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13. ABSTRACT (*Maximum 200 words*)

The objective of this study is to develop more quantitative approaches for the analysis of biological responses to mixtures of toxic materials. The work during the report period focused on developing and extending nonideal modifications to the isobole model for mixture dose-response analysis. Programs to analyze mixture data have been written and used for this purpose. They employ maximum likelihood analysis to the simultaneous determination of dose-response and interaction parameters. The use of spreadsheets to do the same computation has also been investigated, and found promising. This report contains an appendix that enumerates studies from the literature containing mixture dose-response information; many of these studies have been and are currently being used in the project work.

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risk assessment, dose-response, chemical mixtures, toxicity

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Development of Novel Models for Describing Multiple Toxicity Effects

AFOSR 91-0428

Second Year Annual Report
9/20/92 - 9/19/93

RESTATEMENT OF OBJECTIVES

The objective of this project is to develop more quantitative approaches for the analysis of biological responses to mixtures of toxic materials.

STATUS OF THE RESEARCH EFFORT

The effort during the second year was conducted on a no-cost extension from first year funding. During the period covered by this report, the following major activities were accomplished:

- extraction of published data into computer files
- modification of a PASCAL program for the statistical analysis of data sets using a generalized isobole approach, and testing using extracted data sets
- development of alternative solution procedures using spreadsheets

The specifics accomplished are noted below.

Extraction of Published Data

In the first year of the study, the literature was broadly surveyed for studies which potentially contained data sets in which dose-response information amenable to analysis was present. During the second year of the study, the references were physically obtained, and data available in the published papers was compiled in a consistent form usable for analysis. The appendix provides a data base summarizing the individual papers in which usable data was found. In a number of cases, individual references contain multiple data sets. Each data set was extracted from the paper, and entered into a data file.

We classify experimental data into two basic types depending upon the nature of the response. Data in which a known, finite number of experimental subjects are assayed for an all-or-none response (e.g., tumor, death), are termed binomial (since the expected underlying error distribution is expected to be binomial). Data in which the response is graduated (e.g., fractional activity, enzyme level) are termed normal (since the expected underlying error distribution -- at least initially -- might be regarded as normal). This distinction is made since different information is required to describe and analyze the two types of studies.

For binomial data, each data set is described by a following file a file consisting of N+1 lines (records), where N is the number of dose combinations used. The first record is the number of dose combinations. Records 2 through N+1 are the results of each successive dose combination, containing sequentially the concentrations of the two materials in the mixture (which may include 0 for control or single component combinations), followed by the total number of subjects examined, and then the number exhibiting a positive effect.

For normal data, there are also N+1 records, with the first record being identical to the above. The successive records contain the two dose concentrations, the response value, and the standard error of the response. The last term is obtained, where possible, from the experimental data itself (many studies have experimental replicates from which this is or can be determined). In the absence of included standard error information, it is assumed that the standard error is unity (this hinders an absolute goodness of fit determination, but not the parameter estimation process per se).

The data files are coded by reference (see the reference number given in the upper left corner of each record in the appendix), and where multiple data sets are present by the suffixes "e1", "e2", etc., denoting individual experiments within a single published paper. In other words, the data set 288e1 denotes the first data set contained in reference 288.

Modification of PASCAL Program

The initial framework used for data analysis has embodied the generalization of the Berenbaum isobole approach (Berenbaum 1977; Berenbaum 1978; Berenbaum 1981; Berenbaum 1985; Berenbaum 1985; Berenbaum 1989) to toxicity analysis, modified by an excess function. The level of response (on a ratio scale between 0 and 1, with 0 reflecting no toxicity) to a mixture of two components (A and B) is given by:

$$\frac{d_A}{\Phi_A^{-1}(\theta)} + \frac{d_B}{\Phi_B^{-1}(\theta)} = 1 + G$$

where Φ^{-1} is the inverse dose-response function (e.g., multistage, Weibull, logistic, log-probit, etc), θ is the predicted response, d is the dose of the particular component, and G is an excess function. If G is only dependent upon the relative proportions of the two components in the mixture, it can be conveniently expressed as a function of the weight fractions of components, denoted by x_A and x_B. Alternatively, G may also depend upon the level of response (or equivalently, on the total amount of each of the two components).

Some examples of possible functions for G, which satisfy certain necessary properties (if either component is zero, G=0) are:

Model	Function (G)
simple two suffix	Ax_Ax_B
modified two suffix	$\exp(Ax_Ax_B) - 1$
modified two suffix plus	$\exp[(A_0 + A_1\Theta)x_Ax_B) - 1$
three suffix	$x_Ax_B[A_0+A_1(x_A-x_B)]$

NOTE: x_A and x_B represent compositional fractions of the two components

The modified model differs from the other models in allowing a more gradual departure from non-ideal behavior (G=0) at low compositional fractions. This has been found to be useful when data are obtained only at compositions which are relatively low in one component. The "plus" class of models were devised towards the end of the second year of this project to test whether any nonidealities are solely a function of compositional fraction (x's), or are also a function of total mass of toxins (or, equivalently, the level of response, Θ).

The fitting program finds the best set of dose-response (e.g., logistic, probit) parameters for each component in the mixture along with the best interaction parameter(s) for the chosen non-ideality model. The objective function is the minimum value of -2 times the log-likelihood (chosen so that a direct test of significance can be made using the chi-squared distribution). By fitting successively the ideal, two-suffix, and three-suffix models, for example, the significance of added parameters can be determined. By the close of the second year of this project, the PASCAL program was modified to include the logistic, probit and multistage versions of the dose-response models along with the ideal, two suffix and three suffix non-ideality models. The general theory underlying these approaches are described in standard references as well as in the literature on statistical aspects of risk assessment (Kendall and Stuart 1963; Von Mises 1964; Crump and Howe 1985).

The modified program was tested on a number of the extracted data sets to determine program robustness and performance. In this process, a number of general observations were made:

- exponential dose response relationships are more rapidly fitted, due to the simplicity of the computation, although frequently did not yield good fits to the data (i.e., improvement using a logistic fit was often noted)
- when the underlying data was not strictly monotonic (increasing toxic effects with increasing dose), fitting tended to be poor and convergence tended to be slow. Based on this, preliminary screens for monotonicity were incorporated, and subsequent fitting has been restricted to monotonic data sets. In some cases, monotonicity could be obtained by simple transformation of either the dose scale (for example, in dietary studies, from percent protein to percent non protein) or the response scale (for normal data, from percent inhibition to percent of control activity, for example).

Computations were conducted using the THINK PASCAL compiler on Macintosh computers.

Development of Alternative Fitting Procedures Using Spreadsheets

In the course of the second year of the project, Microsoft EXCEL version 3.0 was released. This program as distributed included an optimization engine (the SOLVER add-in macro routine) which is capable of conducting both unconstrained and constrained optimization. It was felt that this might provide a more user-friendly means of conducting the data fitting that was to be undertaken in this project. Accordingly, spreadsheets were developed to conduct the fitting process in this spreadsheet environment. The particular advantages afforded by use of a spreadsheet include ease of modification to include different dose-response and non-ideality relationships, and ready availability of intermediate results for diagnostic purposes. To demonstrate the technique, an extensive study of one data set was conducted.

The data set used was one involving exposure of rats to two liver carcinogens - LAS (an aflatoxin) and CYCA (a food contaminant) reported by NCI (Elashoff et al. 1987). These are found to fit a one and two stage multistage model, respectively. However, the goodness of fits and the specific parameters of the dose-response relationship are clearly influenced by the inclusion of various forms of interaction models in the data analysis procedure. Computations have been performed using EXCEL version 3.0 (and the Solver add-in) on a Macintosh II computer. The following table reports summary statistics for example model fits:

Mixture relationship	summary statistics (L = 2 x log likelihood)
modified two suffix	$\Phi_{LAS} = 1 - \exp(-0.0052 - 0.0348 d_{LAS})$ $\Phi_{CYCA} = 1 - \exp(-0.0052 - 1.05\times10^{-4} d_{CYCA} - 8.398\times10^{-9} d_{CYCA}^2)$ A = -54.74 L = 19.46
modified two suffix plus	$\Phi_{LAS} = 1 - \exp(-0.00536 - 0.0326 d_{LAS})$ $\Phi_{CYCA} = 1 - \exp(-0.00536 - 1.22\times10^{-4} d_{CYCA} - 4.2\times10^{-9} d_{CYCA}^2)$ A_0 = -309.2 A_1 = 277.2 L = 14.28

On the basis of this analysis it is concluded that (1) the non-ideal interactions are highly significant from a statistical point of view as reflected in the significance of the reduction in the likelihood statistic from the ideal model (not shown, but L=30.5 for the ideal model fit) and (2) the modified two suffix plus model is necessary to provide an acceptable degree of fit (for 10 degrees of freedom, this is at about the 5 % significance level). It was found that the spreadsheet, although perhaps slower in terms of execution time, could produce results which are significant, and which are easier to understand. Accordingly, by the end of year 2 of this project, a decision was made to transfer subsequent work to a spreadsheet environment.

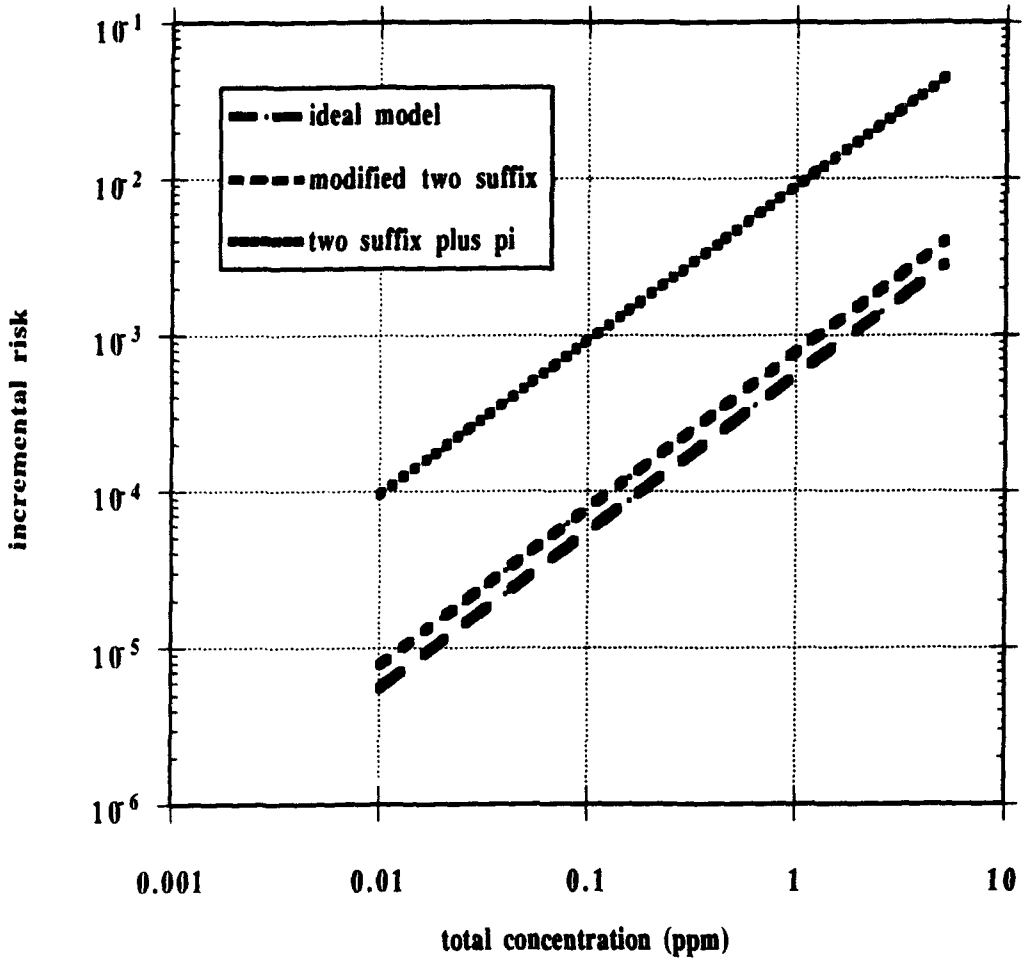

Figure 1 . Predicted Response to a Mixture with 0.01 Weight Fraction of LAS Using Different Mixture Models.

The practical significance of these results are illustrated by Figure 1. In this plot, the dose-response functions described by the three mixture models are shown for a hypothetical mixture consisting of 1 % LAS and 99 % CYCA. It is clear that there is over an order of magnitude difference in the estimated amount of the mixture which assures an incremental risk (above background) in the $< 10^{-2}$ range. Thus, the quantitative incorporation of mixture effects would have a significant effect on setting acceptable exposure limits to such materials. Furthermore, this figure shows that the incorporation of a dependency of the excess function (G) on level of response (θ) has a major effect on the estimated "safe" dosage. Therefore incorporation of these effects, when they are of statistical significance, has major practical consequences.

These findings stand in sharp contrast to the frequently stated assumptions regarding mixture toxicity. Essentially, many individuals, as well as current regulatory practice, believe that although mixture interactive effects may be significant at high doses, they may be ignored at low doses and risks in favor of assumptions of additive toxicity (U.S. Environmental Protection Agency 1986; Krewski et al. 1989).

Based on this work, an AASERT proposal to examine the importance of the level of effect in characterizing the mixture non-idealities was prepared, and was funded. The results of these detailed investigations, as well as the overall summary of dose-response parameters, will be reported upon in the project completion report.

CUMULATIVE LIST OF WRITTEN PUBLICATIONS IN JOURNALS

During the period of this annual report, the following publication appeared based on work performed in this project:

"A New Approach for the Analysis of Mixture Toxicity Data", Water Science and Technology, 26, 9-11, 2345-48 (1992), C.N. Haas.

During the period covered by this report, the following paper was prepared, which was published subsequent to the closure date of the annual report:

"A New Quantitative Approach for the Analysis of Binary Toxic Mixtures", Environmental Toxicology and Chemistry, 13:149-156 (1994), C.N. Haas and B.A. Stirling.

PROFESSIONAL PERSONNEL

In addition to the Principal Investigator, one professional employee was supported by the project during the time period, Mr. Tarik Kamel, an undergraduate co-op student, who was employed as a full time co-op research specialist from April 1, 1993 *until* September 30, 1993.

INTERACTIONS

Papers presented, etc.

"Testing for the Presence of Interactive Toxic Effects: A New Quantitative Procedure Based on Isobole Analysis", presented at the Eastern North America Regional (ENAR) Meeting of the Biometric Society/American Statistical Association/ Institute of Mathematical Statistics, Philadelphia, PA, March 1993, with Bruce A. Stirling.

Consultative and advisory functions, etc.

none

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Elashoff, R. M., T. R. Fears and M. A. Schneiderman (1987). "Statistical Analysis of a Carcinogen Mixture Experiment. I. Liver Carcinogens." Journal of the National Cancer Institute **79**(3): 509-525.

Kendall, M. G. and A. Stuart (1963). The Advanced Theory of Statistics. London, Charles Griffin & Co. Limited.

Krewski, D., T. Thorslund and J. Withey (1989). "Carcinogenic Risk Assessment of Toxic Mixtures." Toxicology and Industrial Health **5**(5): 851-867.

U.S. Environmental Protection Agency (1986). "Guidelines for the Health Risk Assessment of Chemical Mixtures." Federal Register **51**(185): 34014-34025.

Von Mises, R. (1964). Mathematical Theory of Probability and Statistics. New York, Academic Press.

APPENDIX A - SYNOPSIS OF DATA EXAMINED

Study Number: 1
Astrup, A., et.al.
Thermogenic synergism between ephedrine and caffeine in healthy volunteers: a double-blind, placebo-controlled study
Metabolism , 40, 3 323-329 (1991).

compounds studied: Ephedrine and Caffeine
biological response: Thermogenic and metabolic effect levels in humans

# of combinations: 8
dose levels: [10.0-20.0 mg]/[100-200 mg]
data type: Normal

Study Number: 3
Hinks, C.F., Spurr, D.T.
The efficacy and cost benefits of binary mixtures of deltamethrin combined with other insecticides or synergists against grasshoppers at two temperatures
Journal of Agricultural Entomology, 8, 1 29-39 (1991).

compounds studied: Deltamethrin, Malathion, Carbaryl, Diazinon, Chlorpyrifos (8 total)
biological response: Mortality of grasshoppers at limiting temperatures

# of combinations: 7
dose levels: [5.0 g/ha]/[3.13-50.0 g/ha]
data type: Normal

Study Number: 4
Khattak, R.A., and Page, A.L., et al.
Accumulation and Interactions of Arsenic, Selenium, Molybdenum and Phosphorus in Alfalfa
Journal of Enviromental Quality, 20, 165-168 (1991).

compounds studied: Arsenic, Selenium, Molybdenum, Phosphate
biological response: Alfalfa shoot concentrations measured after growth/uptake

# of combinations: 12
dose levels: [0.05-0.1]x[1.0-4.0]x[0-0.1] mg/L
data type: Normal

Study Number: 5
Herkovits, J., and Perez-Coll, C.S.
Synergism and Antagonism Induced by Three Carrier Solvents with t -Retinoic Acid and 6-Aminonicotinamide Using FETAX
Environmental Pollution, 69, 217-221 (1991).

compounds studied:	Lead and Zinc in solution
biological response:	(Bufo arenarum) Amphibian Larvae mortality (%)
# of combinations:	13
dose levels:	[0-16 mg/L]/[0-32 mg/l]
data type:	Normal

Study Number: 6
Rayburn, J.R., et.al.
Synergism and Antagonism Induced by Three Carirer Solvents with t-Retinoic Acid and 6-Aminonicotinamide Using FETAX
Bulletin of Environmental Contamination and Toxicology, 46, 625-632 (1991).

compounds studied:	DMSO, Acetone, Triethylene Glycol
biological response:	(Xenopus) frog embryo mortality (# dead) using FETAX
# of combinations:	9
dose levels:	Multiple dose over 6 seperate experiments
data type:	Binomial

Study Number: 14
Schrenk, D., et.al.
Assessment of biological activities of mixtures of polychlorinated dibenzo-(rho)-dioxins: comparison between polychlorinated dibenzo-(rho)-dioxins: comparison between defined mixtures and their constituents
Archives of Toxicology, 65 , 114-118 (1991).

compounds studied:	Polychlorinated dibenzo-p-dioxin mixtures
biological response:	Inhibition effects on rat hepatocyte and hepatoma cells
# of combinations:	
dose levels:	Multiple dosages of mixtures given
data type:	Normal

Study Number: 29
Vezina, M., et.al.
Potentiation of chloroform-induced hepatotoxicity by methyl isobutyl ketone and two metabolites
Canadian Journal of Physiology and Pharmacology, 68, 1055-1061 (1990).

compounds studied:	Chloroform, Methyl Isobutyl Ketone and two major metabolites
biological response:	Hepatotoxicity potentiation of chloroform in rats
# of combinations:	15
dose levels:	[0.5 mL/kg]/[3.75-7.50 mmol/kg]
data type:	Normal

Study Number: 31
Gupta, S.L.
Interactive effects of nitrogen and copper on growth of cyanobacterium Microcystis
Bulletin of Environmental Contamination and Toxicology, 42, 270-275 (1989).

compounds studied:	Copper and Nitrogen Compounds
biological response:	Cyanobacterium cell cultures, specific growth rate (k)
# of combinations:	10
dose levels:	[0-0.5 uM]/[1.0-10.0 mM]
data type:	Normal

Study Number: 34
Khattak, R.A., et al.
Influence of binary interactions of arsenate, molybdate, and selenate on yield and composition of alfalfa
J. Environmental Quality, 18, 355-360 (1989).

compounds studied:	Arsenate, Molybdenum, and Selenium
biological response:	Alfalfa root and shoot yields and concentrations
# of combinations:	16
dose levels:	[0-1.0 mg/L]/[0.01-5.0 mg/L]/[0-1.0 mg/L]
data type:	Normal

Study Number: 35
Gruden, N., and Matausic, S.
Some factors influencing cadmium-manganese interaction in adult rats
Bulletin of Environmental Contamination and Toxicology, 43, 101-106 (1989).

compounds studied:	Cadmium and Manganese
biological response:	Duodenal transfer and intestinal retention of Mn in rats
# of combinations:	20
dose levels:	[0.0-2.0 mg/d/rat]/[0.64-4.28 mg/ml milk]
data type:	Normal

Study Number: 39
Dikshith, T.S.S., et.al.
Interaction of hexachlorocyclohexane (HCH) and chlorpropham (CIPC) in male rats
Toxicology Letters, 45, 281-288 (1989).

compounds studied: Hexachlorocyclohexane (HCH), Chlorpropham (CIPC)
biological response: Metabolic and biochemical effects of combinations in rats

# of combinations: 3
dose levels: [60.0 mg/kg/d]/[50.0 mg/kg/d]
data type: Normal

Study Number: 41
Umbriet T.H.
Alteration of the acute toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) by estradiol and tamoxifen
Toxicology, 59, 163-169 (1989).

compounds studied: TCDD, Estradiol, and Tamoxifen
biological response: Uterine suppression and acute lethality in mice

# of combinations: 5
dose levels: [0-66 ug/kg/day]/[40 ug/kg]/[1 mg/kd/day]
data type: Binary

Study Number: 45
Brondeau, M.T., et.al.
Acetone compared to other ketones in modifying the hepatotoxicity of inhaled 1,2-dichlorobenzene in rats and mice
Toxicology Letters, 49, 69-78 (1989).

compounds studied: Dichlorobenzene, Acetone, Ketones, Cyclohexanone
biological response: Effects on liver P-450, serum GST, GDLH activity in mice

# of combinations: 8
dose levels: Multiple doseages from [733-14790 ppm]
data type: Normal

Study Number: 48
Davis, D., Safe, S.
Dose-response immunotoxicities of commercial polychlorinated biphenyls (PCBs) and their interaction with 2,3,7,8-tetrachlorodibenzo-p-dioxin
Toxicology Letters, 48, 35-43 (1989).

compounds studied:	Tetrachlorodibenzo-p-dioxin, Polychlorinated Biphenyl mixtures
biological response:	Immunotoxic response using sheep blood cell bioassay
# of combinations:	8
dose levels:	[3.7 nmol/kg]/[5-50 mg/kg]
data type:	Normal

Study Number: 49
Freundt, K.J., et.al.
Decrease of inhaled toluene, ethyl benzene, m-xylene, or mesitylene in rat blood after combined exposure to ethyl acetate
Bulletin of Environmental Contamination and Toxicology, 42, 495-498 (1989).

compounds studied:	Toluene, Ethyl Benzene, m-Xylene, Mesitylene, Ethyl Acetate
biological response:	Blood concentrations in rats after combined exposures
# of combinations:	48
dose levels:	[100-720 ppm]/[0-4000 ppm]
data type:	Normal

Study Number: 51
Harrison, P.T.C., Heath, J.C.
Apparent synergy between chrysotile asbestos and N-nitrosoheptamethyleneimine in the induction of pulmonary tumours in rats
Carcinogenesis, 9, 12 2165-2171 (1988).

compounds studied:	Chrysotile Asbestos, Metalic Cadmium, N-nitrosoheptamethyleneimine
biological response:	Induction of pulmonary tumors in rats
# of combinations:	4
dose levels:	[0-2.0 mg]/[1.0 mg/wk]/[0.18 mg]
data type:	Binomial

Study Number: 52
Stratton, G.W., and Smith, T.M.
Interaction of organic solvents with the green alga Chlorella pyrenoidosa
Bulletin of Environmental Contamination and Toxicology, 40, 736 742 (1988).

compounds studied: Ethanol, Acetone, and Atrazine
biological response: Green Algae (Chlorella pyrenoidosa), (%) inhibition

# of combinations: 30
dose levels: [0.1-5.0 %v/v]/0.05-0.3 ppm]
data type: Normal

Study Number: 54
Bulusu, S., and Chakravarty, I.
Profile of drug metabolizing enzymes in rats treated with paration, malathion, and phosalone under various conditions of protein energy malnutrition
Bulletin of Environmental Contamination and Toxicolgy, 40, 11-118 (1988).

compounds studied: Parathion, Malathion, and Phosalone with Malnutrition
biological response: Enzyme activity in 5 groups of rats fed low protein diets

# of combinations: 15
dose levels: [0-200 ug/kg body wt.] for each chemical
data type: Normal

Study Number: 61
Szepvolgyi, J., et.al.
Examination of the interaction of decis and dithane in rats
Toxicology , 53, 107-111 (1988).

compounds studied: Pyrethroid and Dithiocarbamate
biological response: Serum and bowel biochemical activities measured in rats

# of combinations: 10
dose levels: [2.5-10.0 mg/kg]/[12.5-2500 mg/kg] b.m.
data type: Normal

Study Number: 64
Simmons, J.E., et.al.
Lethality and Hepatotoxicity of Complex Waste Mixtures
Environmental Research , 46, 74-85 (1988).

compounds studied: Complex Waste Combinations: Naphthalene, Phenol, Benzene....
biological response: Male rats evaluated for mortality after 24 hr. period

# of combinations: 0
dose levels: Multiple doses with active ingredients
data type: Binomial

Study Number: 68
Donnelly, K.C., et.al.
Mutagenic potential of binary mixtures of nitro-polychlorinated dibenzo-p-dioxins and related compounds
Journal of Toxicology and Environmental Health, 24, 345-356 (1988).

compounds studied: Nitro-Polychlorinated Dioxins (NMCB, NPCB, NMCDD, NTCDD, BaP...)
biological response: Mutagenic potentials using Samonella/microsome assay

# of combinations: 80
dose levels: [0.15-2.5 ug]/[0.05-5 ug]
data type: Normal

Study Number: 69
Khanna, R.N., et.al.
Effect of repeated exposure to lindane and cadmium on lindane metabolism in rats
Toxicology Letters, 42, 177-183 (1988).

compounds studied: Lindane and Cadmium
biological response: Inhibition of Lindane and heavy metal metabolism in rats

# of combinations: 4
dose levels: [2.0 mg/kg]/[0.2 mg/kg/day] for 35 days
data type: Normal

Study Number: 74
Chakraborty, I.C., et.al.
Antagonistic and synergistic effects of lead and selenium in Rattus norvegicus
Toxicology Letters, 37, 21-26 (1987).

compounds studied: Lead and Selenium
biological response: Chromosomal abnormalities in chronic exposure to rats

# of combinations: 7
dose levels: [0-2.5 mg/100g b.w.]/[0-0.047 mg/100g]
data type: Normal

Study Number: 76
Mandel, R., and Ryser, H.J.-P.
Mechanism of synergism in the mutagenicity of cadmium and N-methul-N-nitrosourea in Salmonella typhimurium: the effect of pH
Mutation Research, 176, 1-10 (1987).

compounds studied: Cadmium and N-methyl-N-Nitrosourea
biological response: Toxic effects on Salmonella typhimurium @ varying pH

# of combinations: 4
dose levels: [0-0.5 mM]/[0-160 uM]
data type: Normal

Study Number: 80
Nikolaev, V., et.al.
Interaction between glucose diet and ethanol on rat liver microsomal induction and liver plasma membrane damage in chronic hexaclorobenzene intoxication
Archives of Toxicology, 60, 112-114 (1987).

compounds studied: Ethanol, Hexachlorobenzene, High/Low Glucose
biological response: Induction of liver plasma membrane damage in male rats

# of combinations: 3
dose levels: [0.104 mol/kg][17.5 mmol/kg]/[63 % diet]
data type: Normal

Study Number: 81
Haake, J.M., et.al.
Aroclor 1254 as an Antagonist of the Teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin
Toxicology Letters, 38, 299-306 (1987).

compounds studied: Aroclor, Tetrachlorodibenzo-p-Dioxin (TCDD)
biological response: Teratogenic effects in pregnant mice

# of combinations: 3
dose levels: [344-750 umol/kg]/[20 ug/kg]
data type: Binary

Study Number: 82
Berger, M.R., et.al.
Combination experiments with very low doses of three genotoxic N-nitrosamines with similar organotropic carcinogenicity in rats
Carcinogenesis, 8, 11 1635-1643 (1987).

compounds studied: N-nitrosodiethylamine, N-nitrosopyrrlidine, N-nitrosodiethanolamine
biological response: Syncarcinogenic activity of very low doses in male rats

# of combinations: 13
dose levels: Multiple doses administered in mg/kg-day
data type: Binomial

Study Number: 95
Nishizumi, M., Masuda, Y.
Enhancing effect of 2,3,4,7,8-pentachlorodibenzofuran and 1,2,3,4,7,8-hexachlorodibenzofuran on diethylnitrosamine hepatocarcinogenesis in rats
Cancer Letters, 33, 333-339 (1986).

compounds studied: Pentachlorodibenzofuran, Hexachlorodibenzofuran, Diethylnitrosamine
biological response: Hepatocarcinogenesis development in rats

# of combinations: 3
dose levels: [10-100 ug/kg body wt.]/[50 ppm]
data type: Binomial

Study Number: 96
Gresele, P., et.al.
Lack of Synergism Between Dazoxiben and Dipyridamole Following Administration to Man
Thrombosis Research , 37, 231-236 (1986).

compounds studied: Dazoxiben and Dipyridamole
biological response: Metabolic levels in man; Plasma, Platelet, Prostaglandin

# of combinations: 2
dose levels: [200 mg]/[200 mg]
data type: Normal

Study Number: 99
Howell, S.R., et.al.
The hepatotoxic potential of combined toluene-chronic ethanol exposure
Archives of Toxicology, 59, 45-50 (1986).

compounds studied: Toluene, Ethanol
biological response: Hepatotoxic potential tested in male rats

# of combinations: 3
dose levels: [10,000 ppm]/[10.1-11.3 g/kg]
data type: Normal

Study Number: 106
Saxena, D.K., et.al.
Embryotoxic and Teratogenic Effects of Interaction of Cadmium and Lindane in Rats
Acta Pharmacology et Toxicology, 59, 175-178 (1986).

compounds studied: Lindane and Cadmium
biological response: Embryotoxic and tetratogenic effects in rats

# of combinations: 4
dose levels: [20 mg/kg/day]/[100 ppm/day]
data type: Normal

Study Number: 113
Arnold, D.L., et.al.
Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary Vitamin A
Food and Chemical Toxicology, 23, 9 779-793 (1985).

compounds studied: Hexacholorobenzene, Vitamin A
biological response: Long-term toxicity (many parameters tested) in rats

# of combinations: 4
dose levels: [0.0-40.0 ppm]/[0-10x normal levels]
data type: Binomial

Study Number: 118
Abou-Donia, B.M., et.al.
The synergism of n-Hexane induced neurotoxicity by methyl isobutyl ketone following subchronic (90 days) inhalation in hens: Induction of hepatic microsomal cytochrome P-450
Toxicology and Applied Pharmacology, 81, 1-16 (1985).

compounds studied: Hexane, Methyl Isobutyl Ketone (MiBK)
biological response: Induction of hepatic microsomal cytochrome P-450 in hens

# of combinations: 7
dose levels: [0-1000 ppm]/[0-1000 ppm]
data type: Normal

Study Number: 121
Hermanutz, R.O., et.al.
Toxicity of endrin and malathion mixtures to flagfish (Jordanella floridae)
Archives of Environmental Contamination and Toxicology, 14, 307-314 (1985).

compounds studied: Endrin and Malathion Mixtures
biological response: Mortality of Flagfish over chronic and acute exposures

# of combinations: 84
dose levels: [0.75-0.99 ug/L]/[265-435 ug/L]
data type: Normal

Study Number: 124
Doeleman, P., et al.
Synergism and Antagonsim in the Analysis of Inseticide Resistance
Bulletin of Environmental Contamination and Toxicology, 32, 717-723 (1984).

compounds studied: Cadmium and Lead tested over time
biological response: Nematode (reproduction) feeding on bacteria in soil

# of combinations: 9
dose levels: [0-12.7 ug/g]/[0-110 ug/g]
data type: Normal

Study Number: 130
Dashiell, O.L., Kennedy Jr., G.L.
The Effect of Fasting on the Acute Oral Toxicity of Nine Chemicals in the Rat
Journal of Applied Toxicology, 4, 6 320-325 (1984).

compounds studied: 9 total (Adiponitrile, Bromobenzene, Caffeine, Methomyl, Lead...)
biological response: Acute toxicity (mortality) using fasted and non-fasted rat

# of combinations: 91
dose levels: Multiple doseage over wide range (mg/kg)
data type: Binomial

Study Number: 132
Chakrabarti, S., Brodeur, J.
Influence of Mercuric Chloride on the Metabolism and Hepatoxicity of Bromobenzene in Rats
Environmental Research, 39, March 13th 50-59 (1984).

compounds studied: Mercuric Chloride and Bromobenzene in various combinations
biological response: Influence on metabolism and hepatotoxicity in rats

# of combinations: 4
dose levels: [1-2 mg/kg]/[1-2.5 mmole/kg]
data type: Normal

Study Number: 136
Stratton, G.W.
Interaction effects of permethrin and atrazine combinations towards several nontarget microorganisms
Bulletin of Environmental Contamination and Toxicology, 31, 297-303 (1983).

compounds studied: Permethrin and Atrazine Combinations
biological response: Toxicity towards non-target soil microorganisms

# of combinations: 30
dose levels: [0-3.0 ppm]/[0-0.1 ppm]
data type: Normal

Study Number: 137
Denda, A., et.al.
Effects of caffeine on pancreatic tumorigenesis by 4-hydroxyamino-quinoline 1-oxide in partially pancreatectomized rats
Carcinogenesis , 4, 1 17-22 (1983).

compounds studied: Caffeine and 4-Hydroxyaminoquinoline-1-oxide
biological response: Reduction of pancreatic tumorigenesis in rats

# of combinations: 6
dose levels: [0-7.0 mg/kg]/[0-120 mg/kg body wt.]
data type: Binary

Study Number: 142
Francis, P.C., and Petersen, R.L.
Synergistic and antagonistic responses of fern spore germination to combinations of copper, cadmium and zinc
Bulletin of Environmental Contamination and Toxicology, 30, 567-574 (1983).

compounds studied: Copper, Cadmium, and Zinc
biological response: Fern spore germination; 2 species used, (%) mortality

# of combinations: 15
dose levels: [0-10.0 ppm] equal weight ratios used
data type: Normal

Study Number: 143
Horvath, P.M., and Ip, C.
Synergistic effect of Vitamin E and selenium in the chemoprevention of mammary carcinogenesis in rats
Cancer Research , 43, 5335-5341 (1983).

compounds studied: Vitamin E and Selenium
biological response: Chemoprevention of mammary carcinogenesis in female rats

# of combinations: 4
dose levels: [50-1000 mg/kg]/[0.1-2.5 mg/kg]
data type: Binomial

Study Number: 153
Zaleska-Freljan, K.I., Kosicka, B.
Influence of Bromfenvinfos Alone and in Mixture with Methoxychlor on the Blood Indices of Laboratory Mice
Polish Journal of Pharmacology and Pharmacy, 34, 187-192 (1982).

compounds studied: Bromfenvinfos, and Methoxychlor
biological response: Influences on blood indices and weights of laboratory mice

# of combinations: 3
dose levels: [12.23 mg/kg/day]/[24.66 mg/kg/day]
data type: Normal

Study Number: 154
Dilley, J.V., et.al.
Short-Term Oral Toxicity of a 2,4,6-Trinitrotoluene and Hexahydro-1,3,5-Trinitro-1,3,5-Triazine Mixture in Mice, Rats, and Dogs
Journal of Toxicology and Environmental Health, 9, 587-610 (1982).

compounds studied: Trinitrotoluene, Hexahydro-Trinitro-Triazine (munitions mixture)
biological response: Short term oral toxicity in mice, rats, and dogs

# of combinations: 5
dose levels: Multiple doseages of mixture [mg/kg*day]
data type: Normal

Study Number: 157
Habs, M., Schmahl, D.
Inhibition of the Hepatocarcinogenic Activity of Diethylnitrosamine (DENA) by Ethanol in Rats
Hepato-gastroenterol , 28, 242-244 (1981).

compounds studied: Diethylnitrosamine and Ethanol
biological response: Inhibition of hepatocarcinogenic activity in male rats

# of combinations: 3
dose levels: [0.0-0.1 mg/kg]/[0-25% in drinking water]
data type: Binomial

Study Number: 158
Clement, L.P.
Factors Influencing the Anticarcinogenic Efficacy of Selenium in Dimethylbenz[a]anthracene-induced Mammary Tumorigenesis in Rats
Cancer Research, 41, 2683-2686 (1981).

compounds studied: Selenium and Dimethylbenz[a]anthracene
biological response: Tumorigenesis in Rats fed low and high fat diets

# of combinations: 8
dose levels: [0.1-5.0 ppm]/[5-10 mg]; 5-25% fat
data type: Binomial

Study Number: 164
Hass, B.S., et.al.
Synergistic, Additive, and Antagonistic Mutagenic Responses to Binary Mixtures of Benzo(a)pyrene and Benzo(e)pyrene as Detected by Strains TA98 and TA100 in the Salmonella/Microsome Assay
Environmental Mutagenesis, 3, 159-166 (1981).

compounds studied: Benzo(a)pyrene, Benzo(e)pyrene
biological response: Mutagenic response using the Salmonella/Microsome assay

# of combinations: 24
dose levels: [0.25-2.5 ug/plate]/[0.2-2.5 ug/plate]
data type: Normal

Study Number: 168
Lamb, J.C., et.al.
Development and Viability of Offspring of Male Mice Treated with Chlorinated Phenoxy Acids and 2,3,7,8-Tetrachlorodibenzo-p-dioxin
Journal of Toxicology and Environmental Health, 8, 835-844 (1981).

compounds studied: 2,4,5-T, 2,4-D, TCDD (Chlorinated Phenoxy Acids)
biological response: Development and offspring viability inhibition in mice

# of combinations: 4
dose levels: [40-80 mg/kg]/[0.16-2.4 ug/kg]
data type: Normal

Study Number: 175
Habs, M., et.al.
Influence of Thioctic Acid (alpha-Lipoic Acid) on N-Nitroso-diethylamine-induced Carcinogenesis in Male Sprague-Dawley Rats
Drug Research, 30(II), Nr.10 1715-1717 (1980).

compounds studied: Thioctic Acid, N-Nitroso-diethylamine
biological response: Inhibition of carcinogenesis in male rats

# of combinations: 3
dose levels: [45-180 mg/kg]/[10 mg/kg]
data type: Binomial

Study Number: 181
Dajani, E.Z., et.al.
Synergistic Actions of Propantheline Bromide with Cimetidine and Thiopropazate Hydrochloride in the Prevention of Stress Ulcer Formation in Rats
The Journal of Pharmacology and Experimental Therapeutics , 210, 3 373-377 (1979).

compounds studied: Bromide, Cimetidine, Thiopropazate
biological response: Prevention of stress ulcer formation in rats

# of combinations: 13
dose levels: [1.0-5.6]/[10-300]/[10-300 mg/kg]
data type: Binomial

Study Number: 183
Dicks, J.W., Abdel-Kawi, A.A.
Antagonistic and Synergistic Interactions between Ancymidol and Gibberellins in Shoot Growth of Cucumber (Cucumis sativus L.)
Journal of Experimental Botany , 30, 117 779-793 (1979).

compounds studied: Ancymidol and Gibberellins
biological response: Shoot growth of Cucumber (Cucumis sativus)

# of combinations: 6
dose levels: [0-2.0 mg/dm]/[0-100.0 mg/dm]
data type: Normal

Study Number: 203
Kurihara, N., et.al.
Metabolic Detoxication and Synergistic Ration of Lindane Analogs in House Flies
Pesticide Biochemistry and Physiology , 7, 332-340 (1977).

compounds studied: Lindane Analogs and Piperonyl Butoxide
biological response: Metabolic detoxication using house flies

# of combinations: 6
dose levels: [Varied Dose]/[0-100% per combination]
data type: Normal

Study Number: 204
Michel, J., et.al.
Bactericidal Synergistic Effect due to Chloramphenicol Induced Inhibition of Staphyloccal Penicillinase
Chemotherapy , 23, 32-36 (1977).

compounds studied: Chloramphenicol and Penicillin-G
biological response: Bactericidal effects on resistant Staphyloccus aureus

# of combinations: 0
dose levels: [0-8.0 ug/ml]/[0-12.0 ug/ml]
data type: Normal

Study Number: 214
Berenbaum, M.C., et.al.
Synergistic effect of cortisol and prostaglandin E2 on the PHA response: Relation to immunosuppression induced by trauma
Clinical and Experimental Immunology, 26, 534-541 (1976).

compounds studied: Cortisol and Prostiglandin E2
biological response: PHA response of human peripheral blood lymphocytes

# of combinations: 30
dose levels: Multiple dose at molar (M) concentrations
data type: Normal

Study Number: 215
Kennedy Jr., G.L., et.al.
Subacute Toxicity Studies with Sodium Saccharin and Two Hydrolytic Derivatives
Toxicology, 6, 133-138 (1976).

compounds studied: Sodium Saccharin, Sulfamoylbenzoic Acid, Ammonium Carboxybenzene
biological response: Subacute toxicity studies in dogs and rats

# of combinations: 14
dose levels: [All compounds tested in 0-20000 ppm]
data type: Normal

Study Number: 216
Wildman, J.M., et.al.
Benzene and Lead Inhibition of Rabbit Reticulocyte Heme and Protein Synthesis: Evidence for Additive Toxicity of These Two Components of Commercial Gasoline
Research Communications in Chemical Pathology and Pharmacology, 13, 3 473-488 (1976).

compounds studied:	Benzene and Lead as components in gasoline
biological response:	Inhibition of rabbit reticulocyte heme/protein synthesis
# of combinations:	2
dose levels:	[0.113 M final conc.]/[100 uM]
data type:	Normal

Study Number: 222
Shinohara, Y., et.al.
Combination effect of citrinin and other chemicals on rat kidney tumorigenesis
Gann, 67, 147-155 (1976).

compounds studied:	Citrinin, N-nitrosodimethylamine, N-(dichlorophenyl)succinimide
biological response:	Combination effect on kidney tumorigenesis in rats
# of combinations:	8
dose levels:	[0.02-0.05%]/[0.05%]/[0.05%] in diet
data type:	Normal

Study Number: 224
Schmahl, D.
Investigations on esophageal carcinogenicity by methyl-phenyl-nitrosamine and ethyl alcohol in rats
Cancer Letters, 1, 215-218 (1976).

compounds studied:	Methyl-Phenyl-Nitrosamine. Ethyl Alcohol
biological response:	Esophageal carcinogenicity in rats
# of combinations:	8
dose levels:	[58-240 mg/kg]/[30 ml/kg]
data type:	Binomial

Study Number: 228
Drewinko, B., et.al.
Combination Chemotherapy In Vitro with Adriamycin. Observations of Additive, Antagonistic, and Synergistic Effects When Used in Two-Drug Combinations on Cultured Human Lymphoma Cells
Cancer Biochemistry and Biophysics, 1, 187-195 (1976).

compounds studied: Adriamycin in combination with 12 other chemotherapeutic drugs
biological response: Lethality and effects on cultured human lymphoma cells

# of combinations: 6
dose levels: [0.25 ug/ml] with multiple doseages
data type: Normal

Study Number: 232
Shabad, L.M., et.al.
On the Influence of Chloramphenicol on the Induction of Lung Adenomas by Urethane in Mice
Neoplasma , 22, 4 347-354 (1975).

compounds studied: Chloramphenicol and Urethane
biological response: Lung adenoma development in different groups of mice

# of combinations: 4
dose levels: [0-4.0 mg/g]/[0-1.0 mg/g]
data type: Binomial

Study Number: 241
Gottlieb, S.F., et.al.
Synergistic Action of Increased Oxygen Tensions and PABA-Folic Acid Antagonists on Bacterial Growth
Aerospace Medicine , 45, 8 829-833 (1974).

compounds studied: Sodium Sulfisoxazole and Trimethoprim
biological response: Effects on bacterial growth @ different oxygen tensions

# of combinations: 20
dose levels: [0-5000 ug%]/[0-100 ug%]
data type: Normal

Study Number: 243
Kaufman, D.G., Madison, R.M.
Synergistic Effects of Benzo (a) pyrene and N-Methyl-N-Nitrosourea on Respiratory Carcinogenesis in Syrian Golden Hamsters
Journal of the National Cancer Institute, 52, 207-218 (1974).

compounds studied:	Methyl-N-Nitrosourea, Benzo(a)pyrene, Ferric Oxide
biological response:	Respiratory carcinogenesis in Syrian Golden Hamsters
# of combinations:	4
dose levels:	[0, 0.5, 5 mg] weekly treatments
data type:	Binomial

Study Number: 245
Nixon, J.E., et.al.
Effect of Cyclopropenoid Compounds on the Carcinogenic Activity of Diethylnitrosamine and Aflatoxin B1 in Rats
Journal of the National Cancer Institute, 53, 2 453-458 (1974).

compounds studied:	Cyclopropenoid, Aflatoxin B, Diethylnitrosamine
biological response:	Effects on carcinogenic activity in rats
# of combinations:	6
dose levels:	[0.04-10.0 %]/[20-100 ppb]/[0.2-1 mg/kg]
data type:	Binomial

Study Number: 246
Cardesa, A., et.al.
Effects of Intraperitoneal Injections of Dimethyl- and Diethlnitrosamine, Alone or Simultaneously on Swiss Mice
Zentral Krebsforschung, 82, 233-238 (1974).

compounds studied:	Diethylnitrosamine, Dimethylnitrosamine
biological response:	Rates of tumor formation and incidence in swiss mice
# of combinations:	4
dose levels:	[3-6 mg/kg]/[3-6 mg/kg-week] x's 10 weeks
data type:	Binomial

Study Number: 254
Pound, A.W., et.al.
Increased Carcinogenic Action of Dimethylnitrosamine After Prior Administration of Carbon Tetrachloride
British Journal of Cancer, 27, 451-459 (1973).

compounds studied: Dimethylnitrosamine with prior treatment of Carbon Tetrachloride
biological response: Potentiation of carcinogenic action in rats

# of combinations: 4
dose levels: [20-40 mg/kg]/[2.5 ml/kg]
data type: Binomial

Study Number: 258
Rodriquez, B.P., Lambeth, V.N.
Synergism and Antagonism of GA and Growth Inhibitors on Growth and Sex Expression in Cucumber
Journal of the American Society of Horticultural Science, 97, 1 90-92 (1972).

compounds studied: Gibberellic Acid, Maleic Hydrazine, SADH, Ethephon
biological response: Inhibition of growth and sex expression in Cucumber

# of combinations: 3
dose levels: Total combinations [100-2000 ppm]
data type: Normal

Study Number: 271
Ito, N., et.al.
The Development of Carcinoma in Liver of Rats Treated with m-Toluylenediamine and the Synergistic and Antagonistic Effects with Other Chemicals
Cancer Research , 29, 1137-1145 (1969).

compounds studied: m-Toluylenediamine with 3-Methylcholanthrene, m-Toluylenediamine...
biological response: Development of carcinoma and liver weight in rats

# of combinations: 4
dose levels: [0.1-0.06]/[0.0067-1.0] % in diet
data type: Binomial

Study Number: 277
Deichmann, W.B., et.al.
Synergism among Oral Carcinogens II. Results of the Simultaneous Feeding of Bladder Carcinogens to Dogs
Toxicology and Applied Pharmacology , 7, 657-659 (1965).

compounds studied: 2-Naphthylamine, 4-Nitrobiphenyl
biological response: Urinary carcinoma development in female Beagle dogs

# of combinations: 3
dose levels: [0.1 g/dog]/[0.1 g/dog]
data type: Binomial

Study Number: 280
Elion, G.B., et.al.
Potentiation by inhibition of drug degradation: 6-substituted purines and xanthine oxidase
Biochemical Pharmacology, 12, 85-93 (1963).

compounds studied: 6 Substituted Purines, Xanthine Oxidase
biological response: Inhibition of adenocarcinoma formation in mice

# of combinations: 48
dose levels: Multiple doses (mg/kg body weight)
data type: Binomial

Study Number: 281
Bieber, S., et.al.
Suppression of the Immune Response by Drugs in Combination
P.S.E.B.M., 111, 334-337 (1962).

compounds studied: Thioguanine, Mercaptopurine, Urethan
biological response: Suppression of immune system response male mice

# of combinations: 24
dose levels: [0-3.0 mg/kg]/[0-75 mg/kg]/[0-675 mg/kg]
data type: Normal

Study Number: 283
Sun, Yun-Pei, and Johnson, E.R.
Analysis of Joint Action Insecticides against House Flies
Journal of Economic Entomology, 53, 5 887-892 (1960).

compounds studied: Dieldrin, Aldrin, Lindane, Chlordane, Pyrethrins, and others
biological response: Mortality of joint action tested against house flies

# of combinations: 12
dose levels: Multiple doseages in binary combinations
data type: Normal

Study Number: 287
Kagy, J.F., and Richardson, C.H.
Ovicidal and Scalicidal Properties of Solutions of Dinitro-o-cyclo-hexylphenol in Petroleum Oil.
Journal of Economic Entomology, 29, 52-59 (1936).

compounds studied: Phenol and Petroleum Oil emulsions
biological response: Mortality of plant bug eggs measured in net kill (%)

# of combinations: 18
dose levels: [0.0-5.0% in oil]/[1.0-3.0% in spray]
data type: Binomial

Study Number: 288
Tattersfield, F., and Martin, J.T.
The Problem of the Evaluation of Rotenone-Containing Plants
Annals of Applied Biology, 22, 578-605 (1935).

compounds studied: Rotenone extracted from Derris Root; to be used as reference only
biological response: Aphid mortality as an indication of concentration

# of combinations: 0
dose levels: [1.0-30.0%] in solution
data type: None

Study Number: 289
Solana. R.P., et.al.
Estimation and Analysis of the Concentration-Response Surfaces Associated with Multiple-Agent Combinations
Toxicology and Applied Pharmacology , 85, 231-238 (1986).

compounds studied: Ethylnitrosourea and D-Dichloroplatinum
biological response: Sister chromatid exchange activity in chinese hamster cell

# of combinations: 16
dose levels: [0-1000 uM]/[0-10.0 uM]
data type: Normal

Study Number: 290
Francis, P.C., and Petersen, R.L.
Effect of Copper, Cadmium, and Zinc on Percent Spore Germination of the Cinnamon Fern (Osmunda cinnamomea) and the Sensitive Fern (Onoclea sensibilis)
Bull. Environ Contam. Toxicol. , 30 , 559-566 (1983).

compounds studied: Copper, Cadmium, Zinc
biological response: Spore germination of Osmunda cinnamomea L. and Onoclea sensibilis L.

# of combinations: None
dose levels: [0-40 ppm]
data type: Normal

Study Number: 291
Lidor, Y.J., et al.
Synergistic Cytotoxicity of Different Alkylating Agents for Epithelial Ovarian Cancer
Int. J. Cancer , 49, 704-710 (1991).

compounds studied: Cisplatin, Thiotepa, Melphalan, 4HC, CBDCA,
biological response: Ovarian Cancer Cell Lines (OVCA 420, 429, 433; and OVCAR-3)

# of combinations:
dose levels:
data type:

Study Number: 292
Gallo, M.A., et. al.
Interactive Effects of Estradiol and 2,3,7,8-Tetrachlorodibenzo-p-dioxin on Hepatic Cytochrome P-450 and Mouse Uterus
Toxicology Letters , 32, 123-132 (1986).

compounds studied: TCDD and Estradiol
biological response: AHH activity, Induction ration, Cytochrome P-450

# of combinations: 10
dose levels: [0 or 72 μg/mouse]x[0-280 ng/mouse]
data type: Normal

Study Number: 293
Weber, H.
Teratogenic Potency of TCDD, TCDF and TCDD-TCDF Combinations in C57BL/6N
Toxicology Letters , 26, 159-167 (1985).

compounds studied: TCDD and TCDF
biological response: Fetal palates and maternal kidneys

# of combinations: 8
dose levels: [12,17,22];[300,600,900]
data type: Binomial and Normal

Study Number: 294
Lu, H.R., et al.
Comparative Thrombolytic Properties of Bolus Injections and Continuous Infusions of a Chimeric (t-PA/u-PA) Plasminogen Activator in a Hamster Pulmonary Embolism Model
Blood , 78, 125-131 (1991).

compounds studied: rt-PA, rscu-PA, rt-PA-ΔFE/scu-PA-e
biological response: Hamster pulmonary embolism model

# of combinations: 22
dose levels: [0,0.016, 0.032, 0.064, 0.125, 0.25, 0.5]; [0,0.25,0.5,1,2]; [0,0.004,0.008,0.016,0.032,0.064]
data type: Normal

Study Number: 295
Witt, P.A. et al
Norepinephrine and ATP are synergistic in the mouse vas deferens preparation
European Journal of Pharmacology , 204, 149-155 (1991).

compounds studied: Norepinephrine and ATP
biological response: Mouse Vas Deferens

# of combinations: 11
dose levels: [0.01,0.03,0.1,0.3,1,3,10,100,1000]; [0.03,0.1,1]
data type: Normal

Study Number: 296
Nikodijevic, O., et al
Behavioral Effects of A1- and A2- Selective Adenosine Agonists and Antagonists: Evidence for Synergism and Antagonism
The Journal of Pharmacology and Experimental Therapeutics, 259, 1 286-294 (1991).

compounds studied: APEC, CHA, NECA
biological response: Locomoter Activity in Mice

# of combinations: 20
dose levels: [0,3.7,30]; [0,29,170]; [0,3.2,6.5]
data type: Normal

Study Number: 297
Withey, R.J. and J.W. Hall
The Joint Toxic Action of Perchloroethylene with Benzene or Toluene in Rats
Toxicology , 4, 5-15 (1974).

compounds studied: Perchloroethylene, Benzene, Toluene
biological response: Rat mortality

# of combinations: 12
dose levels: [0 to 100 by 20]; [0 to 100 by 20]; [0 to 100 by 20]
data type: Binomial

Study Number: 298
Williams, C.H. et al
Studies of Toxicity and Enzyme Activity Resulting from Interaction between Chlorinated Hydrocarbon and Carbamate Insecticides
Toxicology and Applied Pharmacology, 11, 302-307 (1967).

compounds studied: Aldrin, Chlordane, Banol, Mobam
biological response: Brain, Liver, and Serum Enzymes

# of combinations: 8
dose levels: [70]; [300]; [15.8,31.6]; [45,90]
data type: Normal

Study Number: 299
Plummer, J.L. and Short, T.G.
Statistical Modeling of the Effects of Drug Combinations
Journal of Pharmacological Methods *** Data from Finney,1962, 23, 297-309 (1990).

compounds studied: Rotenone and Pyrethrins
biological response: House Flies

# of combinations: 15
dose levels: [0.1 to 0.35 by .05 and .05,.075, 0.1, 0.146, 0.196] x [0 to 1 by 0.25 and 1.5,2,0.375, 0.729, 0.979] mg/mL
data type: Binomial

Study Number: 300
McClune, S. et. al
Synergistic Interaction between midazolam and propofol
British Journal of Anaesthesia , 69, 240-245 (1992).

compounds studied: Midazolam and Propofol
biological response: Patients able to open eyes on command.

# of combinations: 9
dose levels: [0,0.1,0.13,0.16,0.22,0.28,0.34,0.4 and 0.03,0.06,0.12] x [0,0.4,0.8,1.2,1.6,2,2.4,2.8 and 0.3,0.6,0.9]
data type: Binomial

Study Number: 302
Finney, D.J.
Probit Analysis
Cambridge University Press, 2nd Edition, 146-150 (1952).

compounds studied: Rotenone and Pyrethrins
biological response: House Fly mortality

# of combinations: 10
dose levels: [0.25,0.375,0.5,0.729,0.979] X [0.05,0.075,0.1,0.146,0.196] and [0.375,0.5625,0.75,0.125,1.5] X [0.025,0.0375,0.05,0.075,0.1]
data type: Binomial

Study Number: 303
Chou, T.C. and Talalay, P.
Analysis of Combined Drug Effects: A New Look at a Very Old Problem
Trends in Pharmacological Science, 4, 450-454 (1983).

compounds studied: Rotenone and Pyrethrins
biological response: House Fly Mortality

# of combinations: 10
dose levels: [0.25,0.375,0.5,0.729,0.979] X [0.05,0.075,0.1,0.146,0.196] and [0.375,0.5625,0.75,0.125,1.5] X [0.025,0.0375,0.05,0.075,0.1]
data type: Binomial

Study Number: 304
Barrai, I. et al
The analysis of the joint effect of substances on reversion systems and the assessment of antimutagenicity
Mutation Research, 267, 173-182 (1992).

compounds studied:	perylene and cyclopentapyrene
biological response:	Salmonella typhimurium strain TA98
# of combinations:	14
dose levels:	[0.2,0.4,0.6] X [0.25,0.5,1.5,2,3]
data type:	Normal

Study Number: 306
Zaider, M.
Evidence of a neutron RBE of 70 (+/- 50) for solid-tumor induction at Hiroshima and Nagasaki and its implications for assessing the effective neutron quality factor.
Health Physics, 61, 5 631-636 (1991).

compounds studied:	N/A
biological response:	Humans Atomic Bomb Survivors
# of combinations:	N/A
dose levels:	N/A
data type:	N/A
