MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

August 25, 1993

TO: Chlormadinone acetate file (CAS # 302-22-7)

FROM: Gary Butterfield

SUBJECT: ITSL for chlormadinone acetate

A CAS-on-line search conducted July 28, 1993 did not identify any toxicity studies that could be used to calculate an ITSL. This material has been used as a contraceptive drug so that there is considerable amounts of human clinical studies available. RTECS was used to identify potential LD50s, and low dose level reproductive effects in animals and humans. No LD50 by the oral route of exposure was found in RTECS in any English language journal. RTECS also identified this chemical as a potential carcinogen, and cited a review in the IARC monographs.

IARC (1977) has reviewed this material and found limited evidence of carcinogenic potential in animals. However, the IARC discussion includes evidence that most of the positive carcinogenic studies in mice were when chlormadinone acetate was administered with another hormone substitutes (mestranol or ethinyloestradiol). There was little or no carcinogenic activity found in mice administered chlormadinone acetate alone. It should also be noted that all of the authors from long term, carcinogenicity studies state in their conclusions that increased incidence of mammary tumors in non-human species may be of little relevance in projecting potential tumorigenesis in women. This statement in conjunction with IARC's only being able to only conclude that there was limited animal evidence of carcinogenicity, makes the regulation of this material by AQD as a carcinogen questionable.

The following is a short summary of the positive carcinogenicity animal studies, mice fed 8 ppm diets (20 to 30 ug/mouse/day) of a mixture of 97.5% chlormadinone acetate and 2.5% ethinyloestradiol, Rudali et al (1975) reported increased tumor incidence in intact males 0/76 (or 0 %) in controls to 10/32 (or 31 %) in treated mice, and in castrated males 10/61 (16 %) to 23/28 (82 %). Females had no change in mammary tumor incidence or latency period. In a series of reports, Nelson et al (1972), Nelson et al (1973) and Weikel & Nelson (1977), female dogs were reported to have increased incidence of mammary tumors following orally administered, in tablet form, chlormadinone acetate at 0.25 mg/kg. The study reported total number of tumors observed, not the number of tumor bearing animals - making use of this information for quantitative risk assessment difficult. There were 20 dogs per dose level. Four dogs from each dose group were sacrificed after two and four years of exposure, while the remaining chlormadinone acetate dogs were sacrificed at the end of five years due to deteriorating conditions.

Once the question of carcinogenic potential has been dismissed as a basis for screening level development, it is necessary to determine an ITSL for chlormadinone acetate. It can once again be noted that nearly all of the authors who conducted animal studies with chlormadinone acetate indicate that results from animal studies are not necessarily applicable to humans. Among the animal data listed in RTECS is teratogenic effects observed at relatively low doses in mice and rabbits. Following an oral dose of 10 mg/kg on gestation days 8 to 17 in mice and days 8 to 20 in rabbits an increased incidence of malformations was observed (Takano et al 1966).

Because results from animal studies have been reported by many authors as being not applicable for calculation of an ITSL to protect against human adverse reproductive/developmental effects, it is necessary to base the ITSL on human data. Studies in humans, due to ethical reasons, typically don't clearly show NOAELs for adverse effects, as does animal studies. RTECS identified a study which observed changes in humans at low doses. A study that evaluated human cervical mucosal changes in women given oral doses of 50, 100, 200, 300, 400, or 500 ug/day, and the effects on occurrence of pregnancy in women given 100, 200, or 250 ug/day (Martinez-Manautou et al 1967). Maximal effects on cervical mucus appeared between doses of 300 and 400 ug/day. The rate of pregnancy was reduced to less than 5 % at doses of 250 ug/day. (It should be noted that RTECS reported a dose of 80 ug/kg from this study as causing reproductive effects, this dose derivation could not be replicated by this reviewer.) If the dose level of 200 ug/day from this study is assumed to be a NOAEL, and a body weight of 60 kg is assumed for females, the NOAEL can be determined to be 3.3 ug/kg. An ITSL from this dose could be calculated as follows.

ITSL = (3.3 ug/kg)/[100 x 20m3/60kg] = 0.1 ug/m3 annual average

where the above equation is based on Rule 232(1)(e), the 35 fold factor was reduced to 1 because the study evaluated reproductive effects and exposure duration occurred over many reproductive cycles, thus more than a short term exposure. The inhalation rate was assumed to be 20 m3 for a 60 kg woman.

References:

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Takano et al. 1966. Teratogenic effect of chlormadinone acetate in mice and rabbits. Proc Soc Exp Biol Med 121:455-457.

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