MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

March 7, 1994

TO: File for Pirmenol II (61477-94-9)

FROM: Marco Bianchi

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for pirmenol is 3 $\mu g/m^3$ based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS, HEAST, RTECS, IARC, EPB-CCD, EPB-library, CAS-online, NLM-online, NTP Management Status Report, NIOSH Pocket Guide, ACGIH Guide.

Pirmenol hydrochloride or, Pirmenol II as it is known by its tradename is a long-acting antiarrhythmic drug. Preclinical studies from the Warner-Lambert/Parke Davis (WL/PD) Pharmaceutical Research Facility indicated that pirmenol reduced the frequency of preventative contractions in patients with ventricular arrhythmias; while animal studies revealed an increased heart rate, prolonged QRS duration and reduced ST interval (Martin and de la Iglesia 1987, 1988).

A CAS-online and NLM-online search revealed both preclinical and reproductive WL/PD studies that evaluated the toxicity of this drug. One study (Schardein et al., 1980) included a 13 week oral rat study in which a LOAEL could be determined. In this study, no drug-related clinical reactions were observed, but significant mean body weight reductions occurred in both sexes at the 100 mg/kg dose levels. Female rats showed reduced body weights in the 50 and 25 mg/kg groups. With the absence of other adverse effects, reduced body weight at 25 mg/kg/day is considered the LOAEL.

Anderson et al., 1986, showed that reproduction toxicology studies using pirmenol did not affect reproductive performance and did not elicit teratogenic potential in rats and rabbits . Additionally, Martin and de la Iglesia 1987 and 1988, found that several *in vitro* and *in vivo* assay systems evaluating the potential of pirmenol to invoke DNA damage indicated that, pirmenol is not mutagenic and has a low genetic risk potential. Preliminary results from definitive carcinogenesis bioassays indicate that there is no evidence of any carcinogenic potential (Martin and de la Iglesia 1987, 1988).

The ITSL is derived as shown below using a LOAEL of 25 mg/kg/day.

$$\text{ITSL} = \frac{25 \text{ mg/kg/day}}{10 \times 10 \times 100 \times 0.980} \times 1 = 3 \ \mu g/m^3$$

Where:

25 mg/kg/day	=	LOAEL
0.980	=	default inhalation rate (m^3/kg) for female rats
10	=	LOAEL to NOAEL adjustment
10	=	subchronic to chronic adjustment
100	=	a factor of 10 to account for animal to human adjustment and a factor of 10 to account for human sensitivities.

ITSL = 3 $\mu g/m^3$ for an annual average

References:

Martin et al. 1987. Preclinical toxicology of pirmenol hydrochloride. The American Journal of Cardiology 59:10H-14H.

Martin et al. 1988. Preclinical toxicology of pirmenol hydrochloride. Angiology 39:, ISS 3 Pt 2, 299-306.

Schardein et al. 1980. Preclinical toxicology studies with a new antiarrhythmic agent pirmenol hydrochloride (CI-845). Toxicology and Applied Pharmacology 56:294-301.

Anderson et al. 1986. Studies on reproduction in rats with pirmenol, an antiarrhythmic agent. Fundamental and Applied Toxicology 7:221-227.

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