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

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MEMORANDUM

OFFICE OF TOXIC SUBSTANCES

SUBJECT: Clearance of Dowacil 75 as a Preservative under 40 CFR 180.1001(d)

FROM: Gary Burin, Toxicologist GB 6/10/80
Toxicology Branch, HED (TS-769)

TO: Reto Engler, Chief
Disinfectant Branch
Registration Division (TS-767)

THRU: William Burnam, Acting Chief WJB
Toxicology Branch, HED (TS-769)

Background Information

See memos (attached) of April 23, 1980 from K. Bailey and April 16, 1980 from G. Burin for discussions of background information pertaining to use of Dowacil 75 as an inert ingredient. Reto Engler, Chief, Disinfectant Branch, has recently (Memo of May 2, 1980; attached) requested the re-examination of the subchronic dog and rat studies of Dowacil and the classifying of these studies according to the core concept.

Review

90-Day Subchronic Oral Study, Beagle Dogs. Dow Chemical Company, February 13, 1976.

Dowacil 100 was administered in gelatin capsules at dose levels of 0, (7.5,) 15 and 30 mg/kg/day to 4 animals/sex/dose for 90 days. The following parameters were recorded; appearance, behavior, body weight, food consumption, hematology, blood chemistry, urinalysis, ophthalmologic findings, organ weights, mortality, gross and histopathology.

Results

No mortality was observed with the exception of one female of the high dose group that was sacrificed in extremis on day 84. No treatment related observations were reported. Weight gain was not significantly effected at any exposure level. A significant depression in packed cell volume, red and white blood cell count and percent hemoglobin was observed in high dose males and a decrease that was not statistically significant was reported in

those parameters in high dose females. BUN, SGPT, SAP and SGOT were not effected in a manner indicative of compound toxicity. The results of urinalysis are equivocal - a dose related trend in proteinuria is not apparent, however, male animals in the treatment groups appear to have slightly greater proteinuria than control males. (FDA has concluded that due to increased proteinuria a NOEL has not been established in this study). Although proteinuria can be an indication of glomerular damage, it can also be an artifact of collection or analysis of the urine. Submission of pretreatment urinalysis data (reported to have been performed but inexplicably omitted from report) may help in the interpretation of this finding.

The absolute and relative heart weights of males were less than control animals at the 15 and 30 mg/kg/day dose levels. Increased absolute and relative liver weights were observed in high dose males and females compared to controls.

Gross examinations of the sacrificed female found marked abdominal ascites, hemorrhagic foci in the liver, adhesions of the hepatic capsule, thickening of the gall bladder wall and stool contents that were stained with bile. Gross examination of other males and females revealed no other treatment related findings.

Histopathology showed obliterative vasculitis and perivasculities of hepatic blood vessels in 4/4 males and 3/4 females in the 30 mg/kg/day group and 1/4 females in the 15 mg/kg/day group. Moderate perivascular and pericholangiolar infiltration of mononuclear cells and hyperplasia of reticuloendothelial cells lining the hepatic sinusoids was reported in 7/8 animals in the high dose group.

Classification

Supplementary data. The primary deficiency of this study is the use of beagles that were approximately 12 months old. Animals of this age have attained maximum body weight and most organs have fully developed (See Anderson, A. "The Beagle as an Experimental Dog", Iowa State University Press, Ames, Iowa, 1970, p. 43-106).

Proposed Guidelines of August 22, 1978 called for initiation of dosing in dogs 4-6 months old - the rationale being that it is necessary to assess subchronic toxicity in animals during the period of maximum growth.

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90-Day Subchronic Oral Studies, Rats. Dow Chemical Company, December 13, 1972 and August 7, 1972.

Two consecutive 90-day feeding studies of Dowacil 100 were performed; the first using dose levels of 0, 60, 30, 15, and 7.5 mg/kg/day and the second using dose levels of 0, 4, 2 and 1 mg/kg/day. Both studies were conducted in 10 rats/sex/dose. Hematology, urinalysis, blood chemistry, body and organ weights, food consumption, mortality, appearance, gross and histopathology were recorded.

Results

No mortality was observed in either study. Minimal hepatocellular swelling observed in 3/5 60 mg/kg/day males but not in control, 30, 15, or 7.5 mg/kg/day males or females.

A nephroblastoma, accompanied by decreased spermatogenic activity, was found in a single 60 mg/kg/day male. 30, 15, 7.5, 4, 2 and 1 mg/kg/day females and males were not examined microscopically (with the exception of the livers of 30, 15 and 7.5 mg/kg/day males). Other histopathology included intestinal nematodiasis (found in 5/10 control animals and 3/10 high dose animals) and a variety of kidney findings including increased numbers of inflammatory cells and focal mineralized deposits at corticomedullary junctions, mineralized deposits in the renal pelvis of kidneys and eosinophilic casts within renal tubules of kidneys. Kidneys deposits although found in both control and test animals appears to be more prevalent in the control animals. Proteinuria was also found in 19/20 of the control and test animals that were examined.

Weight gain and food consumption were decreased in animals receiving 60, 30, 15, 7.5 and 4 mg/kg/day which the sponsor associates with the unpalatibility of the diet due to the test compound. Because body weight appears to be effected by compound ingestion, organ/body weight ratios are not sensitive indicators of compound toxicity in this study, however, the increased brain to body weight ratios in female rats at 4 mg/kg/day suggests cerebral edema as a compound related effect.

Study Classification

Taken together, both rat studies are inadequate to define compound toxicity and must be classified as supplementary data. The primary deficiency of the first study is the renal pathology and nematodiasis found in most control and test animals. The major deficiency of the second study is the lack of histopathology which is needed to investigate possible compound related brain, liver, heart and kidney alterations. Because tissues were preserved in this study, this is recommended by this reviewer that tissues of at least the high dose group (4 mg/kg/day) and control animals be examined for the posible upgrading of this study to core minimum status.