oftanol were reported to have minor neurological change.~~ Although a number of minor neurological changes (such as small perivascular accumulations of lymphocytes in meninges, occasional perivascular accumulation of lymphocytes in one section (of the spinal cord)) are reported, the conclusion (p. 59, Acc. 096657) is:

"No morphological change or variation from normal was seen in any of the tissues examined that was considered to be related to the administration of the compound under test."

Nervous tissue was examined only from a relatively low number of hens (5 or 6 per dosage level). It is not clear, for example, why 3 hens protected by atropine which survived a dosage level of 100 mg/kg were not so examined. It is noted, however (p. 54)

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that these hens evidenced no symptoms of delayed neurotoxicity.

Before any conclusions can be drawn, it would be appropriate to obtain a copy of the delayed neurotoxicity study conducted by or for the state of California.

2. In addition to possible delayed neurotoxicity effects, this reviewer is concerned that there are indications of brain ChE inhibition at relatively low exposure levels. The statement is made (p. 83, Acc. No. 096657) that groups of 5M rats were treated orally with the test compound at dose levels of 1.0, 2.5 and 3.0 mg/kg and "Measured levels of brain cholinesterase activity depression 24 hours after the application were 0, 23 and 74% respectively." A dosage level of 3 mg/kg is approximately one-tenth the oral LD₅₀ value for the technical active.

In a 13-week feeding study, brain ChE activity inhibition is reported at a dietary dosage level of 25 ppm (p. 164, Acc. 096657). Data on p. 159 suggest there may even be an effect at 5 ppm, but this is not statistically significant, possibly because of the low number of subjects used (3 rats/sex/exposure level).

3. It would be appropriate for the Toxicology Branch, HED, to address both the delayed neurotoxicity issue (once a copy of the California study is provided) and the question of brain ChE inhibition. A copy of the data in Acc. 096657 should be provided.

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