MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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November 3, 2015

To: File for Lincomycin Hydrochloride

From: Michael Depa, Air Quality Division, Toxics Unit

Subject: Screening Level Update

Previously, the averaging time (AT) assigned to lincomycin hydrochloride was 24 hours, as per the default methodology (Rule 232(2)(b))(see attached memo from Robert Sills dated September 17, 1993). The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is set to annual.

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

September 17, 1993

To: File for lincomycin hydrochloride (CAS No. 859-18-7)

From: Robert Sills, Surface Water Quality Division

Subject: Screening Level Development

The available literature (CAS-online, NTIS, NLM-Toxline, and standard references) was reviewed to determine the toxic effects of lincomycin hydrochloride. Occupational exposure guidelines and an EPA RfD or RfC were unavailable. Lincomycin is an antibacterial drug with narrow-spectrum effectiveness against gram-positive bacteria (Kucers and Bennett, 1987; Sanders, 1970). The usual adult dosage is 0.5 g every 6 or 8 hours; it is not recommended for newborn babies (Kucers and Bennett, 1987). Adverse effects (presumably after repeated-dose, subchronic dosing regimen) include nausea, vomiting, abdominal cramps and diarrhea. The diarrhea may be severe, simulate ulcerative colitis, and persist for 1 or 2 weeks after the drug is stopped (Kucers and Bennett, 1987). Diarrhea of varying severity may be encountered in from 5 to 50% of patients (Sanders, 1970). Less common side effects include hypersensitivity reactions (rare), mild hepatotoxicity, and neutropenia. Safety in pregnancy has not been established, but there is no evidence of harm during pregnancy (Kucers and Bennett, 1987).

Gray, et al. (1966) reported that oral doses of lincomycin-HCl at 800 and 1000 mg/kg were well tolerated by dogs and rats, and that teratogenic effects were not observed in term fetuses from rat dams injected with 300 mg/kg. The oral rat LD50 was 15.645 g/kg.

The ITSL is derived from the lowest adult therapeutic human dose of 0.5 g every 8 hours. This dose is considered a short term repeated-dose LOAEL due to the common occurrence of diarrhea, which may be severe in some cases, and occasionally other side effects. A total uncertainty factor of 1000 is applied to the short-term LOAEL dose. This total UF consists of a factor of ten for LOAEL-to-NOAEL adjustment and to account for intraspecies variability, and a factor of 100 to adjust the short-term exposure regimen to a chronic exposure duration. A LOAEL-to-NOAEL adjustment appears appropriate, given that the side-effects of antibiotic treatment have been documented and are serious. It is noted that the effects are moderate in severity, and the frequency of occurrence is <50%. It is reasonable to couple this concern with the uncertainty for intraspecies sensitivity, because the LOAEL reflects effects appearing in the more sensitive individuals under treatment. Other sensitive groups, e.g. the young and the elderly, may also exist. Therefore, it is concluded appropriate to combine the

uncertainties for LOAEL-to-NOAEL conversion and intraspecies sensitivity in a single 10-fold UF.

The other UF of 100-fold is to adjust the short duration of the available human toxicity data to chronic conditions. The commonly used UF to adjust subchronic (e.g., 90 day) rodent data to chronic (2 year) rodent data is ten, and an additional UF may be used if the duration is substantially less than 90 days. Because the key data involve repeated human exposures for presumably a short duration (as is typical for antibiotics), this represents a small fraction of the human lifespan. Therefore, a 100-fold UF is considered appropriate in this case for adjustment to chronic exposures. The resulting composite UF of 1000 is used to derive the ITSL as follows:

LOAEL= (500 mg x 3doses/d)/70kg = 21.4 mg/kg/d
Oral RfD = (21. 4mg/kg-d) /1000 = 0.0214 mg/ kg-d
ITSL = 0.0214 mg/kg-d x 70kg/20m^3
ITSL = 0.0749 mg/m^3
ITSL = 75 µg/m^3, 24 hour averaging time

REFERENCES

Kucers, A. and N. McK. Bennett. 1987. The Use of Antibiotics. 4th Ed. William Heinemann Medical Books. London.

Sanders, B. 1970. Lincomycin: Fact, Fancy and Future. In: Conn, H.F. (ed.) The Medical Clinics of North America; Efficacy of Antimicrobial and Antifungal Agents. 54(5). W.B. Saunders Co., Philadelphia.

Gray, J.E., A. Purmalis and W.J. Mulvihill. 1966. Further toxicologic studies of lincomycin. Toxicol. Appl. Pharmacol. 9(3): 445-54.

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