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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

3-30-98

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Chlorothalonil, Registrant's Comments re Dermal Absorption

TO: Mary Rust
Risk Characterization and Analysis Branch
Health Effects Division (7509C)

Is this what you are looking for?

FROM: Robert P. Zendzian Ph.D.
Senior Pharmacologist
Science Analysis Branch
Health Effects Division (7509C)

3/30/98

on Bill's desk

THROUGH: William Burnam
Chief
Science Analysis Branch
Health Effects Division (7509C)

*WJ Burnam
4/18/98*

DP Barcode #D244482 Case #819269 Submission #S539414

Chemical #Chlorothalonil ID #081901

Registrant #ISK -MRID 44493601

Action Requested

Respond to the registrant's comments on the use of dermal absorption by the agency in the chlorothalonil RED of November 20, 1996.

Conclusions

The Agency has erred in its use of dermal absorption in the chlorothalonil RED as modified on November 13, 1996. Valid data on the dermal absorption of chlorothalonil are not available (Zendzian 1995). The 5% dermal absorption given by Zendzian was an upper limit estimate based on the physical properties of chlorothalonil. In his memo Zendzian recommended that a repeated dose dermal toxicity study, up to 90-days, be performed in the rat if this dermal absorption rate did not produce an acceptable MOE. The NOEL from this study was to be used directly for dermal risk assessment. Subsequently it was determined that a 21-day dermal toxicity study would be

sufficient for agency risk assessment purposes and such a study was performed by the registrant. A NOEL of 600 mg/kg/day (HDT) was determined for the systemic toxicity of chlorothalonil (physical damage to the proximal convoluted tubule of the kidney). The study also determined an LOEL of 60 mg/kg/day (LDT) for damage to the skin. These data are suitable for risk assessment following dermal exposure to chlorothalonil.

The correct agency notation under dermal absorption in the chlorothalonil RED should be as follows;

1. No valid dermal absorption data on chlorothalonil are available.
2. An acceptable dermal toxicity study (21-day) is available for dermal risk assesment.
3. Therefore, Dermal absorption data are not necessary or required.

The registrant's calculation of 'virtual' or 'apparant' dermal absorption rates from the results of oral and dermal toxicity studies is kinetically interesting. Lacking more directly useful information such a value could be used, carefully in dermal risk assessment of chlorothalonil. However, the 21-day dermal toxicity study provides definitive primary data for dermal risk assessment and must be used for that process.

Background

Chlorothalonil is a fungicide with acute oral and dermal toxicities greater than 10,000 mg/kg. It is a dermal irritant and a severe eye irritant. The primary target of oral chlorothalonil is the digestive tract (esophagus, forestomach/stomach and duodenum). This appears to be a direct toxic effect. The systemic target of chlorothalonil toxicity is the kidney. Kidney toxicity has been demonstrated in rats and mice in both subchronic and chronic studies and in the dog in a chronic study; all by the oral route. The lesion is a primary toxic effect on the proximal convoluted tubule. The effect is first observed as irregular intracytoplasmic inclusion bodies, advancing to tubular vacuolization, tubular hyperplasia and ultimately renal tumors in both rats and mice. The effects were dose and duration related.

In 1995 I was asked to assess the the dermal absorption data available on chlorothalonil and determine aproprate dermal absorption rates. I concluded that the studies available do not allow determination of dermal absorption. However, I further concluded "Based on the physical/chemical properties of chlorothalonil and its vehicle(s) used in agriculture, we can make a reasonable estimate that no more than 10% of the chlorothalonil deposited on the skin, during a 10 hour working day, will enter the skin. Based on the distribution of the total amount of chlorothalonil to enter the skin from the

latex base paint in MRID 436001-03, we can reasonably estimate that no more than half of that material will pass through the skin and be available systemically to effect the kidney. Therefore; five percent dermal absorption of chlorothalonil can be used for a threshold risk assessment of toxicity to the kidney. As this assumption is based on absorption by the rat it can be expected to overestimate human absorption."

"If this assumption of 5% dermal absorption does not produce an acceptable MOE(s), it is recommended that a repeated dose dermal toxicity study of appropriate duration, up to 90-days, be performed in the rat to determine a NOEL for toxicity to the systemic target organ, the proximal convoluted tubule of the kidney. This NOEL can be used directly, with the agricultural worker exposure data, to calculate the MOE(s)."

In 1996 the registrant commented on this evaluation. In response to these comments "A meeting was held on Friday March 22, 1996 to discuss the matter of the dermal absorption of chlorothalonil and a number of unacceptable margins of exposure (MOEs) derived therefrom in the reregistration eligibility document (RED). Attending were Baetcke, Burnam, Ioannou and Zendzian. It was decided that further pursuit of information on the dermal absorption of chlorothalonil up to and including a new study cannot be expected to significantly effect MOEs for certain use patterns."

"It was recommended that the Registrant perform a 90-day dermal toxicity study in the rat, with an intermediate sacrifice at 21-days, on the most sensitive sex with particular attention to histopathological evidence of toxicity to the kidney. A no observable effect level (NOEL) from this study can be used directly with dermal exposures to determine MOEs. It was recommended that the Registrant consult with the Agency in designing the dermal toxicity study." (Zendzian 1996a).

"On Wednesday April 3, 1996 a meeting was held on Chlorothalonil with representatives of the Registrant (ISK) to discuss the dermal risk assessment and the role of dermal absorption. Attending were Dr. William Busey of Experimental Pathologies Laboratories Inc. and Dr. Maija Mizens of Ricerca Inc. representing ISK and Drs. Mike Ioannou and Robert Zendzian and Ms Mary Clock representing the Agency."

"In the meeting it was decided to abandon the pursuit of data on the dermal absorption of chlorothalonil and perform a short term dermal toxicity study in the rat. The study will be designed to provide a dermal NOEL that can be used directly in risk assessment calculations following dermal exposure. Such a study will avoid a variety of assumptions that must be made in applying dermal absorption data and provide a simpler and more realistic risk assessment." (Zendzian 1996b)

A 21-day dermal toxicity study of chlorothalonil was designed, performed and submitted to the agency. The study clearly showed a NOEL for kidney toxicity at 600 mg/kg/day, the highest dose tested. The study also showed dermal irritation at 60 mg/kg/day, the lowest dose tested. The Toxicology Endpoint Selection Document on chlorothalonil was revised on 11/13/96 to reflect this new data. The NOEL of 600 mg/kg/day was used as the end points for short and intermediate term occupational or residential exposures. However, no change was made in the summary of dermal absorption data to reflect that this was an estimate that could no longer be supported.

The registrant has now proposed a dermal absorption rate obtained by comparing the doses at which a common toxic effect is observed following oral and dermal dosing in the same species. This procedure produces a percent value which I have named the Apparent Dermal Absorption. The value is derived by the following method which is abstracted from a draft document on using dermal absorption data.

"Estimating Dermal Absorption"

"2. Comparison of acute oral and dermal toxicities."

"If an acute LD₅₀ has been determined for a compound by the oral and the dermal route in the same species one may estimate a percentage dermal absorption rate. I have called this percent the apparent dermal absorption. One assumes that 100 percent of the compound is absorbed by the oral route at the oral LD₅₀ to produce the systemic dose and that the same systemic dose is produced at the dermal LD₅₀. Three criteria must be met to use this approach;

1. The same test material, technical or a similar high concentration material, must be used for the oral and dermal studies.

2. The same species and sex must be used so that we are assured of similar qualitative metabolic processes in each test.

3. There must be the same toxicological end-point in the oral and dermal test. In this example we are using lethality because this data is commonly generated but other end-points may be used.

One calculates the apparent percent absorbed at the LD₅₀s as;

$$\text{Apparent Percent Absorbed} = \frac{\text{Oral LD}_{50} \text{ in mg/kg}}{\text{Dermal LD}_{50} \text{ in mg/kg}} \times 100$$

This calculation produces an apparent dermal absorption. The resulting figure is called apparent because it includes the differences in absorption, distribution and metabolism that can be expected to occur by the different routes. This percent number has several problems in application to the exposure data. 1) Dermal exposure for a dermal LD₅₀ is usually 4 or 24 hours so that the apparent dermal absorption rate is percent /4 or /24 hours. 2) Since, in the usual case, the percent absorbed per unit time varies inversely with the dose applied this calculated rate will under estimate the true rate at lower doses per unit area of skin than those used in determination of the dermal LD₅₀. 3) For some compounds the dermal LD₅₀ is less than the oral LD₅₀ producing an apparent dermal absorption rate of greater than 100%. This is usually, due to quantitative differences in metabolism by the two routes.

In cases where there is a difference by sex, one should be conservative and use the highest apparent dermal absorption rate. In cases where a dermal LD₅₀ was not determined one can make a better estimate of the apparent dermal absorption rate, if the individual dose data are available, by comparing the lowest oral dose which produced death with the highest dermal dose which produced no deaths. The resultant apparent dermal absorption rate will be lower than that calculated in the table. However, one must never use an oral no effect dose. There is no lower limit to no effect doses, the smaller they are the smaller the apparent dermal absorption rate and the greater the likelihood of underestimating the true dermal absorption rate. The error of underestimating dermal absorption is never allowable in risk assesment."

The registrant used this approach with the data from a rat subchronic oral study, a rat metabolism study and the rat 21-day dermal toxicity study. The end point, is toxicity to the kidney.

Given

1. Lowest effect dose from subchronic oral study 3 mg/kg/day
2. Oral absorption in the rat 30%.
3. Lowest effect dose from 21-day dermal toxicity study >600 mg/kg/day.

$$\text{Apparant Dermal Absorption} = 100 \times \frac{3 \text{ mg/kg/day} \times 0.30}{>600 \text{ mg/kg/day}}$$

Therefore: the Apparant Dermal Absorption = <0.15%

The registrant extended this approach by adding the following assumptions;

Given

4. Kidney toxicity is produced by absorbed nephrotoxic thiols.
5. Metabolism studies show only 1.6% of the oral dose is absorbed as nephrotoxic thiols.

$$\text{Apparant Dermal Absorption} = 100 \times \frac{3 \text{ mg/kg/day} \times 0.016}{>600 \text{ mg/kg/day}}$$

Therefore: the Apparant Dermal Absorption = <0.008%

This is an interesting approach and could be considered for risk assessment purposes in the absence of preferred data. In all cases of dermal exposure the preferred data set is the NOEL from a dermal toxicity study that matches or exceeds the exposure duration which occurs during field use. In this case the approach is superceeded by the data from the dermal toxicity study.

references

- Memo: Chlorothalonil, dermal absorption and metabolism studies Zendzian to Clock 9/15/95.
- Memo: Chlorothalonil, risk assessments and dermal absorption Zendzian to Clock and Deschamp 3/28/96
- Memo: Chlorothalonil Meeting with registran's scientists re dermal absorption, dermal risk assessment and dermal toxicity Zendzian to Clock and Ertman 4/9/96