UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TITLE: Supplementary Data and Replies to Our Recommendations for the Two-Generation Inhalation Reproduction Study with Telone II

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Action Requested:

Review the supplementary data to upgrade the 2-generation inhalation reproduction study in Fischer rats, dated 2/11/88.

Background:

In the memo from S. Stolzenberg to L.A. Rossi, dated 2/11/88, the study was classified as Core Supplementary. Six recommendations or issues were discussed by the reviewing toxicologist with a suggestion that the study may be upgraded if an acceptable explanation for a discrepancy in the data, indicated in the sixth recommendation, is provided.

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RECOMMENDATIONS:

The applicant has adequately responded to our request for historical control reproduction data (Issue # 2) and has provided us with an acceptable explanation for the discrepancies in the data (Issue # 6). The study should be upgraded as follows.

Core Classification: Minimum

Reproductive NOEL: ≥ 90 ppm

Systemic LEL: 90 ppm
NOEL: 30 ppm

Systemic LEL and NOEL are based on histopathologic lesions observed in the stomach and nasal tissues and a decrease in body weight gain.

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Replies by the applicant to the six issues of EPA pertaining to the study.

EPA Issue #1. We were not able to assign a systemic toxicity NOEL or LEL to F1 and F2 parents. In two previous studies by the applicant reviewed at EPA, increased liver and kidney weights were observed in rats after only 12 weeks of exposure by the inhalation route at 5 ppm (LDT) in one study and 50 ppm in the second study. In a 6 month inhalation study, cloudy swelling of renal epithelium was seen in rats at a 3 ppm dose. Organ weight data for the present study must be submitted if available.

Registrant's reply: The most sensitive indicator of toxicity to inhaled 1,2-dichloropropene in rodents is nasal epithelial hyperplasia, which has been repeatedly demonstrated in subchronic and chronic studies. References are cited in which it is claimed that NOELs for subchronic nasal lesions were found to be 10 ppm (Torkelson and Rowe, In: Patty's Industrial Hygiene and Toxicology, 3rd Ed., Vol. 2B, 1981) and 30 ppm (Stott et al, Report of a Dow Chemical 13 week inhalation study in rats and mice, 1984). Decreased body weight was found only in a 2-year rat test, after 6 and 12 months. Organ weight changes, if they occurred, were secondary to body weight depression. Organ weight or body weight changes were not sensitive indicators of toxicity, nor were renal or hepatic histopathology changes, up to exposre levels of 150 ppm. "Cloudy swelling of renal tubular epithelium" was claimed to be an infrequent occurrence and was attributed to a contaminant in material used in the 1950's, or to the animals bred at Dow's facilities at that time.

In the present inhalation reproduction study, liver and renal weights were not obtained but both organs were examined microscopically. No histopathology changes in these organs were evident.

EPA Issue #2. A table of historical control data on reproductive indices for this strain of rat at the applicant's testing facility was requested because conception indices in the four F1 and F2 generations were low.

Registrant's reply. Historical control data for conception index and other reproduction indices in 22 reproduction and teratology studies with Fischer 344 rats conducted at Dow facilities between 1981 to 1987, were presented. Conception index, defined as "number of females delivering a litter/number of sperm positive females", ranged between 70.0 to 96.8% with a mean of 84.8% for the 12 historical control groups. The conclusion was that the data for the present reproduction study was well within historical control data for conception index.

EPA Issue #3. The applicant concluded that the stomach lesions observed in the 90 ppm group was the result of general stress and was not a compound effect. We do not accept this conclusion. Our reasons were 1). None of the rats in control and lower dose treated groups developed these stomach lesions even though they were subjected to the same stress of the handling and exposure conditions, 2). Macromolecular binding by non-glandular stomach was found to be about twice as high as for glandular stomach and 4- to 5-times higher than for other organs such as liver, kidney and bladder, 3). Telone II is a dermal and eye irritant and a highly reactive compound. Thus, because of high uptake by non-glandular stomach and its high irritancy, it is not surprising that this area of the stomach would be particularly sensitive to lesions by this compound, 4). In both rat and mouse carcinogenicity tests, the stomach is a highly susceptible target organ for tumor development.

Applicant's reply: The applicant believes that the stomach lesions were the result of stresses associated with pregnancy, whelping and lactation superimposed on the stress of the irritative effects of the Telone II vapors on the nasal passages in the rat which is an obligate nose breather. Even though the rats in all four groups were handled the same, the 90 ppm exposure was more stressful. Agency guidelines call for toxicity, preferably without mortality at the highest selected dose level. Histopathological nasal passage changes and slightly lower body weight gain were seen only in the group with the 90 ppm exposure (HDT).

In a 90-day subchronic inhalation study, exposures at 90 and 150 ppm caused no observable stomach lesions in either males or females. In an interim report for a 2-year study, stomach lesions were not seen after exposure of rats to 60 ppm for 6 or 12 months.

The stomach lesions, as stated in the report, were not "limited entirely to nonglandular region, mainly the mucosa but it sometimes included the submucosa". The glandular mucosa of F1 adult females as well as the nonglandular mucosa were affected. The diagnoses were ulcer, edema, and submucosal inflammation represented a continuum of focal damage associated with gastric ulceration. A diagnosis of acanthosis was employed in areas which contained increased thickness of stratified squamous epithelium. In addition, two females in the F1 generation developed stomach ulcers that resulted in death.

The applicant recognizes that Telone II has the ability to bind and react with the stratified epithelium of the nonglandular stomach as shown in gavage studies by NTP and their own data on macromolecular binding and organ distribution studies. Some of the test compound, although minor, would be expected to be ingested in this inhalation study. "However, the data from the 2-generation inhalation study appears inconclusive with regard to a direct

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effect on the glandular gastric mucosa. The incidences and site of gastric lesions, i.e. non-glandular vs. glandular, in the F1 generation adults, does not correspond closely with the F0 generation adults. If the effect were only a consequence of Telone II administration, we would have expected a much greater agreement between the two generations. Also, if reactivity of Telone II with stratified squamous epithelium was great at these dose levels, lesions should have been apparent in the oral cavity, a site with a large expanse of stratified squamous epithelium. No lesions were seen in the oral mucosa of these rats."

A table is attached which summarizes the gross and microscopically observed gastric lesion incidence for both sexes in the F0 and F1 generations. The incidence in males was much less than in females. In the NTP 2-year rat study, males were more sensitive than females with regard to incidence of gastric tumors. Therefore, the applicant claimed that the NTP study results are a contradiction of their study results, even though the route for the NTP study was by oral gavage compared to inhalation in the present reproduction study. There were also other differences. The applicant interpreted these differences in results between the two studies to be due to the results of stress associated with pregnancy, whelping and lactation superimposed on high exposure to Telone II.

EPA Issue #4. In nasal tissue of exposed adults, hyperplasia of respiratory epithelium and focal degeneration of olfactory tissue were seen at 90 ppm (HDT). Males and females were equally sensitive.

Applicant's reply. Dow did not adress the issue of male-female sensitivity but they agree that the data in the report indicates similar sensitivity.

EPA Issue #5. Decreased body weight gain was seen in males and females exposed at 90 ppm. Males were more sensitive to this effect.

Applicant's reply. The same conclusion was drawn by Dow and was stated in their Discussion and Conclusion section.

EPA Issue #6. There are discrepancies in the data of Tables 17 and 18 in volume 1, page 50 and 51 of the report. The values for N (number of liters) are surprisingly low for body weight and body weight gain of the dams on day 21 of pregnancy compared to all other time periods. In tables 19 and 20 (pages 52 and 53), for body weight and body weight gain of the same animals during lactation, the values of N are much higher and correspond more to such values during the earlier part of the gestational period seen in Tables 17 and 18. The applicant should be requested to address these discrepancies and submit a full explanation together with data to support the explanation.

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Applicant's reply. The length of gestation for animals represented in Tables 17 and 18 ranged from 20 to 24 days, as can be seen in the Appendix, Table 15 of the original report. The majority had a gestational period of 21-22 days. In general, parturition began prior to the completion of the exposure period 3:30 pm. Once parturition began, the dams were considered to be in day 0 of lactation. For consistency of data collection, body weights of all animals, whether or not they were exposed, were obtained following the 6 hour exposure period (approx. 3:30 p.m.). Therefore, body weights on gestation Day 21 could not be obtained from dams that delivered on gestation Day 21 prior to the completion of exposure of any dams that delivered litters on gestation Day 20.

Discussion:

Issue #1. The applicant's explanations that the most sensitive indicators of toxicity by this compound is the nasal epithelium is backed by literature citations and references to experimental data. Cloudy swelling seen in renal epithelium of rats in a 6 month inhalation study was attributed to a contaminant which was present in Telone preparations during the 1950's. Organ weight or body weight changes are not sensitive indicators of toxicity with this compound nor are renal or hepatic histopathology changes.

We accept these as plausible explanations. With regard to our request for organ weight data if they were obtained in the present rat reproduction study, we were told they were not obtained.

Issue #2. The applicant provided historical control data on reproduction indices obtained in studies at their facilities with Fischer 344 rats, as had been requested by EPA. We consider the conception index of most of the historical control groups to be exceptionally low for studies with rats. Nevertheless, the Telone II data for the present reproduction study is well within the historical control data that has been provided.

Issue #3. The applicant reiterated their view that the stomach lesions observed in the 90 ppm exposure group were the result of stresses associated with pregnancy, whelping and lactation superimposed on the nasal irritative effects of the Telone II vapors. They recognize that Telone II has the ability to bind and react with tissues of the nonglandular stomach but they presented evidence to support their hypothesis that it is a stress related phenomenon. We have no argument with their hypothesis but it should not be taken as a conclusion. Gastric lesions have been observed in rats when the compound was administered by either of two routes, oral or inhalation. It also appears possible that in some of their experiments, at sufficiently high respiratory levels, the stomach lesions observed may be a direct effect of the compound absorbed through the lungs and which is preferentially accumulated in cells within the stomach.

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Issue #4. We have no further comment.

Issue #5. We have no further comment.

Issue #6. The applicant's explanation for the discrepancies in the data that we observed is considered valid. We have no further comment.

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