Short communications

Correlation of the cardiac sensitizing potential of halogenated hydrocarbons with their physicochemical properties

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The cardiac sensitizing potencies of a range of 14 halogenated hydrocarbons were assessed in conscious dogs by comparing the partial pressures (Pcs) needed to sensitize the heart to adrenaline. These were found to be directly related to their saturated vapour pressures (Ps) and the ratio Pcs/Ps was approximately constant although the values of partial pressures differed nearly 700-fold. It is suggested that cardiac sensitization is probably a structurally non-specific action and may be regarded as another example of physical toxicity.

Cardiac sensitization is an increased susceptibility of the heart to catecholamines, resulting in arrhythmias such as ventricular fibrillation or ventricular tachycardia. It has been shown to occur after the inhalation of a wide range of unsubstituted or halogenated hydrocarbons (Reinhardt, Azar, Maxfield, Smith & Mullins, 1971) and is a well known phenomenon in the field of anaesthetics. It has recently been the subject of detailed toxicological investigations following the suggestion that it was responsible for the sudden deaths of asthmatics using isoprenaline and a halogenated hydrocarbon pressurizing agent as an aerosol spray (Silverglade, 1972).

Although many chemicals have been studied in attempts to correlate cardiac sensitizing activity with chemical structure, no general pattern has emerged. Suggestions have been made that the degree of saturation (Carr, Burgison, Vitcha & Krantz, 1949), the molecular size and shape (Burgison, O'Malley, Heisse, Forest & Krantz, 1955), the degree and type of halo-

genation (Reinhardt *et al.*, 1971), or the carbon-halogen interatomic distance (Hopkins & Krantz, 1968) may be important.

In a recent series of experiments on the toxicity of the fluorinated hydrocarbons used as aerosol propellants, fire extinguishants and solvents (Clark & Tinston, 1972; Beck, Clark & Tinston, 1973) we observed that whereas cardiac sensitization could not be related to chemical structure, it did seem to be related to the physicochemical properties of the molecule. The present paper, therefore, describes the results of a more detailed investigation of this observation, using a range of chemical types, varying widely in their boiling points.

Methods.—Conscious beagle dogs (10–13 kg body weight) were exposed to atmospheres of the chemicals by means of a face mask. Oxygen was added when high concentrations of chemicals were used. During the last 10 s of the 5 min exposure period a bolus injection of adrenaline (5 µg/kg) was given via a cephalic vein, and the E.C.G. (lead II) changes were recorded. A further injection of adrenaline was also given 10 min after the end of exposure. As a control injection of adrenaline given during air exposure often produced some unifocal ventricular ectopic beats, only the appearance of more serious arrhythmias such as multifocal ventricular ectopic beats or ventricular fibrillation was taken as evidence of cardiac sensitization. Several dose levels of the chemical being tested were used, each differing by a factor of two, and the concentration at which 50% of the animals could be sensitized (EC₅₀ cardiac sensitization) calculated by the moving average interpolation technique of Thompson (1947). Separate groups of 4 to 7 dogs were used at each dose level.

Results.—None of the chemicals produced cardiac arrhythmias on inhalation without an injection of adrenaline, but all were able to cause cardiac sensitization when the adrenaline was injected during exposure to a sufficiently high concentration. The post exposure injection of adrenaline, however, never resulted in arrhythmias even when it followed a challenge injection that had caused ar-

TABLE 1. Concentrations of the chemicals causing cardiac sensitization and their physicochemical properties

Chemical	EC ₅₀ cardiac sensitization and 95% confidence intervals (volume %)	Molecular weight	Boiling point (°C)	Vapour pressure at 37°C (mmHg)	Partial pressure at EC ₅₀ (mmHg)	Relative saturation for cardiac sensitization Pcs/Ps
Tetrachlorodifluoromethane	CFCl ₃ CFCl ₂	206	93	99	2	0.02
Carbon tetrachloride	CCl ₄	156	77	190	4	0.02
Trichloroethane	CH ₃ CCl ₃	135	74	210	6	0.03
Haloethane	CF ₃ CHCl Br	198	50	480	15	0.03
Trichlorotrifluoroethane	CFCl ₂ CF ₂ Cl	189	48	524	8	0.02
Methylene chloride	CH ₂ Cl ₂	86	40	661	18	0.03
Trichlorofluoromethane	CFCl ₃	139	24	1186	10	0.01
Dichlorofluoromethane	CHCl ₂	104	9	2052	19	0.01
Dichlorotetrafluoroethane	CF ₂ ClCF ₂ Cl	172	4	2310	76	0.03
Vinylchloride	CH ₂ :CHCl	63	-14	4218	38	0.01
Dichlorodifluoroethane	CF ₂ Cl ₂	122	-30	6764	61	0.01
Propane	CH ₃ CH ₂ CH ₃	44	-42	9538	153	0.02
Bromotrifluoromethane	CF ₃ Br	149	-58	15276	153	0.01
Chlorotrifluoromethane	CF ₃ Cl	105	-81	40698**	610	0.02

*Estimate (3/6 showed cardiac sensitization); **extrapolated.

rhythmias. As these hydrocarbons are rapidly eliminated from the body following a brief exposure (Clark & Tinston, 1972; Morgan, Black, Walsh & Belcher, 1972), cardiac sensitization would therefore seem to be only a transient phenomenon dependent on some temporary interaction between the effects of the chemical and the adrenaline, and not to structural damage of the heart cells.

The chemicals varied widely in their ability to cause cardiac sensitization (Table 1), their EC_{50} 's ranging from 0.4–12% to 80% in the inspired air. The cardiac sensitizing potency could not be correlated with the molecular structure, the degree of fluorination, the degree of saturation or the molecular weight, but was directly related to the saturated vapour pressure or inversely related to the boiling point.

Discussion.—A direct relationship between vapour pressure and narcotic potency is well known for anaesthetic agents. On the basis of this relationship Ferguson (1939) developed his theory that substances present in a given medium at equal thermodynamic activities have the same degree of biological action. Using the ratio of the partial pressure of the chemical causing cardiac sensitization (P_c) to the saturated vapour pressure (P_s) as a measure of the thermodynamic activity, it can be seen that despite a 6–700 fold variation in potency when expressed as volumes percent, all the chemicals we tested produced cardiac sensitization at approximately the same relative saturation (P_c/P_s).

That such a wide range of relatively inert, stable, lipid soluble chemicals producing a rapidly reversible effect, are equipotent when expressed on a thermodynamic scale, would indicate that cardiac sensitization is very likely to be a structurally non-specific action, occurring as soon as the chemical occupies a constant

fraction of the critical biophase. Cardiac sensitization may therefore be regarded as another example of 'physical toxicity' (Ferguson, 1939), and may be predictable from the saturated vapour pressure or the boiling point, or any physico-chemical property that is a measure of intermolecular attraction.

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