MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

November 2, 2015

TO: Novobiocin (CAS # 303-81-1)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: ITSL Derivation

Previously, the averaging time (AT) assigned to Novobiocin was 24 hours, as per the default methodology (Rule 232(2)(b))(see attached memo from Dennis Bush 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 ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

September 17, 1993

TO: Novobiocin (CAS # 303-81-1)

FROM: Dennis Bush, Surface Water Quality Division

SUBJECT: ITSL Derivation

Novobiocin ($C_{13}H_{36}N_2O_{11}$) is an antibiotic which was isolated from Streptomyces niveus in 1955. Novobiocin is normally administered to adults at a dose of 0.5 grams novobiocin every 6 hours (2 grams/day). There is a high incidence of adverse side effects following administration of this antibiotic. The most frequent adverse effects are hypersensitivity reactions such as skin rashes. The rash occurs in approximately 12% of treated patients. Hematological changes such as eosinophilia and rarely anemia, leukopenia, agranulocytosis, thrombocytopenia and pancytopenia have also been reported. Eosinophilia and leukopenia occur in approximately 1% of patients. Gastrointestinal side-effects such as nausea, abdominal pain and diarrhea are also common, but are usually not severe enough to terminate treatment. Treatment of young children with novobiocin may result in hyperbilirubinemia (Riley, 1970) (Kucers and Bennett, 1987).

No inhalation studies using novobiocin were found in the literature. Many clinical studies using the oral route of exposure were conducted in the 1950s. Only one clinical study was found which had a long exposure duration. In this clinical study reported by Blackmon and Curry (1956), a 41-year-old woman was given an initial dose of 250 mg novobiocin 4 times a day for 3 days, followed by one 250 mg tablet administered daily for 6 months. Urinalysis, icterus index and blood cell counts were normal. No allergic reactions were observed even though the woman had a history of allergic reactions. Other human studies which used low doses and which had exposure periods which lasted more than a week are presented below.

Welch, et al. (1956) administered 0.5 grams of novobiocin orally twice daily to a group of 208 healthy adult male volunteers. The drug was administered for 5 days followed by a rest period of 2 days and then it was administered again for 5 days. Of the 208 subjects given novobiocin, 37% had loose stools, 2% had skin eruptions and 1% exhibited yellowing of the sclerae.

David and Burgner (1956) exposed 28 patients (ages 6 to 76) suffering from a variety of infections to doses ranging from 1 to 2 grams/day for an average of 8.7 days. Of the 8 patients given 1 gram/day, 5 patients exhibited side-effects. One patient each had a rash, eight eosinophilia and leukopenia. Two patients had an increase in the icteric index which may have been due to a yellow pigment produced by the metabolism of novobiocin.

Hughes, et al. (1958) treated 26 patients (5 males and 21 females of unknown ages) suffering from chronic urinary infections to 250 mg novobiocin 4 times/day for 7 to 14 days. Five patients developed a diffuse maculopapular rash 7 to 10 days after treatment. No other adverse reactions were observed.

Breese, et al. (1957) dosed 23 children (average age was 6-years-old) suffering from beta-hemolytic infections with various oral doses of novobiocin for an average of 8 days. The

children received an average dose of 10 mg/lb (22 mg/kg). Mild diarrhea and vomiting occurred in some of the patients while skin eruptions occurred in 15 of 23 patients. White blood cell counts were within normal limits.

The screening level for novobiocin was based on an oral RfD which was calculated using the LOAEL of 1 g/day found in healthy adult males by Welch, et al. (1956). This LOAEL is equivalent to 14 mg/kg if it is assumed that an average male weighs 70 kg. Similar LOAELs were found in studies by David and Burgner (1956), Breese, et al. (1957) and Hughes, et al. (1958). The ITSL was derived using the LOAEL of 14 mg/kg (12 mg/kg/d) with an uncertainty factor of 1000x. This uncertainty factor consists of 10x for each LOAEL-to-NOAEL and subchronic-to-chronic extrapolation, an additional uncertainty factor of 10x is used because the study was substantially less than chronic in duration. An additional uncertainty factor of 10x was not used for intraspecies variability because the LOAEL was based on studies of people of all ages, both sexes and people weakened by infections.

ITSL Derivation:

ITSL = Oral RfD x 70 kg/20 m^3

ITSL = LOAEL(mg/kg/d)/UF x 70 kg/20m^3

ITSL = (14 mg/kg)(10 days/12 days)/1000 x 70 kg/20m^3

ITSL = 0.041 mg/m^3, 24 hour averaging time

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