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

JAN 29 1982

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE: January 28, 1982

SUBJECT: Addendum to Metolachlor Memo of October 7, 1981; Risk Assessment for Additional New Uses (Including Potatoes, PP#9F2203) & 100-597
Tox. Chem.#188DD

FROM: Gary J. Burin, Toxicologist
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TO: Richard Mountfort (23)
Registration Division (TS-767)

THRU: Orville E. Paynter, Chief
Toxicology Branch/HED (TS-769)

Background Information: The registrant, Ciba-Geigy Corporation, has requested the establishment of permanent tolerances for residues of metolachlor on sunflowers (0.3 ppm), sunflower meal and hulls (0.6 ppm), seed and pod vegetables (0.3 ppm), sweet corn and popcorn (0.1 ppm), cottonseed (0.1 ppm), flaxseed (0.2 ppm), flaw straw (0.6 ppm), flaxseed meal (0.4 ppm) flax hulls (0.4 ppm) and potatoes (0.2 ppm - received on 9/30/81). In my memo of October 7, 1981, I noted the IBT chronic rat study was positive in females for primary liver tumors and that a risk assessment would be required for these additional new uses. Comments from the registrant regarding the oncogenicity of Metolachlor were addressed in the memo of December 10, 1981 from this reviewer and Dr. Louis Kasza. A risk assessment for the requested uses has recently been completed and is discussed below.

Recommendations: A risk assessment based on the chronic rat feeding study conducted at IBT indicates that the point estimate of oncogenic risk resulting from dietary exposure to existing and proposed tolerances is 2.167×10^{-7}; The upper 95% bound on this increased risk estimate is 8.0×10^{-7}.

Additional risk estimates expressed at the upper 95% confidence level are as follows (assuming 10% dermal absorption):

Mixer/Loader (Farmer)	4.5×10^{-8}
Mixer/Loader (Custom Applicator)	6.7×10^{-7}
Applicator (Farmer)	3.3×10^{-6}
Applicator (Custom Applicator)	4.9×10^{-5}

(Exposure estimates are based on the memo of January 22, 1982 from Ed Moroski of Environmental Fate Branch.) Toxicology Branch defers to the Administrator regarding the acceptability of the oncogenic risks. Aside from the issue of acceptability of oncogenic risk, Toxicology Branch does not object to the aforementioned proposed tolerances. It is recommended that the oncogenic potential of Metolachlor be reassessed after the chronic rat feeding study, which is now underway, is submitted and evaluated.

Discussion: (See memos of October 7, 1981 and December 12, 1981 from this reviewer for evaluation and additional discussion of this study.) The following data was used in the estimation of oncogenic risk:

TABLE I

Primary Liver Tumors in Females from IBT No. 622-07926

	PPM				
	0	30	300	1000	3000
Hypertrophic-Hyperplastic nodule	0	1	2	1	3
Hypertrophic-Hyperplastic nodules (two or more)	1	0	1	2	6
Cholangioma	0	0	1	0	0
Cystic cholangioma	2	2	1	2	6
Hepatocellular carcinoma	0	0	0	0	2
Total (# animals with primary liver tumors)	3	3	5	5	14*
Number examined (month 13-Final sacrifice)	54	58	60	60	60

*Three animals each bore two primary liver tumors.

A mathematical risk assessment, was performed by Toxicology Branch statistician, Mr. Bertram Litt using a multistage (Crump), multihit (van Ryzin) model and the Mantel-Bryan procedure. The multistage model was selected because it presents a reasonable fit to the data and represent the most conservative approach i.e. a "worst case" approach. The program output is as follows:

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        TITLE :   METPAT.FEMALE/LIVER TUMORS SET #1 (MULT 9 EDOSES)

 CLASS( 1) HAS   54 MEMBERS WITH    3 RESPONSES TO DOSE OF          0.0
 CLASS( 2) HAS   58 MEMBERS WITH    3 RESPONSES TO DOSE OF          1.40000
 CLASS( 3) HAS   60 MEMBERS WITH    5 RESPONSES TO DOSE OF         14.60000
 CLASS( 4) HAS   60 MEMBERS WITH    5 RESPONSES TO DOSE OF         54.00000
 CLASS( 5) HAS   60 MEMBERS WITH   14 RESPONSES TO DOSE OF        140.00000
0KOP = 1 GRADIENT MOVES = 25

 THE COEFFICIENTS OF THE POLYNOMIAL OF DEGREE  4 THAT MAXIMIZES THE LIKELIHOOD OF THE DATA ARE :
                    Q( 0) = 0.6086202896D-01
                    Q( 1) = 0.5557076728D-03
                    Q( 2) = 0.0
                    Q( 3) = 0.0
                    Q( 4) = 0.3295329161D-09
-     TEST OF HYPOTHESIS: Q(1) = 0
0     PR(>TEST STATISTIC) =  0.3490624176D+00
0     LIKELIHOOD RATIO  0.1504299350D+00
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 0CONFIDENCE LIMITS ON EXTRA RISK AT THE  9 ENVIRONMENTAL DOSES INPUT
                                                                                  Flax Seed
 0CONFIDENCE LIMITS FOR DOSE OF  0.667000D-06  M.L.E. FOR EXTRA RISK IS  0.370657D-09
 0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:
              90%              95%              97.5%             99%
          0.120428D-08     0.136230D-08     0.149434D-08     0.164808D-08
 0CONFIDENCE LIMITS FOR DOSE OF  0.889000D-06  M.L.E. FOR EXTRA RISK IS  0.494024D-09
 0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:                                   Popcorn
              90%              95%              97.5%             99%
          0.160511D-08     0.181572D-08     0.199170D-08     0.219662D-08
 0CONFIDENCE LIMITS FOR DOSE OF  0.100000D-05  M.L.E. FOR EXTRA RISK IS  0.555708D-09
 0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:                                   Sunflower
              90%              95%              97.5%             99%
          0.180552D-08     0.204243D-08     0.224039D-08     0.247089D-08
 0CONFIDENCE LIMITS FOR DOSE OF  0.167000D-05  M.L.E. FOR EXTRA RISK IS  0.928032D-09
 0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:                                   Cottonseed
              90%              95%              97.5%             99%
          0.301522D-08     0.341086D-08     0.374144D-08     0.412638D-08
 0CONFIDENCE LIMITS FOR DOSE OF  0.159000D-04  M.L.E. FOR EXTRA RISK IS  0.883575D-08
 0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:                                   Sweet Corn
              90%              95%              97.5%             99%
          0.287078D-07     0.324746D-07     0.356221D-07     0.392871D-07
 0CONFIDENCE LIMITS FOR DOSE OF  0.121000D-03  M.L.E. FOR EXTRA RISK IS  0.672406D-07
 0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:                                   Potatoes
              90%              95%              97.5%             99%
          0.218468D-06     0.247134D-06     0.271087D-06     0.298977D-06
 0CONFIDENCE LIMITS FOR DOSE OF  0.122000D-03  M.L.E. FOR EXTRA RISK IS  0.677963D-07
 0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:                                   Seed and Pod Vegitables
              90%              95%              97.5%             99%
          0.220273D-06     0.249176D-06     0.273327D-06     0.301448D-06
 0CONFIDENCE LIMITS FOR DOSE OF  0.127000D-03  M.L.E. FOR EXTRA RISK IS  0.705749D-07
 0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:                                   All Existing Tolerances
              90%              95%              97.5%             99%
          0.229301D-06     0.259389D-06     0.284529D-06     0.313803D-06
 0CONFIDENCE LIMITS FOR DOSE OF  0.390000D-03  M.L.E. FOR EXTRA RISK IS  0.216726D-06
 0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:                                   Total Existing & Proposed Tolerances
              90%              95%              97.5%             99%
          0.704153D-06     0.796548D-06     0.873750D-06     0.963646D-06
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0CONFIDENCE LIMITS BASED ON THE MULTI-STAGE MODEL  ( KOP = 1 )
-CONFIDENCE LIMITS FOR A RISK OF  0.100000D+00  M.L.E. DOSE =  0.1082302496D+03
0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:
            90%             95%             97.5%           99%
        0.213866D+00    0.233767D+00    0.250009D+00    0.268488D+00
0       LOWER CONFIDENCE LIMITS ON SAFE DOSE:
            90%             95%             97.5%           99%
        0.564954D+02    0.505337D+02    0.463490D+02    0.422171D+02
-CONFIDENCE LIMITS FOR A RISK OF  0.100000D-01  M.L.E. DOSE =  0.1802308212D+02
0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:
            90%             95%             97.5%           99%
        0.320509D-01    0.361751D-01    0.396077D-01    0.435892D-01
0       LOWER CONFIDENCE LIMITS ON SAFE DOSE:
            90%             95%             97.5%           99%
        0.556637D+01    0.492068D+01    0.448592D+01    0.406746D+01
-CONFIDENCE LIMITS FOR A RISK OF  0.100000D-02  M.L.E. DOSE =  0.1800401398D+01
0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:
            90%             95%             97.5%           99%
        0.324539D-02    0.367045D-02    0.402547D-02    0.443871D-02
0       LOWER CONFIDENCE LIMITS ON SAFE DOSE:
            90%             95%             97.5%           99%
        0.554134D+00    0.489858D+00    0.446575D+00    0.404915D+00
-CONFIDENCE LIMITS FOR A RISK OF  0.100000D-03  M.L.E. DOSE =  0.1799597250D+00
0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:
            90%             95%             97.5%           99%
        0.324868D-03    0.367488D-03    0.403098D-03    0.444562D-03
0       LOWER CONFIDENCE LIMITS ON SAFE DOSE:
            90%             95%             97.5%           99%
        0.553835D-01    0.489637D-01    0.446374D-01    0.404733D-01
-CONFIDENCE LIMITS FOR A RISK OF  0.100000D-04  M.L.E. DOSE =  0.1799516273D-01
0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:
            90%             95%             97.5%           99%
        0.324901D-04    0.367532D-04    0.403153D-04    0.444631D-04
0       LOWER CONFIDENCE LIMITS ON SAFE DOSE:
            90%             95%             97.5%           99%
        0.553860D-02    0.489615D-02    0.446354D-02    0.404715D-02
-CONFIDENCE LIMITS FOR A RISK OF  0.100000D-05  M.L.E. DOSE =  0.1799508175D-02
0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:
            90%             95%             97.5%           99%
        0.324904D-05    0.367536D-05    0.403158D-05    0.444637D-05
0       LOWER CONFIDENCE LIMITS ON SAFE DOSE:
            90%             95%             97.5%           99%
        0.553857D-03    0.489613D-03    0.446352D-03    0.404713D-03
-CONFIDENCE LIMITS FOR A RISK OF  0.100000D-06  M.L.E. DOSE =  0.1799507365D-03
0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:
            90%             95%             97.5%           99%
        0.324905D-06    0.367537D-06    0.403159D-06    0.444638D-06
0       LOWER CONFIDENCE LIMITS ON SAFE DOSE:
            90%             95%             97.5%           99%
        0.553857D-04    0.489613D-04    0.446352D-04    0.404713D-04
-CONFIDENCE LIMITS FOR A RISK OF  0.100000D-07  M.L.E. DOSE =  0.1799507365D-04
0       UPPER CONFIDENCE LIMITS ON EXTRA RISK:
            90%             95%             97.5%           99%
        0.324905D-07    0.367537D-07    0.403159D-07    0.444638D-07
0       LOWER CONFIDENCE LIMITS ON SAFE DOSE:
            90%             95%             97.5%           99%
        0.553857D-05    0.489613D-05    0.446352D-05    0.404713D-05
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$\therefore Q_1^* = 2.04 \times 10^{-3}$