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

JUL 5 1988

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Dietary Exposure Analysis of Maneb and Maneb Derived Ethylenethiourea

FROM: J. Robert Tomerlin, Ph.D.
Tolerance Assessment System Staff
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and

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THRU: Karl Arne, Ph.D. *Karl Arne*
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TO: Valerie M. Bael, EBDC Fungicide Review Manager
Special Review Branch
Registration Division (TS 767C)

and

Amy Rispin, Director, Science Integration Staff
Hazard Evaluation Division (TS 769C)

Action Requested

Provide TAS routine chronic dietary exposure analyses for maneb and maneb derived ethylenethiourea (ETU) and an oncogenic risk assessment for maneb derived ETU as part of the EBDC/ETU Special Review Process.

Discussion

1. Toxicology Endpoints: A routine chronic TAS analysis was conducted with a reference dose (PADI) of 0.005 mg/kg body weight/day, based upon a NOEL of 5.0 mg/kg body weight/day and a safety factor of 1000 from a 6 month monkey feeding study. This value has been approved (10/15/86) and later reassessed (9/28/87) by TOX Branch and verified by Agency (10/14/87) reference dose committees.

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A routine chronic TAS analysis was also conducted for maneb derived ETU using a reference dose (PADI) of 0.00008 mg/kg body weight/day, based upon an LEL (NOEL has not been established) of 0.25 mg/kg body weight/day and a safety factor of 3000 from a 2 year rat feeding study. This value was approved (9/26/88) and reassessed (10/30/87) by the TOX Branch reference dose committee. The value was originally verified (12/9/86) by the Agency reference dose committee; the Agency subsequently deferred a decision pending review of data from a monkey study (2/25/88).

Ethylenethiourea has been implicated in oncogenesis in rats and mice and has been categorized as a Class B2 oncogen (probable human carcinogen). An upper bound potency estimate (Q_1^*) of 0.14 (mg/kg/day)⁻¹ has been assigned to ETU (personal communication, J. Hauswirth).

2. Residue Values Used in the TAS Analyses: Maneb tolerances used in the analysis were the published tolerances from 40 CFR 180.110; no pending or new action tolerances were included in the analysis. Per cent crop treated (Pelletier and Ballard memo, 5/27/88) and anticipated residue (AR) data (Hummel memo, 6/30/88) were also used for the maneb analysis. A per cent crop treated value of 10 was used for all commodities for which the estimated per cent crop treated was less than 10 (personal communication, G. Ballard). Ten per cent of meat and milk were assumed to contain maneb residues, a figure extrapolated from residue data for animal feed commodities (Hummel memo, 6/30/88). Residue data were unavailable for some food commodities and residues from these commodities were extrapolated from similar crops having similar usage patterns. For example, maneb residues on collards were assumed to be the same as on spinach (Hummel memo, 6/30/88). A summary of the residue information used in the maneb analysis is attached as Table 1. NOTE: AR data were available for meat, milk, and poultry, for which tolerances have not been established.

Per cent crop treated (Pelletier and Ballard memo, 5/27/88) and AR data (Hummel memo, 6/30/88) were used to conduct the analysis for maneb derived ETU. A summary of the residue information used in the maneb derived ETU analysis is attached as Table 1a. NOTE: the tolerance values in Table 1a are for maneb and should be ignored. Tolerance values were included solely to allow the TAS AR analysis to execute properly.

3. Routine Chronic Analysis for Maneb: The TAS routine chronic analysis estimates the Theoretical Maximum Residue Contribution (TMRC) for the U.S. population and 22 population subgroups. The maneb TMRC, assuming maneb residues at tolerance levels and 100 per cent crop treated, for the U.S. population is 0.030265 mg/kg body weight/day, which represents 605% of the PADI. Non-nursing

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infants and children aged 1 to 6 had TMRCs of 0.1145 mg/kg body weight/day (2290% of the ADI) and 0.064401 mg/kg body weight/day (1288% of the ADI), respectively.

The analysis incorporating both AR and per cent crop treated data significantly reduced exposure to maneb. The Anticipated Residue Contribution (ARC) for the U.S. population is 0.003652 mg/kg body weight/day, representing 73% of the PADI. The ARCs for non-nursing infants and children aged 1 to 6 were 0.015801 mg/kg body weight/day (316% of the ADI) and 0.006509 mg/kg body weight/day (130% of the ADI), respectively. The TMRC and ARC exposure summary for maneb is attached as Table 2. The contribution of selected agricultural commodities to the total maneb ARC for three population subgroups is shown in the table below.

Anticipated Residue Contributions of Selected Raw Agricultural Commodities for Maneb

	U.S. Population	Non-Nursing Infants	Children 1 to 6
Peaches	1.035544 ^a 20.7 ^b	10.016346 200.3	2.268672 45.4
Spinach	0.543267 10.9	2.304994 46.1	0.682781 13.7
Tomatoes	0.369370 7.4	0.167824 3.4	0.525871 10.5
Apples	0.348097 7.0	0.812710 16.3	0.961593 19.2
Lettuce	0.339591 6.8	0.015111 0.3	0.287229 5.7
Brassica Leafy Vefs	0.278880 5.6	0.163594 3.3	0.380194 7.6
Celery	0.237749 4.8	0.091467 1.8	0.311723 6.2
Root/Tuber Vefs	0.146938 2.9	0.743719 14.9	0.253349 5.1

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Anticipated Residue Contribution ... Maneb, Continued

	U.S. Population	Non-Nursing Infants	Children 1 to 6
Apricots	0.086673 1.7	0.924857 18.5	0.256501 5.1
Milk	0.068470 1.4	0.424281 8.5	0.201115 4.0
Grapes	0.045690 ^a 0.9 ^b	0.028619 0.6	0.137249 2.7
Bulb Vegetables	0.032679 0.7	0.011851 0.2	0.053818 1.1
Cucurbits	0.024009 0.5	0.029514 0.6	0.034549 0.7
Red Meat	0.016668 0.3	0.015066 0.3	0.030917 0.6
Beans	0.011977 0.2	0.025931 0.5	0.020965 0.4
Poultry	0.006170 0.1	0.012776 0.3	0.012519 0.3
Eggs	0.004063 0.1	0.004230 0.1	0.009100 0.2
Other ^c	0.056206 1.1	0.009045 0.2	0.081593 1.6
Total	3.652041 73.0	15.801935 316.0	6.509738 130.2

^aARC in ug/kg body weight/day

^bARC expressed as per cent of the PADI

^cAlmonds, bananas, cranberries, eggplant, endive, figs, nectarines, papaya, peppers, rhubarb, and sweet corn

4. Routine Chronic Analysis for Maneb Derived ETU: The Tas routine chronic analysis for maneb derived ETU using ARs and per

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cent crop treated calculated an ARC for the U.S. population of 0.000462 mg/kg body weight/day (578% of the PADI). The two most highly exposed population subgroups, non-nursing infants and children aged 1 to 6, had ARCS of 0.001845 mg/kg body weight/day (2306% of the ADI) and 0.000903 mg/kg body weight/day (1130% of the PADI), respectively. The ARC summary for manebo derived ETU is attached as Table 2a.

Oncogenic risk attributable to manebo derived ETU was calculated only for the overall U.S. population, in accordance with HED policy. Risk was estimated according to the relationship:

$$\text{Risk} = \text{Exposure} \times Q_1^*$$

where Exposure is the ARC. The ARCs of selected commodities and commodity groups with their associated oncogenic risk is shown in the table below.

Anticipated Residue Contribution of Selected Raw Agricultural Commodities and Associated Oncogenic Risk for Maneb Derived ETU

	U. S. Population	Non-Nursing Infants	Children 1 to 6	Oncogenic ^a Risk
Spinach	0.093926 ^b 117.4 ^c	0.464214 580.3	0.116723 145.9	1.3 X 10 ⁻⁵
Grapes	0.093348 116.7	0.109382 136.7	0.210641 263.3	1.3 X 10 ⁻⁵
Brassica Leafy Veggies	0.056283 70.4	0.034020 42.5	0.077438 96.8	7.9 X 10 ⁻⁶
Milk	0.052670 65.8	0.326369 408.0	0.154704 193.4	7.4 X 10 ⁻⁶
Root/Tuber Veggies.	0.037753 47.2	0.201936 252.4	0.068624 85.8	5.3 X 10 ⁻⁶
Peaches	0.033656 42.1	0.349300 436.6	0.074016 92.5	4.7 X 10 ⁻⁶

Table Continued on Next Page

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Anticipated Residue Contribution ... Maneb Derived ETU, Continued

	U. S. Population	Non-Nursing Infants	Children 1 to 6	Oncogenic ^a Risk
Apples	0.017536 21.9	0.177105 221.4	0.060081 75.1	2.5 X 10 ⁻⁶
Beans	0.016504 20.6	0.036370 45.5	0.028916 36.1	2.3 X 10 ⁻⁶
Celery	0.012330 15.4	0.016297 20.4	0.018588 23.2	1.7 X 10 ⁻⁶
Apricots	0.009311 11.6	0.099756 124.7	0.027515 34.4	1.3 X 10 ⁻⁶
Bulb Vegetables	0.008596 10.7	0.003779 4.7	0.015845 19.8	1.2 X 10 ⁻⁶
Lettuce	0.007275 ^b 9.1 ^c	0.000669 0.8	0.007830 9.8	1.0 X 10 ⁻⁶
Poultry	0.004552 5.7	0.009471 11.8	0.009274 11.6	6.4 X 10 ⁻⁷
Red Meat	0.004302 5.4	0.004592 5.7	0.007888 9.9	6.0 X 10 ⁻⁷
Tomatoes	0.004256 5.3	0.003282 4.1	0.008415 10.5	6.0 X 10 ⁻⁷
Eggs	0.003484 4.4	0.003626 4.5	0.007799 9.7	4.9 X 10 ⁻⁷
Cucurbits	0.000970 1.2	0.001841 2.3	0.001311 1.6	1.4 X 10 ⁻⁷
Other ^d	0.005317 6.6	0.003148 3.9	0.008029 10.0	7.4 X 10 ⁻⁷
Total	0.462069 577.6	1.845157 2306.4	0.903637 1129.5	6.5 X 10 ⁻⁵

^aOncogenic risk is estimated for the U.S. population only, in accordance with HED policy

^bARC in ug/kg body weight/day

^cARC expressed as per cent of the PADI

^dAlmonds, bananas, cranberries, eggplant, endive, figs, nectarines, papaya, peppers, rhubarb, and sweet corn

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5. Several factors must be considered when interpreting this TAS analysis. A NOEL has not been established for maneb derived ETU. A relatively high safety factor has been applied to an LEL to arrive at a PADI. Consequently, the PADI used as the standard to which the maneb derived ETU exposure figures are compared may change if additional toxicology data are received.

Note that eleven food commodities or commodity groups have estimated oncogenic risks exceeding 1×10^{-6} . Therefore, oncogenic risk is distributed over a range of foods for which anticipated residues adjusted for per cent crop treated were taken into consideration. Of these, grapes, root and tuber vegetables, peaches, apples, celery, apricots, and bulb vegetables had estimated per cent crop treated less than 10, which was considered to be 10 in these analyses.

Exposure to maneb derived ETU was relatively high for milk, which contributed 11 per cent of the total ARC and consequently 11 per cent of the total oncogenic risk. Ten per cent of the milk was assumed to contain maneb derived ETU residues. This figure was derived from the per cent of apples treated with maneb.

Finally, the analyses were conducted assuming that maneb and maneb derived ETU residues were uniformly present in the food commodities at levels defined as the product of the anticipated residue and the per cent crop treated.

Attachments

CC: J. R. Tomerlin (RCB), S. Hummel (RCB), TAS File, Maneb SF,
ETU SF, TOX, Circulation (7), RF

Table 1

ANTICIPATED RESIDUE INFORMATION FOR CASWELL NUMBER 539

DATE: 06/28/88

PAGE: 1

FOOD CODE	FOOD	FOOD FORM	PET. #	TOLERANCE (ppm)	ANTICIPATED RESIDUE (ppm)	AR TYPE	% CROP TREATED	REFERENCE DOSES		DATA GAPS/COMMENTS	STATUS
								OPP RFD= 0.005000	EPA RFD= 0.005000	Chronic feeding- rat	TOX reassess 9/28/87.
Maneb										Reproduction	EPA Verified 10/14/87
Caswell #539										Teratology- 2 species	
CAS No. 12427-38-2											WHO last reviewed 1980;
A.I. CODE: 014505											see Mancozeb.
CFR No. 180.110											
ONCO: Undetermined.					No adequate oncogenicity data available (see EU).						
CHEMICAL	STUDY TYPE										
	6mo feeding- monkey				Increased thyroid weight, inhibition of I-131 uptake at 3000 ppm.	[PADD SF -->]	1000	Chronic feeding- dog		TOX complete 10/15/86.	
	NOEL= 5.0000 mg/kg							Chronic feeding- rat		TOX reassess 9/28/87.	
	LEL= 100.00 ppm							Reproduction		EPA Verified 10/14/87	
	LEL= 15.0000 mg/kg							Teratology- 2 species			
	LEL= 300.00 ppm										
	ONCO: Undetermined.										

Table 1 (Con't.)

ANTICIPATED RESIDUE INFORMATION FOR CASEMILL NUMBER 539

DATE: 06/28/88

PAGE: 8

FOOD CODE	FOOD	STUDY TYPE	EFFECTS	REFERENCE DOSES	DATA GAPS/COMMENTS	STATUS
Maneb	6mo feeding- monkey	Increased thyroid weight, inhibition of I-131 uptake at 3000 ppm.	PADI SF --> 1000 Chronic feeding- dog	OPP RED= 0.005000 Chronic feeding- rat	TOX complete 10/15/86.	
Caskelli #539	NOEL= 5.0000 mg/kg		OPP RED= 0.005000 Reproduction	EPA RED= 0.005000 Teratology- 2 species	TOX reassess 9/28/87.	
CS No. 12427-38-2	100.00 ppm				EPA verified 10/14/87	
A.I. CODE: 014505	LEL= 15.0000 mg/kg				WHO last reviewed 1980;	
CFR No. 180.110	300.00 ppm	No adequate oncogenicity data available (see ETU).			see Manczez.	
ONCO: Undetermined.						

FOOD CODE	FOOD	FOOD FORM	PET. #	TOLERANCE RESIDUE (ppm)	ANTICIPATED RESIDUE (ppm)	AR TYPE	% CROP TREATED	RES. VALUE USED IN TAS RUN (ppm)
55014AA	EGGS-WHOLE	10 RAW-FRESH OR NFS		P 0.000000	0.007000			100.00
55014AA	EGGS-WHOLE	21 COOKED-NFS		P 0.000000	0.007000			100.00
55014AA	EGGS-WHOLE	22 COOKED-FRESH-BAKED		P 0.000000	0.007000			100.00
55014AA	EGGS-WHOLE	23 COOKED-FRESH-BOILED		P 0.000000	0.007000			100.00
55014AA	EGGS-WHOLE	25 COOKED-FRESH-FRIED		P 0.000000	0.007000			100.00
55014AB	EGGS-WHITE ONLY	10 RAW-FRESH OR NFS		P 0.000000	0.007000			100.00
55014AB	EGGS-WHITE ONLY	21 COOKED-NFS		P 0.000000	0.007000			100.00
55014AB	EGGS-WHITE ONLY	22 COOKED-FRESH-BAKED		P 0.000000	0.007000			100.00
55014AB	EGGS-WHITE ONLY	62 COOKED-FRESH OR FROZEN-BAKED		P 0.000000	0.007000			100.00
55014AB	EGGS-WHITE ONLY	81 COOKED-FROZEN		P 0.000000	0.007000			100.00
55014AC	EGGS-YOLK ONLY	10 RAW-FRESH OR NFS		P 0.000000	0.007000			100.00
55014AC	EGGS-YOLK ONLY	21 COOKED-NFS		P 0.000000	0.007000			100.00
55014AC	EGGS-YOLK ONLY	25 COOKED-FRESH-FRIED		P 0.000000	0.007000			100.00
55014AC	EGGS-YOLK ONLY	31 COOKED-FRESH OR CANNED		P 0.000000	0.007000			100.00
55015BA	CHICKEN-BPY	00 NOT SPECIFIED (NO CONSUMPTION)		P 0.000000	0.020000			100.00
55015LA	CHICKEN-ORGAN	21 COOKED-NFS		P 0.000000	0.020000			100.00
55015LA	CHICKEN-ORGAN	25 COOKED-FRESH-FRIED		P 0.000000	0.020000			100.00
55015LA	CHICKEN-ORGAN	26 COOKED-FRESH-PICKLED, CORNED, OR CURED		P 0.000000	0.020000			100.00
55015MA	CHICKEN-W/O SKIN	21 COOKED-NFS		P 0.000000	0.012000			0.012000
55015MA	CHICKEN-W/O SKIN	22 COOKED-FRESH-BAKED		P 0.000000	0.012000			0.012000
55015MA	CHICKEN-W/O SKIN	25 COOKED-FRESH-FRIED		P 0.000000	0.012000			0.012000
55015MA	CHICKEN-W/O SKIN	31 COOKED-FRESH OR CANNED		P 0.000000	0.012000			0.012000
55015MA	CHICKEN-W/O SKIN	53 COOKED-CANNED-BOILED		P 0.000000	0.012000			100.00
55015MB	CHICKEN+SKIN	21 COOKED-NFS		P 0.000000	0.012000			100.00
55015MB	CHICKEN+SKIN	25 COOKED-FRESH-FRIED		P 0.000000	0.012000			100.00

Table 1a (Con't.)

ANTICIPATED RESIDUE INFORMATION FOR CASWELL NUMBER 443AA

PAGE: 8

DATE: 06/29/88

FOOD CODE	FOOD	FOOD FORM	PET. #	TOLERANCE (ppm)	ANTICIPATED RESIDUE (ppm)	AR STATISTIC TYPE	% CROP TREATED	RES. VALUE USED IN TAS RUN (ppm)	
55014AA	EGGS-WHOLE	10 RAW-FRESH OR NFS	P	0.000000	0.000000		100.00	0.006000	
55014AA	EGGS-WHOLE	21 COOKED-NFS	P	0.000000	0.000000		100.00	0.006000	
55014AA	EGGS-WHOLE	22 COOKED-FRESH-BAKED	P	0.000000	0.000000		100.00	0.006000	
55014AA	EGGS-WHOLE	23 COOKED-FRESH-BOILED	P	0.000000	0.000000		100.00	0.006000	
55014AB	EGGS-WHOLE	25 COOKED-FRESH-FRIED	P	0.000000	0.000000		100.00	0.006000	
55014AB	EGGS-WHITE ONLY	10 RAW-FRESH OR NFS	P	0.000000	0.000000		100.00	0.006000	
55014AB	EGGS-WHITE ONLY	21 COOKED-NFS	P	0.000000	0.000000		100.00	0.006000	
55014AB	EGGS-WHITE ONLY	22 COOKED-FRESH-BAKED	P	0.000000	0.000000		100.00	0.006000	
55014AB	EGGS-WHITE ONLY	62 COOKED-FRESH OR FROZEN-BAKED	P	0.000000	0.000000		100.00	0.006000	
55014AB	EGGS-WHITE ONLY	81 COOKED-FROZEN	P	0.000000	0.000000		100.00	0.006000	
55014AC	EGGS-YOLK ONLY	10 RAW-FRESH OR NFS	P	0.000000	0.000000		100.00	0.006000	
55014AC	EGGS-YOLK ONLY	21 COOKED-NFS	P	0.000000	0.000000		100.00	0.006000	
55014AC	EGGS-YOLK ONLY	25 COOKED-FRESH-FRIED	P	0.000000	0.000000		100.00	0.006000	
55014AC	EGGS-YOLK ONLY	31 COOKED-FRESH OR CANNED	P	0.000000	0.000000		100.00	0.006000	
55015BA	CHICKEN-BYP	00 NOT SPECIFIED (NO CONSUMPTION)	P	0.000000	0.000000		100.00	0.008000	
55015LA	CHICKEN-ORGAN	21 COOKED-NFS	P	0.000000	0.000000		100.00	0.008000	
55015LA	CHICKEN-ORGAN	25 COOKED-FRESH-FRIED	P	0.000000	0.000000		100.00	0.008000	
55015LA	CHICKEN-W/O SKIN	26 COOKED-FRESH-PICKLED, CURED, OR CURED	P	0.000000	0.000000		100.00	0.009000	
55015MA	CHICKEN-W/O SKIN	21 COOKED-NFS	P	0.000000	0.000000		100.00	0.009000	
55015MA	CHICKEN-W/O SKIN	22 COOKED-FRESH-BAKED	P	0.000000	0.000000		100.00	0.009000	
55015MA	CHICKEN-W/O SKIN	25 COOKED-FRESH-FRIED	P	0.000000	0.000000		100.00	0.009000	
55015MA	CHICKEN-W/O SKIN	31 COOKED-FRESH OR CANNED	P	0.000000	0.000000		100.00	0.009000	
55015MA	CHICKEN-W/O SKIN	53 COOKED-CANNED-POILED	P	0.000000	0.000000		100.00	0.009000	
55015MB	CHICKEN+SKIN	21 COOKED-NFS	P	0.000000	0.000000		100.00	0.009000	
55015MB	CHICKEN+SKIN	25 COOKED-FRESH-FRIED	P	0.000000	0.000000		100.00	0.009000	

