



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

Rec'd 11-10-92

NOV 10 1992

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Chlorothalonil & HCB: ISK Biotech Waiver Requests
in Response to Chlorothalonil DCI dated 7/31/91:
CBRS Nos 9562 & 9806: DP Barcodes D175650 &
D177592: MRID No 42272101.

FROM: William O. Smith, Ph.D., Chemist *William O. Smith*
Reregistration Section I
Chemistry Branch II-Reregistration Support (CBRS)
Health Effects Division (H7509C)

THROUGH: Paula Deschamp, Acting Section Head *Paula Deschamp*
Reregistration Section I
Chemistry Branch II-Reregistration Support
Health Effects Division (H7509C)

TO: Lois Rossi/Andrew Ertman
Reregistration Branch
Special Review & Reregistration Division (H7508W)

CBRS has been asked to evaluate waiver requests regarding the chemical chlorothalonil. ISK Biotech is requesting waivers for all HCB field trials and livestock feeding studies that were required in the 7/31/91 Chlorothalonil DCI.

CONCLUSIONS

1. The conclusions in this review apply only to Chlorothalonil formulations proposed by ISK Biotech. Any changes in the data requirements as stated in the 7/31/91 Chlorothalonil DCI apply only to ISK Biotech and are contingent upon the registrant documenting that they are indeed manufacturing chlorothalonil with the specifications claimed in the present submission.
2. The dietary risk assessment for HCB from chlorothalonil is not affected by this review. All Chlorothalonil formulations presently on the market are certified to contain HCB in concentrations [REDACTED] those discussed in this review.

COMMERCIAL/FINANCIAL INFORMATION IS NOT INCLUDED
3. If ISK Biotech produces chlorothalonil formulations with the reduction in HCB contamination claimed in this submission, a



Recycled/Recyclable
Printed on paper that contains
at least 75% recycled fiber

significant reduction in dietary risk would be accomplished for crops treated with their formulations. However, other manufacturers of chlorothalonil will still be producing formulations with HCB contamination unchanged from present conditions; therefore, any changes in the dietary exposure to the overall population from HCB in chlorothalonil would become a function of the relative market share of the registrant's product.

4. HCB field trial data required of ISK Biotech in the 7/31/91 Chlorothalonil DCI should be placed in reserved status.
5. For purposes of risk assessment, and in the absence of further HCB field trial data, the Agency will continue to assume that HCB residues on food crops from the application of chlorothalonil are present at a 10-fold greater level relative to chlorothalonil residues than in the formulations applied to the crops.
6. The data requirement for an HCB ruminant feeding study, as specified in the Chlorothalonil DCI of 7/31/91, remains outstanding. An analytical method with a limit of detection of 0.0005 ppm or less should be used and the study must be conducted with exaggerated levels of HCB so bioaccumulation estimations can be based on actual measurements.
7. The HCB poultry feeding study required in the Chlorothalonil DCI of 7/31/91 is placed in reserved status pending results of the ruminant feeding study. A decision will be made at that time whether a poultry study is needed.

RECOMMENDATIONS

We recommend, contingent upon the registrant documenting that they have reduced HCB contamination in their chlorothalonil formulations as claimed in this submission, that HCB field trials and poultry feeding studies be held in reserve. The waiver request for ruminant feeding studies should be denied.

DETAILED CONSIDERATIONS

HCB Field Trial Data

-Background

The Agency has conducted dietary exposure analyses to estimate the oncogenic risk resulting from the presence of HCB in chlorothalonil formulations applied to food crops. In the absence of data indicating actual levels of HCB on many food

crops, analyses were conducted in which average expected dietary residues of chlorothalonil were multiplied by 0.5% to obtain a estimate of HCB residues. The 0.5% value was based on the limited data available that indicated that HCB may dissipate more slowly on crops than chlorothalonil resulting in an increased percent of HCB relative to chlorothalonil in the harvested commodity (0.5% on the crop vs. 0.05% in the chlorothalonil formulation). Although it was recognized that these data were limited and additional data were needed prior to making a final determination, this 10-fold concentration factor was used as an interim value to estimate dietary exposure to HCB as a result of chlorothalonil use. This approach resulted in an estimated risk of 10^{-6} (excluding risk from meat and milk) for chlorothalonil formulations containing 0.05% contaminating HCB.

Subsequently, the Agency required crop field trial data depicting uptake and decline of HCB residues relative to chlorothalonil from several representative crops. The data were required to reflect residues at various intervals (including the PHI) during an application regimen in which the crop was treated at exaggerated rates such that HCB was measurable at several harvest intervals after treatment and the rate of degradation of HCB relative to that of chlorothalonil could be determined.

-Registrant's Response

ISK Biotech has informed the Agency that they are improving the Chlorothalonil manufacturing process, thereby reducing the maximum level of contaminating HCB in their technical product from [REDACTED]. It was anticipated that the new production facilities would be completed and the improved technical product characterized by mid 1992; however, the Agency has received no data to confirm this. The registrant feels that this improvement in their technical product will reduce the level of potential HCB residues on agricultural commodities treated with chlorothalonil below levels which could pose significant carcinogenic risk.

The registrant also cites storage stability studies (MRIDs 415648-20 through -27) in which chlorothalonil was applied to crops at exaggerated rates. They claim that these studies demonstrate that HCB residues decline at a rate equal to that of chlorothalonil on treated crops; therefore, the 10-fold concentration factor used by the Agency for HCB relative to chlorothalonil residues in recent dietary risk analysis is inappropriate.

The registrant requests that the HCB field trial data requirement be waived for the above described reasons.

-CBRS Comments

The storage stability studies cited by the registrant involve

exaggerated applications of chlorothalonil to wheat, carrots, potatoes, celery, soy beans, tomatoes, cucumbers and cherries. The HCB was present in the chlorothalonil formulation at a level of [REDACTED]. All of the crops were treated with multiple foliar applications and harvested immediately after the last application. The limit of detection for the HCB analytical method was 0.003 ppm. These studies are not suitable to address the HCB data requirement because they were not conducted in a manner that would be expected to reveal the relative rates of dissipation of HCB and chlorothalonil. In the cases of wheat, cherries, cucumbers, tomatoes, soy beans, and celery the relative ratio of HCB and Chlorothalonil would be expected to be the same as in the formulation applied because the crops were harvested immediately after application of an exaggerated foliar application; thus the analysis would most likely determine the HCB/chlorothalonil ratio in the fresh surface residues. Additionally, the data for cucumbers, celery and potatoes are not useful because the HCB residues were below the limit of detection of the analytical method. The only crop that may be considered marginally useful is carrots. It is possible that the residues on the carrots are not just contamination from the last foliar application and therefor may represent an actual comparison of relative decline of chlorothalonil and HCB similar to what may occur under normal cropping procedures. In this case the residues of chlorothalonil were reported as 1.84 ppm and HCB was reported as 0.005 ppm. The ratio of HCB to chlorothalonil residues is 0.0027 as compared to a ratio of [REDACTED] in the formulation; this is an apparent [REDACTED] relative concentration of HCB on the carrots. Therefore, CBRS does not accept the registrant's argument that these data show that HCB does not concentrate relative to chlorothalonil in crop residues. We do recommend that the crop field trial requirement for ISK Biotech be held in abeyance contingent upon the registrant providing product chemistry data proving that they have lowered HCB levels in their formulations to [REDACTED] and pending receipt of data on secondary residues in livestock. The fact that the registrant has reduced the level of HCB contamination to [REDACTED] in their formulations will lower the risk from crop commodities in the most recent DRES analysis to $<10^{-6}$. We do note that other registrants are manufacturing chlorothalonil at the higher level of HCB contamination. These registrants should either lower the level of HCB in their formulations or be required to submit the required HCB field trial data as specified in the chlorothalonil DCI of 7/31/91.

Meat, Milk, Poultry and Egg Feeding Studies

-Background

The Chlorothalonil DCI of 7/31/91 required feeding studies in which ruminants and poultry must be dosed with HCB at three

levels representative of 1X, 3X and 10X the anticipated average concentration in the diet resulting from use of chlorothalonil on feed items.

-Registrant's Response

In a meeting between ISK Biotech and the Agency held on October 30, 1991 it was agreed that it may not be necessary to feed HCB alone but it may be necessary to monitor for HCB when the registrant conducts feeding studies with chlorothalonil/SDS-3701.

The registrant submitted copies of published articles (MRID 42272101) concerned with HCB in animal tissues in support of their claim that residues of HCB will concentrate in livestock tissue by about 10-fold relative to the level in the animal diet. CBRS cannot accept these studies because the registrant has not provided raw data from these publications nor certified that they have access to these data. We note that the relative concentration of HCB in animal tissues varied from about 1X to greater than 50X in these studies and seemed to be dependant, among other factors, on dose level. That is, at lower dose levels the relative concentration in tissues seems greater. The lowest dosing level of HCB reported was 0.03 ppm, a level considerably higher than what would be expected to occur as residues on animal feeds. Therefore, even if the registrant had access to the raw data from these studies their usefulness would be limited for the purposes of dietary risk assessment.

The registrant has provided livestock dietary burden calculations for chlorothalonil and HCB (MRID 42272101). They estimate tissue-to-feed ratios of chlorothalonil in milk and red meat based on a study with the SDS-3701 metabolite (MRID 0008677). Tissue-feed-ratios in poultry were obtained from a ¹⁴C-chlorothalonil feeding study (MRID 00127866). The poultry study was conducted at dose levels up to 20 ppm with essentially no transfer of radiolabel to eggs or meat. The dietary burden of chlorothalonil was estimated to be less than 0.001 ppm for poultry.

The registrant submitted an estimate of anticipated residues and a chronic dietary exposure analysis for chlorothalonil and HCB (MRID 42272101) in support of their contention that HCB residues from chlorothalonil uses are too low to contribute significantly to oncogenic risk in the diet. This analysis was performed by Technical Assessment Systems, Inc. Among the assumptions made in this analysis were the following:

1. HCB residues on crops resulting from applications of chlorothalonil are present at the same relative ratio to the active ingredient residues as in the formulation applied. [The Agency has made the assumption that HCB residues on crops should be estimated to concentrate 10-fold relative to residue of chlorothalonil.]

2. The relative concentration of HCB in Chlorothalonil formulations is [REDACTED]. This level represents a [REDACTED] reduction from the maximum level that is presently certified to be present in chlorothalonil formulations.

3. The HCB residue in animal tissue was estimated on the chlorothalonil dietary burden multiplied by an appropriate tissue-to-feed ratio, the [REDACTED] chlorothalonil-to-HCB impurity ratio, and a 10-fold concentration factor taken from the above mentioned published studies.

The registrant requests that poultry and meat/milk feeding studies be waived. As discussed at the meeting with the Agency of Oct 30, 1991, the registrant requests a waiver of the meat/milk study with HCB alone but indicates the HCB residues may be monitored if a feeding study is required for chlorothalonil.

-CBRS Comments

The registrant estimates that maximum dietary burden for beef cattle, dairy cattle and poultry would be 0.044 ppm, 0.072 ppm and 0.001 ppm respectively. CBRS neither accepts nor rejects these estimates at this time but for the sake of considering the present submission these estimates seem reasonable. We do not agree with the registrant's calculation of HCB dietary burden or worst case estimation of residues in animal tissues. To estimate HCB residues in red meat we multiply the maximum dietary burden of chlorothalonil [REDACTED] to obtain the level of HCB contaminant in the proposed new formulation. Then we multiply by another factor of 10 to account for our best estimate of concentration of HCB in crop residues (see above for our rationale). Based on a perusal of the published literature provided by the registrant we will assume that a conservative estimate of concentration of HCB in animal tissues is 100x rather than the 10x proposed by the registrant. Thus, in red meat we calculate the worst-case estimated residues as:

[REDACTED]

for milk the same assumptions yield:

[REDACTED]

and for poultry we have:

[REDACTED]

Because the Q* of 1.7 for HCB is so high, these levels of HCB are an unacceptable risk for red meat and milk. In fact the red meat contribution alone would result in a risk of 3.1×10^{-5} . These estimates are based on assumptions that may or may not prove to be too conservative; therefore, it seems prudent to not waive the

requirement for a ruminant feeding study as specified in the 7/31/91 Chlorothalonil DCI. These studies must include feeding levels exaggerated enough to ensure that detectable HCB levels will occur. This will also require the use of an analytical method with a limit of detection of 0.0005 ppm or better. Such a limit of detection has been reported by this registrant for HCB analyses on crops. Because of the low levels of poultry residues predicted in our estimates above (0.00004 ppm) we will hold the HCB poultry feeding study in reserve status. A decision as to the necessity of a poultry feeding study will be made on completion of the ruminant feeding study.

cc: W. Smith, Chlorothalonil Reg. Std. File, SF, RF.

H7509C:CB-II:WOS:wos:Rm805A:CM#2:X5353:09/29/92
RDI: PDeschamp(09/30/92) MMetzger(11/9/92) EZager(11/9/92)