RECOMMENDATIONS OF THE SCIENTIFIC ADVISORY PANEL

ISOFLUPREDONE ACETATE

CAS # 338-98-7
DECEMBER 8, 1994

Basis for ITSL:

A CAS- and NLM-online literature search was conducted for isoflupredone acetate February 1993, but did not produce any relevant information to calculate an ITSL. The search found one LC50 study in RTECS but the route of exposure was by injection. This data was inappropriate for use in calculating an ITSL. Due to the lack of available toxicity data meeting the criteria of Rule 232(1), the ITSL for isoflupredone acetate was determined to be 0.04 µg/m³ with an annual averaging, based on Rule 232(1)(i).

Summary of Public Comment:

A public comment for this compound was only received from The Upjohn Company. They suggested to AQD that publishing a screening level of 0.04 µg/m³ when other toxicological information was available to derive a higher screening level. A NOAEL from a 90-day feeding study was proposed for use in calculating an ITSL. This feeding study was conducted by Upjohn, and a brief summary was provided in the public comment.

Subsequent to their public comment, The Upjohn Company requested a formula modification for Rule 336.1232(1)(c) which is used to calculate ITSLs for a 7-day oral exposure. This formula modification involved adjusting the 35-fold safely (uncertainty) factor downwards to 2.73 (35 x 7/90) based on a dietary study where rats were exposed to isoflupredone for 90-days. This factor of 35 is used to account for the uncertainty of extrapolating from a 7-day study versus a chronic lifetime study.

Response to Public Comment:

In response to the formula modification request, while Ride 232(1)(e) allows the adjustment of the factor 35 on a case-by-case basis from repeated dose studies other that 7day studies, this factor was not intended to be adjusted downward below 10 for a subchronic 90-day study, unless specific data was available to support a different uncertainty factor.

When the Michigan Air Toxics Policy Committee (1989) recommended its proposed rules for regulating emissions of air toxics, they endorsed the uncertainty factor methodology established by EPA. The Policy Committee stated, “EPAs inhalation reference methodology is currently one of the best generic methodologies available tot determining screening levels. It provides for consideration of all relevant data and specifies guidelines for consistent determination of safe exposure levels. EPA’s inhalation reference dose methodology, incorporating uncertainty or safety factors applied to a NOAEL, is also consistent with the methods used by other scientific and regulatory groups, including the National Academy of Sciences and the Food and Drug Administration”. These groups have all traditionally used a factor of 10 to account for the uncertainty of extrapolating front a subchronic 90-day study versus a lifetime chronic study.

The 90-day study submitted by Upjohn is more appropriate to use for determining the ITSL than the default value of 0.04 µg/m³. The AQD recommends that this study be used for determining the ITSL according to Rule 232(1)(e) with the adjustment of the 35-fold uncertainty factor to 10. A summary of the 90-day study and the ITSL determination is given below.

Upjohn provided an internal dietary 90-day study for isoflupredone. Isoflupredone is the active portion of the isoflupredone-acetate complex, with the acetate moiety used primarily to enhance solubility. The parent compound was administered via the diet to groups of UPJ:TUC(SD) rats at approximate concentrations of 0, 100, 200, 1,000, and 2,000 ppb for 90 days. A total of 40 rats/sex/group were dosed and observed for body weight changes, food consumption, clinical observations, clinical pathologic changes, plasma corticosterone levels and gross and microscopic observations.

Comparisons of results among the treated and control groups indicated no treatment differences between control, 100 and 200 ppb dosed groups, whereas, significant decreases occurred in body weight, mean cholesterol values and food consumption in the 1000 and 2000 ppb dosed groups. This data corresponds with literature data, indicating that corticosteroids have a marked effect on body weight as a function of growth. The data from this study indicated that 200 ppb of isoflupredone in the diet was the maximum "no effect level".

Because isoflupredone is the active portion of isoflupredone acetate, the screening level for isoflupredone will also be adjusted by a ratio of the molecular weights of these two compounds.

The ITSL was derived as follows using Rule 232(l)(e):

isoflupredone MW 378.5 g/mol
isoflupredone acetate MW 420.5 g/mol

NOAEL: 200 ppb 0.200 ppm

Average body weight (90-day study): 0.358 kg
Average daily food intake (90-day study): 0.022 kg/day

0.200 ppm feed x 0.022 kg (feed eaten)/(0.358 kg body weight) = 0.0123 mg/kg/day

Calculation of the ITSL:
UF of 10 data from a subchronic rather than chronic study
UF of 100 animal rather than animal data; sensitive individuals
Daily inhalation rate of rats in m^3/day = 0.344
Absorption efficiency by oral exposure route 1
Absorption efficiency by inhalation exposure route 1

0.0123 mg/kg/day/(10 x 100) x 0.358kg/(0.344) x 1/1 = 0.0000127 mg/m^3

0.00001 mg/m^3 x 1000 µg/mg = 0.01 $µg/m^3$

Molecular Weight Ratios:

0.01 $µg/m^3$/(378.5 g/mol) = x $µg/m^3$/(420.5 g/mol)

X = 0.011 $µg/m^3$

Isoflupredone acetate is a compound that is used for supportive therapy in cattle, horses, and swine. It is not intended for human use, but it is uncertain if this compound would exert any therapeutic effect in humans. This ITSL was derived using very conservative assumptions yielding a screening level four-fold lower than a trace value of 0.04 ug/m^3. Therefore, it is reasonable to conclude that the ITSL would be protective of public health at 0.01 $µg/m^3$

The ITSL for Isoflupredone Acetate = 0.01 $µg/m^3$ based on annual averaging.