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Project Summary

In Vitro and *In Vivo* Mutagenicity Studies of Environmental Chemicals

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The objectives of this project were to evaluate the mutagenicity of various compounds, mostly pesticides, using microbial and mammalian cell *in vitro* techniques, as well as *in vivo* techniques in *Drosophila* and mice, and to further develop and refine these procedures for application as test batteries.

Seventy-nine compounds were evaluated for mutagenicity in one or more of 11 test systems: *S. typhimurium* plate incorporation assay; *E. coli* WP-2 reverse mutation assay; *S. cerevisiae* D3 mitotic recombination assay; *S. cerevisiae* D7 assays; *E. coli, B. subtilis,* and *S. typhimurium* relative toxicity assays; sister-chromatid exchange in Chinese hamster ovary cells assay; L5178Y mouse lymphoma cell forward mutation assay; unscheduled DNA synthesis assay; mouse micronucleus assay; *Drosophila* sex-linked recessive lethal assay; and mouse dominant lethal assay.

The data from the evaluation of 41 pesticides and 10 industrial chemicals are presented, and qualitative interpretations of these data and of data obtained under a previous contract, including those for an additional 28 pesticides, are summarized.

This Project Summary was developed by EPA's Health Effects Research Laboratory, Research Triangle Park, NC, to announce key findings of the research project that is fully documented in a separate report of the same title (see Project Report ordering information at back).

Introduction

Under contract to the U.S. Environmental Protection Agency (EPA), SRI International evaluated the mutagenicity of various compounds using microbial and mammalian cell *in vitro* techniques, as well as *in vivo* techniques in *Drosophila* and mice. Simultaneously, these test procedures were further developed and refined.

This report includes a compilation of all the quantitative data and a description of the test results for each of the 51 chemicals (41 pesticides and 10 industrial chemicals) evaluated under the contract, together with a summary table listing the qualitative interpretation of the results. In addition, the summary table includes the qualitative interpretations of the results of a previous contract in which 27 of these 51 chemicals and 28 other chemicals were evaluated.

The qualitative interpretations for all 79 chemicals are based on a review of all of the data generated under both contracts, using the criteria described in the methods section of this report. In some cases, this process resulted in qualitative interpretations that differed from those in previous reports. For example, in previous reports, results for the relative toxicity studies in *E. coli* and *B. subtilis* were scored as positive when there was a clear compound effect or as negative when there was not. In the present evaluation, positive or negative interpretation was limited to clear effect or no-effect results, which any other finding interpreted as inconclusive. Those cases in which retesting and/or reevaluation was done are specified in the test and in the summary table.

Materials and Methods

Battelle Memorial Laboratories (Columbus, Ohio) obtained the pesticides from the manufacturers and subsequently provided samples to SRI International (Menlo Park, California) or to WARF Institute, Inc. (Madison, Wisconsin) for the tests reported here. A few of the chemicals were obtained from the manufacturers by the EPA Office of Pesticide Programs, Washington, D.C. Each pesticide was a "technical grade" product or its equivalent. Monocrotophos was tested as a formulated product, Azodrin 5 (Shell). Mancozeb was tested as two different products: Dithane M-45 (Rohm and Haas) and Manzate 200 (Du Pont). Maneb was also tested as two different products: Dithane M-22 (Rohm and Haas) and Manzate D (Du Pont).

Seventy-nine compounds (69 pesticides and 10 industrial chemicals) were examined for mutagenicity in one or more of 11 test systems. The pesticides are listed alphabetically in Table 1 by their common name, action, and chemical class. Nearly a third of the compounds are organophosphate insecticides; other classes include carbamates, chlorinated hydrocarbons, halogenated aromatics, arsenic compounds, urea derivatives and natural plant products, and synthetic derivatives. The mode of action of these compounds ranges from general contact and systemic poisons to specific preemergence and postemergence herbicides.

The 11 assay systems employed are listed in Table 2, along with references to complete descriptions of the assay procedures. The following bioassays were carried out both in the presence and absence of an Aroclor-1254 induced rat liver metabolic activation system: *S. typhimurium* plate incorporation, *E. coli* WP-2 *uvrA* reverse mutation, *S. cerevisiae* D7 reverse mutation, mouse lymphoma L5178Y cell forward mutation, *S. cerevisiae* D3 enhanced mitotic recombination, *S. cerevisiae* D7 gene conversion and mitotic crossing-over, human lung fibroblast (WI-38) unscheduled DNA synthesis, and Chinese hamster ovary cell sister-chromatid exchange. All experiments were performed with concurrent positive (known mutagen) and negative (solvent) control chemicals.

Results and Discussion

Table 3 summarizes the test results for each of the 79 chemicals evaluated. Cases involving a retest are identified by footnotes, as are cases in which the reexamination of previous data resulted in a different interpretation. The *S. typhimurium* plate incorporation results were scored as positive when the results of any of the individual

Table 1. *Pesticides Assayed for Genotoxic Effects*[a]

Name (action)	*Chemical class*
Acephate (I)	*Thio/dithiophosphoramidate*
Allethrin (I)	*Pyrethroid*
Aspon (I)	*Organothio/dithiophosphate*
Azinphos-methyl (I)	*Organothio/dithiophosphate*
Benomyl (F)	*Carbamate*
Biphenyl (F)	*Aromatic*
Botran (F)[b]	*Chlorinated nitroaniline*
Bromacil (H)	*Diazine*
sec-*Butylamine AB (F)*	*Aliphatic amine*
sec-*Butylamine AB•H_{3PO4} (F)*	*Aliphatic amine*
Cacodylic acid (H)	*Organoarsenical*
Captan (F)	*Phthalimide*
Carbofuran (I)	*Carbamate*
Chlordimeform (I)	*Haloaromatic amidate*
Chlorpyrifos (I)	*Organothio/dithiophosphate*
Creosote P1[c]	
Creosote P2[c]	
Crotoxyphos (I)	*Organothio/dithiophosphate*
2,4-D acid (H)	*Halophenoxy*
2,4-DB acid (H)	*Halophenoxy*
Demeton (I)	*Organothio/dithiophosphate*
Diallate (H)	*Thiocarbamate*
Diazinon (I)	*Organothio/dithiophosphate*
Dicamba (H)	*Halophenoxy*
m-Dichlorobenzene (I)	*Haloaromatic*
o-Dichlorobenzene (I)	*Haloaromatic*
p-Dichlorobenzene (I)	*Haloaromatic*
Dinoseb (H)	*Dinitrophenol*
Disulfoton (I)	*Organothio/dithiophosphate*
DL-cis/trans *chrysanthemic acid (I)*	*Pyrethroid*
DSMA (H)	*Organoarsenical*
Endrin (I)	*Chlorinated hydrocarbon*
Ethion (P)	*Organothio/dithiophosphate*
Ethyl chrysanthemate (I)	*Pyrethroid*
Fensulfothion (I)	*Organothio/dithiophosphate*
Fenthion (I)	*Organothio/dithiophosphate*
Folpet (F)	*Phthalimide*
Fonofos (I)	*Phosphonate/thiophosphonate*
Formetanate hydrochloride (I)	*Carbamate*
Malathion (I)	*Organothio/dithiophosphate*
Mancozeb (F)[d]	*Ethylenebisdithiocarbamate*
Maneb (F)[e]	*Ethylenebisdithiocarbamate*
Methomyl (I)	*Carbamate*
Methoxychlor (I)	*Aromatic*
Monocrotophos (I)[f]	*Organophosphate*
Monuron (H)	*Urea*
MSMA (H)	*Organic arsenical*
Parathion (I)	*Organothio/dithiophosphate*
Parathion-methyl (I)	*Organothio/dithiophosphate*
PCNB (F)	*Haloaromatic*
Pentachlorophenol (H)	*Haloaromatic*
Permethrin (I)	*Pyrethroid*
Phorate (I)	*Organothio/dithiophosphate*
Polyram (F)	*Ethylenebisdithiocarbamate*
Propanil (H)	*Haloaromatic*
Resmethrin (I)	*Pyrethroid*
Rotenone (I)	*Hydrocarbon*
Siduron (H)	*Urea*
Simazine (H)	*Triazine*
Sumithrin (I)	*Pyrethroid*
2,4,5-T (H)	*Halophenoxy*
Triallate (H)	*Thio/dithiocarbamate*
Trichlorfon (I)	*Phosphonate/thiophosphonate*
Trifluralin (H)	*Nitroaromatic*
Vegadex (H)[g]	*Thio/dithiocarbamate*

Table 1. (Continued)

Name (action)	Chemical class
Zineb (F)	Ethylenebisdithiocarbamate

[a] I = insecticide, F = fungicide, H = herbicide.
[b] Botran is the chemical name used in report; dichloran is the common name.
[c] Compound is actually a complex coal tar mixture containing phenol, creosote, and other compounds.
[d] Tested as two products, Dithane M-45 and Manzate 200.
[e] Tested as two products, Dithane M-22 and Manzate D.
[f] Azodrin 5 is the chemical name used in this report; sulfallate is the common name.
[g] Vegadex is the chemical name used in this report; sulfallate is the common name.

Table 2. Assay Systems Used for Genotoxic Studies

Assay	Reference to method employed
S. typhimurium *plate incorporation*	Ames et al. (1)
E. coli *WP-2* uvrA *reverse mutation*	Bridges (2)
S. cerevisiae *D3 mitotic recombination*	Brusick and Mayer (3)
S. cerevisiae *D7*	
Reverse mutation	Zimmerman (4)
Gene conversion	Zimmerman (5)
Mitotic crossing-over	Zimmerman (5)
Relative toxicity	
E. coli, *strains W3110 and p3478*	Slater et al. (6)
B. subtilis, *strains H17 and M45*	Kada (7)
S. typhimurium, *strains SL4525* (rec$^+$), *SL4700* (rec$^-$), *TA1978* (uvrB$^+$), *and TA1538* (uvrB$^-$)	Ames et al. (1)
Sister-chromatid exchange in CHO cells	Perry and Evans (8)
L5178Y TK$^{+/-}$ Mouse lymphoma cell forward mutation	Stetka and Wolff (9) Clive et al. (10)
Unscheduled DNA synthesis in WI-38 cells	Simmon (11, 12)
Mouse micronucleus	Schmid (13)
Drosophila *sex-linked recessive*	Wurgler et al. (14)
Mouse dominant lethal	Simmon (15)

Table 3. Summary Data for 79 Chemicals

PESTICIDES	S.typh Pl. Inc	E coli WP-2	S cere D3	S. cere D7 MCO	MGC	RM	Relative Toxicity E coli PolA	B subt Rec	S typh uvrB	Rec	SCE CHO	L5178Y Lymph	UDS WI-38	Mouse Micro	Dros SLRL	Mouse DL	No. ± Tests	No. Pos.
Acephate	+ +[a]	− −	+ +	+ +	+ +	− +	?[b]	?	−	−	+ +	+ +	+ −	−			12	8
Allethrin	− +	− −	− −				?	−					− −				5	1
Aspon	− −	− −	− −				?	?					− −				4	0
Azinphos-Methyl	−[c] −[c]	− −	+[c] −[d]	− −	− −	− −	?	?	−	−	? −	− +	−[c] −[d]	−		−	13	2
Benomyl											+ +	+ + *		+			3	3
Biphenyl	− −	− −	− −				?	?					− −				4	0
Botran[e]	− −	− −	− −				−	−									5	0
Bromacil	− −	− −	− −	− −	− −	− −	−	−	−	−	− −	+ +	− −	−		−	15	1
sec Butylamine 2AB	− −	− −	− −				+	−									5	1
sec Butylamine 2AB H_3PO_4	− −	− −	− −				−	−									5	0
Cacodylic Acid	− −	− −	+[c] +[c]	+ +	+ +	+ +	?	?	−	−	− −	+ +	− −	+			12	6
Captan	+[c] +[c]	+ +	+[c] +[c]				+	+	+	+		+ +	−[c] −[d]			−	10	8
Carbofuran	− −	− −	− −				?	?					− −				4	0
Chlordimeform	− −	− −	− −				?	−					− −				5	0
Chlorpyrifos	−[c] −[c]	− −	− −				+	+	+	+			− −				8	4
Creosote P1	− +	− −	− −				−	−				? +					6	2
Creosote P2	− +	− −	− −				−	−				? +					6	2
Crotoxyphos	− −	− −	+ +	− −	− −	− −	?	?	−	−	− −	+ +	− −	−			12	2
2,4-D Acid	− −	− −	− −				−[d]	+[c]	−	−			− −				8	1
2,4-DB Acid	− −	− −	− −				+	−[c]	−	−			− −				8	1
Demeton	+ +	+ +	+ +	+ +	+ +	+ +	−[d]	+	−	−	+ +	+ −	+ +	−			14	10
Diallate	−[c] +[c]	− −	− +	− −	− −	− −						+ +			+		8	4
Diazinon	− −	− −	− −				?	?					− −				4	0
Dicamba	− −	− −	− −				+	+	−	−			− −				8	2
m-Dichlorobenzene	− −	− −	+ +				+	−									5	2

strains were positive. The totals indicate the numbers of tests conducted, excluding inconclusive tests, and the numbers of tests with positive results. For computing the totals, tests with and without activation were scored as positive when either result was positive. For purposes of this analysis, each of the three parameters in the *S. cerevisiae* D7 system and each of the four strain pairs in the relative toxicity assays was counted as a separate test.

The general problem addressed by this research was the classification of pesticides according to their genotoxic effects. Genotoxicity was assessed by prokaryotic and eukaryotic test systems that measured gene mutation, DNA damage, or chromosomal effects. The chemicals studied can be divided into two groups: those that displayed no genotoxic response and require little further testing, and those that displayed some positive response and require further evaluation. The chemicals that elicited positive responses in several kinds of genetic bioassays are of greatest concern, particularly as regards their potential effect on humans.

Attempts to relate the results of *in vitro* and *in vivo* bioassays to potential human health hazards lead naturally to a more specific classification or ranking of individual chemicals. The present assessment falls short of a definitive ranking of the chemicals studied for the following reasons:

- In most cases technical grade chemicals were used. While this level of purity is

Table 3. *(continued)*

PESTICIDES	S.typh. Pl. Inc.	E. coli WP-2	S. cere. D3	S cere D7 MCO	MGC	RM	Relative Toxicity: E. coli PolA	B. subt Rec	S. typh. uvrB	Rec	SCE CHO	L5178Y Lymph	UDS WI-38	Mouse Micro	Dros SLRL	Mouse DL	No. ± Tests	No. Pos.
o-Dichlorobenzene	--	--	--				+	-									5	1
p-Dichlorobenzene	--	--	--				-	-									5	0
Dinoseb	--	--	-[c]-[c]				+	+	+	+			--				8	4
Disulfoton	--	--	--	--	--	--	?	?	-	-	-+	+-	+-	-			12	3
DL-cis/trans Chrysanthemic Acid	--	--	--				-	+					--				6	1
DSMA	-[c]-[c]	--	-[c]-[c]				-	-					--				6	0
Endrin	--	--	--				-	-					--				6	0
Ethion	--	--	--				-	-					--				6	0
Ethylchrysanthemate	--	--	++				-	-					--				6	1
Fensulfothion	--	--	--				?	?					--				4	0
Fenthion	--	--	--				?	?					--				4	0
Folpet	+[c]+[c]	++	+[c]+[c]				+	+	+	+		++	-[c]-[d]			-	10	8
Fonofos	--	--	--				?	?					--				4	0
Formetanate Hydrochloride	--	--	--				-	-									5	0
Malathion	-[c]-[c]	--	--				-	-					--			-	6	0
Mancozeb (Dithane M-45)	--	--	++				-	-					--				6	1
Mancozeb (Manzate 200)	--	--	++				-	-					+-				6	2
Maneb (Dithane M-22)	--	--	+-				-	-					--				7	1
Maneb (Manzate D)	--	--	++				-	-					+-				6	2
Methomyl	--	--	-[c]-[c]				-	-					--				6	0
Methoxychlor	--	--	--				?	?					--				4	0
Monocrotophos	+[f]+[f]	--	+[c]+[c]	++	++	++	?	?	-	+	++	++	-[d]+[c]	-		-	13	9
Monuron	--	--	--	--	--	--	-	-			-+	++	-[c]-[d]	+			12	3
MSMA	-[c]-[c]	--	--				-	-					--				6	0
NRDC 149	--	--	--				?	?					--				4	0
Parathion	-[c]-[c]	--	--				-	-					-[d]-[c]			-	7	0
Parathion-Methyl	--	--	++	--	--	--	?	?	-	-	-+	++	--			-	12	3
PCNB	--	--	--				?	?					--			-	5	0
Pentachlorophenol	--	--	++				-	+									5	2
Permethrin	--	--	--				?	?					--				4	0
Phorate	-[c]-[c]	--	--				-	-					--			-	7	0
Polyram	--	--	--				-	-					--				6	0
Propanil	--	--	--				-[d]	+	+	-			--				8	2
Resmethrin	--	--	--				?	?					--				4	0
Rotenone														-			1	0
Siduron	--	--	--				?	?					--				4	0
Simazine	-[c]-[c]	--	--	--	--	--	?	?	-	-	--	?+	--	-			12	1
Sumithrin	--	--	--				?	?					--				4	0
2,4,5-v	--	--	--				-	+									5	1
Triallate	-+	--	-+	--	--	--						++			-		8	3
Trichlorfon	+[c]+[c]	++	++	++	++	++	?	?	+	+	++	++	+-	-			12	11
Trifluralin	-[c]-[c]	-[c]-[c]	--				-	-					--				6	0
Vegadex[g]	-+	--	--				-	-									5	1
Zineb	--	--	++				-	-					--					
INDUSTRIAL CHEMICALS																		
Acetonitrile	--	--	--				-	-									5	0
Chlorobenzene	--	--	-+				-	-									5	1
Coal Tar - Flaked Pitch	++	-+	--				-	-									5	2
Coal Tar - Bitumastic A	++	-+	+-				-	-									5	3
Coal Tar - Bitumastic B	++	-+	-+				-	-									5	3
Coal Tar - Bitumastic A + B	++	-+	++				-	-									5	3
Ethanol	--	--	--				-	-									5	0
Methanol	--	--	--				-	-									5	0
Toluene	--	--		--	--	--	--			--	--			-			9	0
Vinyl Fluoride	--	--	--														3	0
No. ± Tests	77	77	76	15	15	15	49	51	19	20	14	19	53	14	2	10	526	
No. Positive	16	8	23	5	5	5	9	11	6	6	8	19	7	3	1	0		132

[a] Positive response, +; negative response, -; inconclusive response, ?; two symbols in one column indicates without activation, with activation.
[b] For relative toxicity tests, results marked inconclusive were previously reported as negative, but reexamination of data using more stringent criteria indicates results should have been reported as inconclusive (see text).
[c] Retested with same results as previously reported.
[d] Previous results reported as positive, but retest and/or reexamination of data indicates results are negative.
[e] Botran used as chemical name in this report — common name is Dicloran.
[f] Previous results reported as negative, but retest and/or reexamination of data indicates results are positive.
[g] Vegadex used as chemical name in this report — common name is Sulfallate.
* MBC instead of Benomyl was tested in mouse lymphoma forward mutation assay.

most relevant to commercial products, it is possible that the genotoxic activity of the technical grade chemicals may be related to the presence of contaminants.

- The data base is incomplete; not all chemicals were evaluated in all test systems.
- The quantitative dose-response data that exist for each chemical in each test have been used only to establish whether the test was positive or negative.
- No dosimetry studies have been performed; only the quantity of chemical to which the organism was exposed has been recorded.

Despite these limitations, a great deal of preliminary information has been gleaned from this examination of the qualitative data. Undoubtedly, much can be gained from a careful analysis of the quantitative data.

Thirty-nine of the pesticides examined were positive in one or more the 11 test systems employed. Of these 35 pesticides, 21 caused point/gene mutation and 31 caused DNA damage. Nine pesticides produced chromosomal effects; however, they also caused gene mutation and/or primary DNA damage, and relatively few tests for chromosomal effects were performed.

Six pesticides evaluated in this study displayed genotoxic acitivity in three or more eukaryotic bioassay systems. These compounds are acephate, cacodylic acid, demeton, diallate, monocrotophos, and trichlorfon. Cacodylic acid also caused chromosomal damage in the *in vivo* mouse micronucleus test; monocrotophos was negative in the relatively insensitive mouse dominant lethal test. With further testing, other compounds may also show similar effects; nonetheless, because of their diverse genotoxic activities, these six compounds should be assessed carefully.

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*The complete report, entitled "*In Vitro *and* In Vivo *Mutagenicity Studies of Environmental Chemicals," (Order No. PB 84-138 973; Cost: $41.50, subject to change) will be available only from:*

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