Validation and Subsequent Development of the Derek Skin Sensitization Rulebase by Analysis of the BgVV List of Contact Allergens

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The DEREK knowledge-based computer system contains a subset of approximately 50 rules describing chemical substructures (toxophores) responsible for skin sensitization. This rulebase, based originally on Unilever historical in-house guinea pig maximization test data, has been subject to extensive validation and is undergoing refinement as the next stage of its development. As part of an ongoing program of validation and testing, the predictive ability of the sensitization rule set has been assessed by processing the structures of the 84 chemical substances in the list of contact allergens issued by the BgVV (German Federal Institute for Health Protection of Consumers). This list of chemicals is important because the biological data for each of the chemicals have been carefully scrutinized and peer reviewed, a key consideration in an area of toxicology in which much unreliable and potentially misleading data have been published. The existing DEREK rulebase for skin sensitization identified toxophores for skin sensitization in the structures of 71 out of the 84 chemicals (85%). The exercise highlighted areas of chemistry where further development of the rulebase was required, either by extension of the scope of existing rules or by generation of new rules where a sound mechanistic rationale for the biological activity could be established. Chemicals likely to be acting as photoallergens were identified, and new rules for photoallergenicity have subsequently been written. At the end of the exercise, the refined rulebase was able to identify toxophores for skin sensitization for 82 of the 84 chemicals in the BgVV list.

INTRODUCTION

Relationships between the structure and properties of chemicals can be programmed into knowledge-based systems. DEREK (an acronym for "Deductive Estimation of Risk from Existing Knowledge")[1,2] is one such system for the qualitative prediction of chemical toxicity that is now in widespread use in the chemical industry. The system covers various toxicological endpoints including mutagenicity, carcinogenicity, skin sensitization, neurotoxicity, and reproductive toxicity, with the rulebase for the latter two endpoints in early stages of development.

DEREK embodies both a controlling program and a chemical rulebase. The chemical rulebase consists of descriptions of molecular substructures previously found to correlate with specific toxicological endpoints. The user communicates with DEREK via interactive computer graphics by drawing the 2-dimensional (2D) chemical structure of the query chemical on the screen. The rulebase is then searched against the query structure and any structural alert is highlighted together with a message indicating the nature of the toxicological hazard.

The DEREK rulebase is under constant development, particularly in the area of skin sensitization. Rulebase development takes place in collaboration with existing DEREK users with the result that rules are based both on commercial in-house data as well as the published literature.

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THE SKIN SENSITIZATION RULEBASE

For a chemical to be biologically active, it must first be transported from its site of administration to its site of action and then it must bind to or react with its receptor or target;[3] that is, biological activity is a function of partition and reactivity. DEREK contains a subset of approximately 50 rules that describe chemical substructures known or believed to be responsible for the chemical reactivity component of skin sensitization. This rulebase was initially derived from Unilever historical in-house guinea pig maximization test data for 294 single chemical substances of known chemical purity.[4,5] Those chemicals that classified as skin sensitizers by EC criteria[6] (135 of the 294) were arranged in groups according to their most likely mechanism of reaction with skin proteins. Where the chemical mechanism could not be clearly identified, structural alerts were derived for groups of chemicals with similar functional groups. This process resulted in the generation of around 40 structure−activity rules.[5] As a result of further development, the number of structural alerts for skin sensitization has now been increased to >50.[7]

THE BgVV LIST OF CONTACT ALLERGENS

In 1995, the German Federal Institute for Health Protection of Consumers (BgVV) published a list of 84 chemical substances identified as contact allergens.[8] This list is important because the biological data for each chemical had been carefully scrutinized and peer-reviewed—a key consideration in an area of toxicology in which much unreliable and poten-

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tially misleading data are published. The names and CAS numbers of the chemicals in this list are shown in Table 1.

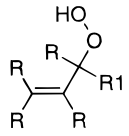
THE VALIDATION EXERCISE

As part of an ongoing program of validation and testing of the DEREK system, the predictive ability of the skin sensitization rulebase has been assessed by processing the structures of the 84 chemicals on the BgVV list. The results of that analysis are shown in Table 2. The DEREK rulebase for skin sensitization initially identified toxophores in the structures of 71 out of the 84 chemicals (85%). DEREK was unable to process one chemical, a mercury compound, because its molecular weight is beyond the scope of the program. The 12 contact allergens not identified by the rulebase as containing structural alerts for skin sensitization are three photoallergens, four organic hydroperoxides, one phenolic compound, one thiol exchange agent, one hydroxylamine precursor, one cyclopropenone derivative, and one chemical (*N*-vinylcarbazole) for which the sensitization potential cannot at this stage be unequivocally explained. The structures of these 12 chemicals are shown in Figure 1. This exercise highlighted several areas of chemistry where further development of the rulebase was required. A sound mechanistic rationale can be established for the biological activity of the three photoallergens, four organic hydroperoxides, and the hydroxylamine precursor, which results in the generation of three new rules. A review of the skin sensitization literature was carried out relating to these specific chemical classes; further examples were discovered that supported the proposed mechanisms of action, and these were used to support the structure−activity relationships described in the new rules.

There were existing rules in DEREK that covered skin sensitization by phenolic compounds, thiol exchange agents, and α,β-unsaturated ketones. On the basis of the knowledge available when they were written, these rules did not cover the three chemicals from these classes in the current dataset.

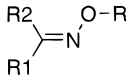
RULEBASE MODIFICATION

1. Organic Hydroperoxides. The new DEREK rule for organic hydroperoxides contains the following structural alert

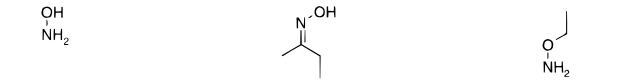


where R = H, aliphatic carbon; R1 = aliphatic carbon. The rule is supported by the known sensitization potential of the hydroperoxides of α-pinene,[9] abietic acid,[10] Δ^3-carene,[11] α-terpineol,[9] and limonene.[12] Reaction between the haptens and skin proteins has been shown to take place via free radical mechanisms.[13]

2. Hydroxylamine and Precursors. The new DEREK rule for hydroxylamine and precursors contains the following structural alert



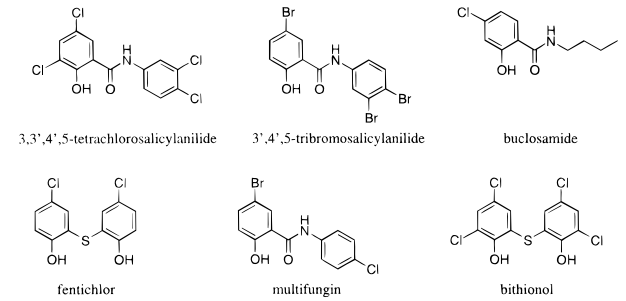
where R = H or alkyl and R1 and R2 are alkyl or aryl. The rule is supported by the known sensitization potentials of hydroxylamine,[14] butanone oxime,[14,15] and *O*-ethylhydroxylamine.[16] The basis of this rule is the skin sensitization potential of hydroxylamine and the ability of the precursors to be metabolised in vivo to give hydroxylamine. The chemical mechanism of hydroxylamine sensitization remains to be elucidated.



hydroxylamine butanone oxime O-ethylhydroxylamine

3. Photoallergens. There are three new DEREK rules covering photoallergens. The first, which is for halogenated phenolic compounds, contains the following structural alerts

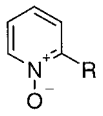
where X = Cl, Br, I and R = S or amido. The rule is supported by the known photoallergenicity of 3,3′,4′,5-tetrachlorosalicylanilide,[17] 3′,4′,5-tribromosalicylanilide,[18] buclosamide,[19] fentichlor,[20] multifungin,[20] and bithionol.[21] Halogenated phenolic compounds of this type have been shown to react covalently with proteins on irradiation with ultraviolet light.[22,23] The mechanism of protein conjugate formation is thought to proceed via free radical mechanisms; free radicals have been detected and characterized using electron spin resonance spectroscopy on ultraviolet irradiation of several of these chemicals [e.g., ref 24].



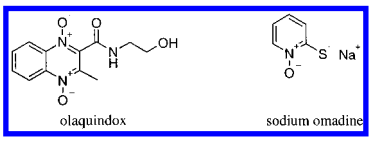
3,3',4',5-tetrachlorosalicylanilide 3',4',5-tribromosalicylanilide buclosamide

fentichlor multifungin bithionol

The second photoallergen rule contains the structural alert



where R = S, O, N, or amido; alkyl or aryl substituents are allowed on other positions of the aromatic ring. This rule is supported by the known photoallergenicity of olaquindox[25] and sodium omadine.[26] Sodium omadine has been shown to bind covalently to human serum albumin on irradiation with ultraviolet light.[22]



olaquindox sodium omadine

The third photoallergen rule contains the structural alerts

Table 1. BgVV Skin Sensitizers, CAS Numbers and DEREK Skin Sensitization Rules Fired

name	CAS no.	DEREK rules fired
	Category A	
formaldehyde	50-00-0	419 aldehyde
4-aminophenylazobenzene	60-09-3	427 aromatic primary amine 428 amine precursor - aromatic azo compound
2,4-dinitrofluorobenzene	70-34-8	415 halo-di/trinitro aromatic compound
N,*N*′ -diphenyl-*p*-phenylenediamine	74-31-7	427 aromatic secondary amine
choroacetamide	79-07-2	413 haloalkane
musk ambrette	83-66-9	**I**
naphthol AS	92-77-3	**II**
benzocaine	94-09-7	427 aromatic primary amine
dicyclopentamethylenethiuramdisulphide	94-37-1	442 thiuram disulphide
p-toluenediamine and salts	95-70-5	427 Primary aromatic amine
3-thioglycerol	96-27-5	**III**
2,4-dinitrochlorobenzene	97-00-7	415 halo-di/trinitro aromatic compound
tetramethylthiurammonosulphide	97-74-5	442 thiuram monosulphide
tetraethylthiuramdisulphide	97-77-8	442 thiuram disulphide
phenylhydrazine	100-63-0	448 hydrazine or hydrazine precursor
4-aminodiphenylamine	101-54-2	427 aromatic primary/secondary amine
N-isopropyl-*N*′-phenyl-*p*-phenylenediamine	101-72-4	427 aromatic secondary amine
4,4′-diaminodiphenylmethane	101-77-9	427 aromatic primary amine
N-cyclohexyl-*N*′-phenyl-*p*-phenylenediamine	101-87-1	427 aromatic secondary amine
cinnamaldehyde	104-55-2	419 aldehyde
p-phenylenediamine	106-50-3	427 aromatic primary amine
allylglycidylether	106-92-3	433 epoxide
ethylenediamine	107-15-3	435 1,2-diamine
glyoxal	107-22-2	419 aldehyde
diethylenetriamine	111-40-0	435 1,2-diamine
triethylenetetramine	112-24-3	435 1,2-diamine
phenylglycidylether	122-60-1	433 epoxide
p-aminophenol	123-30-8	427 primary aromatic amine 439 phenol
tetramethylthiuramdisulphide	137-26-8	442 thiuram disulphide
2-mercaptobenzothiazole	149-30-4	410 isothiocyanate 432 thiol
hydrazine and salts	302-01-2	448 hydrazine or hydrazine precursor
isoalantolactone	470-17-7	421 α,*β*-unsaturated ester
2-chloroacetophenone	532-27-4	413 haloalkane
alantolactone	546-43-0	421 α,*β*-unsaturated ester
tulipalin A	547-65-9	421 α,*β*-unsaturated ester
costunolide	553-21-9	421 α,*β*-unsaturated ester
thioglycolic acid hydrazide	760-30-5	432 thiol 448 hydrazine or hydrazine precursor
diphenylcyclopropenone	886-38-4	**IV**
3,3′,4′,5-tetrachlorosalicylanilide	1154-59-2	**V**
N-vinylcarbazole	1484-13-5	**VI**
bisphenol A diglycidyl ether	1675-54-3	433 epoxide
carabrone	1748-81-8	421 α,*β*-unsaturated ester
1,4-butanediol diglycidyl ether	2425-79-8	433 epoxide
n-butylglycidyl ether	2426-08-6	433 epoxide
2-chloro-*N*-hydroxymethylacetamide	2832-19-1	413 haloalkane 426 formaldehyde donor
pentaerythritol triacrylate	3524-68-3	421 α,*β*-unsaturated ester
deoxylapachol	3568-90-9	416 quinone
R-3,4-dimethoxydalbergione	3755-64-4	416 quinone 421 α,*β*-unsaturated ketone
3,4-diethoxycyclobutenedione	5231-87-8	425 enol precursor of a ketone
2-nitro-*p*-phenylenediamine	5307-14-2	427 aromatic primary amine
helenalin	6754-13-8	421 α,*β*-unsaturated ester 421 α,*β*-unsaturated ketone
t-butylglycidyl ether	7665-72-7	433 epoxide
mansonon A	7715-94-8	416 quinone
potassium dichromate	7778-50-9	443 metal salt containing Co, Cr, Ni, Be
nickel and its salts	7718-54-9	443 metal salt containing Co, Cr, Ni, Be
turpentine oil (α-terpineol)	8006-64-2	**VII**
colophony (abietic acid)	8050-09-7	**VIII**
Δ3-carene	13466-78-9	**IX**
primin	15121-94-5	416 quinone
trimethylol propane triacrylate	15625-89-5	421 α,*β*-unsaturated ester
parthenolide	20554-84-1	421 α,*β*-unsaturated ester 433 epoxide
organomercury compounds	22967-92-6	(cannot process)
olaquindox	23696-28-8	**X**
2-methyl-4-[(methylphenyl)azo]aniline	41576-40-3	427 aromatic primaryamine 428 amine precursor - aromatic azo compd
l,1-dimethylallyl caffeate	100884-13-7	418 catechol

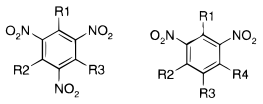
Table 1 (Continued)

name	CAS no.	DEREK rules fired
	Category B	
bisphenol A	80-05-7	439 phenol
α-pinene and oxidation products	80-56-8	**XI**
morpholinyldithiobenzothiazole	95-32-9	410 isothiocyanate
methylethylketoxime	96-29-7	**XII**
p-tert-butylcatechol	98-29-3	418 catechol
resorcinol	108-46-3	440 resorcinol
piperazine	110-85-0	435 1,2-diamine
tetraethylenepentamine	112-57-2	435 1,2-diamine
4,4′-diaminodiphenylamine	537-65-5	427 aromatic primary and secondary amine
4,4′-diaminoazobenzene	538-41-0	427 aromatic primary amine 428 amine precursor - aromatic azo compd
N-dimethylbutyl-*N*′-phenyl-*p*-phenylenediamine	793-24-8	427 aromatic secondary amine
4-diethylaminoazobenzene	2481-94-9	428 amine precursor - aromatic azo compd
grotan BK	4719-04-4	426 formaldehyde donor
	Category C	
dipropylenetriamine	56-18-8	435 1,3-diamine
n-butylmethacrylate	97-88-8	421 α,β-unsaturated ester
4,4′-diaminodiphenylether	101-80-4	427 aromatic primary amine
N,*N*′-diethylaminopropylamine	104-78-9	435 1,3-diamine
tetrahydrofurfurylmethacrylate	2455-24-5	421 α,β-unsaturated ester
bisphenol A dimethacrylate	253-39-2	421 α,β-unsaturated ester

Table 2. The BgVV Contact Allergen List: Performance of the DEREK Skin Sensitization Rulebase[a]

parameter	category A (strong)	category B (moderate)	category C (weak)	total
structural alert for skin sensitization	54	11	6	71
no structural alert for skin sensitization	10	2	0	12
cannot process	1	0	0	1
total	65	13	6	84

[a] Eight-four chemicals in three categories; 71 out of 84 chemicals identified as containing a structural alert for skin sensitization represents a "hit rate" of 85%.



For the dinitro compounds, R1 can be a primary substituent (not secondary or tertiary) up to four carbon atoms long, R2, R4 = H, methyl, or methoxy, and R3 = any sp^2 or sp^3 carbon. For the trinitro compounds, R1 can be can be a primary substituent up to four carbon atoms long, R2, R3 = H, methyl, or methoxy. These requirements are based on the hypothesis proposed by Motten et al.[27] that to be a photoallergen, the chemicals must be capable, on photolysis, of forming a nitro radical anion that is coplanar with the aromatic ring. The coplanar nitro radical anion can then go on to be metabolized into a reactive intermediate. Because of steric constraints, the related chemicals musk xylene and musk ketone, which are not reported to cause any photoallergic reactions, can only form nitro radical anions which are out of plane with the aromatic ring.

Diphenylcyclopropenone is a cyclic α,β-unsaturated ketone that probably reacts with nucleophiles by 1,4-addition. Indeed, the highly strained nature of the cyclopropene ring would lead to a large gain in enthalpy from this reaction and make this particularly reactive. However, according to the DEREK chemical perception routines, the cyclopropenone ring system is aromatic because it conforms to the Huckel $(4n + 2)$,g electrons rule ($n = 0$) for determining

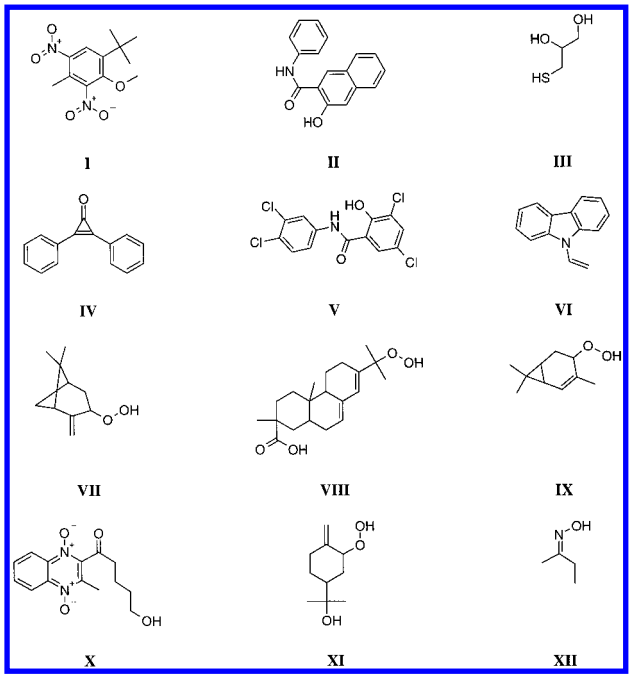


Figure 1.

aromaticity. For this reason, the existing rule for α,β-unsaturated ketones was not activated for diphenylcyclopropenone. It was a simple task to extend the rule to allow any cyclopropenone to fire this rule.

ANALYSIS AFTER RULEBASE MODIFICATION

Following the modifications to the rulebase just mentioned, DEREK was able to identify toxophores for skin sensitization in 82 of the 84 chemicals (98%). We can currently find no basis in mechanistic organic chemistry for the sensitization potential of *N*-vinylcarbazole as a direct acting allergen. One possibility is that the vinyl group may be oxidized to an epoxide, which could then react with skin protein. In the absence of any evidence, however, this explanation is purely speculative. The atomic weight of mercury is currently too high for the mercury compounds to be processed by the

DEREK operating system. This deficiency is due to be remedied in the near future.

CONCLUSIONS

This validation exercise demonstrates the accuracy of the predictions for skin sensitization made by the DEREK system and exemplifies the process by which the rulebase is undergoing continuous development in the light of new knowledge. The process is illustrated whereby specific compound data coupled with a thorough literature review of a chemical class can be used as the basis of a mechanistic hypothesis for toxicity. Following peer review by the DEREK collaborative group (using proprietary data where available), this leads to the development of new structure activity rules for the DEREK rulebase.

Although the data in the BgVV list are of good quality, they are limited by the fact that only positive data relating to skin sensitization are listed. Analysis of further high quality datasets, which consist of negative as well as positive skin sensitization data, is an essential part of the development process.

Analysis of datasets that contain only positive skin sensitization data requires consideration only of whether or not the chemicals have the potential to react with a contact allergens either directly or after appropriate skin metabolism. For datasets containing both positive and negative data, consideration of the physicochemical properties of the chemicals that influence partition either into the skin, or into biological compartments relevant for skin metabolism, is also required. Partition parameters assume a greater importance in evaluating skin sensitization data from protocols that employ only topical application of test chemicals (e.g., the mouse local lymph node assay and the human maximization test), than in procedures such as the guinea pig maximization test, which involve the use of subcutaneous injections with adjuvant. The structural alerts for skin sensitization contained in the DEREK system provide only information about the reactivity component of skin sensitization. The StAR system, currently under development by LHASA Limited, in addition to containing the functionality of DEREK, will also contain the tools necessary for analyzing the partition properties of chemicals.

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