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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Folpet Registration Standard Correction.
Caswell #464

TO: Henry Jacoby (21)
Registration Division (TS-767)

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THRU: Laurence D. Chitlik, DABT
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and
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Please find attached corrections to pages 10, 17, and 18, and page 3 of 10 of the "one-liners" of the Folpet Registration Standard. These old pages in the standard should be replaced by the new pages. The corrections reflect changes in the NOEL for maternal toxicity in the 2-generation rat reproduction study, and the inclusion of a calculation of oncogenic risk to mixer/loader/applicators.

data for this effect are necessary in order to fully evaluate this study. Other findings noted included decreases in pup body weight gain in second generation (F1) rats fed diets containing 3600 ppm nominal (3200 ppm actual). The NOEL for parental toxicity was therefore 800 ppm nominal (690 ppm actual). The study was classified as Core-Supplementary data, pending the submission of requested additional data.

84 Series Mutagenicity

84-2 Mutagenicity Tests

(1) Gene Mutation- Acceptable studies have been submitted to satisfy the Guideline requirement for gene mutation testing. Data have been submitted to demonstrate that folpet is mutagenic in Salmonella (Bullock et al., MRID #DSF005; Simmon et al., MRID #132582), E. coli (Simmon et al., MRID #132582), mouse L5178Y/TK lymphoma cells (Jotz et al., MRID #DSF006), and in the in vivo Drosophila sex-linked recessive lethal assay (Valencia, MRID #143567). Folpet is mutagenic in these test systems without metabolic activation. In general, addition of rat liver S-9 fraction (commonly used for metabolic activation) diminishes the mutagenic activity of folpet. This effect is presumed to be due to binding of folpet (or its active metabolite) to sulfhydryl groups (Machado et al., MRID #149469).

Folpet was negative for in vivo gene mutations in the mouse somatic cell mutation assay (mouse spot test) (Moore and Brusick, MRID #148625, 149567). However, significant pup mortality was noted in this assay, and further evaluation of this non-mutagenic finding is required (see section D. "Toxicological Issues").

(2) Chromosomal Aberrations- Folpet is negative for in vivo chromosome damage in the rat bone marrow cytogenetics assay (Carver, MRID #DSF007, 151085), and in the mouse dominant lethal assay (Simmon et al., MRID #132582). These studies were classified as Acceptable data.

A mouse micronucleus assay (Jacoby, MRID #150558) was negative, however was classified as Inconclusive due to inadequate dose levels.

A dominant lethal study in rats (Bradfield, MRID #93462) was negative, but classified as Unacceptable due to the lack of a rationale for the selection of dose levels, and the lack of individual animal data.

Although acceptable in vivo studies have been submitted, because of the demonstrated lability of folpet in blood, and the fact that this compound has been shown to cause intestinal tumors, additional testing for chromosomal aberrations in an in vitro test system is required to further elucidate the genotoxic properties of folpet. Therefore, the available data only par-

fact that folpet induced a high incidence of a rare tumor type in two strains of mouse, and clear evidence of genotoxicity in a number of test systems.

The analysis of exposure to mixer/loader/applicators, provided by EAB, indicated that the greatest chronic exposure resulted from the treatment of grapes, 30 mg/kg/yr. This value is due solely to dermal exposure, and is not corrected for penetration through the skin. The analysis conducted by EAB assumed that inhalation exposure is insignificant. The oncogenic risk to mixer/loader/applicators is calculated (Risk = Exposure X Q*) as:

$$\frac{30 \text{ mg/kg/yr}}{365 \text{ days/yr}} \times (3.49 \times 10^{-3}) = 2.9 \times 10^{-4}$$

The risk calculated above is based on the incidence of duodenal tumors observed in the mouse feeding studies. Since the half-life of folpet per se in the blood is approximately 1 minute, there is little likelihood, in the opinion of this reviewer, that dermal exposures could result in duodenal tumors. However, the induction of skin tumors as a result of dermal exposures is a possibility that must be considered. Further, it is noted that a high degree of skin toxicity (hyperkeratosis, etc.) was noted in the mouse oncogenicity study, which suggests that skin may also be a target for folpet toxicity in humans.

(2) Developmental Toxicity- Folpet was demonstrated to cause an increased incidence of hydrocephalus in the New Zealand White rabbit, using a standard treatment protocol (treatment over the entire gestation period). This finding was not reproduced in the same strain of rabbit when treatment was administered for short periods during gestation. A teratology study in the HY/CR rabbit, using standard treatment protocols, also failed to reproduce this teratogenic effect, although the NOELs for maternal and developmental toxicity were the same in either study, 10 mg/kg/day. These studies were all fully acceptable, and were classified as Core-Minimum data.

An acceptable study in the rat also failed to produce any evidence of teratogenicity, and the NOEL for overall developmental toxicity was 60 mg/kg/day in this study.

Published data provide little additional useful information, and are not acceptable as only summary data were provided, insufficient numbers of animals were tested, and/or non-standard protocols were used. Data reported for the New Zealand White rabbit indicated that folpet was negative for malformations under the conditions of these studies (Fabro et al., MRID #42391, 62643; McLaughlin et al., MRID #93760, 41400). As only summary data were presented, and small numbers of animals were tested, these data are of limited utility and do not offset the positive findings noted in this strain in a fully acceptable study.

3

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Data reported for the mouse indicated that the results were equivocal by gavage, (Kotin et al., MRID #27598), and negative by the oral, subcutaneous, or inhalation routes (Courtney et al., MRID #133325).

A published study in the hamster (Robens, MRID #DSF008), indicated that folpet was teratogenic in this species, causing apparent increases in fetal incidences of exencephaly and fused ribs. Although suggestive of a developmental effect, these data are of limited utility as an inadequate number of animals was tested, and only summary data were provided in the published report.

After consideration of all available data, it is concluded that folpet possesses teratogenic potential in the rabbit, with a NOEL for overall developmental toxicity in this species of 10 mg/kg/day. As this value was also the NOEL for maternal toxicity, the available data suggest that folpet presents a developmental hazard only at exposure levels that also produce maternal toxicity.

An acute exposure analysis performed by the Exposure Assessment Branch (memo Reiter to Saunders, 7-1-86), indicated that an acute exposure of 7 mg/kg/day would be predicted for female mixer/loader/applicators of child-bearing age. This exposure would result in a Margin-of-Safety (MOS) of only 1.4 based on the NOELs for maternal and developmental toxicity of 10 mg/kg/day noted in the two rabbit studies. The highest predicted acute dermal exposure for homeowner uses is 0.05 mg/kg/day, which produces a MOS of 200. An acceptable dermal penetration study is necessary to further refine these risk estimates.

(3) Reproductive Effects- A study has been submitted in the rat which failed to establish a NOEL for potential male fertility effects, and additional data have been requested to complete the assessment of this study. In addition, a mouse somatic cell mutation assay, which is in essence a one-generation feeding study, demonstrated statistically significant decreases in mouse pup survival at all dose levels, with a LEL of 76 ppm (10.9 mg/kg/day), the lowest dose tested. Therefore, it is possible that the NOEL for this apparent effect will be lower in the mouse than the value which may be ultimately established in the rat. Further, no histopathological examinations of mouse pups were conducted, and other toxicologically significant effects may become apparent after all relevant endpoints are assessed in a full reproduction study in this species. The Registrant should submit a protocol for this study prior to initiation, as the standard protocol used in the rat study may not be sufficient to answer all relevant questions.

4

Tox Chem No. 464 Folpet

Study/Lab/Study #/Date	Material	EPA Accession /MRID No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Teratology - mice ; Courtney et al., Toxicol. Appl. Pharmacol 45:292 (1978)	Purity unknown	251885 MRID # 133325	Published abstract. Dosen tested: 100 mg/kg by gavage or subcut. injection, or 483, 830 ug/m^3, over days 6-13 of gestation. Reported as negative for teratogenicity. Summary data only, NOELs for developmental, maternal toxicity could not be determined.		Supplementary 005308
Teratology - mice ; Bionetics Research Labs; #NCI-TOCP-CG-1973-1-2; August, 1968.	Technical	225529 MRID # 27598	Screening study, summary data only. (Kotin et al., Innes report). Dose tested: 100 mg/kg subcutaneous Reported as "conflicting results", no conclusion was reached. NOELs for developmental, maternal toxicity could not be determined.		Supplementary 005308
2-Gen. Reproduction- rat Chevron Environmental Health Center; #Socal 2140; 9-19-85.	Technical 89.5%	259585 to 259596 MRID # 151489	Doses tested: 0, 200, 800, 3600 ppm (nominal) in the diet (150, 690, 3200 analytical concentrations) in Sprague-Dawley rats. Parental NOEL = 690 ppm (analyt.) Parental LEL = 3200 ppm Decreased weight gain in F1 offspring. Reproductive NOEL not determined. Historical control data for male fertility requested.		Supplementary