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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT **2,4-Dichlorophenoxyacetic Acid:** Toxicological Significance of **Dioxins/Furans** Present in **Technical 2,4-D Acid and Technical 2,4-D IOE of Nufarm, U.S.A**

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PROJECT IDENTIFICATIONS: Submission No. 8411157
Caswell No(s). 315 & 315-AS HED Project No. 2-1355

ACTION REQUESTED: Evaluate the toxicological significance of the level of two of the dioxin-p-dibenzofuran compounds present in 2,4-D acid, and one of the compounds present in 2,4-D acid IOE at or above LOQ limit in the Nufarm products [Memo: S. Funck, CBRS, to E. Feris, RD, 11/26/91; MRID No. 416819-01].

RESPONSE: The toxicological significance of **1,2,3,7,8-PCDD** was evaluated using the Agency's Toxicity Equivalency Factor [TEF] concept.

CDD / Isomer	Non-cancer Risk [TCDD Equivalent]	Unit Cancer Risk [TCDD Equivalent]
TCDD / Acid	1.5×10^{-11} mg TCDD/kg/day	2.4×10^{-16}
PCDD / Acid	2.2×10^{-12} mg TCDD/kg/day	3.5×10^{-17}
PCDD / IOE	5.6×10^{-13} mg TCDD/kg/day	9.0×10^{-18}

When expressed in terms of TCDD TEF, both the non-cancer risk from maximum dietary exposure **and the quantitative unit cancer risk indicate negligible risk to humans.** Therefore, the Toxicology Branch II concludes that the levels of 2,3,7,8-TCDD and 1,2,3,7,8-PCDD present in the technical 2,4-D and 2,4-D IOE are of no toxicological concern.

I. BACKGROUND

The registrant, Nufarm U.S.A, Inc., in response to a 06/87 Data Call-In notice submitted analytical chemistry data on polychlorinated dibenzo-p-dioxins and dibenzofurans in technical 2,4-D Acid and in technical 2,4-D IOE.

The concentrations of dioxins/furans were determined for seven 2,4-D samples and seven 2,4-IOE samples. The samples were reextracted and reanalyzed [in duplicates]. Based on the reanalyzes presented, the CBRS, concluded that 14 of the 15 2,3,7,8-tetra to 1,2,3,4,6,7,8-hepta chlorinated dibenzo-p-dioxins and dibenzofurans were detected in technical 2,4-D Acid and 2,4-D IOE. **However, only two of the compounds were present in 2,4-D Acid at or above the EPA Lowest Quantification [LOQ] limits, and only one of the compounds was present in the 2,4-D IOE at or above LOQ limit, as follows:**

2,4-ACID

Compound	Maximum Concentration Present [ng/g]	LOQ [ng/g]
2,3,7,8- TCDD	0.12	0.1
1,2,3,7,8-PCDD	3.4	0.5

2,4-D IOE

Compound	Maximum Concentration Present [ng/g]	LOQ [ng/g]
1,2,3,7,8-PCDD	0.93	0.5

The CBRS deferred to the Toxicology Branch on the toxicological significance of the level of these compounds in the technical products.

II. EVALUATION OF THE LEVEL OF TCDD and PCDD.

Assuming the ratio of dioxin/dibenzofuran to active ingredient remains constant from technical through the end-use product, through plant application, and through animal/human consumption of the treated raw agricultural commodities [RAC's], the amount of 2,3,7,8-TCDD and 1,2,3,7-8 PCDD expected on a RAC can be calculated.

The ratios of TCDD and PCDDs to 2,4-D Acid and 2,4-D IOE are as follows:

2,4-D ACID [2,3,7,8-TCDD and 1,2,3,7,8-PCDD]

- Technical 2,4-D has 0.98 g of 2,4-D acid / 1 g Technical
- 1 g of Technical 2,4-D contains 0.12 ng of 2,3,7,8-TCDD
- 1 g of Technical 2,4-D contains 3.4 ng of 1,2,3,7,8-PCDD
- Therefore, 0.98 g of 2,4-D corresponds to 0.12 ng of TCDD and 3.4 ng of PCDD
- **The ratio of TCDD and PCDD to 2,4-D are:**

0.12 ng/0.98 g = **0.12 ng of TCDD/1 g of 2,4-D [0.12×10^{-9}**

3.4 ng/0.98 g= **3.5 ng of PCDD/1 g of 2,4-D [3.5×10^{-9}]**

2,4-D IOE [1,2,3,7,8-PCDD ONLY

- Technical 2,4-D IOE has 0.98 g of 2,4-D IOE/1 g Technical
- 1 g of Technical 2,4-D IOE has 0.93 ng of 1,2,3,7,8-PCDD
- Therefore, 0.98 g of 2,4-D IOE corresponds to 0.93 ng of PCDD
- **The ratio of PCDD to 2,4-D IOE is:**

0.93 ng/0.98 g = 0.95 ng of PCDD/1 g of Tech. **[0.95×10^{-9}]**

RATIOS OF TCDD AND PCDD	
2,4-D ACID	**2,4-D IOE**
TCDD: 0.12×10^{-9} g TCDD/g Tech	
PCDD: 3.5×10^{-9} g PCDD/g Tech	**PCDD: 0.95×10^{-9} g PCDD/g Tech**

III. ANTICIPATED TCDF RESIDUES FROM THE USE OF NUFARM TECHNICAL 2,4-D and 2,4-D IOE

The ratio established above can be applied to the established tolerances [40 CFR 180.142] to calculate maximum anticipated TCDD and PCDD residues in the commodities as shown below:

2,4-D Acid

Anticipated TCDD Residues [ppm] =
Tolerance [ppm] x Ratio [0.12×10^{-9} g TCDD / g Technical]

Anticipated PCDD Residues [ppm] =
Tolerance x Ratio [3.5×10^{-9} g PCDD / g Technical]

Commodity	Established Tolerances of 2,4-D [ppm]	Anticipated Residues from 2,3,7,8-TCDD [ppm][a]	Anticipated Residues from 1,2,3,7,8-PCDD [ppm]
Eggs	0.05	$.006 \times 10^{-9}$	0.175×10^{-9}
Fruits	**5.0**	**0.6×10^{-9}**	**17.5×10^{-9}**
Grains	1.0	0.12×10^{-9}	3.5×10^{-9}
Kidney [hogs]	2.0	0.24×10^{-9}	7.0×10^{-9}
Meat [hogs]	0.2	0.024×10^{-9}	0.7×10^{-9}
Milk	0.1	0.012×10^{-9}	0.35×10^{-9}
Nuts	0.2	0.024×10^{-9}	0.7×10^{-9}
Poultry	0.05	0.006×10^{-9}	0.175×10^{-9}
Sugar cane	2.0	$0.24 \times 10^{-9}0$	7.0×10^{-9}

a: ppm = mg/kg

The maximum anticipated TCDD and PCDD residues in the commodities reflect worst case levels when the 2,4-D products are used according to label specifications. However, the anticipated actual levels, if any, of the TCDD or PCDD in commodities should be significantly lower.

From the above table, it is evident that the **maximum anticipated residues of TCDD [0.6×10^{-9} ppm] and PCDD [17.5×10^{-9}]** from 2,4-D acid may occur in fruits due to a higher tolerance level [5.0 ppm]. These maximum anticipated TCDD and PCDD residues may be applied, as a worst case scenario, to calculate the anticipated TCDD and PCDD dietary exposure in a 60 kg man consuming a diet consisting of 100% fruit.

2,4-D IOE

Anticipated PCDD Residues [ppm] =

Tolerance [ppm] x Ratio [0.93×10^{-9} g PCDD / g Technical]

Commodity	Established Tolerances of 2,4-D [ppm]	Anticipated Residues from 1,2,3,7,8-PCDD [ppm][a]
Eggs	0.05	0.05×10^{-9}
Fruits	**5.0**	**4.65×10^{-9}**
Grains	1.0	0.93×10^{-9}
Kidney [hogs]	2.0	1.86×10^{-9}
Meat [hogs]	0.2	0.19×10^{-9}
Milk	0.1	0.09×10^{-9}
Nuts	0.2	0.19×10^{-9}
Poultry	0.05	0.05×10^{-9}
Sugar cane	2.0	1.9×10^{-9}

a: ppm = mg/kg

The maximum anticipated PCDD residues in the commodities reflect worst case levels when the 2,4-D IOE is used according to label specifications. However, the anticipated actual levels, if any, of the PCDD in commodities should be significantly lower.

From the above table, it is evident that the **maximum anticipated PCDD residues [17.5×10^{-9}] from 2,4-D IOE** may occur in fruits due to a higher tolerance level [5.0 ppm]. These maximum anticipated PCDD residues may be applied, as a worst case scenario, to calculate the anticipated PCDD dietary exposure in a 60 kg man consuming a diet consisting of 100% fruit.

IV. ANTICIPATED TCDD and PCDD DIETARY EXPOSURE

Applying the worst case scenario discussed above [i.e., a 60 kg human on a diet consisting of 100% fruits], the Anticipated TCDD and PCDD Dietary Exposure is calculated as follows:

Maximum Anticipated TCDD Dietary Exposure from 2,4-D Acid	
1 ppm in diet = 0.025 mg/kg/day	
Therefore, 0.6×10^{-9} ppm = $0.025 \times 0.6 \times 10^{-9}$	
1.5×10^{-11} mg/kg/day	
Anticipated TCDD Dietary Exposure= 1.5×10^{-11} mg TCDD/kg/day	
Where:	
0.025 mg/kg/day =	Equivalent to 1 ppm in the diet for a 60 kg man.
0.6×10^{-9} ppm =	Maximum Anticipated TCDD residue level in fruits.

Maximum Anticipated PCDD Dietary Exposure from 2,4-D Acid	
1 ppm in diet = 0.025 mg/kg/day	
Therefore, 17.5×10^{-9} ppm = $0.025 \times 17.5 \times 10^{-9}$	
4.4×10^{-10} mg/kg/day	
Anticipated PCDD Dietary Exposure= 4.4×10^{-10} mg PCDD/kg/day	
Where:	
0.025 mg/kg/day =	Equivalent to 1 ppm in the diet for a 60 kg man.
17.5×10^{-9} ppm =	Maximum Anticipated PCDD residue level in fruits.

Maximum Anticipated PCDD Dietary Exposure from 2,4-D IOE

1 ppm in diet = 0.025 mg/kg/day

Therefore, 4.65×10^{-9} ppm = $0.025 \times 4.65 \times 10^{-9}$

1.17×10^{-10} mg/kg/day

Anticipated TCDD Dietary Exposure= 1.7×10^{-10} mg PCDD/kg/day

Where:

0.025 mg/kg/day = Equivalent to 1 ppm in the diet for a 60 kg man.

4.65×10^{-9} ppm = Maximum Anticipated PCDD residue level in fruits.

V. ESTIMATION OF TCDD TOXICITY EQUIVALENT FOR 1,2,3,7,8-PCDD

Neither a Reference Dose [RfD] nor a Q_1* has been established for 1,2,3,7,8-PCDD. Therefore, the Agency uses the Toxicity Equivalent Factor [TEF] for estimating risks associated with exposure to mixtures of chlorinated dibenzo-p-dioxins [CDDs] and dibenzofurans [CDFs].

According to the Agency's 1989 Risk Assessment Form[1] Toxicity Equivalents [TEQs] can be generated by using the TEF to convert the concentration of a given CDD/CDF into an equivalent concentration of 2,3,7,8-TCDD.

Therefore, employing the TEF, the 2,3,7,8-TCDD toxicity equivalent is calculated as follows:

2,3,7,8-TCDD Toxicity Equivalent for PCDD from 2,4-D Acid:

$= 4.4 \times 10^{-10}$ mg/kg/day x 0.005

$= 2.2 \times 10^{-12}$ mg/kg/day

Where:

4.4×10^{-10} mg/kg/day = Maximum Anticipated PCDD Dietary Exposure

0.005 = The Toxicity Equivalent Factor for PCDDs

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[1] Update Of Toxicity Equivalency Factors [TEFs] for Estimating Risks Associated with Exposure to Mixtures of Chlorinated Dibenzo-p-Dioxins and Dibenzofurans [CDDs and CDFs]. Risk Assessment Forum, February, 1989. U.S. Environmental Protection Agency.

2,3,7,8-TCDD Toxicity Equivalent for PCDD from 2,4-D IOE:

$= 1.17 \times 10^{-10}$ mg/kg/day x 0.005

$= 5.9 \times 10^{-13}$ mg/kg/day

Where:

1.17×10^{-10} mg/kg/day = Maximum Anticipated PCDD Dietary Exposure

0.005 = The Toxicity Equivalent Factor for PCDDs

V. PCDD RISK CHARACTERIZATION BASED ON TCDD "TOXICITY EQUIVALENT FACTORS"

a. Non-Cancer End Point

For PCDD Present in 2,4-D Acid and 2,4-D IOE:

The risk for non-cancerous effects are negligible since the maximum anticipated dietary exposure levels of **2.2×10^{-12} mg TCDD equivalent/kg/day from the 2,4-D acid and 5.9×10^{-13} mg TCDD equivalent/kg/day from 2,4-D IOE** are lower than the 2,3,7,8-TCDD Reference Dose [RfD] of **1×10^{-9} mg/kg/day.**

For TCDD Present in 2,4-D Acid

Similarly, the risk for non-cancerous effects are negligible since the maximum anticipated dietary exposure level of **1.5×10^{-11} mg TCDD/kg/day from the 2,4-D acid** is lower than the 2,3,7,8-TCDD RfD **[1×10^{-9} mg/kg/day].**

b. Carcinogenic Potency

Using the **Q_1^* of 1.6×10^{-5} $[mg/kg/day]^{-1}$ for 2,3,7,8-TCDD**, the quantitative unit cancer risk is estimated as follows:

For TCDD Present in 2,4-D Acid:

Unit Risk = 1.6×10^{-5} $[mg/kg/day]^{-1}$ x 1.5×10^{-11} mg/kg/day

= 2.4×10^{-16}

Where:

1.6×10^{-5} $[mg/kg/day]^{-1}$ = Q_1^* of 2,3,7,8-TCDD

1.5×10^{-11} mg/kg/day = Maximum Anticipated TCDD Dietary Exposure

For PCDD Present in 2,4-D Acid:

Unit Risk = 1.6×10^{-5} $[mg/kg/day]^{-1}$ x 2.2×10^{-12} mg/kg/day

= 3.5×10^{-17}

Where:

1.6×10^{-5} $[mg/kg/day]^{-1}$ = Q_1^* of 2,3,7,8-TCDD

2.2×10^{-12} mg/kg/day = 2,3,7,8-TCDD Toxicity Equivalent

For PCDD in 2,4-D IOE:

Unit Risk = 1.6×10^{-5} $[mg/kg/day]^{-1}$ x 5.9×10^{-13} mg/kg/day

= 9.4×10^{-18}

Where:

1.6×10^{-5} $[mg/kg/day]^{-1}$ = Q_1^* of 2,3,7,8-TCDD

5.9×10^{-13} mg/kg/day = 2,3,7,8-TCDD Toxicity Equivalent

VI. CONCLUSION

When expressed in terms of 2,3,7,8-TCDD Toxicity Equivalency Factors as follows, **the risk for non-cancer efffects are:**

1.5×10^{-11} mg TCDD/kg/day [from 2,4-D Acid]

2.2×10^{-12} mg TCDD equivalent/kg/day [from PCDD in Acid]

5.6×10^{-13} mg TCDD equivalent/kg/day [from PCDD in IOE].

These levels are lower than the RfD of 1×10^{-9} mg/kg/day established for 2,3,7,8-TCDD.

Based on the cancer potency of 2,3,7,8-TCDD, **the quantitative unit cancer risks are:**

2.4×10^{-16} [from TCDD in 2,4-D Acid]

3.5×10^{-17} [from PCDD in 2,4-D Acid]

9.4×10^{-18} [from PCDD in 2,4-D IOE].

These unit risks are lower than the 1×10^{-6} [acceptable risk from life time exposure].

When expressed in terms of TCDD TEF, both the non cancer risk and the unit cancer risk indicate negligible risk to humans. Therefore, the Toxicology Branch II concludes that the levels of 2,3,7,8-TCDD and 1,2,3,7,8-PCDD present in the technical 2,4-D and technical 2,4-D IOE are of no toxicological concern at this time.

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