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WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Assessment of the Dietary Cancer Risk of Hexachlorobenzene and Pentachlorobenzene as impurities in Chlorothalonil, PCNB, Picloram, and several other pesticides. DP Barcode D243499. Chemical codes 061001 (Hexachlorobenzene) & 081901 (Chlorothalonil).

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This memorandum is primarily in response to issues arising related to reregistration of chlorothalonil and registration of some new uses for the same chemical. To date, in assessment of human health risks associated with chlorothalonil, the Agency has addressed the cancer risk due to the presence of hexachlorobenzene (HCB) as a minor impurity in the formulated products. Hexachlorobenzene is considered to be a B2 possible human carcinogen with a Q* of 1.02 $(mg/kg/day)^{-1}$. This memorandum is being written in response to requests from RD and SRRD to provide a cumulative cancer risk for the dietary exposure to HCB. Four pesticides that are used on food/feed crops have been assessed for cancer risk due to contamination with HCB. These are chlorothalonil, dacthal, picloram, and pentachloronitrobenzene (PCNB).

Pentachlorobenzene (PCB) has also been found from use of PCNB. HED has concluded that, based on the similarities of the chemical structures and toxicities of HCB and PCB, it is reasonable to assume that the carcinogenic potential of PCB is comparable to HCB. Thus, for the PCNB dietary risk assessment the Q* for PCB has been assumed to be equal to that for HCB.

The Agency has also issued a DCI (10/92) for analytical data on the possible presence of HCB or

PCB in 26 other pesticidal active ingredients. Based on data reviewed to date, one or both of these impurities have been detected in five active food-use pesticides.

In the discussion provided below we are providing estimates of dietary exposure/risk for HCB and PCB in nine chemicals.

CONCLUSIONS:

Table 1 contains estimated dietary cancer risks from all known pesticidal sources of HCB and PCB. The cumulative estimated dietary cancer risk for HCB is 1.34×10^{-6}. An additional 0.46×10^{-6} may be attributed to PCB. If this total is adjusted for the potential cancellation of dacthal (personal communication, Jill Bloom, SRRD), then the cumulative dietary cancer risk is estimated to be 1.1×10^{-6}. The assumptions and methods that are incorporated in these assessments can be found in the discussion section that follows.

Table 1. Estimated Dietary Cancer Risk of the Pesticide Impurities, HCB and PCB[1].

Source Pesticide	Oncogenic Risk[2]		
	HCB	PCB	Combined
Chlorothalonil	2.4×10^{-7}	None	2.4×10^{-7}
PCNB	1.6×10^{-7}	4.3×10^{-7}	5.9×10^{-7}
Picloram	1.5×10^{-7}	None	1.5×10^{-7}
Dacthal[3]	[7.1×10^{-7}]	None	[7.1×10^{-7}]
Five Other Chemicals[4]	7.5×10^{-8}	2.75×10^{-8}	1.0×10^{-7}
Total	**6.3×10^{-7} [1.34 x 10-6]**	**4.6×10^{-7}**	**1.1×10^{-6} [1.81×10^{-6}]**

1. See discussion section below for source of assessment and any new assumptions or calculations contained in this consideration.

2. Q* for HCB and PCB assumed to be 1.02 $(mg/kg\ bwt/day)^{-1}$

3. Uses of this chemical may be voluntarily canceled in the near future. Cancer risks that include the potential contribution from dacthal are enclosed in brackets

4. Five pesticides that are currently used on food/feed crops and were identified in the product chemistry DCI of 10/92 as containing either HCB or PCB. The chemicals are endosulfan, chlorpyrifos-methyl, atrazine, simazine, and clopyrilid.

DISCUSSION:

General Considerations: For purposes of this cumulative assessment we have added the individual assessments for picloram, dacthal, PCNB and chlorothalonil, each with its individual set of data and assumptions. For the five additional chemicals obtained from responses to the DCI of 10/92 we made a first cut screening assessment based on the most recent DRES run for the active ingredient. The assumption was made that the impurities would occur on food commodities at the same ratio to the active ingredient as was present in the formulation applied to crops. Further refinement of anticipated residues was not attempted for the five additional chemicals because of limited resources available at this time. It is the judgement of this reviewer that given the low levels of HCB and PCB in the DCI chemicals relative to picloram, PCNB, chlorothalonil, and dacthal, any errors in the simple screening approach taken here would be insignificant compared to the overall dietary exposure assessment including all nine chemicals.

The major problem in attempting to estimate the dietary exposure to HCB is that it is generally present in food commodities, if at all, at levels that are below the limit of detection of analytical methods. In such situations the general rule for exposure assessment has been to make the assumption that residues are present at one half the limit of quantitation or one half the limit of detection. Given the high Q* of HCB, this assumption can lead to the appearance of an unacceptable risk, depending on the sensitivity of the analytical method. In some cases levels of HCB have been estimated based on levels of the active ingredient in food commodities. In these cases it was assumed that the impurity would dissipate from the food commodity at an equal or greater rate than the active ingredient. There are some data available from exaggerated use rates of chlorothalonil, picloram and DCPA that support this approach.

The sources of data for each chemical and any new refinements introduced in this memo, are summarized below.

Picloram: The most recent DRES analysis (4/12/94, J. Bazuin) yielded an estimate of oncogenic risk of 0.6698×10^{-6}. The anticipated residues for HCB from picloram were included in the Residue Chemistry Chapter of the RED (W. Smith, 3/7/94). The estimated cancer risk in the diet from uses of picloram is essentially all from the consumption of meat and milk and was based on a number of conservative assumptions including tolerance level picloram on feed items and worst case animal diets. Also, the transfer factors used in estimating residues in meat, milk, poultry and eggs were more conservative than those used for similar dietary exposure assessments for HCB in dacthal, PCNB and chlorothalonil, even though the factors were derived from the same HCB feeding study. These factors are shown below. The lower numbers in the third column were derived from a linear regression analysis of multidose feeding study data while the numbers used in the picloram assessment were rounded up based on visual inspection of the same data. In the interest of consistency the same transfer factors are taken into account here as that were used for assessments of HCB in animal commodities due to use of chlorothalonil, dacthal and PCNB on feed items (Table 2, column 3).

Table 2. Transfer factors used in estimating anticipated residues of HCB in meat milk, poultry and eggs.

Commodity	Factor used in picloram RED for deriving anticipated residues of HCB (DRES run of 4/12/94)	Factor used for deriving anticipated residues of HCB from uses of dacthal, chlorothalonil, and PCNB
Cattle fat	10x	4x
Milk	0.2x (with residues confined to fat)	0.08x (with residues confined to fat)
Cattle meat, liver and kidney	0.5x	0.2x
Poultry fat	10x	6x
Poultry liver	2x	2x
Poultry meat	0.2x	0.1x
Egg yolk	3x	2x
Egg white	0.01x	0.004x

Based on the revised factors shown in Table 2 refinements can be made in the cancer risk assessment for HCB in picloram.

The contribution of HCB residues in beef fat to the cancer risk in the DRES run of 4/12/94 was 0.2856×10^{-6}. Since this value is directly related to anticipated residue and we can reduce the anticipated residue by a factor of 4/10 (Table 2) , a refined risk due to these food items is 0.1142×10^{-6}.

In the cancer assessment of 4/12/94, milk-non-fat-solids contributed 0.1343×10^{-6}. This should be removed from the cancer risk because the anticipated residues of HCB are restricted to milk fat only. The risk due to milk-fat solids was 0.1938×10^{-6}. This can be refined by a factor of 0.08/0.2 (Table 2). Thus a revised estimate for risk from milk fat products would be 0.07752×10^{-6}.

The revisions are summarized in the following table.

Table 3. Revisions in the assessment of cancer risk from HCB in Picloram based on changes in transfer factors for estimating residues in meat and milk.

Foods	Cancer risk (4/12/94)	Cancer risk based on present revision in anticipated residues
Beef fat	0.2856×10^{-6}	0.1142×10^{-6}
Milk-non-fat	0.1343×10^{-6}	-
Milk-fat	0.1938×10^{-6}	0.07752×10^{-6}
Sum	0.6137×10^{-6}	0.19172×10^{-6}

The difference in estimated cancer risk from beef fat and milk is 0.42198×10^{-6}.. Therefore, adjusting the total cancer risk for these revisions yields (0.66980×10^{-6}) - (0.42198×10^{-6}) = 0.2478×10^{-6}. Finally, the assessment of 4/12/94 used a Q* for HCB of 1.7, which has subsequently been revised to 1.02. Thus the cancer risk can be adjusted by a factor of 1.02/1.7 resulting in a revised value of 0.15×10^{-6}.

Pentachloronitrobenzene: A refinement of anticipated residues for HCB and PCB was completed by HED in 1994 (W. Smith, D203453, 5/25/94); however, a dietary risk assessment had not been performed. The latest anticipated residue data were entered into the DRES for this assessment (B. Steinwand, 2/18/98) and the oncogenic risk calculated. These data yield revised risks of 1.6×10^{-7} for HCB and 4.3×10^{-7} for PCB. It should be noted that in deriving these anticipated residues it was assumed that HCB is present in PCNB at levels not to exceed 0.1 %. Since that time the two producers of PCNB have certified that levels of HCB will not exceed 0.05% and that levels of PCB will not exceed 0.01%.

Chlorothalonil: The latest refinements in the dietary risk assessment for HCB in chlorothalonil were performed in conjunction with the RED. An oncogenic risk of 2.4×10^{-7} has been estimated assuming that all chlorothalonil used on food or feed crops contain[redacted]HCB. The major producer, ISK has certified that the level is actually lower than[redacted] It has been argued by the producer that if one considers the relative market share of different chlorothalonil products chronic risk assessments using the[redacted]level result in a considerable overestimate of the risk.

The most recent risk assessment for chlorothalonil included the anticipated risk from all proposed new tolerances also.

Dacthal: The latest dietary risk assessment for HCB in dacthal resulted in an oncogenic risk of 7.1×10^{-7}. It has been indicated that uses of dacthal will soon be canceled. At present this chemical has the highest allowable level of HCB[redacted]of any of the pesticides known to contain HCB.

Responses to the DCI of 10/92:

The 10/92 DCI was sent to producers of pesticides that had been identified as being potentially contaminated with HCB or PCB, based on knowledge of the manufacturing process. A total of 26 pesticide active ingredients were included in the DCI. The producers of these pesticides were required to submit analytical data on possible contamination using an analytical method capable of quantifying residues at levels as low as 0.1 ppm (1×10^{-5}%). If quantifiable levels of either contaminant were found then certified upper limits were required for its presence in the active ingredient involved. Several of the responses to the DCI indicated the presence of either HCB or PCB but at levels considerably lower than those assessed for the four food-use chemicals above. There are five additional food-use chemicals that have been identified as contaminated with HCB or PCB at levels not to exceed those indicated in Table 4 below. These levels are considerably lower than those previously certified for pesticides (0.01%-0.3%). The potential dietary risk from these additional pesticides was estimated based on the most recent DRES runs for the active ingredient. It was assumed that the dietary exposure to the contaminant would be directly correlated to the estimated exposure to the active ingredient based on the level of the contaminant in the formulation applied to food/feed crops. It was assumed that the contaminant would be present in all formulations at the maximum concentration reported or at the certified limit set for that active ingredient. See Table 4 for the dietary risk estimates.

Table 4. Estimation of cancer risk from the presence of hexachlorobenzene or pentachlorobenzene in pesticides identified in data call in of 10/92. The "anticipated residues" of the impurities are estimated as being directly proportional to their level in the pesticide formulation applied to food crops, i.e., residues of the active ingredient and the impurity dissipate at the same rate on all food commodities.

Pesticide[1]	Daily Dietary Intake[2] [TMRC/ARC] (mg/kg/day)	Level of Impurities in Technical (%)		Estimated Oncogenic Risk[3]	
		HCB	PCB	HCB	PCB
Endosulfan	0.012144/ 0.001227	7×10^{-5}	0.0006	8.7×10^{-9} 8.8×10^{-10}	7.4×10^{-8} 7.5×10^{-9}
Chlorpyrifos-methyl	0.012672/ NA[4]	-	3×10^{-5}	None	3.9×10^{-9}
Atrazine	0.0009902/ 0.0001981	0.0017	2.5×10^{-5}	1.7×10^{-8} 3.4×10^{-9}	2.5×10^{-10} 5.1×10^{-11}
Simazine	0.002506/ 0.000113	0.002	-	5.1×10^{-8} 2.3×10^{-9}	None
Clopyrilid	0.008295/ NA	0.0008	0.00019	6.8×10^{-8}	1.6×10^{-8}
Sum of estimated dietary risk based on TMRC Sum of estimated dietary risk using ARC when available				1.5×10^{-7} 7.5×10^{-8}	9.4×10^{-8} 2.75×10^{-8}
Total estimated dietary risk (sum of HCB and PCB based on TMRC)				**2.4×10^{-7}**	
Total estimated dietary risk (sum of HCB and PCB using ARC where available)				**1.0×10^{-7}**	

1. These pesticides were identified in the DCI of 10/92 as containing detectable levels of either HCB or PCB. The highest level detected in the given pesticide technical grade was used for this assessment.

2. Daily dietary intake is based on the most recent DRES analysis for the active ingredients listed. The TMRC represents the daily dietary intake for the U.S. population - 48 states assuming tolerance level residues and 100% crop treated. The ARC values are based on the most recent refinement of anticipated residues available.

3. Estimated as the TMRC, or ARC, multiplied by the percent of impurity and the Q* (1.02 $(mg/kg/day)^{-1}$) for HCB.

4. NA indicates not available.

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