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Authors

ABRAHAM, MICHAEL H
KUMARSINGH, RACHEL
COMETTO-MUNIZ, J. ENRIQUE
et al.

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Draize eye scores and eye irritation thresholds in man can be combined into one QSAR.

MICHAEL H. ABRAHAM[1], RACHEL KUMARSINGH[1], J. ENRIQUE COMETTO-MUÑIZ[2], AND WILLIAM S. CAIN[2]

[1]Department of Chemistry, University College London, 20 Gordon Street, London WC1H OAJ, UK

[2]Chemosensory Perception Laboratory, Department of Surgery (Otolaryngology), University of California, San Diego, La Jolla, CA 92093-0957, USA

Abstract

Draize eye scores (DES) of 37 pure organic liquids have been converted into scores for the corresponding vapors, DES/P^0, where P^0 is the liquid vapor pressure in atmospheres at 298K. It is shown that there is a constant difference of 6.7 between values of $\log(DES/P^0)$ and log(1/ET), where ET is the eye irritation threshold in ppm of eight vapors for human subjects. The 37 $\log(DES/P^0)$ values can be combined with log(1/ET) values for 17 vapors into one QSAR for sensory potency (SP) using our general solvation equation,

$$\log SP = -7.979 + 1.016\pi_2^H + 3.678 \sum(alpha)_2^H + 1.730 \sum(beta)_2^H + 0.838 \log L^{16}$$

$$n = 54, \quad r2 = 0.924, \quad sd = 0.369, \quad F = 149.3,$$

where π_2^H is the compound polarizability-dipolarity, $\sum(alpha)_2^H$ and $\sum(beta)_2^H$ are the compound hydrogen-bond acidity and basicity, and $\log L^{16}$ is the gas-hexadecane partition coefficient. n is the number of data points, r the correlation coefficient, sd the standard deviation, and F the F-statistic. LogSP is then either $\log(DES/P^0 - 6.7)$, or log(1/ET), confirming the result for the eight common compounds. It is suggested that eq. i can be used to predict eye irritancy of organic vapors and pure liquids. It is further suggested that for the compounds in the data set, the main process in eye irritation is transfer of the compound from the vapor or pure liquid to a biological phase, and a number of chemical properties of the biological phase have been mapped out through eq. i. These properties are consistent with corresponding properties for a number of organic liquid phases.

This work concerns the use of a quantitative structure-activity relationship (QSAR) to account for eye irritation in humans and rabbits. The data for humans comprised eye irritation thresholds (EIT). The data for rabbits comprised scores on the Draize test, and in particular a set of scores used by various researchers to search for chemical or molecular correlates of ocular inflammation. The human and animal data differed in an important way. The human data came from vapor-phase stimulation with various volatile organic compounds (VOCs), whereas the animal data came from direct application of VOCs as bulk liquids. The two sets had eight members in common. In order to compare the sets, we expressed the Draize scores relative to the saturated vapor pressures of the VOCs which essentially converted the data into scores for vapor stimulation. We then inquired whether a QSAR based upon solvation energy could describe both sets of data. This QSAR has already shown itself able to describe human nasal irritation thresholds[1]. Its extension to the description of Draize scores adds substantially to its usefulness. The particulars of the comparison follow.

Draize eye scores (DES) for 37 pure organic liquids[2] were converted into scores for the corresponding vapors, DES/P^o, where P^o is the liquid vapor pressure in ppm at 298K. After that conversion, there was a constant difference (0.66) between values of log(DES/P^o) and log(1/EIT), where EIT is the eye irritation threshold in ppm of eight vapors for human subjects. The 37 log(DES/P^o) values can be combined with 17 log(1/EIT) values[3] to give one QSAR for sensory potency (SP) using our general solvation equation[4],

$$\log SP = - 7.918 - 0.482\, R_2 + 1.420\, \pi_2^H + 4.025\, \sum\alpha_2^H + 1.219\, \sum ß_2^H + 0.853\, \log L^{16} \quad (1)$$

$$n = 54, \quad r^2 = 0.93, \quad sd = 0.36, \quad F = 124$$

where R_2 is an excess molar refraction, π_2^H is the compound polarizability/dipolarity, $\sum\alpha_2^H$ and $\sum ß_2^H$ are the compound hydrogen-bond acidity and basicity, and L^{16} is the gas-

hexadecane partition coefficient at 298K; n equals the number of data points, r the correlation coefficient, sd the standard deviation, and F the F-statistic. LogSP is then either [log(DES/P^o) - 0.66], or log(1/EIT). A plot of logSP(obs) vs logSP(calc) on eq. 1 appears as Fig.1, with the substances listed in Table 1. The scatter appears random along the line of identity, confirming the result suggested by the eight common compounds.

Eq. 1 therefore encompasses two quite different measures, the Draize eye test on rabbits and eye irritation thresholds on human subjects. To our knowledge this is the first time that Draize scores have been satisfactorily matched to any *in vivo* test, let alone to tests on human subjects.

The quest for structure-activity relationships between chemical or molecular properties and Draize scores has focused on liquid-phase stimulation. Fig. 1 shows that vapor and liquid phase stimulation have comparable bases. The solvation equation can serve to describe liquid-phase stimulation (logDES) by the following relationship:

$$\log(\text{DES, calc}) = \log(\text{SP, calc on eq.1}) + 0.66 + \log P^o \qquad (2)$$

For the 37 compounds with DES scores used in eq.1, the calculated log(DES) scores reproduce the observed values to 0.33 log units,

$$\log(\text{DES, obs}) = -0.028 + 1.036 \log(\text{DES, calc}) \qquad (3)$$

$$n = 37, \quad r^2 = 0.74, \quad sd = 0.33, \quad F = 98$$

In view of the large errors associated with observed DES values[5], this agreement is as good as can be expected. Whatever the limitations based upon the reliability of the data, the fit of eq. 3 to DES exceeds that of any previous QSAR by a considerable margin. Equation 3 accounts for 74% of the variance in observed logDES.

The success of the present approach suggests that for the compounds in this set, the main process in eye irritation involves transfer of the compound from the vapor or pure liquid to a biophase, and a number of chemical properties of the biophase have been implicated through eq. 1. These are consistent with corresponding properties for a number of organic phases, which could then effectively simulate the biophase for eye irritation. For a number of terpenes not included in the present set, log(1/EIT) predicted on eq. 1 shows the same trend as that of the observed values[6].

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References

1. ABRAHAM, M.H. *et al*. 1996. An analysis of nasal irritation thresholds using a new solvation equation. Fund. Appl. Toxicol. **31**: 71-76.

2. CRONIN, M.T.D., D.A. BASKETTER & M. YORK. 1994. A quantitative structure-activity relationship (QSAR) investigation of a Draize eye irritation database. Toxicol. in Vitro **8**: 21-28.

3. COMETTO-MUÑIZ, J.E. & W.S. CAIN. 1995. Relative sensitivity of the ocular trigeminal, nasal trigeminal, and olfactory systems to airborne chemicals. Chem. Senses **20**: 191-198.

4. ABRAHAM, M.H. 1994. Scales of solute hydrogen-bonding: their construction and application to physicochemical and biochemical processes. Chem. Soc. Revs. **22**: 73-83.

5. BALLS, M. *et al*. 1995. The EC/HO international validation study on alternatives to the Draize eye irritation test. Toxicol. in Vitro **9**: 871-929.

6. COMETTO-MUÑIZ, J.E. *et al*. 1997. Sensory properties of selected terpenes: Threshold for odor, nasal pungency, nasal localization, and eye irritation. Ann. N.Y. Acad. Sci. (this volume).

TABLE 1. Draize Eye Scores (DES) referred to saturated vapor pressure (P°) and human eye irritation thresholds (EIT), indicated by H, for human, after the stimuli. The second column of data contains the observed values in Figure 1 and the third column the calculated values.

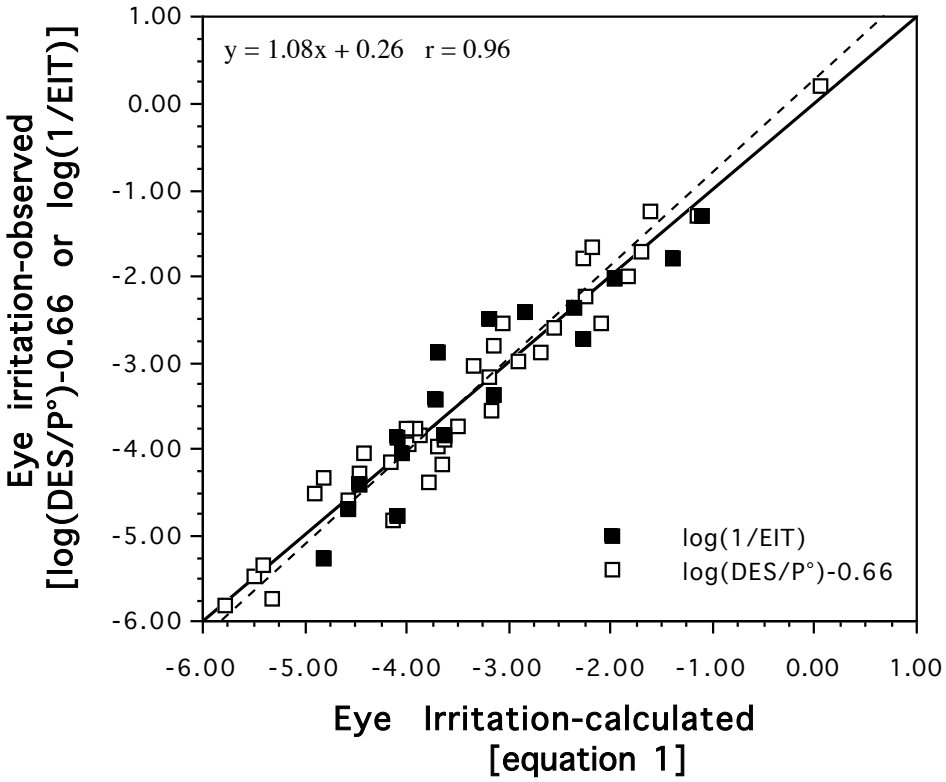
Stimuli	log(DES/P°) or log(1/EIT)	log(DES/P°)–0.66 or log(1/EIT)	calculated (eq.1)
Ethanol (H)	–4.76	–4.76	–4.10
Propan–1–ol (H)	–3.84	–3.84	–3.63
Butan–1–ol (H)	–3.37	–3.37	–3.14
Hexan–1–ol (H)	–2.71	–2.71	–2.27
Octan–1–ol (H)	–1.78	–1.78	–1.40
Ethyl acetate (H)	–4.69	–4.69	–4.57
Butyl acetate (H)	–2.87	–2.87	–3.69
Hexyl acetate (H)	–2.41	–2.41	–2.83
Octyl acetate (H)	–2.02	–2.02	–1.96
Decyl acetate (H)	–1.30	–1.30	–1.10
Propanone (H)	–5.27	–5.27	–4.81
Pentan–2–one (H)	–4.05	–4.05	–4.05
Heptan–2–one (H)	–2.49	–2.49	–3.18
Nonan–2–one (H)	–2.35	–2.35	–2.35
Toluene (H)	–4.41	–4.41	–4.46
Ethylbenzene (H)	–3.87	–3.87	–4.08
Propylbenzene (H)	–3.43	–3.43	–3.71
Methyl trimethylacetate	–4.16	–4.82	–4.13
Ethyl trimethylacetate	–3.51	–4.17	–3.66
Butyl acetate	–3.30	–3.96	–3.69
Ethyl acetate	–3.92	–4.58	–4.57
2–Ethoxyethylacetate	–2.21	–2.87	–2.68
Ethyl 2–methylacetoacetate	–1.58	–2.24	–2.24
Methyl acetate	–3.86	–4.52	–4.90
2,2–Dimethylbutanoic acid	–0.64	–1.30	–1.14
Glycerol	0.86	0.20	0.05
Propan–2–ol	–3.27	–3.93	–3.99
2–Ethylhexan–1–ol	–0.58	–1.24	–1.61
2–Methylpropan–1–ol	–2.36	–3.02	–3.34
Butan–1–ol	–2.13	–2.79	–3.14
Hexan–1–ol	–1.13	–1.79	–2.27
2–Butoxyethanol	–1.33	–1.99	–1.84
Cyclohexanol	–1.00	–1.66	–2.18
4–Bromophenetole	–1.88	–2.54	–2.09
1,3–Diisopropylbenzene	–2.32	–2.98	–2.90
sec–Butylbenzene	–3.08	–3.74	–3.49
3–Ethyltoluene	–3.22	–3.88	–3.63
2,4–Difluoronitrobenzene	–1.94	–2.60	–2.55
Styrene	–3.11	–3.77	–3.92
Toluene	–3.62	–4.28	–4.46
m–Xylene	–3.11	–3.77	–4.01
4–Fluoroaniline	–1.06	–1.72	–1.70
3–Methylhexane	–5.08	–5.74	–5.32
2–Methylpentane	–5.14	–5.80	–5.78
Deca–1,9–diene	–3.17	–3.83	–3.88

Stimuli	log(DES/P°) or log(1/EIT)	log(DES/P°)-0.66 or log(1/EIT)	calculated (eq.1)
Dodecane	-1.89	-2.55	-3.06
1,5-Dimethylcyclooctadien	-2.90	-3.56	-3.17
Cyclooctene	-3.48	-4.14	-4.16
Methylcyclopentane	-4.69	-5.35	-5.40
Hexa-1,5-diene	-4.80	-5.46	-5.49
4-Methylpentan-2-one	-3.73	-4.39	-3.79
Heptan-2-one	-2.49	-3.15	-3.18
Butanone	-3.38	-4.04	-4.43
Propanone	-3.67	-4.33	-4.81

Figure Legend

Figure 1. Observed vs. calculated eye irritation values for the substances listed in Table 1. The observed values are either derived from Draize eye scores (DES) (empty squares) or reflect the reciprocal of eye irritation thresholds (EIT) in humans (filled squares). The unbroken line represents the line of identity. The broken line represents the obtained relationship including all data with its equation shown at the top of the graph.

FIGURE 1


y = 1.08x + 0.26 r = 0.96
log(1/EIT)
log(DES/P°)-0.66
Eye irritation-observed
[log(DES/P°)-0.66 or log(1/EIT)]
Eye Irritation-calculated
[equation 1]
1.00
0.00
-1.00
-2.00
-3.00
-4.00
-5.00
-6.00
-6.00
-5.00
-4.00
-3.00
-2.00
-1.00
0.00
1.00

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