RECOMMENDATIONS OF THE SCIENTIFIC ADVISORY PANEL

METHYLPREDNISOLONE ACETATE

CAS # 53-36-1
DECEMBER 8, 1994

Basis for ITSL:

A CAS- and NLM-online literature search was conducted for methylprednisolone acetate in February 1993, but it did not produce any relevant information to calculate an ITSL. The Upjohn Company provided a MSDS which stated that corticosteroids, as a group, are generally considered to be teratogenic. A search of studies listed in RTECS found some reproductive effects following an injection route of exposure. In addition, some LD_{50}s were identified by an injection route of exposure and an oral LD_{50} from a foreign journal - not available for review. All of this data was considered inadequate for use in calculating an ITSL. Due to the lack of available toxicity data meeting the criteria of Rule 232(1), the ITSL for hydrocortisone acetate was determined to be 0.04 $\mu g/m^3$ based on annual averaging (Rule 232(1)(i)).

Summary of Public Comment:

The only public comment received for this compound was from The Upjohn Company. They commented that other toxicological information was available to derive a screening level, rather than use the default value of 0.04 ug/m^3. This data consisted of a LD_{50} of >12 g/kg which was published in the company MSDS.

Response to Public Comment:

A complete reference check was conducted for methylprednisolone acetate, but because there was no information with which to derive an ITSL, methylprednisolone was also investigated. Methylprednisolone is the active portion of the methylprednisolone-acetate complex, with the acetate moiety used primarily to enhance solubility.

Upjohn provided an in-house oral LD_{50} study for methylprednisolone. A total of 5 rats/sex/group were given a single oral dose of 0, 4000, 8000, 10,000, or 12,000 mg/kg body weight of methylprednisolone suspended in a 25% methylcellulose vehicle. After an observation period of 7-days, no deaths were noted in any of the dose groups. A surrogate LD_{50} will be set at 12,000 mg/kg for ITSL determination. Additionally, because methylprednisolone is the active portion of methylprednisolone acetate, the screening level for methylprednisolone will be adjusted by using a ratio of the molecular weights of methylprednisolone and methylprednisolone acetate to account for the addition of the acetate group. Because no deaths were observed in the "surrogate LD_{50}", the ITSL derived by this method should provide a conservative estimate of the ITSL derived from an actual LD_{50}. However, if methylprednisolone acetate is absorbed to a greater degree than methylprednisolone, the LD_{50} for the acetate compound could be lower than that for methylprednisolone, lessening the amount of this conservatism.

The ITSL was derived as follows using Rule 232(1)(h):

methylprednisolone MW = 374.5 g/mol
methylprednisolone acetate MW = 416.5 g/mol

LD_{50} = 12,000 mg/kg
W_A = Body weight of experimental animal in kilograms (kg).
I_A = Daily inhalation rate of experimental animal in cubic meters/day.
Since body weights and daily inhalation rates were not available, assume a default value of 0.931 m^3/kg.

$$ITSL = \frac{1}{500} \times \frac{1}{40} \times \frac{1}{100} \times \frac{LD_{50}\ mg/kg \times W_A}{0.167 \times I_A}$$

$$ITSL = \frac{1}{500} \times \frac{1}{40} \times \frac{1}{100} \times \frac{12{,}000\ mg/kg}{0.167 \times 0.931\ m^3/kg} = 0.0386\ mg/m^3$$

0.0386 mg/m^3 x 1000 = 39 $\mu g/m^3$ based on annual averaging.

Molecular Weight Ratios:

$$\frac{39\ \mu g/m^3}{374.5\ g/mol} = \frac{x\ \mu g/m^3}{416.5\ g/mol}$$

x = 43.4 or 43 $\mu g/m^3$ = ITSL

Because of the many uncertanties in using an oral rat LD_{50} to derive an ITSL, the ITSL derived in this manner was compared to the therapeuptic dose level for methylprednisilone acetate. A therapeutic dose doesn't imply that the dose is safe from adverse effects. Methylprednisilone acetate is a glucocorticoid causing profound and varied physiologic effects at therapeutic doses. However, since the therapeutic dose is based upon human experience, such a comparison can help provide confidence as to whether or not the ITSL will be protective of public health. To make the comparison between the ITSL and the therapeutic dose, the ITSL was converted to a delivered dose as shown below. A comparison was made by determining the ratio of the therapeutic dose to the delivered dose. Therapeutic doses are not necessarily no effect doses. However, the ratio of calculated ITSLs and therapeutic doses were so large as to preclude, in the judgement of the committee, the existence of even a therapeutic effect at the ITSL.

COMPARISON OF DELIVERED DOSE[A] TO THERAPEUTIC DOSE

Compound Name	Proposed ITSL (ug/m3)	Therapeutic Dose[B] Range (mg/kg/day)	Delivered Dose (mg/kg)	Ratio of Doses[D] (Range)
methylprednisilone acetate	43	0.57 - 2.86[C]	0.012	48 - 238

A. Based on the formula: Delivered dose = {ITSL (mg/m3) x 20 m3}/70 kg

B. No implications are made that a therapeutic dose is a safe dose.

C. Medrol (methylprednisilone tablets): 80 mg every other day for 30 days (=40 mg/day; or =200 mg/day for 1 week). Based on a 70 kg person = 40 mg/70 kg (or 200 mg/70 kg). Dose regimen for treatment of multiple sclerosis.

D. Therapeutic Dose/Delivered Dose = Ratio of Doses.

The ITSL for methylprednisolone acetate = 43 $\mu g/m^3$ based on annual averaging.