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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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MAY 17 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPTC Registration Standard - Review of Subchronic Inhalation Study Submitted by Stauffer January 17, 1985, Assigned Accession No. 256485
EPA Registration No. 476-2140

Caswell No. 435
EPA Chem. No. 041401

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05-07-86

TO: Robert J. Taylor, PM 25
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THRU: Jane E. Harris, Ph.D., Head
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5/8/86

5/7/86

Registrant: Stauffer Chemical Company.

Action Requested:

Review and evaluate the following study, submitted as supplementary information by the registrant, January 17, 1985:

Subchronic Inhalation Toxicity of EPTAM® in Rats, Study No. T-10422, dated March 5, 1982, conducted at the Environmental Health Center, Stauffer Chemical Company, 400 Farmington Avenue, Farmington, CT 06032.

TB Conclusions:

The study is graded Core-Minimum Data, and reports the following treatment-related effects from 13 weeks exposure (6 hrs/day, 5 days/week) at levels of 0, 8.3, 58, and 290 mg/m^3:

At the HDT (290 mg/m^3) - In both sexes: increased SGOT, related to histological finding of an increased incidence

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and severity at termination of myocardial degeneration (cardiopathy); ocular irritation; decreased brain AChE activity, unrelated to plasma or erythrocyte activities; decreased food consumption; and transient histopathological changes in the nasal epithelium and sinuses. In addition, but only in females, increased prothrombin time (PT) and hepatocellular lipoidosis ("fatty degeneration").

At the mid-dose (58 mg/m^3) - In both sexes, ocular irritation, decreased food consumption and transient histopathological changes in nasal epithelium and sinuses; additionally, but only in females, increased PT; and in males only, decreased brain cholinesterase values. At the LDT (8.3 mg/m^3) - No clinical or histopathological alterations.

It is concluded that the NOEL is 8.3 mg/m^3. A detailed Data Review follows:

Toxicology Branch: Data Review

Test Material: Eptam Technical (EHC 0081-31), 98.6% ai, a light-yellowish cloudy liquid.

Procedures:

Groups of 24 male and 24 female 7- to 8-week-old Sprague-Dawley rats were exposed to aerosolized test material (particle size, MMADar = 2.8 um) 6 hr/day, 5 days/week for 13 weeks (for a total of 65 exposure days) at mean inhalation chamber concentrations of 0, 8.3, 58, and 290 mg/m^3. All animals were observed daily and weighed weekly, at which times food consumption was estimated. Six/sex/group were bled prior to treatment and again during week-8 of exposure for hematological (hct, hb, and CBC) and clinical chemistry (glu, BUN, LDH, SP, bili, SGPT, SGOT, AP, chol) values; at terminal necropsy (week-14), these animals were evaluated for treatment-related changes in these parameters, as well as for brain cholinesterase activity. Two subgroups of six/sex/treatment were sacrificed during weeks 3 and 9-10 and evaluated for clotting parameters (prothrombin time, Russell viper, partial thromboplastin time) and cholinesterase inhibition (plasma, rbc, brain). All surviving animals were necropsied during week-14, body and organ weights recorded, and all Guidelinesprescribed tissues examined both grossly and histologically.

Results:

One animal died during week-5 of the exposure period, a low-dose male (cause undetermined). Treatment-related ocular irritation, chromodacryorrhea, and alopecia were observed at all exposure levels, but earlier and in more mid- and high-dose animals than in controls (or the low-dose group). Significantly lower than control (by Dunnett's t-test) food consumption was recorded at the two higher dose levels at various time points. No treatment-related effects were apparent in body weight gain at study termination. Several scattered statistically significant changes in hematology and clinical chemistry values considered of little or no biological significance were recorded at all exposure levels. However, the increase in SGOT for the highdose group measured at termination (especially in females, at 135 u/L vs. 88 u/L for controls) was considered biologically significant since it correlated with increased incidence and severity of myocardial degeneration (observed in both sexes). Consistent depression in brain cholinesterase activity (but not in erythrocyte or plasma values) in terminal high-dose males and females as well as in mid-dose males was recorded. On the other hand, only females exposed to 58 and 290 mg/m^3 Eptam had increased PT at termination, whereas only in high-dose males were increased PTT values considered biologically relevant, since the latter was accompanied by a statistically mean increase in stypven time measurements.

Slight but statistically significant lower mean terminal organ weights and organ weight-to-body weight ratios recorded in mid- and high-dose animals were considered to have no biological significance. These changes were mainly associated with lower terminal body weights (especially in the high-dose group), and further, had no correlation to histopathological findings.

Whereas a variety of gross and histopathological changes were found among all animals on study, the incidences for the majority of such changes were comparable among all test groups and controls. However, as tabulated on the following page, histological alterations with a significant incidence and/or severity pattern were considered treatment related for the heart (in both sexes), liver (in females), and portions of the upper respiratory tract (the latter considered typical responses to inhalation exposure of a "mildly toxic material"). Additionally, all animals had evidence of "murine pneumonia" (as indicated in Report Tables 29, 30):

Myocardial degeneration was observed in animals sacrificed at 3, 9-10, and 14 weeks, with increased severity and incidence in high dose animals of both sexes shown at termination.

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Significant Histopathological Findings in
Eptam-treated Rats* (24 animals/sex/treatment)
Sacrificed at 3, 9-10 and 14 Weeks.

Organ/Lesion	No. affected at exposure level of (mg/m^3):							
	0		8.3		58		290	
	Males	Females	Males	Females	Males	Females	Males	Females
HEART: Myocardial degeneration	17 (71%)	18 (75%)	7 (29%)	14 (58%)	20 (83%)	14 (58%)	24 (100%)	24 (100%)
LIVER:								
Focal subchronic lymphocytic pericholangitis	1	1	-	-	-	-	-	-
Focal nonsuppurative hepatitis	16	18	17	8	22	18	24	12
Telangiectasis	1	-	-	-	-	-	1	-
Focal bile duct proliferation	3	-	3	11	-	3	-	1
Multifocal necrosis with hemorrhage	1	-	-	-	-	-	-	-
Focal hepatocellular lipidosis	-	1	-	5	1	-	-	15
NASAL TURBINATES:								
Subepithelial lymphoid tissue present	20	18	13	19	19	19	20	14
Necrotizing rhinitis	-	-	-	-	-	-	2	-
Paranasal sinusitis	1	-	-	-	1	-	3	-
Focal basal cell hyperplasia with squamous metaplasia	-	2	-	-	3	-	-	6
Segmental degeneration and attenuation of olfactory epithelium	-	-	-	-	4	2	-	3
Suppurative rhinitis	-	-	-	-	-	1	-	-
Mucosa Focal epithelial cell degeneration and microcyst formation	-	-	-	-	1	-	-	-

* Extracted from individual microscopic findings of the Report's Appendix XXIII, and summary Tables 29 and 30. The severity and incidence of specific treatment-related lesions were stated to have been summarized in "Table 31" but no such tabulation was included in the Report, nor listed in the table of contents.

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The early stage was described as involving "multiple focal hyaline or smooth deeply eosinophilic staining of myocardial muscle bundles . . .," developing in later stages into degenerative ". . . loss of structure, vacuolization of muscle fibers and increased numbers of sarcolemma or fibrocytic cells, and infiltration of a few macrophages and lymphocytes." This lesion (found more commonly in aged rats) is ascribed by the authors to ". . . one of the rat viruses. . . [exacerbated by]. . . exposure of rats to 290 mg/m^3 Eptam."

Hepatocellular lipidosis ("fatty degeneration") was found in a total of 15/24 high-dose females (but in no high-dose males) and at each of the sacrifices (5/6 at 3 weeks; 6/6 at 10 weeks; 4/12 at termination). This alteration was considered a response to the mild systemic toxicity induced by Eptam.

The authors concluded that rats exposed to Eptam vapor at average levels of 8.3, 58, and 290 mg/m^3 manifested the following treatment-related effects:

At the HDT (290 mg/m^3) - both sexes: ocular irritation, chromodacryorrhea and alopecia; occasional decreased food consumption; increased SGOT; decreased brain cholinesterase; transient histopathological changes in nasal epithelium and sinuses; increased severity and incidence of myocardial degeneration at termination. In addition, but in females only: increased prothrombin time; higher incidence of hepatocellular lipoidosis. In males only: increased partial thromboplastin time accompanied by increased stypven time.

At the mid dose (58 mg/m^3) - both sexes: ocular irritation, chromodacryorrhea and alopecia; occasional decreased food consumption; transient histopathological changes in nasal epithelium and sinuses. Additionally, but only in males, decreased brain cholinesterase values; while in females only, increased prothrombin time.

At the low dose (8.3 mg/m^3) - no alterations compared to controls, hence this level was suggested as the NOEL.

TB Evaluation:

The study is graded Core Minimum Data. The increased severity and incidence of myocardial degeneration (a necrotic lesion more commonly found in aged rats) at the HDT may very well be associated with a viral infection in this colony, considering that, except for one mid-dose EPTAM-treated male, all animals in the study, including the controls, were diagnosed with murine pneumonia.

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