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A Systematic Search for Structure-Activity Relationships of Skin Contact Sensitizers: Methodology

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A computerized resource for the systematic evaluation of the structure-activity relationships and other aspects of contact allergens is described. This resource consists of a data base of results of contact dermatitis tests and a structural classification scheme for contact allergens that is called a Structure-Activity (S/A) Tree. The data base now contains approximately 2200 test results extracted from the journal *Contact Dermatitis* (1975–1982) and is continually being expanded. The S/A Tree is being developed to provide an index to structure-activity relationships of contact allergens; 63 structural groups are currently indexed. Analyses of benzoquinones and gallic acid esters are presented as examples of the potential application of this resource to such problems as the identification of potential cross-reactants, appropriate test concentrations and vehicles, and the reliability of available test results.

One of the most vexing and frequent problems encountered in patients with allergic contact dermatitis (ACD) is understanding potential cross-sensitization reactions. Often, patients react to compounds that are not the *primary sensitizers* (i.e., the ones that initially induced the ACD). These compounds, or *cross-reactants*, are generally structurally related to the primary sensitizer. Knowledge of structure-activity relationships involved would enable the dermatologist to do some preventive medicine, that is, to teach the patient what compounds he or she should avoid contacting. Furthermore, structure-activity relationships are critical in designing new molecules having no or little sensitization potential.

Thus, there is a need for a systematic analysis of known contact sensitizers to find features that make a chemical a sensitizer and to identify minimal structural requirements for the recognition of the allergen.

The dermatologist and other investigators are faced with many other questions in evaluating specific allergens and classes of allergens, such as, "At what concentrations is the allergen effective?", "In what vehicles?", and, most important, "How reliable are the results cited in the literature?"

We are developing a computerized resource for the systematic analysis of the structure-activity relationships and other aspects of contact allergens to address the problems described above. This resource has two components. The first component is a data base of ACD test results on chemicals and the second is a structural classification scheme for contact allergens that is called a Structure-Activity (S/A) Tree.

This paper describes the data base and S/A Tree that we are developing and presents examples of the potential applications of this resource to problems in ACD.

MATERIALS AND METHODS

Data Base of ACD Test Results

The data base of ACD test results and the S/A Tree for Contact Allergens are stored in the PROPHET computer system [1,2].

Description of the data base: The data base of test results is being compiled from the open literature. Currently the data base contains information extracted from articles appearing in the journal *Contact Dermatitis*, Volumes 1–8 (1975–1982). Retrospective and current literature searches are being conducted to identify additional material for the data base. The test results covered are primarily on single chemicals of known structure; substances of undefined composition generally are not cited. Each entry is a single test result and, for many chemicals, multiple tests are included in the data base. The data base contains chemicals identified by name, structure, and CAS Registry Number, together with information from their tests as contact allergens that we have extracted and evaluated.

Entering the data: Each entry in the data base is a single test result on a chemical. Table I is a sample entry from the data base. The following data elements are included: *Col. 1—Chemical name and CAS Registry Number. Col. 2—Type of reactant.* This entry indicates how the chemical is being evaluated. P = primary sensitizer (in experimental sensitization it is known whether or not the chemical is being evaluated as a primary sensitizer; in natural sensitization it is a reasonable guess); X = cross-reactant (where known, the name and CAS Registry Number of the primary sensitizer are listed in brackets following the X); U = unknown, for cases where the sensitization status of the subject being tested is not evident. *Col. 3—No. cases.* This is the number of cases being evaluated, including systematic consecutive patient testing. *Col. 4—Type of cases.* The sensitization status of the subject is indicated as follows: 1 = subject with eczema; 2 = subject has other disease—skin or systemic; 3 = subject is "normal," that is, the study is an experimental induction in humans or is being carried out in animals. *Col. 5—No. pos.* This is the number of positive responses observed among the cases studied. *Col. 6—Type of test.* The test methodology is cited as follows: OET = open epicutaneous test, PT = patch test. *Col. 7—Conc.* This is the concentration of the substance tested. Most concentrations are cited as a percent (molar concentrations are also cited frequently); ND = no data provided by the investigator. *Col. 8—Veh.* This is the vehicle in which the test substance is applied. The vehicles cited in this report are ETOH = ethanol, LANO = lanolin, OLIV = olive oil, PEG = polyethylene, PET = petroleum, and VAS = vaseline. *Col. 9—Skin Rx. intens.* The skin reaction intensity is recorded where provided by the investigator as 0.5+ to ++++. *Col. 10—Anim. model.* The test models used are HU = human and GP = guinea pig. Other information in Col. 10 includes specific test system identifiers, e.g., GPMT = guinea pig maximization test. *Col. 11—No. contr.* The numbers of vehicle and untreated controls are listed here. ND = no data reported; YES? = controls were included, but the size of the control group was not reported. *Col. 12—Ref.* This column contains a 12-digit abbreviation for the journal article in which the test result is cited. The abbreviation is as follows: JJJJYYVVPPPP where JJJJ = an abbreviation for the title of the journal (CODE = *Contact Dermatitis*); YY = the year of publication; VV = the volume number of the journal; PPPP = the number of the first page of the article. *Col. 13—Degree of conf.* This is a number (0–5) assigned to indicate how well the test result demonstrates that the chemical does or does not induce ACD. This Degree of Confidence is by no means a judgment of the overall quality of the research reported, but is strictly an evaluation of the evidence provided by the test result for classifying the chemical as a contact allergen.

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Abbreviations:
ACD: allergic contact dermatitis
S/A Tree: Structure-Activity Tree

TABLE I. *Biologic data sample entry*

(1) Chemical name (CAS no.)	(2) Type of reactant	(3) No. cases	(4) Type of cases	(5) No. pos.	(6) Type of test	(7) Conc. %	(8) VEH.	(9) Skin Rx. intens.	(10) Anim. model	(11) No. contr.	(12) Ref.	(13) Degree of conf.
P-PHENYLENEDIAMINE (106-50-3)	U	131	1	11	PT	1	PET		HU	YES?	CODE 7602 0089	2
P-PHENYLENEDIAMINE (106-50-3)	P	20	3	16	OET	0.05	VAS		GP	YES?	CODE 7703 0001	5
P-PHENYLENEDIAMINE (106-50-3)	X [N-ISOPROPYL-N′-PHENYL-P-PHENYLENEDIAMINE (104-72-4)]	20	3	19	OET	0.05	VAS		GP		CODE 7703 0001	5
P-PHENYLENEDIAMINE (106-50-3)	X [BENZOCAINE (94-09-7)]	4	1	1	PT	ND		+++	HU	0	CODE 7703 0170	3

See text for explanation of data.

The criteria for assigning Degree of Confidence are presented below.

Criteria for evaluation of test results: The Degree of Confidence in a given test result is dependent on the following conditions: (i) the presence of vehicle-treated or untreated controls, (ii) a concentration of test substance judged sufficient to elicit a response, (iii) use of an appropriate vehicle, (iv) a sufficient purity of the substance tested to ensure that the response obtained is for the chemical under consideration and not for contaminants, and (v) a sufficient number of cases evaluated to ensure a meaningful response.

The Degree of Confidence is then assigned to the test results as follows: 5 (the highest) = the test result is judged to meet all of the criteria; 4 = meets all of the criteria except that the number of cases tested is marginal; 3 = meets the criteria for 4, but there may also be questions about other parameters (if controls are absent, there is enough evidence from other studies to indicate the sensitization potential of the test substance); 2 = controls are absent and evidence from other studies is inadequate to indicate the sensitization potential of the test substance; 1 = fails several of the criteria, results are not considered to be reliable; 0 = test essentially fails all of the criteria (such results are included in the data base for completeness and because of the possibility that they may contribute to an overall evaluation of a chemical or class of chemicals that is based primarily on other test results). It is evident that these criteria are somewhat subjective; hence, the Degree of Confidence most probably should be viewed as a range within ±1 of the number assigned.

Searching the data base: Chemical names, CAS Registry Numbers, structures, and all of the biologic parameters cited in the data base can be searched by computer, singly or in combination. For example, all occurrences of chemicals assessed in patch tests where the Degree of Confidence is 4 or 5 could be identified. Similarly, all chemicals that have been found to be cross-reactants in humans with chemicals assigned to a specific chemical class can be identified.

S/A Tree for Contact Allergens

Definition of the S/A Tree: The S/A Tree is a hierarchical index of structure classes and substructures within these classes that are judged to be relevant in mediating the activity of chemicals as contact allergens. This component is being developed to provide a systematic analysis of structure-activity relationships of chemicals as contact allergens. The S/A Tree method was first defined in the early 1970s [3], and since that time it has been redefined, developed, and applied to the analysis of chemical carcinogens (e.g., [4–6]). The initial S/A Tree classification for contact allergens is based on 250 chemicals that one of the investigators (C. B., see [7,8]) had previously identified as being associated with contact dermatitis. It includes classes and subclasses judged to represent the significant structure groups in the chemicals analyzed (Table II). The S/A Tree will be continually developed by incorporating analyses of new chemicals added to the data base of test results. We expect that many of these initial groups, as well as those added in further development, will also prove to reflect different characteristics of behavior as contact allergens. As we continue the development of the S/A Tree through analysis of the data base of the test results, each of the structural classifications will be annotated with the attributes of the class or substructure relevant to ACD; that is, classes of cross-reactants, effective concentrations, appropriate vehicles, and Degree of Confidence in the available data will be added to each structural grouping.

Development of the S/A Tree: The methodology for development of the S/A Tree for contact allergens is depicted schematically in Fig 1. The S/A Tree physically consists of sets of fragment structures representing the classes and subclasses judged to be relevant to ACD. A sample of these structure fragments is shown in Fig 2. These structures are stored in PROPHET and are used in a computer procedure that we have written to classify chemicals into the appropriate structural groups on the S/A Tree. The computer procedure takes advantage of the substructure search and data base management capabilities in PROPHET to search for the chemical structures according to the hierarchical framework of the S/A Tree. Both the structure fragment tables and classification procedures are designed so that new structure groups can be readily accommodated. To better define the groups on the S/A Tree, we plan to incorporate other physicochemical properties into the classification scheme (e.g., lipophilicity, electrophilicity, steric effects).

We already have data bases of relevant substituent constants (e.g., Hammett electronic constants) stored in PROPHET that can be searched and matched with the chemical structures from the data base of test results. Furthermore, we have computerized procedures that we have written and that are provided by the developers of PROPHET for calculating various properties (e.g., logP [9] and bond angles and distances [1]).

As indicated in Fig 1, the major steps in the development of the S/A Tree are classification of chemicals in the current data base of test results using the current S/A Tree structure groups and analysis of the results to (i) identify new subgroups or classes that should be added to the S/A Tree, (ii) redefine groups currently on the S/A Tree, and (iii) evaluate the attributes of each class and subclass, including cross-reactants, effective test concentrations, and Degree of Confidence in the available data. The process of developing the S/A Tree is iterative and will be repeated as warranted by the addition of new information to the data base of test results.

EXPERIMENTS AND RESULTS

We describe the uses of the data base and S/A Tree for ACD by applying them to two sample problems. The problems are to identify what is known about benzoquinones and about gallic acid esters as contact allergens based on the information available in our data base and S/A Tree. We feel that it is necessary to remind the reader that the current scope of the data base is *Contact Dermatitis*, 1975–1982. The sensitizing potentials of benzoquinones and gallic acid esters have been well documented in literature not yet incorporated into the data base and, hence, not all of the appropriate test results are available for these sample studies.

Sample 1: Benzoquinones

The following questions might be asked relevant to evaluating the potential sensitizing effects of benzoquinones.

Do the chemicals belong to a class that has demonstrated

TABLE II. *Contact allergens: structure classes and subgroups*

ALCOHOLS/THIOLS
  Benzylic alcohols
  Enols
ALDEHYDES
  Aldehydes, conjugated
  Aldehydes, aromatic
  Hydrazones, aldehydic
ALKENES
  Vinyl/allyl benzenes
AMINES
  Azides
  Imides
ARYL AMINO/NITRO/AZO COMPOUNDS
  Single ring aryl amino/nitro compounds
  Fused ring aryl amino compounds
  Aryl azo compounds
  Aryl diazonium compounds
ARYL HALIDES
CARBOXYLIC ACIDS, ESTERS, AND RELATED COMPOUNDS
  Amides
  Carbamates
  Benzylic acids and esters
ETHERS/THIOETHERS
FATTY HYDROCARBONS (C > 4)
KETONES
  Ketones, conjugated
  Ketones, aromatic
  Quinones
  Hydrazones, ketonic
METALS
NITRILES, THIOCYANATES, ISOTHIOCYANATES
NITRO COMPOUNDS
NITROGEN-CONTAINING HETEROCYCLES
  Pyrimidines
  Quinolines
  Thiazines
  Thiazoles
  Triazines
OXYGEN-CONTAINING HETEROCYCLES
  Cyclic anhydrides
  Furans
  Lactones
PEROXIDES
PHENOLS
  Phenolic acids
PHOSPHATES, THIOPHOSPHATES, ARSENATES
STEROIDS
SULFONES, SULFONAMIDES
SULFUR-CONTAINING HETEROCYCLES
  Sultones
  Thiazines
  Thiazoles
TERPENES
  Monoterpenes
  Sesquiterpenes
  Diterpenes
  Triterpenes
TRIATOMIC HETEROCYCLES
  Imines
  Oxiranes
  Thiiranes
UREAS, THIOUREAS, GUANIDINES
VINYL HALIDES

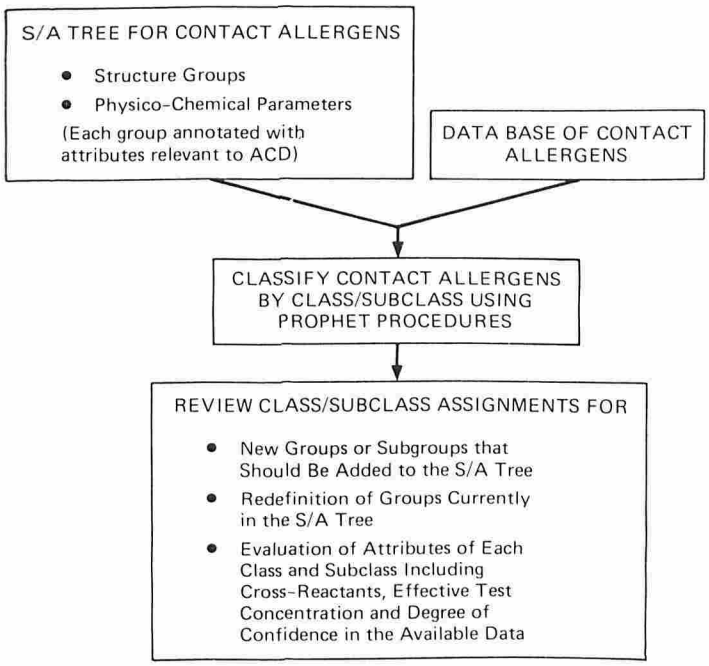

FIG 1. Development of an S/A Tree for Contact Allergens.

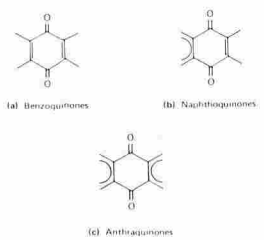

FIG 2. Quinone structure fragments from S/A Tree for Contact Allergens.

sensitizing potential? Yes, quinones per se are a structure group on the current S/A Tree for Contact Allergens (see Table II). Furthermore, by searching the data base of test results using the benzoquinone structure (see Fig 2a), the results shown in Table III are obtained. Tests of 6 benzoquinones have been reported in *Contact Dermatitis.* Of 29 cases in tests for primary sensitization, 16 were positive.

With what chemicals are benzoquinones likely to be cross-reactants? Thus far, only limited information is available in the data base to address this question. Two dalbergiones, R,S-4-methoxydalbergione and S-4,4′-dimethoxydalbergione, produced positive responses in 3/5 and 1/5 cases, respectively, when tested as cross-reactants to R-3,4-dimethoxydalbergione. In the same study, 2,6-dimethoxybenzoquinone did not produce a response when tested as a cross-reactant to R-3,4-dimethoxydalbergione. Also, 2,5-dimethoxybenzoquinone did not produce a response when tested as a cross-reactant to 2,6-dimethoxybenzoquinone. No other studies were found in the data base in which chemicals were found to cross-react with quinones. Although these data do not provide conclusive results, it is interesting that cross-reactions were seen only where the positions of substituents relative to the quinone moieties were similar.

What concentrations of benzoquinones are effective? What vehicles are appropriate? The data from *Contact Dermatitis* are clearly too sparse to allow a definitive conclusion to be drawn; however, some information can be obtained from the positive responses that are cited. A positive response was obtained for 2,6-dimethoxybenzoquinone at 0.1%; however, this result was in a guinea pig maximization test and no positive responses in humans were reported at 10%. Positive responses with dalbergiones were seen at a concentration of 1%. These results suggest that relatively high concentrations (e.g., 10%) may be needed to test unknown benzoquinones. For all of the benzoquinones, petrolatum was the vehicle and hence would appear to be one of the appropriate choices.

How reliable are the available data? None of the test results cited provide unequivocal evidence that the benzoquinones are sensitizers. Most of the results, however, including those of 2,6-dimethoxybenzoquinone as a primary sensitizer in guinea pigs, are assigned a Degree of Confidence of 3 and can be considered to provide evidence that the tested compounds are most probably sensitizers.

Sample 2: Gallic Acid Esters

Similar questions might be asked in evaluating the sensitizing potential of gallic acid esters.

Are gallic acid esters members of a class of chemicals generally

TABLE III. *Contact allergens: biologic data on benzoquinones, from Contact Dermatitis volumes 1–8*

Chemical name (CAS no.)	Type of reactant	No. cases	Type of cases	No. pos.	Type of test	Conc. %	VEH.	Skin Rx. intens.	Anim. model	No. contr.	Ref.	Degree of conf.
2,5-DIMETHOXY-P-BENZOQUINONE (3117-03-1)	X [2,6-DIMETHOXY-P-BENZOQUINONE (116-71-4)]	ND	3	0	OET	ND	ND		GP GPMT	YES?	CODE 7804 0204	3
2,6-DIMETHOXY-BENZOQUINONE (116-71-4)	P	1	1	0	PT	10	PET		HU	0	CODE 8208 0077	3
2,6-DIMETHOXY-BENZOQUINONE (116-71-4)	X [R-3,4-DIMETHOXY-DALBERGIONE (3744-64-4)]	5	1	0	PT	10	PET		HU	0	CODE 006 0246	2
2,6-DIMETHOXY-P-BENZOQUINONE (116-71-4)	P	10	3	2	OET	ND	ND		GP	YES?	CODE 7804 0204	3
2,6-DIMETHOXY-P-BENZOQUINONE (116-71-4)	P	10	3	7	OET	0.1	ND		GP GPMT	YES?	CODE 7804 0204	3
R-3,4-DIMETHOXY-DALBERGIONE (3744-64-4)	P	1	1	1	PT	1	PET	+++	HU	0	CODE 8208 0077	3
R-3,4-DIMETHOXY-DALBERGIONE (3744-64-4)	P	5	1	5	PT	1	PET	+++	HU	0	CODE 8006 0246	2
S-4,4-DIMETHOXY-DALBERGIONE (66821-68-9)	X [R-3,4-DIMETHOXY-DALBERGIONE (3744-64-4)]	5	1	1	PT	1	PET	+	HU	0	CODE 8006 0246	2
R,S-4-METHOXY-DALBERGIONE (28396-75-0)	X [R-3,4-DIMETHOXY-DALBERGIONE (3744-64-4)]	5	1	3	PT	1	PET	+, ++	HU	0	CODE 8006 0246	2
R,S-4-METHOXY-DALBERGIONE (28396-75-0)	P	1	1	1	PT	1	PET	+++	HU	0	CODE 8208 0077	2
2-METHYL-1,4-NAPHTHOQUINONE (58-27-5)	P	2	1	1	PT	ND	ND		HU	20	CODE 8006 0355	3
PRIMIN (119-38-0)	P	1	1	0	PT	0.01	PET		HU	0	CODE 8208 0077	3

regarded as having sensitizing potential? Yes, gallic acid esters are phenolic acid derivatives. Phenolic acids are a subgroup on the S/A Tree for Contact Allergens under the phenols class. Tests of 13 chemicals classified as phenolic acids are cited in the data base; these chemicals include parabens, salicylic acids, and atranorin and related compounds, as well as gallic acid esters. Studies of three gallic acid esters were found: propyl gallate, octyl gallate, and lauryl gallate (see Table IV). Of 904 cases reported on these chemicals, 123 (13.6%) were positive responses.

What concentrations of gallic acid esters are effective? Can the potency of these compounds be characterized on the basis of the available data? As for the benzoquinones, the data are inadequate for conclusive evaluation; however, some useful observations can be made. The octyl ester produced a positive response when tested at 0.1% in olive oil; both the octyl and lauryl esters produced significant positive responses at 0.25 and 0.5% in petrolatum, and the propyl ester produced a response at 1% in petrolatum. Based on this information, 1% may be an adequate concentration for detecting activity of gallates. Although it is difficult to generalize from the limited data cited, the gallic acid esters appear to be somewhat more potent than the benzoquinones on the basis of effective concentrations. The results presented in one study cited in the data base [10] indicate that the potency of the gallates increases with increasing alkyl chain length in the alcohol moiety. That is, when the compounds were tested in 200 cases at a concentration of 1%, the percentage of positive responses increased in the order propyl gallate (4%) < octyl gallate (16.5%) < lauryl gallate (21%). It will be interesting to see whether this observation is verified as additional data are entered.

How reliable are the available data? As for benzoquinones, none of the individual test results cited provide unequivocal evidence that the gallic acid esters are sensitizers. However, the large number of cases cited (904) and the assignment of a Degree of Confidence of 3 to all but one of these results provide strong evidence that the tested compounds are contact sensitizers.

DISCUSSION

The evaluation of benzoquinones and gallic acid esters presented as an example are the type of analysis that we will do in developing the S/A Tree for Contact Allergens. However, there are additional uses of this resource in assessing ACD. For example, one could search for all of the cross-reactants to a particular primary sensitizer or structural class of sensitizers. The reliability of various test methods could be compared for different classes of sensitizers. Similarly, one could search for results obtained in a specific test system, at a particular concentration, with selected vehicles, or that were assigned a high Degree of Confidence. Searches combining two or more of these parameters could be carried out and could be done for specific chemicals, for groups of chemicals, or without regard to the chemicals tested. We hope that such versatility will enhance the utility of this resource as a knowledge base.

TABLE IV. *Sample of evaluation of three gallic acid esters for sensitizing potential*

Chemical name (CAS no.)	Type of reactant	No. cases	Type of cases	No. pos.	Type of test	Conc. %	VEH.	Skin Rx. intens.	Anim. model	No. contr.	Ref.	Degree of conf.
LAURYL GALLATE (1166-52-3)	X [OCTYL GALLATE (1034-01-1)]	1	1	0	PT	0.1	OLIV		HU	30	CODE 7804 0060	3
LAURYL GALLATE (1166-52-3)	X [OCTYL GALLATE (1034-01-1)]	1	1	0	PT	1	OLIV		HU	30	CODE 7804 0060	3
LAURYL GALLATE (1166-52-3)	U	200	1	42	PT	1	PET		HU	0	CODE 7501 0393	3
LAURYL GALLATE (1166-52-3)	U	100	1	16	PT	0.5	PET		HU	0	CODE 7501 0393	3
LAURYL GALLATE (1166-52-3)	U	50	1	4	PT	0.25	PET		HU	0	CODE 7501 0393	3
OCTYL GALLATE (1034-01-1)	U	200	1	33	PT	1	PET		HU	0	CODE 7501 0393	3
OCTYL GALLATE (1034-01-1)	U	100	1	12	PT	0.5	PET		HU	0	CODE 7501 0393	3
OCTYL GALLATE (1034-01-1)	U	50	1	4	PT	0.25	PET		HU	0	CODE 7501 0393	3
OCTYL GALLATE (1034-01-1)	P	1	1	1	PT	1	OLIV		HU	0	CODE 7804 0060	3
OCTYL GALLATE (1034-01-1)	P	1	1	1	PT	0.1	OLIV		HU	30	CODE 7804 0060	3
PROPYL GALLATE (121–79-9)	P	1	1	1	PT	1	ETOH	++	HU	0	CODE 7501 0257	1–2
PROPYL GALLATE (121-79-9)	U	200	1	8	PT	1	PET		HU	0	CODE 7501 0393	3
PROPYL GALLATE (121-79-9)	P	1	1	1	PT	2	PET	+	HU	12	CODE 8006 0213	3

In *Materials and Methods* we describe plans to incorporate physicochemical parameters other than structure into the analysis of structure-activity relationships. Similarly, we expect to include parameters based on the biochemical characteristics of the substances tested. For example, Dupuis and Benezra [11], have cited the cross-reactivity of the structurally dissimilar chemicals hydroquinone and *para*-phenylenediamine and have noted that the formation of a common metabolite, benzoquinone, has been suggested as an explanation. Observations of such cross-reactivity among chemicals in the data base might indicate the need for new structural subgroups to contain *para*-substituted aryl compounds capable of being metabolized to quinones (e.g., hydroquinones, aminophenols, aryldiamines).

We readily acknowledge that we have only begun to tap the information available to build the data base and S/A Tree. We know that the material extracted thus far from *Contact Dermatitis* does not adequately cover test data on many of the widely known contact allergens that we have already incorporated into the S/A Tree (e.g., deoxylapachol, urushiol). The retrospective and ongoing literature search and review should help remove this limitation, especially as relevant textbook data will be added. However, we also realize that much useful data are not published in forms accessible through the open literature, and we would like to invite other investigators to contact us regarding appropriate data that they would be willing to contribute to the development of the data base.

We have no illusion that the computer will improve the quality of biologic data but we do have confidence that wise use of its powers will provide structure-activity relationships in ACD that are not obvious using prior methods. This has certainly been the case in other biologic areas.

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