

QSARs for the skin sensitization potential of aldehydes and related compounds

Patlewicz Grace^{a*}, Roberts David W^b and Walker John D^c

^a Safety and Environmental Assurance Centre (SEAC), Unilever Research & Development, Colworth House, Sharnbrook, Bedford MK44 1LQ, UK

^b Unilever Research Port Sunlight, Bebington, Wirral, Merseyside, UK

^c TSCA Interagency Testing Committee (ITC), U.S. Environmental Protection Agency (7401M), 1200 Pennsylvania Avenue, NW, Washington, DC 20460

Abstract

Although not all aldehydes are skin sensitizers, many of them, covering a diverse range of structures, show varying degrees of sensitization potential. Based on consideration of their reaction chemistry, it is possible to identify structural features associated with sensitization potential or the lack of it. Many aldehydes, including several fragrance allergens, can sensitize by Schiff base formation. A QSAR based on reactivity and hydrophobicity param-

eters has been developed for these aldehydes. The QSAR can be extended to include 1,2-diketones, which can also react by Schiff base formation. The findings indicate that for skin sensitization, as for several other areas of toxicology, chemicals are better classified in terms of their reaction chemistry rather than in terms of their functional groups, i.e., based on mechanisms of action as opposed to chemical class.

1 Introduction

Skin sensitizing chemicals (contact allergens) cause allergic contact dermatitis via a number of biochemical and physiological events. The induction or elicitation of contact allergy involves the interaction of a hapten, a small low molecular weight molecule, with a protein to form an antigenic complex. This interaction involves the formation of a covalent bond between the hapten and the protein. Correlations between the ability of chemicals to react with proteins to form covalently linked conjugates and their skin sensitization ability form the basis for Quantitative Structure Activity Relationships (QSARs) that have been developed to predict skin sensitization potential. Physico-chemical parameters for different chemical classes have been used to develop these skin sensitization QSARs [1], while other QSAR approaches take advantage of the fact

that a mechanism of action approach can be used to predict skin sensitization. [2, 3]

Roberts and Williams [4] established QSARs to predict skin sensitization based on electrophilicity and hydrophobicity parameters using the Relative Alkylation Index (RAI) mathematical model. The RAI quantifies the relative extent of sensitizer binding to the skin protein as a function of the dose. The chemical reactivity may be expressed in terms of: 1) measured rate constants for reaction with a model nucleophile, 2) Taft or Hammett substituent constants or 3) computed molecular orbital indices. Hydrophobicity expressed as the octanol/water partition coefficient may be calculated e.g. by the method of Hansch and Leo [5]. The general form of the RAI expression is:

$$\text{RAI} = \text{Log } D + a\text{Log } k + b\text{Log } P$$

where *D* is dose, *k* is the relative rate constant and *P* is the octanol/water partition coefficient. Log *P* can model both penetration and lipid/polar fluid partitioning.

This RAI model has been used to evaluate data on various sets of skin sensitizing chemicals [6, 7, 8].

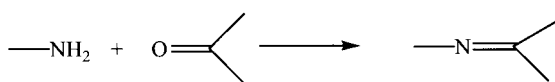
The development of the local lymph node assay (LLNA) has facilitated the use of QSARs to predict skin sensitization potential because it provides unambiguous, well-defined endpoints [9]. The LLNA is described in detail in numerous publications; for the present paper, it suffices to state that it involves repeated topical application of the test chemical to

* To receive all correspondence, Tel.: +44 1234 264826, Fax: +44 1234 264722, e-mail: Grace.Patlewicz@unilever.com

Key words: Structure activity relationship, skin sensitization, local lymph node assay, aldehydes, ketones

Abbreviations: QSAR: Quantitative Structure Activity Relationship, LLNA: Local Lymph Node Assay, RAI: Relative Alkylation Index, SI: Stimulation Index, DK: Diketone, SB: Schiff Base.

Schiff base formation



Michael addition

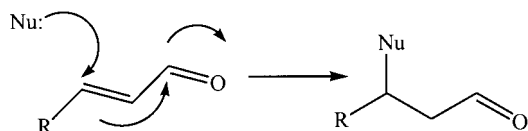


Figure 1. Related mechanisms for Schiff base and Michael acceptor aldehydes

mouse ear skin followed by quantitative assay of T-cell response in the draining lymph node, measured as a function of the incorporation of tritiated thymidine. The sensitization response is quantified in terms of the stimulation index (SI) or the ratio of the activity in draining lymph nodes of treated mice compared to that of the vehicle treated mice. A given chemical is tested over a range of concentrations such that a dose response relationship can be determined from which the sensitization potential is defined in terms of the concentration required to give a specified SI value. Currently the preference is to estimate the concentration of a chemical required to generate a SI of 3, the EC3 value [10].

This paper expands on the work on aldehydes in Patlewicz et al. [11]. This previous study investigated the skin sensitization potential of various aldehydes in relation to the development of structure activity relationships (SARs) using the RAI model. Seventeen aldehydes were evaluated for which different reaction mechanisms were suspected. It was established that the dataset could be classified by chemical reactivity considerations into four discrete classes: aryl-substituted aliphatic aldehydes (class 1), aryl aldehydes (class 2), aryl aldehydes with “special features” such that they could be actively metabolized (class 3) and α,β -unsaturated aldehydes (class 4). The sensitization potential of each aldehyde was subsequently rationalised in terms of this classification. A QSAR was defined for a subset of these compounds where the mechanism of action was considered to be the same. Class 1 aldehydes are aryl-substituted aliphatic or simple aliphatic aldehydes which are expected to react via Schiff base formation. Class 4 aldehydes are α,β -unsaturated aldehydes which are able to utilize the conjugated C=C double bond to act by a Michael addition mechanism.

Class 1 and Class 4 aldehydes will be termed Schiff base and Michael addition aldehydes for the remainder of the text.

In a further study this hypothesis was examined through identification of suitable candidate aldehydes to test in the LLNA and the development of predictive QSAR models.

QSAR models were investigated for both Schiff base and Michael addition aldehydes and these will be the subject of a separate publication [12].

This paper focuses on the reactivity of the carbonyl group and its contribution to skin sensitization potential. Carbonyl groups in simple aldehydes and ketones can react as hard electrophiles, e.g., by Schiff base formation. Carbonyl groups in more complex aldehydes and ketones, as well as ester and amide groupings, may have the potential to activate other groups, e.g., unsaturated C=C bonds which can undergo Michael addition reactions when activated by carbonyl groups in the alpha position. These reactions are shown in Figure 1. This publication examines the Schiff base QSAR model in further detail and studies its domain applicability to other carbonyl compounds. Specifically the Schiff base QSAR model developed in [12] will be used to make predictions of 1,2-diketones studied in [13] and a comparison of the two QSAR models will be made.

2 Materials and Methods

The 17 aldehydes examined in [11] were supplemented with additional aldehydes identified from the internet catalogue <http://www.execpc.com/~goodscent/index.html> which specialises in the sale of fragrances. This provided a list of fragrance materials from which a total of 71 fragrance aldehydes were identified. These are listed in Table 1. Structures for these aldehydes were drawn or downloaded from www.chemfinder.com and imported into the 2D-drawing package Chemdraw (Version 6, CambridgeSoft). These structures were collated into one (sd) file and Log P values for each of the chemicals were estimated using CLog P (Version 4, BioByte Corp). The structures were energy minimized to generate 3D representations. A number of physicochemical parameters were calculated that were considered relevant using Cerius 2 software (Version 4.6, Accelrys). These included: LUMO (lowest unoccupied molecular orbital), Dipole, Heat of Formation (Hf), HOMO (highest occupied molecular orbital), Molar Refractivity (MR), number of hydrogen bond acceptor groups (HBA), number of hydrogen bond donors (HBD), number of rotatable bonds (RotB) and molecular volume (Mol Vol). Number of rotatable bonds are defined as the number of bonds in the molecule possessing rotations that are meaningful for molecular mechanics. All terminal H atoms are ignored. Default parameters within Cerius 2 were used to calculate the descriptors, LUMO and HOMO energies were calculated using MOPAC AM1.

Each of the 71 aldehydes was then rationalised according to its reaction chemistry into one of the 4 classes previously hypothesised in [11]. A cluster analysis was used to select subsets of 10 materials from the two classes where there were an abundance of chemicals from which to make a selection. Class 1 (Schiff base aldehydes) and Class 4 (Michael addition aldehydes) were targeted and two sets of 10 materials were proposed. A set of ten aldehydes was

Table 1. 71 fragrance aldehydes

CAS#	Name	Class	Log-P	V _m /l ³	Rotl-bonds	HBA	HBD	MR/cm ⁻³	LUMO/eV	Dipole/debye	Hf/kcal	HOMO/eV
100-52-7	Benzaldehyde	2	1.47	102.971289	1	1	0	31.528824	-0.40159	2.776	-6.84446	-9.95975
101-39-3	Methyl cinnamic aldehyde	4	2.21	143.309568	2	1	0	37.923405	-0.35922	2.667	130.24414	-9.26177
101-86-0	Hexyl cinnamic aldehyde	4	4.85	231.790455	7	1	0	51.960022	-0.3817	2.69	-25.51034	-9.38832
103-95-7	Cyclamen aldehyde	1	3.46	204.589849	4	1	0	60.987328	0.55615	2.407	-36.02279	-9.06022
104-09-6	4-methylphenylacetaldehyde	1	2.28	136.457703	2	1	0	42.807201	0.18363	2.689	-20.30003	-9.37093
104-53-0	Phenyl propionaldehyde, 3-	1	1.72	136.891783	3	1	0	41.948486	0.30932	2.476	-17.81264	-9.5398
104-55-2	Cinnamic aldehyde	4	1.9	130.968193	2	1	0	41.831543	-0.64885	3.369	8.89344	-9.44624
106-23-0	Citronellal, (r)-(+)-	1	3.26	177.206134	5	1	0	49.011894	0.98234	2.914	-59.06848	-9.39153
106-26-3	Cis-citral	4	2.95	171.230179	4	1	0	51.261002	-0.03736	3.977	-33.036	-9.5353
106-72-9	Dimethyl-2-hepten-7-al, 2,6-	1	2.64	160.52715	4	1	0	44.496365	0.94409	2.733	-53.93415	-9.43696
107-22-2	Ethandial	1	-1.66	50.22004	1	2	0	11.829566	-0.81635	0	-55.62293	-10.77962
107-75-5	Hydroxycitronellal	1	1.54	190.988351	7	2	1	47.998024	1.0072	3.72	-126.56885	-10.47749
110-41-8	Aldehyde c12 mna	1	4.85	217.434245	9	1	0	56.813614	0.93886	2.671	-103.44836	-10.43809
111-30-8	Glutaric dialdehyde	1	-0.61	101.541479	4	2	0	24.836775	0.8679	4.835	-80.58523	-10.51699
111-71-7	Heptyl aldehyde	1	2.42	133.133285	5	1	0	34.176964	0.9536	2.671	-72.9481	-10.55426
112-31-2	Aldehyde c10	1	4.01	183.832064	8	1	0	47.723549	0.95283	2.682	-92.96472	-10.54713
112-44-7	Aldehyde c-11 undecylic	1	4.54	200.379035	9	1	0	52.239075	0.94787	2.443	-99.4369	-10.53344
112-45-8	Aldehyde c-11 undecylenic	1	4.05	194.45498	9	1	0	53.354229	0.93921	2.403	-67.33528	-9.96384
112-54-9	Aldehyde c12 lauric	1	5.07	217.008992	10	1	0	56.754612	0.9471	2.458	-106.09949	-10.53303
116-26-7	Trimethyl-2-formyl cyclohexa-2,4-diene, 1,1,3-	4	2.63	159.61864	1	1	0	28.841396	-0.259	2.721	-19.08621	-9.1286
120-57-0	Heliotropine	2	1.05	126.824485	1	3	0	32.769135	-0.62987	2.371	-60.47803	-9.35553
121-32-4	Ethyl vanillin	3	1.8	154.571882	4	3	1	47.36829	-0.42179	4.014	-89.24014	-9.13997
121-33-5	Vanillin	3	1.21	137.233554	3	3	1	42.852764	-0.4757	4.585	-79.14394	-9.11206
122-03-2	Cuminaldehyde	2	2.92	153.703899	2	1	0	45.993134	-0.36568	3.073	-23.60048	-9.72337
122-40-7	Amyl cinnamaldehyde, alpha-	4	4.32	214.901767	6	1	0	55.985523	-0.33608	2.79	-22.31463	-9.40225
122-78-1	Phenylacetaldehyde	1	1.78	119.648857	2	1	0	37.432953	0.18453	2.502	-12.73333	-9.62575
123-11-5	P-anisic aldehyde	2	1.76	128.723711	2	2	0	40.125347	-0.35297	3.901	-42.47205	-9.43577
123-72-8	Butanal	1	0.88	82.396897	2	1	0	20.630377	0.95094	2.608	-52.89957	-10.58241
124-13-0	Octanal	1	2.95	149.706239	6	1	0	38.692497	0.95335	2.674	-79.64273	-10.5509
124-19-6	Nonanal	1	3.48	165.869467	7	1	0	43.208019	0.94865	2.445	-86.0158	-10.53872
124-25-4	Myristaldehyde	1	6.12	251.139982	12	1	0	65.785675	0.94705	2.456	-119.46838	-10.53045
1321-89-7	Dimethyloctanal, 2,6-	1	3.88	183.236258	7	1	0	47.782558	0.95665	2.689	-90.29717	-10.5458
142-83-6	Trans, trans-2,4-hexadien-1-al	4	1.15	103.772114	2	1	0	34.702824	-0.47589	3.696	-9.62159	-9.54809
	Trans-cinnamic aldehyde	4	1.9	130.634531	2	1	0	40.852192	-0.64895	3.369	8.89293	-9.4462
15764-16-6	1-formyl-2,4-dimethyl benzene	2	2.49	136.342106	1	1	0	42.277328	-0.35428	3.158	-20.40981	-9.55323
18031-40-8	Perillaldehyde	4	2.46	160.453804	2	1	0	47.760033	-0.01557	2.962	-22.30662	-9.82933
18127-01-0	Bourgeonal (4-tert-butyl-dihydrocin-namaldehyde)	1	3.55	204.024045	4	1	0	57.632969	0.42108	2.46	-34.01464	-9.17849
18829-55-5	Trans-2-heptenal	4	2.11	126.714245	4	1	0	36.427967	-0.03892	3.427	-43.80499	-10.39978
19009-56-4	Methyl octyl acetaldehyde	1	4.32	200.509925	8	1	0	52.298077	0.94988	2.611	-96.05175	-10.45457
21661-97-2	Cis-7-decenal	1	3.52	177.539159	7	1	0	48.895798	0.92478	2.595	-62.89154	-9.6602
21662-09-9	Decen-1-al, cis-4-	1	3.52	177.679735	7	1	0	48.895794	0.9171	2.213	-61.8437	-9.64914
21662-13-5	Trans, cis-2,6-dodecadien-1-al	1	4.27	205.100744	8	1	0	60.17786	-0.06301	3.516	-46.96011	-9.81007
21834-92-4	2-phenyl-5-methyl-2-hexenal	4	3.66	197.676115	4	1	0	61.528496	-0.14526	3.245	-11.25797	-9.33312

Table 1. (cont.)

CAS#	Name	Class	Log-P	V _m /l ³	Rotl-bonds	HBA	HBD	MR/cm ⁻³	LUMO/eV	Dipole/debye	Hf/kcal	HOMO/eV
2277-19-2	Cis-6-nonenal	1	2.99	160.541166	6	1	0	44.380264	0.93818	2.689	-56.20247	-9.70722
2363-88-4	Decadien-1-al, trans, trans-2,4-	4	3.27	171.530986	6	1	0	52.495258	-0.4602	3.845	-36.07137	-9.51335
26643-91-4	Methyl-2-phenyl-2-pentenal, 4-	4	3.14	181.556255	3	1	0	57.012966	-0.17158	3.155	-5.03141	-9.31782
31906-04-4	Landolal	1	2.15	224.956651	6	2	1	59.540783	0.88672	2.839	-110.69958	-9.50053
35158-25-9	2-isopropyl-5-methyl-2-hexenal	4	3.21	176.940555	4	1	0	50.149662	0.04095	3.045	-55.44854	-9.9883
3913-71-1	Trans-2-decenal	4	3.69	177.463256	7	1	0	49.97456	-0.03902	3.452	-63.82266	-10.39761
4313-03-5	2,4-heptadienal	4	1.68	120.637127	3	1	0	39.218353	-0.36716	2.855	-16.2419	-9.46436
4501-58-0	Trimethylcyclopentenyl acetaldehyde	1	2.94	166.89833	2	1	0	44.498268	0.94645	2.671	-34.72317	-9.77701
472-66-2	Homocyclocitral, beta-	1	3.5	182.887343	2	1	0	49.009995	0.8119	2.782	-51.05398	-9.29751
	Formalin	1	0.35	31.159754	0	1	0	7.026683	0.83574	2.293	-30.41206	-10.8206
5392-40-5	Citral	4	2.95	171.111346	4	1	0	51.261002	-0.06286	3.638	-34.51034	-9.4786
5406-12-2	P-methyl hydrocinnamic aldehyde	1	2.22	153.839888	3	1	0	47.322739	0.30292	2.667	-25.3714	-9.28029
623-36-9	Methyl-beta-ethyl acrolein, alpha-	4	1.36	109.428565	2	1	0	31.969543	0.00348	3.121	-36.97755	-10.03072
66-25-1	Caproaldehyde	1	1.78	115.878244	4	1	0	29.661436	0.95397	2.653	-66.25461	-10.55907
6728-26-3	Propyl acrolein, beta-	4	1.58	109.814344	3	1	0	31.642748	-0.04043	3.395	-37.13708	-10.40071
6789-80-6	Cis-3-hexenal	1	1.41	110.086975	3	1	0	30.833675	0.88296	2.587	-36.10155	-9.95666
68039-49-6	Acroval	1	2.36	148.934931	1	1	0	41.322186	0.93552	2.538	-45.74892	-9.3714
7492-44-6	Butyl cinnamic aldehyde	4	3.79	198.284542	5	1	0	42.928974	-0.38624	2.709	-12.04336	-9.38347
764-39-6	Ethyl acrolein, 3-	4	1.05	92.915648	2	1	0	27.396908	-0.04538	3.359	-30.45162	-10.40825
78-84-2	Isobutyric aldehyde	1	0.61	81.916007	1	1	0	20.689375	0.95154	2.509	-50.74453	-10.50549
8028-48-6	Dimethyl-10-methylene-2,6,11-dodecatrienal, 2,6- (natural)	1	4.47	243.884619	8	1	0	77.744179	-0.03675	2.957	-0.52338	-9.37924
80-54-6	Para-tert-butyl-alpha-methylhydrocinnamic aldehyde	4	3.86	220.868294	4	1	0	62.207512	0.56657	2.356	-35.70348	-9.04111
90-02-8	Hydroxybenzaldehyde, 2-	2	1.81	111.210136	2	2	1	34.256245	-0.52945	1.591	-45.94507	-9.53394
93-53-8	Alpha-methyl phenylacetaldehyde	1	2.09	136.777897	2	1	0	42.007481	0.21526	2.478	-15.1367	-9.56826
97-96-1	Diethyl acetaldehyde	1	1.67	116.142056	3	1	0	29.720436	0.98042	2.465	-61.58178	-10.39462
98-01-1	Furfuraldehyde, alpha-	2	0.41	84.494569	1	2	0	13.664425	-0.26023	3.155	-7.87719	-9.6627
	3-(3-hydroxy-3-methyl-butyl-cyclohex-3-enecarbaldehyde	1	1.62	207.990936	5	2	1	55.025257	1.04303	1.482	-101.54791	-9.12691
	3,5-dimethyl-cyclohex-3-enecarbaldehyde	1	2.36	149.000978	1	1	0	41.322189	0.91651	2.454	-46.70276	-9.44447

selected from these classes for LLNA testing, data for previously tested aldehydes from [11] were added to the resulting dataset.

LLNA tests were conducted using a 4:1 acetone:olive oil vehicle to generate dose-response data for the aldehydes in order to determine EC3 values. The EC3 value, expressed as a weight % was converted into a molar basis by dividing by the molecular weight. The negative logarithm of this molar EC3, $\text{Log}(1/\text{EC3})$ (or pEC3) is a quantitative measure of sensitizing potential. Using these experimentally derived $\text{Log}(1/\text{EC3})$ values we investigated how sensitization potential varied with chemical reactivity and lipophilicity. Chemical reactivity of these aldehydes was modelled conveniently using Taft σ^* values. The Taft σ^* constant for a substituent R is a measure of the inductive effect of R. The σ^* values used here are taken from the extensive compilation by Perrin et al. [14]. Lipophilicity was modelled by Log P . Log P values were computed using Clog P (Version 4, BioByte Corp.). Modified Log P took into account the branching effects of the methyl or ethyl (e.g., for diethyl acetaldehyde, CAS No. 97-96-1) groups on a straight alkyl chain by applying the position dependent branching factor [15]. Average values were used for the repeat EC3 measurements.

3 Results and Discussion

3.1 Assessment of Relative Potency of the Schiff Base aldehydes

The 11 Class 1 Schiff Base aldehydes tested are listed in Table 2 in addition to two Class 4 Michael addition aldehydes which we considered to be sufficiently deactivated as such that they would preferentially act as Schiff Base formers. Myristaldehyde was tested but failed to generate an EC3 value.

Landolal (Lyr^{al}) (CAS No. 31906-04-4) and hydroxycitronellal (CAS No. 107-75-5) both have tertiary hydroxyl

groups, which were expected to be very susceptible to acid catalysed dehydration *in vivo*. Therefore the log P values used for the QSAR are those for the corresponding olefinic dehydration products. Landolal (Lyr^{al}) and hydroxycitronellal both fitted the Schiff base QSAR very well when entered as the olefinic derivatives (Figure 2).

Citral (CAS No. 5392-40-50) and farnesal (CAS No. 502-67-0) also fitted the Schiff base QSAR indicating that they were so deactivated sterically as Michael acceptors that they react as Schiff bases instead.

Regression analysis yielded a good correlation. The QSAR equation (1) was:

$$\text{Log}(1/\text{EC3}) = 0.25 + 0.28 * \text{Modified-Log-P} + 0.86 * \text{R } \sigma^* (1) \\ n = 12 \text{ R}^2 = 0.825 \text{ s} = 0.17 \text{ F} = 21.2$$

The plot of measured and predicted values is shown in Figure 3.

Previous work by Roberts et al. [13] established a RAI based combined (Q)SAR/dose response relationship for a small dataset of α,β -diketones where RAI was defined as

$$\text{RAI} = \text{Log}(\text{D/M}) + \text{RP} + 0.5 \text{Log P}$$

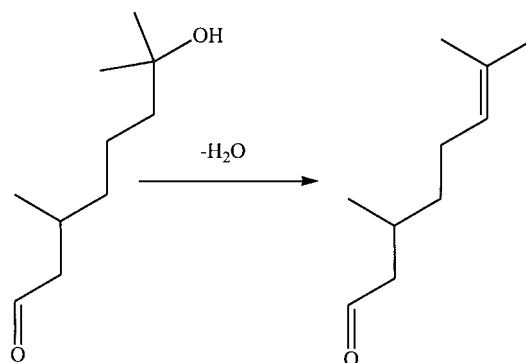


Figure 2. Proposed mechanism for the loss of water from aldehydes possessing a terminal hydroxy group

Table 2. Schiff base (SB) aldehydes tested using LLNA

Name	CAS Number	EC3%	$\text{Log}(1/\text{EC3})$	Modified-LOG-P	R σ^*
Cyclamen aldehyde	103-95-7	20.5	0.968	2.86	-0.16
Glyoxal	107-22-2	1.4	1.618	-1.66	2.15
Hydroxycitronellal	107-75-5	25.25	0.834	0.94	-0.19
2-Methylundecanal	110-41-8	10	1.266	4.55	-0.19
Undec-10-enal	112-45-8	6.8	1.394	4.05	-0.23
Myristaldehyde (a)	124-25-4	*		6.12	-0.23
Cis-6-nonenal	2277-19-2	23.1	0.783	2.99	-0.25
Landolal (Lyr ^{al})	31906-04-4	17.1	1.09	1.85	-0.19
Para-tert-butyl- α -methylhydrocinnamic aldehyde	80-54-6	19.7	1.016	2.96	-0.16
α -Methylphenylacetaldehyde	93-53-8	6.3	1.328	1.79	0.37
Diethyl acetaldehyde	97-96-1	68.15	0.167	1.1	-0.19
Citral (b)	5392-40-5	13.2	1.062	2.35	0.19
Farnesal (b)	502-67-0	11.7	1.275	4.081	0.19

(a) Myristaldehyde failed to generate an EC3 value as the material was insoluble in the vehicle. This compound has been therefore excluded from the mathematical analyses.

(b) Deactivated Michael addition reacting aldehydes included in the final Schiff base QSAR

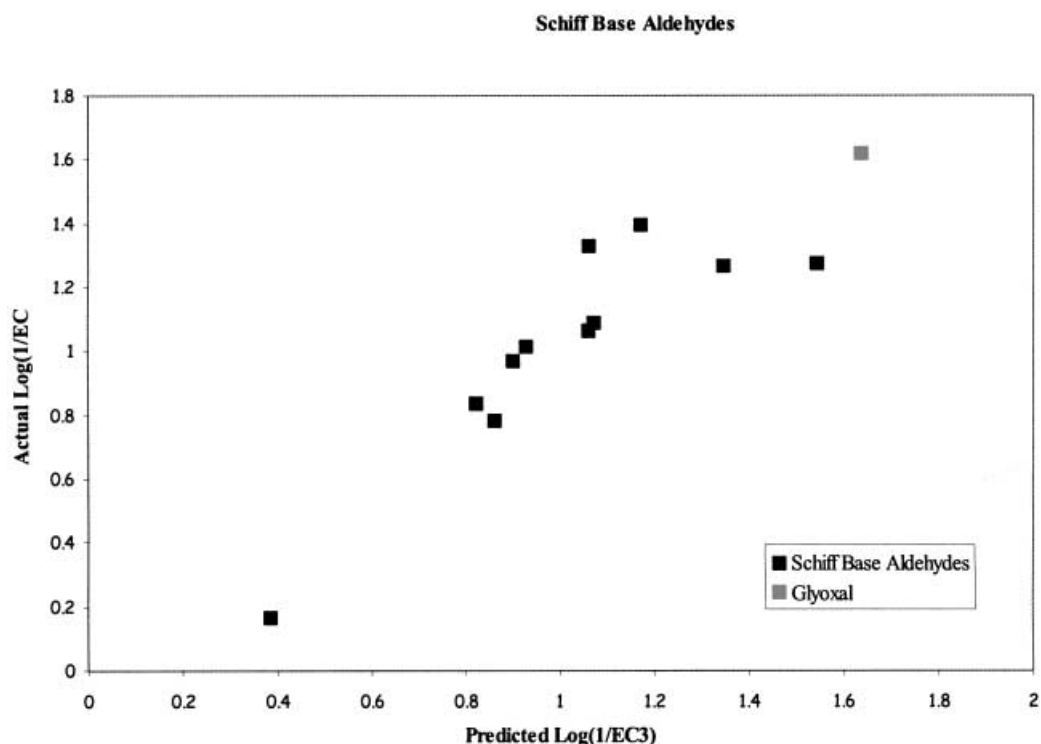


Figure 3. Structure activity relationship for mechanistically related Schiff base aldehydes

Table 3. pEC3 QSAR predictions for 1,2-diketones (DK)

Compound	pEC3 (DK/QSAR)
Furil	0.802
Camphorquinone	1.557
Butane-2,3-dione	0.792
PhCOCOMe	2.302
glyoxal	1.402

Table 4. Comparison of Schiff base (SB) and DK pEC3 QSAR predictions

Name	LogP	σ^*	SB-pEC3	DK-pEC3
butane-2,3-dione	-1.22	1.32	1.044	0.792
PhCOCOMe	1.02	1.71	2.003	2.302
camphorquinone	0.69	1.13	1.411	1.557
furil	1.42	0.01	0.648	0.802

D is the concentration in weight % and M is the molecular weight.

Like α,β -diketones, Schiff base aldehydes can react with skin proteins either by simple Schiff base formation and there is also the possibility of a cyclisation reaction with guanidine units as proposed by Bundgaard [16] α,β -Diketones possess the general structure R_1COCOR_2 , where at least one of the carbonyl groups reacts directly. A reasonable QSAR model was achieved using stimulation indices (SI indices) for all four α,β -diketones. The DK/QSAR (2) equation was:

$$\text{Log (T/C)} = 0.50 \text{ RAI} + 0.24 \quad (2)$$

$$n = 11, R^2 = 0.963, s = 0.09, F = 235$$

Glyoxal (CAS No. 107-22-2), a 1,2-dial was found to fit well in the Schiff base aldehyde QSAR. This compound like the 1,2-diketones has the potential to react by Schiff base

formation or with guanidine as per the Bundgaard [16] route. This suggested that perhaps the Schiff Base aldehydes and the 1,2-diketones could sensitize via the same reaction mechanism.

The DK/QSAR (3) was modified to account for reaction at the acetyl for PhCOCOMe.

$$\text{Log (T/C)} = 0.60 \text{ RAI} + 0.23 \quad (3)$$

$$n = 11, R^2 = 0.944, s = 0.11, F = 152.1$$

A prediction was made using this modified QSAR for glyoxal. pEC3 from the DK/QSAR gave a value of 1.402 for glyoxal compared with the experimental value of 1.61. These pEC3 values appear to agree reasonably well.

The four 1,2-diketones were hence predicted with the Schiff base QSAR. pEC3 values for the four 1,2-diketones were first derived using the DK/QSAR. The values are given in Table 3. These values were compared with pEC3 values

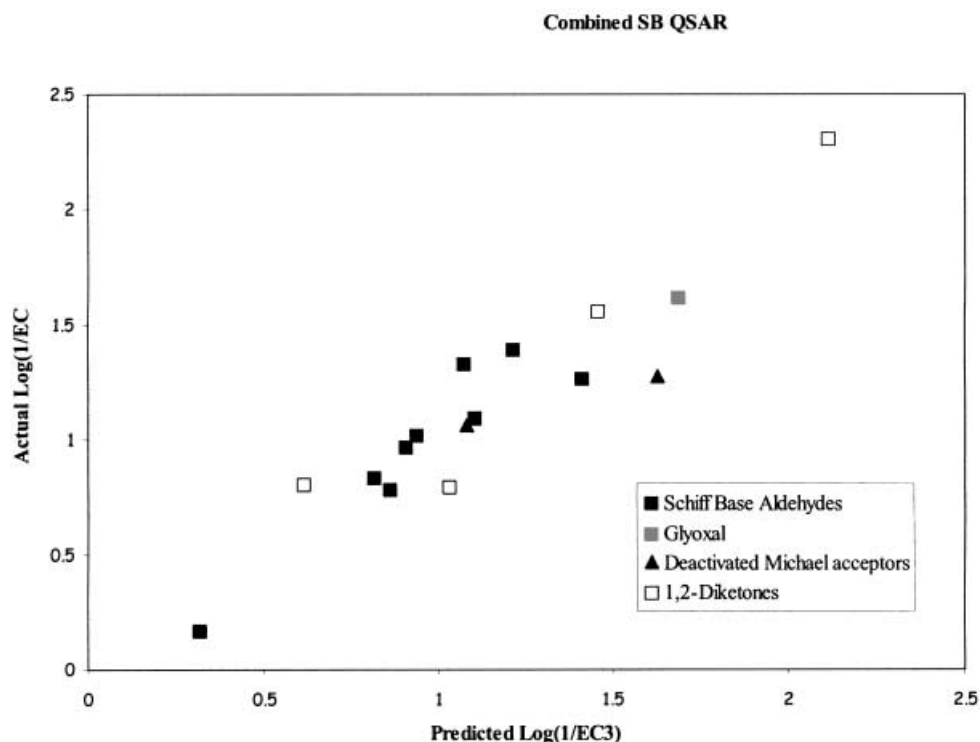


Figure 4. Structure activity relationship for mechanistically related Schiff base aldehydes and 1,2-diketones

estimated using the SB/QSAR. In order to make the comparison the Taft σ^* values were modified to account for the presence of a ketone group by subtraction of 0.49 (the σ^* value of hydrogen). The predictions shown in Table 4 show reasonable correlations implying that the Schiff base QSAR for aldehydes could be potentially extended to include 1,2-diketones. These initial findings suggest that for skin sensitization, chemicals are perhaps better classified in terms of their reaction chemistry rather than in terms of their functional groups.

The pEC3 values of the Schiff Base aldehydes and 1,2-diketones were then combined to investigate the feasibility of a new overall QSAR (Figure 4).

The regression equation (4) takes the form:

$$\text{pEC3} = 0.16 + 0.32 \cdot \text{Log-P} + 0.96 \cdot \sigma^* \quad (4)$$

$$n = 16, R^2 = 0.873, s = 0.18, F = 44.5$$

4 Conclusions

These initial findings suggest that both aldehydes and 1,2-diketones sensitize via the same rate-determining step. If the diketones sensitize via heterocyclic formation resulting from attack of guanidine, it follows that guanidine units must be the nucleophiles for Schiff base aldehydes as well. This seems to us inherently unlikely (as guanidine is more highly protonated than lysine), and it seems more plausible

that both aldehydes and 1,2-diketones react by Schiff base formation with lysine units.

Despite the structural diversity between and within the two sets of carbonyl compounds, the differences in sensitization potential are well explained solely by differences in chemical reactivity and partitioning. It appears that the criterion for congenericity is having the same rate determining reaction chemistry rather than a common functional group.

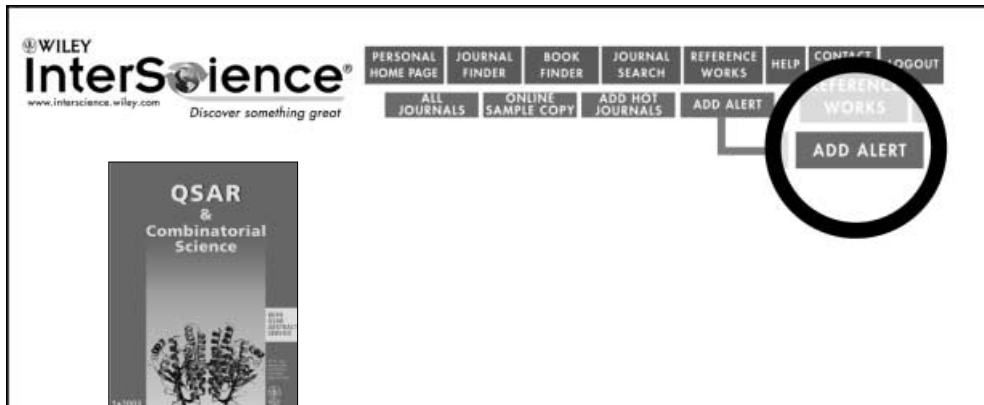
These initial findings indicate that for skin sensitization, chemicals should be classified by their reaction mechanisms rather than their functional groups. More carbonyl compounds need to be identified in order to investigate this potential generic extension. This is the subject of ongoing work.

References

- [1] Barratt, M. D., Basketter, D. A. and Roberts, D. W. in: Lepoittevin, J-P., Basketter, D.A., Goossens, A., Karlberg, A-T., (Eds.), *Allergic Contact Dermatitis, the Molecular Basis, Structure-Activity Relationships for contact hypersensitivity*, Springer, Heidelberg, 1997, pp. 129–154.
- [2] Ashby, J., Basketter, D. A., Paton, D., Kimber, I., Structure activity relationships in skin sensitization using the murine local lymph node assay, *Toxicology* 103(3), 177–94 (1995).
- [3] Payne M. P., Walsh P. T. Structure-activity relationships for skin sensitization potential: development of structural alerts

- for use in knowledge-based toxicity prediction systems. *J Chem Inf Comput Sci.* 34(1), 154–61 (1994).
- [4] Roberts, D. W. and Williams, D. L., The derivation of quantitative correlations between skin sensitization and physico-chemical parameters for alkylating agents and their application to experimental data for sultones, *J. Theor. Biol.* 99, 807–825 (1982).
- [5] Hansch, C. and Leo, A., *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley-Interscience, (1979).
- [6] Roberts, D. W., Structure activity relationships for skin sensitization potential of diacrylates and dimethacrylates, *Contact Dermatitis* 17(5), 281–289 (1987).
- [7] Roberts, D. W. and Benezra, C., Quantitative structure activity relationships for skin sensitization potential of urushiol analogues, *Contact Dermatitis* 29(2), 78–83 (1993).
- [8] Roberts, D. W. and Basketter, D. A., Quantitative structure activity relationships: sulfonate esters in the LLNA, *Contact Dermatitis* 42(3), 154–161 (2000).
- [9] Basketter, D. A., Roberts, D. W., Cronin, M. T. D and Scholes, E. W., The value of the local lymph node in quantitative structure activity investigations. *Contact Dermatitis* 27, 137–142 (1992).
- [10] Basketter, D. A., Gerberick, G. F., Kimber, I. and Loveless, S. E., The local lymph node assay: a viable alternative to currently accepted skin sensitisation tests. *Food and Chemical Toxicology* 34, 331–336 (1996).
- [11] Patlewicz, G., Basketter, D. A., Smith, C. K., Hotchkiss, S. A. M. and Roberts, D. W., Skin-sensitization structure-activity relationships for aldehydes, *Contact Dermatitis* 44, 331–336 (2001).
- [12] Patlewicz, G., Wright, Z., Basketter, D. A., Pease, C., Lepoittevin, J-P. and Giménez Arnau, E. Structure-activity relationships for selected fragrance allergens, *Contact Dermatitis* 47(4), 219–226 (2002).
- [13] Roberts, D. W., Basketter, D. A. and York, M., Structure-activity relationships in the murine local lymph node assay for skin sensitization: α,β -diketones, *Contact Dermatitis* 41, 14–17 (1999).
- [14] Perrin, D. D., Dempsey, B., Serjeant, E. P., *pKa prediction for organic acids and bases*. London, Chapman and Hall, 1981, pp. 109–126.
- [15] Roberts, D. W. and Marshall, S. J., Applications of hydrophobicity parameters to prediction of the aquatic toxicity of commercial surfactant mixtures, *SAR and QSAR in Env. Res.* 4, 167–76 (1995).
- [16] Bundgaard, H., The possible implication of steroid-glyoxal degradation products in allergic reactions to corticosteroids, *Arch. Pharm. Chem. Sci. Ed.* 8, 83–90 (1980).

Received on June 24, 2002; Accepted on September 20, 2002



The image shows a screenshot of the Wiley InterScience website. At the top, the Wiley logo and 'InterScience' branding are visible. Below this is a navigation bar with buttons for 'PERSONAL HOME PAGE', 'JOURNAL FINDER', 'BOOK FINDER', 'JOURNAL SEARCH', 'REFERENCE WORKS', 'HELP', 'CONTACT', and 'LOGOUT'. A secondary bar contains 'ALL JOURNALS', 'ONLINE SAMPLE COPY', 'ADD HOT JOURNALS', and 'ADD ALERT'. The 'ADD ALERT' button is circled in black. Below the navigation bar is a thumbnail image of the 'QSAR & Combinatorial Science' journal cover. The main text area contains the heading 'Tables of Contents by E-Mail' followed by a paragraph explaining the free email alert service. At the bottom, a black bar contains the URL 'www.interscience.wiley.com/alerts'. A vertical text string '44303023_vo' is visible on the right side of the page.

Tables of Contents by E-Mail

Find out what's in the latest issue through automatic notification. Wiley InterScience now offers free content alerts to all Registered Users – no subscription required. To activate your e-mail alerts for this journal, login to Wiley InterScience, go to the journal, and click on the ADD ALERT button on the “Available Issues” page.

www.interscience.wiley.com/alerts