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SPECIAL REPORT

Risk Assessment of Chlordimeform and Two Metabolites

STUDY IDENTIFICATION:

1. Chlordimeform HCl. Lifetime Feeding in Mice. Final Report. CIBA-GEIGY, Ltd., Basle, Switzerland. Project No. Siss M 04761/1, February 8, 1978. RS-MRID #00081913.

2. N-formyl-4-chloro-o-toluidine. Lifetime Feeding Study in Mice. Final Report CIBA-GEIGY, Ltd., Basle, Switzerland. Project No. Siss M 04762/1, June 7, 1978. RS-MIRD #00070979.

3. 4-chloro-o-toluidine HCl. Lifetime Feeding Study in Mice. Final Report. CIBA-GEIGY, Ltd., Basle, Switzerland. Project No. Siss M 04760/1, June 7, 1978. RS-MRID #00070980.

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1. CHEMICAL: Chlordimeform HCl and two metabolites, N-formyl-4-chloro-o-toluidine and 4-chloro-o-toluidine HCl.

2. TEST MATERIAL: All three chemicals are described as a white powders, 99.7% pure.

3. STUDY/ACTION TYPE: Three lifetime feeding and oncogenicity studies in mice for use in risk assessment.

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1. Chlordimeform HCl. Lifetime Feeding in Mice. Final Report. CIBA-GEIGY, Ltd., Basle, Switzerland. Project No. Siss M 04761/1, February 8, 1978. RS-MRID #00081913.

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3. 4-Chloro-o-toluidine HCl. Lifetime Feeding Study in Mice. Final Report. CIBA-GEIGY, Ltd., Basle, Switzerland. Project No. Siss M 04760/1, June 7, 1978. RS-MRID #00070980.

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I. INTRODUCTION

This document describes the procedures and calculations used to quantify human carcinogenic risk due to exposure to the pesticide chlordimeform. Three lifetime animal oncogenicity studies were available for this risk assessment in which mice were fed either chlordimeform HCl, or two of its metabolites, N-formyl-4-chloro-o-toluidine or 4-chloro-o-toluidine HCl. The dose-response incidence of benign hemangiomas and malignant hemangioendotheliomas from these studies was used to predict human exposure levels corresponding to selected levels of human risk. Various low-dose extrapolation models, including a model incorporating time-to-tumor information, were fitted to these data to estimate the probability of cancer as a function of dose. Estimates corresponding to extra risks of 10^{-4} and 10^{-6} as well as lower 95% confidence bounds on these doses are presented. In addition, a survival analysis was performed to assess differences in survival between dose groups.

This report is divided into three sections: 1) a description of the oncogenicity studies, 2) a characterization of the dose-response relationship, and 3) the low-dose extrapolation.

II. DESCRIPTION OF STUDIES

Three chronic toxicity studies were conducted on chlordimeform HCl and two of its metabolites (Gross, S., EPA 1984). Results have shown higher incidences of benign hemangiomas and malignant hemangioendotheliomas. All three studies were conducted in mice (Tif: MAG, SPF-bred) by CIBA-GEIGY, Ltd., Basle Switzerland.

Chlordimeform HCl, N-formyl-4-chloro-o-toluidine, or 4-chloro-o-toluidine HCl (all 99.7% pure) were administered to mice continuously in their feed for a period of 24 months in 3 lifetime carcinogenicity studies. Mice for the chlordimeform HCl study were approx. 3 weeks old while the other two studies used mice approx. 4 weeks old. Groups of 100 mice (50 males and 50 females) received 20 ppm (Group 2), 100 ppm (Group 3) and 500 ppm (Group) for chlordimeform HCl and N-formyl-4-chloro-o-toluidine. The 4-chloro-o-toluidine HCl study was carried out with an additional low dose group. For this experiment the groups of 100 mice (50 males, 50 females) received 2 ppm (Group 2), 20 ppm (Group 3), 100 ppm (Group 4), and 500 ppm (Group 5). An additional group of 100 mice (50 of each sex) served as a control (Group 1) receiving ground diet without chlordimeform for all 3 studies.

Animals were administered the test substance for 104 weeks. There were no interim sacrifices. The animals were kept alive and observed until 90% of the animals in each dose and sex group had died; then the remaining 10% of the animals were sacrificed.

No specific beginning or ending dates were included in the study reports. A description of the randomization of animals to dose groups was not included.

For the purposes of this risk assessment the studies will be referred to as Study 1, Study 2, or Study 3, where the chemicals are chlordimeform HCl, N-formyl-4-chloro-o-toluidine, and 4-chloro-o-toluidine HCl, respectively. Estimates will be presented for males and females separately as well as combined sexes.

III. CHARACTERIZATION OF THE DOSE-RESPONSE RELATIONSHIP

Using the computer program of Thomas and Breslow (1977), each of the six sets of data (male and female data for three studies) was examined for differences in survival between the dose groups. This program analyzes the overall homogeneity of the data using a chi-square statistic for the unadjusted data as well as Cox's test and the generalized Kruskal-Wallis (Gehan-Breslow) test for the life table adjusted data. The Cox test places equal weight on all deaths while the Gehan-Breslow uses inversely proportional weighting, putting more weight on earlier deaths. Pairwise comparisons between dose groups and controls are also tested using these statistics. As shown in Tables 1-3, each of the six data sets show a statistically significant difference ($p < 0.001$) in survival between the dose groups. This difference indicates the life-shortening effect of chlordimeform. The pairwise comparisons indicate which dose groups exhibit significantly decreased survival compared to the control group with $p \leq 0.001$ for each of the two higher dose groups for both sexes. The only exception was Study 3 low dose females, where the test for the unadjusted data only suggested a significant shortening of length of life ($p = 0.0523$).

Tables 4-6 show the dose-response incidence data for benign hemangiomas and malignant hemangioendotheliomas for the three studies. These values reflect the omission of animals which died of other causes six or more weeks before the occurrence of the first tumor of interest in any of the dose groups and are assumed not to be at risk. For both sexes a significant dose-response relationship was shown for malignant hemangioendotheliomas, while the incidence of benign hemangiomas appears to be greater in the lower dose groups. In all cases the combination of benign hemangiomas and malignant hemangioendotheliomas exhibited a positive dose-response relationship. These data are used to estimate cancer risk using the low-dose extrapolation models. Table 7 gives the day of the first occurrence of benign hemangioma or malignant hemangioendothelioma for each study and sex.

TABLE 1. P-values by Statistical Test for Differences in Survival Among Dose Groups for Mice Fed Chlordimeform for Two Years (Study 1)

	Unadjusted Data	Adjusted Data	
		Cox's Test	Kruskal-Wallis Test
Males			
Overall Comparison	< 0.001	< 0.001	< 0.001
Pairwise Comparisons			
Control vs. 20 ppm group	1.0000	0.8312	0.4990
Control vs. 100 ppm group	< 0.001	< 0.001	< 0.001
Control vs. 500 ppm group	< 0.001	< 0.001	< 0.001
Females			
Overall Comparison	< 0.001	< 0.001	< 0.001
Pairwise Comparisons			
Control vs. 20 ppm group	0.8075	0.9252	0.7425
Control vs. 100 ppm group	< 0.001	< 0.001	< 0.001
Control vs. 500 ppm group	< 0.001	< 0.001	< 0.001

TABLE 2. P-values by Statistical Test for Differences in Survival Among Dose Groups for Mice Fed Chlordimeform for Two Years (Study 2)

	Unadjusted Data	Adjusted Data	
		Cox's Test	Kruskal-Wallis Test
Males			
Overall Comparison	< 0.001	< 0.001	< 0.001
Pairwise Comparisons			
Control vs. 20 ppm group	0.6845	0.7544	0.4815
Control vs. 100 ppm group	< 0.001	< 0.001	< 0.001
Control vs. 500 ppm group	< 0.001	< 0.001	< 0.001
Females			
Overall Comparison	< 0.001	< 0.001	< 0.001
Pairwise Comparisons			
Control vs. 20 ppm group	0.3357	0.7789	0.3636
Control vs. 100 ppm group	< 0.001	< 0.001	< 0.001
Control vs. 500 ppm group	< 0.001	< 0.001	< 0.001

TABLE 3. P-values by Statistical Test for Differences in Survival Among Dose Groups for Mice Fed Chlordimeform for Two Years (Study 3)

	Unadjusted Data	Adjusted Data	
		Cox's Test	Kruskal-Wallis Test
Males			
Overall Comparison	< 0.001	< 0.001	< 0.001
Pairwise Comparisons			
Control vs. 2 ppm group	0.6561	0.9760	0.4503
Control vs. 20 ppm group	0.0180	0.0023	0.0122
Control vs. 100 ppm group	< 0.001	< 0.001	< 0.001
Control vs. 500 ppm group	< 0.001	< 0.001	< 0.001
Females			
Overall Comparison	< 0.001	< 0.001	< 0.001
Pairwise Comparisons			
Control vs. 2 ppm group	0.6110	0.6570	0.8632
Control vs. 20 ppm group	0.0532	0.0018	0.0035
Control vs. 100 ppm group	< 0.001	< 0.001	< 0.001
Control vs. 500 ppm group	< 0.001	< 0.001	< 0.001

TABLE 4. Incidence of Benign Hemangiomas and Malignant Hemangioendotheliomas in Mice Fed Chlordimeform for Two Years (Study 1) by Sex

	Dose Group (ppm)			
	0	20	100	500
Males				
Benign Hemangioma	1/44	1/44	2/49	0/48
Malignant Hemangioendothelioma	1/44	0/44	15/49	39/48
Crude Total	2/44	1/44	17/49	39/48
Effective Total[a]	2/41	1/43	17/48	39/47
Females				
Benign Hemangioma	4/43	3/46	2/47	0/49
Malignant Hemangioendothelioma	0/43	2/46	22/47	35/49
Crude Total	4/43	5/46	24/47	35/49
Effective Total[a]	4/38	5/34	24/37	35/41

[a] Reflects animals omitted that died of other causes six or more weeks before occurrence of first tumor of interest.

TABLE 5. Incidence of Benign Hemangiomas and Malignant Hemangioendotheliomas in Mice Fed Chlordimeform for Two Years (Study 2) by Sex

	Dose Group (ppm)			
	0	20	100	500
Males				
Benign Hemangioma	3/42	1/48	2/46	1/47
Malignant Hemangioendothelioma	1/42	6/48	17/46	40/47
Crude Total	4/42	7/48	18/46[a]	40/47[a]
Effective Total[b]	4/41	7/44	18/42	40/45
Females				
Benign Hemangioma	8/46	3/47	1/43	0/48
Malignant Hemangioendothelioma	0/46	1/47	24/43	38/48
Crude Total	8/46	4/47	25/43	38/48
Effective Total[b]	8/43	4/44	25/41	38/46

[a] One animal that had both a benign hemangioma and a malignant hemangioendothelioma was counted only once in the totals.

[b] Reflects animals omitted that died of other causes six or more weeks before occurrence of first tumor of interest.

TABLE 6. Incidence of Benign Hemangiomas and Malignant Hemangioendotheliomas in Mice Fed Chlordimeform for Two Years (Study 3) by Sex

	Dose Group (ppm)				
	0	2	20	200	500
Males					
Benign Hemangioma	1/50	1/47	2/47	1/47	1/48
Malignant Hemangioendothelioma	2/50	0/47	10/47	31/47	40/48
Crude Total	3/50	1/47	12/47	32/47	40/48[a]
Effective Total[b]	3/47	1/46	12/46	32/47	40/47
Females					
Benign Hemangioma	0/45	0/45	3/47	0/48	0/49
Malignant Hemangioendothelioma	3/45	1/45	8/47	31/48	34/49
Crude Total	3/45	1/45	11/47	31/48	34/49
Effective Total[b]	3/38	1/35	11/42	31/39	34/41

[a] One animal that had both a benign hemangioma and a malignant hemangioendothelioma was counted only once in the totals.

[b] Reflects animals omitted that died of other causes six or more weeks before occurrence of first tumor of interest.

TABLE 7. Day of First Death Due to Occurrence of Either Benign Hemangioma or Malignant Hemangioendothelioma by Study and Sex in Mice Fed Chlordimeform for Two Years

	Males	Females
Study 1	231	376
Study 2	311	291
Study 3	357	356

IV. LOW-DOSE EXTRAPOLATION

Various low-dose extrapolation models were fit to the dose-response incidence data presented in Tables 4-6 after appropriate conversions of the experimental dose concentrations in ppm to human equivalent dose in mg/kg/day. This is accomplished by first converting the ppm to mg/kg/day for the test animals, then applying a species-to-species conversion factor to extrapolate mice to humans. The conversion of ppm to mg/kg/day for the experimental animals in these studies was provided in each oncogenicity study reports and are presented in Table 8. These values are then converted to human equivalent doses based on work by Mantel and Schneiderman (1975), and is given in the following equation:

$$\text{Human Equivalent Dose (mg/kg/day)} = \text{Animal Dose (mg/kg/day)} \times \left(\frac{30}{60{,}000}\right)^{1/3}$$

where 30 is the average weight of the mouse in grams and 60,000 is the average human weight in grams. Table 9 presents the human equivalent doses used in this assessment.

Table 10 shows chi-square goodness of fit statistics and associated p-values for the various models for each dataset. Values are presented for the multistage model with all doses and also with the high dose omitted. In general the data for male mice from Study 2 provide an adequate fit for all models, while the models provides a poor fit for all other datasets. The fit of the multistage model to most datasets is improved when the high dose is omitted from consideration. The exceptions are the combined sexes datasets.

As no environmental doses were available, doses and associated lower 95% confidence bounds were estimated for levels of extra risk of 10^{-4} and 10^{-6} for the probit, logit, Weibull, multihit, and multistage models.

Estimates based on the multistage model are based on extra risk and include the datasets with and without the high dose included. These were run with the Global 83 program of Howe and Crump. The other model estimates were run using the Risk81 program of Krewski and Kovar and include both the independent and additive background estimate of dose. Estimates were calculated for each sex group and also for combined sexes. These data are presented in Tables 11-19.

In addition, the RANK81 program of Crump, et al. was used to account for time-to-tumor information. These calculations use the multistage model but adjust the estimates by making use of the time it took for the tumor to occur. For these data it is assumed that benign hemangiomas and malignant hemangioendotheliomas are rapidly lethal tumors; that the time period between tumor onset and death is very short. The time periods used are 365, 475, 548, 639, and 720 days. Also included was the day prior to the occurrence of the last tumor of interest. This day differs for each dataset and is shown in Tables 20-22 along with the estimates for the other time periods.

TABLE 8. Average Dose Levels in mg/kg/day by Study and Sex for Mice Fed Chlordimeform for Two Years as reported by CIBA-GEIGY

	Nominal Dose (ppm)			
	2	20	200	500
Study 1				
Males	-[a]	2.15	9.82	56.36
Females	-	2.25	9.88	57.57
Study 2				
Males	-	2.18	11.10	57.05
Females	-	2.27	10.78	62.11
Study 3				
Males	0.29	1.80	10.44	61.95
Females	0.35	1.87	11.33	68.11

[a] Studies 1 and 2 did not employ a dose concentration of 2 ppm.

TABLE 9. Human Equivalent Doses in mg/kg/day by Study and Sex for Mice Fed Chlordimeform for Two Years

	Nominal Dose (ppm)			
	2	20	200	500
Study 1				
Males	-[a]	0.17	0.79	4.51
Females	-	0.18	0.79	4.61
Study 2				
Males	-	0.17	0.89	4.56
Females	-	0.18	0.86	4.97
Study 3				
Males	0.023	0.14	0.84	4.96
Females	0.028	0.15	0.91	5.45

[a]Studies 1 and 2 did not employ a dose concentration of 2 ppm.

TABLE 10. Chi-square Goodness-of-Fit Statistics and Associated p-Values for Various Models Fitted to Chlordimeform Mice Data.

	MODEL					
Data	Probit	Logit	Weibull	Multihit	Multistage (all doses)	Multistage (high dose omitted)
Study 1						
Males	3.146 0.0761	3.055 0.0805	3.922 0.0476	3.973 0.0462	3.8784 0.0489	1.0150 0.3137
Females	4.313 0.0378	3.896 0.0484	5.539 0.0186	6.546 0.0105	7.5051 0.0058	8.0001 1.000
Both Sexes	16.506 0.0055	16.112 0.0065	18.278 0.0026	18.692 0.0022	19.9886 <0.001	11.3422 0.0034
Study 2						
Males	0.006 0.9377	0.000 0.9917	0.067 0.7956	0.130 0.7189	0.1190 0.7301	<0.0001 1.000
Females	9.276 0.0023	8.940 0.0028	10.223 0.0014	10.705 0.0011	13.1069 0.0003	2.7275 0.0986
Both Sexes	11.873 0.0366	11.444 0.0433	13.007 0.0227	14.504 0.0127	15.2046 0.0005	6.1647 0.0459
Study 3						
Males	5.145 0.0763	4.738 0.0936	7.948 0.0188	11.017 0.0041	27.5675 <0.001	3.0319 0.0816
Females	9.968 0.0068	9.266 0.0097	13.240 0.0013	18.733 0.0001	36.1111 <0.001	2.2603 0.3230
Both Sexes	15.318 0.0321	14.155 0.0485	21.537 0.0031	29.932 0.001	65.1701 <0.001	6.0062 0.0496

TABLE 11. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra R for Various Models for Male Mice Fed Chlordimeform for Two Years (Study 1)

Model	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB
Additive Probit	4×10^{-4}	2×10^{-4}	4×10^{-6}	2×10^{-6}
Additive Logit	4×10^{-4}	2×10^{-4}	4×10^{-6}	2×10^{-6}
Additive Weibull	3×10^{-4}	1×10^{-4}	3×10^{-6}	1×10^{-6}
Additive Multihit	3×10^{-4}	2×10^{-4}	3×10^{-6}	2×10^{-6}
Independent Probit	2×10^{-2}	1×10^{-2}	7×10^{-3}	3×10^{-3}
Independent Logit	3×10^{-3}	1×10^{-3}	2×10^{-4}	4×10^{-5}
Independent Weibull	4×10^{-4}	1×10^{-4}	5×10^{-6}	9×10^{-7}
Independent Multihit	6×10^{-4}	2×10^{-4}	9×10^{-6}	2×10^{-6}
Multistage (all doses)	3×10^{-4}	2×10^{-4}	3×10^{-6}	2×10^{-6}
Multistage (high dose omitted)	1×10^{-2}	3×10^{-4}	1×10^{-2}	3×10^{-5}

[a]Maximum likelihood estimate of dose.

[b]Lower 95% confidence bound on dose.

TABLE 12. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Female Mice Fed Chlordimeform for Two Years (Study 1)

Model	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Additive Probit	1×10^{-6}	5×10^{-5}	1×10^{-8}	5×10^{-7}
Additive Logit	1×10^{-4}	5×10^{-5}	1×10^{-6}	5×10^{-7}
Additive Weibull	6×10^{-5}	3×10^{-5}	6×10^{-7}	3×10^{-7}
Additive Multihit	4×10^{-5}	1×10^{-5}	4×10^{-7}	1×10^{-7}
Independent Probit	4×10^{-3}	1×10^{-3}	8×10^{-4}	2×10^{-4}
Independent Logit	3×10^{-4}	7×10^{-5}	5×10^{-6}	9×10^{-7}
Independent Weibull	3×10^{-6}	5×10^{-7}	3×10^{-9}	4×10^{-11}
Independent Multihit	2×10^{-7}	4×10^{-8}	5×10^{-11}	6×10^{-12}
Multistage (all doses)	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Multistage (high dose omitted)	5×10^{-3}	8×10^{-5}	8×10^{-5}	8×10^{-7}

[a] Maximum likelihood estimate of dose.
[b] Lower 95% confidence bound on dose.

TABLE 13. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Mice (Both Sexes) Fed Chlordimeform for Two Years (Study 1)

Model	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Additive Probit	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Additive Logit	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Additive Weibull	1×10^{-4}	7×10^{-5}	1×10^{-6}	7×10^{-7}
Additive Multihit	1×10^{-4}	8×10^{-5}	1×10^{-6}	8×10^{-7}
Independent Probit	8×10^{-3}	3×10^{-3}	2×10^{-3}	7×10^{-4}
Independent Logit	5×10^{-4}	2×10^{-4}	1×10^{-5}	2×10^{-6}
Independent Weibull	4×10^{-5}	1×10^{-5}	1×10^{-7}	3×10^{-8}
Independent Multihit	[c]			
Multistage (all doses)	2×10^{-4}	2×10^{-4}	2×10^{-6}	2×10^{-6}
Multistage (high dose omitted)	3×10^{-2}	2×10^{-4}	4×10^{-3}	2×10^{-6}

[a] Maximum likelihood estimate of dose.
[b] Lower 95% confidence bound on dose.
[c] Model did not converge.

TABLE 14. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Male Mice Fed Chlordimeform for Two Years (Study 2)

Model	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Additive Probit	3×10^{-4}	2×10^{-4}	3×10^{-6}	2×10^{-6}
Additive Logit	3×10^{-4}	2×10^{-4}	3×10^{-6}	2×10^{-6}
Additive Weibull	2×10^{-4}	1×10^{-6}	2×10^{-6}	1×10^{-8}
Additive Multihit	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Independent Probit	2×10^{-2}	7×10^{-3}	6×10^{-3}	2×10^{-3}
Independent Logit	3×10^{-3}	8×10^{-4}	1×10^{-4}	3×10^{-5}
Independent Weibull	2×10^{-4}	4×10^{-5}	1×10^{-6}	2×10^{-7}
Independent Multihit	5×10^{-4}	1×10^{-4}	7×10^{-6}	1×10^{-6}
Multistage (all doses)	2×10^{-4}	2×10^{-4}	2×10^{-6}	2×10^{-6}
Multistage (high dose omitted)	3×10^{-4}	1×10^{-4}	3×10^{-6}	1×10^{-6}

[a] Maximum likelihood estimate of dose.
[b] Lower 95% confidence bound on dose.

TABLE 15. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Females Mice Fed Chlordimeform for Two Years (Study 2)

Model	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Additive Probit	2×10^{-4}	8×10^{-5}	2×10^{-6}	8×10^{-7}
Additive Logit	2×10^{-4}	9×10^{-5}	2×10^{-6}	9×10^{-7}
Additive Weibull	1×10^{-4}	6×10^{-5}	2×10^{-6}	6×10^{-7}
Additive Multihit	1×10^{-4}	5×10^{-5}	1×10^{-6}	5×10^{-7}
Independent Probit	9×10^{-3}	3×10^{-3}	2×10^{-3}	6×10^{-4}
Independent Logit	7×10^{-4}	2×10^{-4}	2×10^{-5}	3×10^{-6}
Independent Weibull	3×10^{-5}	5×10^{-6}	1×10^{-7}	1×10^{-8}
Independent Multihit	1×10^{-5}	2×10^{-6}	2×10^{-8}	3×10^{-9}
Multistage (all doses)	3×10^{-4}	2×10^{-4}	3×10^{-6}	2×10^{-6}
Multistage (high dose omitted)	1×10^{-4}	2×10^{-4}	1×10^{-5}	2×10^{-6}

[a] Maximum likelihood estimate of dose.
[b] Lower 95% confidence bound on dose.

TABLE 16. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Both Sexes Fed Chlordimeform for Two Years (Study 2)

Model	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Additive Probit	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Additive Logit	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Additive Weibull	2×10^{-4}	9×10^{-5}	2×10^{-6}	9×10^{-7}
Additive Multihit	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Independent Probit	1×10^{-2}	4×10^{-3}	3×10^{-3}	1×10^{-3}
Independent Logit	1×10^{-3}	3×10^{-4}	2×10^{-5}	6×10^{-6}
Independent Weibull	6×10^{-5}	2×10^{-5}	3×10^{-7}	6×10^{-8}
Independent Multihit	[c]			
Multistage (all doses)	2×10^{-4}	2×10^{-4}	2×10^{-6}	2×10^{-6}
Multistage (high dose omitted)	3×10^{-2}	2×10^{-4}	4×10^{-3}	2×10^{-6}

[a] Maximum likelihood estimate of dose.

[b] Lower 95% confidence bound on dose.

[c] Model did not converge.

TABLE 17. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Males Fed Chlordimeform for Two Years (Study 3)

Model	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Additive Probit	5×10^{-5}	3×10^{-5}	5×10^{-7}	3×10^{-7}
Additive Logit	5×10^{-5}	2×10^{-5}	5×10^{-7}	2×10^{-7}
Additive Weibull	2×10^{-5}	9×10^{-6}	2×10^{-7}	9×10^{-8}
Additive Multihit	4×10^{-5}	1×10^{-5}	4×10^{-7}	1×10^{-7}
Independent Probit	8×10^{-4}	3×10^{-4}	1×10^{-4}	4×10^{-5}
Independent Logit	4×10^{-5}	1×10^{-5}	4×10^{-7}	7×10^{-8}
Independent Weibull	5×10^{-7}	1×10^{-7}	3×10^{-10}	4×10^{-11}
Independent Multihit	1×10^{-8}	3×10^{-9}	8×10^{-13}	1×10^{-13}
Multistage (all doses)	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Multistage (high dose omitted)	7×10^{-5}	6×10^{-5}	7×10^{-7}	6×10^{-7}

[a] Maximum likelihood estimate of dose.
[b] Lower 95% confidence bound on dose.

TABLE 18. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Females Fed Chlordimeform for Two Years (Study 3)

Model	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Additive Probit	4×10^{-5}	2×10^{-5}	4×10^{-7}	2×10^{-7}
Additive Logit	4×10^{-5}	2×10^{-5}	4×10^{-7}	2×10^{-7}
Additive Weibull	2×10^{-5}	7×10^{-6}	2×10^{-7}	7×10^{-8}
Additive Multihit	2×10^{-5}	6×10^{-6}	2×10^{-7}	6×10^{-8}
Independent Probit	7×10^{-4}	2×10^{-4}	1×10^{-4}	3×10^{-5}
Independent Logit	1×10^{-5}	9×10^{-6}	3×10^{-7}	5×10^{-8}
Independent Weibull	1×10^{-7}	2×10^{-8}	4×10^{-11}	5×10^{-12}
Independent Multihit	4×10^{-9}	7×10^{-10}	1×10^{-13}	2×10^{-14}
Multistage (all doses)	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Multistage (high dose omitted)	7×10^{-4}	5×10^{-4}	7×10^{-6}	5×10^{-6}

[a] Maximum likelihood estimate of dose.

[b] Lower 95% confidence bound on dose.

TABLE 19. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for Various Models for Both Sexes Fed Chlordimeform for Two Years (Study 3)

Model	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Additive Probit	4×10^{-5}	3×10^{-5}	4×10^{-7}	3×10^{-7}
Additive Logit	5×10^{-5}	3×10^{-5}	5×10^{-7}	3×10^{-7}
Additive Weibull	2×10^{-5}	1×10^{-5}	2×10^{-7}	1×10^{-7}
Additive Multihit	4×10^{-5}	2×10^{-5}	4×10^{-7}	2×10^{-7}
Independent Probit	4×10^{-4}	2×10^{-4}	5×10^{-5}	2×10^{-5}
Independent Logit	1×10^{-5}	3×10^{-6}	4×10^{-8}	9×10^{-9}
Independent Weibull	1×10^{-7}	3×10^{-8}	3×10^{-11}	4×10^{-12}
Independent Multihit	[c]			
Multistage (all doses)	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Multistage (high dose omitted)	7×10^{-5}	1×10^{-4}	7×10^{-7}	1×10^{-6}

[a] Maximum likelihood estimate of dose.

[b] Lower 95% confidence bound on dose.

[c] Model did not converge.

TABLE 20. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for the Multistage Model at Specific Days of Death for Mice Fed Chlordimeform for Two Years (Study 1)

	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Males				
Day 365	1×10^{-2}	6×10^{-3}	1×10^{-4}	6×10^{-5}
Day 475	3×10^{-3}	2×10^{-3}	3×10^{-5}	2×10^{-5}
Day 548	8×10^{-4}	6×10^{-4}	8×10^{-6}	6×10^{-6}
Day 639	4×10^{-4}	3×10^{-4}	4×10^{-6}	3×10^{-6}
Day 720	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Day 862	8×10^{-5}	6×10^{-5}	8×10^{-7}	6×10^{-7}
Females				
Day 365	[c]	[c]	[c]	[c]
Day 475	2×10^{-3}	1×10^{-3}	2×10^{-5}	1×10^{-5}
Day 548	4×10^{-4}	3×10^{-4}	4×10^{-6}	3×10^{-6}
Day 639	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Day 720	9×10^{-5}	7×10^{-5}	9×10^{-7}	7×10^{-7}
Day 953	2×10^{-5}	1×10^{-5}	2×10^{-7}	1×10^{-7}

[a]Maximum likelihood estimate of dose.
[b]Lower 95% confidence bound on dose.
[c]Model did not converge.

TABLE 21. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for the Multistage Model at Specific Days of Death for Mice[a] Fed Chlordimeform for Two Years (Study 2)

	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[b]	Lower 95% CB[c]	MLE[b]	Lower 95% CB[c]
Males				
Day 365	1×10^{-1}	2×10^{-2}	1×10^{-2}	3×10^{-4}
Day 475	4×10^{-2}	4×10^{-3}	4×10^{-3}	4×10^{-5}
Day 548	2×10^{-2}	1×10^{-3}	8×10^{-4}	1×10^{-6}
Day 639	1×10^{-2}	5×10^{-3}	1×10^{-3}	5×10^{-6}
Day 720	9×10^{-3}	2×10^{-4}	9×10^{-4}	2×10^{-6}
Day 862	2×10^{-3}	2×10^{-5}	2×10^{-4}	2×10^{-7}

[a]Female data would not converge.
[b]Maximum likelihood estimated dose.
[c]Lower 95% confidence bound on dose.

TABLE 22. Estimated Doses (mg/kg/day) Associated with Specific Levels of Extra Risk for the Multistage Model at Specific Days of Death for Mice Fed Chlordimeform for Two Years (Study 3)

	Extra Risk			
	10^{-4}		10^{-6}	
	MLE[a]	Lower 95% CB[b]	MLE[a]	Lower 95% CB[b]
Males				
Day 365	4×10^{-3}	2×10^{-3}	4×10^{-5}	2×10^{-5}
Day 475	7×10^{-4}	5×10^{-4}	7×10^{-6}	5×10^{-6}
Day 548	3×10^{-4}	2×10^{-3}	3×10^{-6}	2×10^{-6}
Day 639	1×10^{-4}	1×10^{-4}	1×10^{-6}	1×10^{-6}
Day 720	8×10^{-5}	6×10^{-5}	8×10^{-7}	5×10^{-7}
Day 962	1×10^{-5}	8×10^{-6}	1×10^{-7}	8×10^{-8}
Females				
Day 365	3×10^{-3}	2×10^{-3}	3×10^{-5}	2×10^{-5}
Day 475	4×10^{-4}	3×10^{-4}	4×10^{-6}	3×10^{-6}
Day 548	2×10^{-4}	1×10^{-4}	2×10^{-6}	1×10^{-6}
Day 639	7×10^{-5}	5×10^{-5}	7×10^{-7}	5×10^{-7}
Day 720	4×10^{-5}	3×10^{-5}	4×10^{-7}	3×10^{-7}
Day 872	9×10^{-6}	5×10^{-6}	9×10^{-8}	5×10^{-8}

[a]Maximum likelihood estimate of dose.
[b]Lower 95% confidence bound on dose.

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Subject: Three-Generation Rat Reproduction Study

MRID No.: 66881

Classification: Supplementary

Comment: This study was classified as core-supplementary data during the course of the development of the Registration Standard. Sufficient overall detail was not available to the reviewer to classify it otherwise.

Subject: Chronic Feeding/Oncogenicity Study in the Rat

MRID No.: 67569

Classification: Supplementary

Comment: This study was classified as core-supplementary data during the course of the development of the Registration Standard, for reasons some of which are as follows:

1. There was no NOEL established.

2. There were not enough tisues available at final sacrifice for histopathological examination.

Subject: Two-Year Dog Feeding Study.

MRID No.: 66887

Classification: Core-Minimum

Comment: This study was classified as core-minumum data during the course of the development of the Registration Standard.