

## Metered dose pressurized aerosols and the ozone layer

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### Historical perspective

The term "aerosol" has a precise scientific definition as liquid or solid particles suspended in air [1], but has in the last few decades acquired a new non-scientific meaning as a self-contained, sprayable product in which the propellant force is supplied by liquefied gas [2]. The propellants used in these aerosol canisters are of several types, namely: a) chlorofluorocarbons (CFCs); b) hydrocarbons, such as propane and isobutane; c) mixtures of CFCs and hydrocarbons, which are used in many proprietary brands of household aerosol spray; and d) other substances including dimethyl ether, nitrogen and carbon dioxide.

The oldest reference to a product propelled by the energy derived from one of its own constituents is in a US Patent of 1899 [2], utilizing methyl and ethyl chlorides as propellants to deliver paints and varnishes. Further Patents of 1903 and 1921 described devices for perfume and antiseptic spraying, using carbon dioxide as the propellant. CFCs were developed in the early 1930s as "safe" alternatives to ammonia in the refrigeration industry [3], being first used as propellants in a fire extinguisher in 1933, and subsequently in insecticide sprays during World War II [4]. Household sprays containing CFCs were introduced in the 1950 [5] and six years later, Riker Laboratories developed the first pressurized metered dose inhaler (MDI) for asthma therapy [6], containing the adrenergic agents isoprenaline (isoproterenol) or adrenaline (epinephrine). Subsequently, CFC-powered MDIs have become the mainstay of asthma therapy, for delivery of selective beta-agonists, topical corticosteroids and anti-allergic agents.

The propellants used in MDIs are CFCs 11 ( $\text{CCl}_3\text{F}$ ), 12 ( $\text{CCL}_2\text{F}_2$ ) and 114 ( $\text{CClF}_2\text{CClF}_2$ ); mixtures of two or three of these substances being selected, in order to achieve the desired vapour pressure and spray characteristics. The numbering system for CFCs is a code which indicates the number of carbon, hydrogen, chlorine and fluorine atoms present in the molecule. CFCs are also known as Freons and Arctons, these being trade names imposed by two of the leading chemical companies. Although most CFCs are gases under normal ambient conditions, they can be liquefied either by cooling or by pressurization. Each CFC has a characteristic boiling

point and (at a given temperature) vapour pressure. Raoult's Law and Dalton's Law of partial pressures can be used to calculate the vapour pressures of various propellant mixtures [7], and the pressure inside an MDI is typically 300-500 kPa at 20°C, depending on the blend used. A saturated vapour is formed inside the can and the vapour pressure remains constant throughout the life of the MDI, an essential requirement. By contrast, hydrocarbons are unsuitable for inhalation, whilst gaseous nitrogen and carbon dioxide cannot be used because the canister pressure would fall steadily during the life of the MDI and spray characteristics would not be reproducible. Liquefied nitrogen and carbon dioxide could be used, but safety problems would arise from the very high vapour pressures created.

### Safety of CFCs

For many years, CFCs were regarded as inert and non-toxic [7, 8]. However, in the 1960s, fears about the safety of CFCs arose following an increase in the incidence of asthma deaths in the UK, which could be correlated statistically with the increased use of some pressurized bronchodilators. It was suggested [9] that this epidemic of asthma deaths might have been caused by the sensitization of the heart to cardiac arrhythmias induced by CFCs in asthma inhalers. The same authors [10] also noted as increased risk of heart palpitations in laboratory staff who used CFCs to prepare tissue sections. BASS [11] reported 110 sudden "sniffing" deaths in American youths, many of which involved CFCs.

By contrast, however, DOLLERY *et al.* [12] found that except with grossly excessive use of an MDI in a short period of time, the predicted myocardial concentrations of CFCs in man are much less than those shown in animal studies to provoke arrhythmias. Thus, cardiac toxicity is likely to be a problem only for the occasional adult [13] or child [14, 15] who deliberately abuses his/her MDI, apparently to satisfy a craving for CFCs. Although MDIs themselves were probably not directly responsible for the epidemic in asthma deaths [16], concern was sufficiently great in the 1970s for an editorial in *The Lancet* to recommend the gradual replacement of MDIs with alternative devices, such as the salbutamol Rotahaler [17]. In addition to problems of safety, there are occasional reports of bronchoconstriction following inhalation from MDIs, but it is unclear whether this effect is caused by the CFCs.

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### Environmental problems

Paradoxically, it is some of the very factors that make CFCs ideal propellants that contribute to the environmental hazards that they present. Since CFCs are chemically stable and have a low solubility in water, they slowly diffuse into the upper atmosphere once released into the environment. In 1974, MOLINA and ROWLAND [18] suggested that decomposition of CFCs by ultraviolet radiation in the stratosphere, 10–50 km above the earth's surface, might lead to a build-up of chlorine and, subsequently, to the depletion of stratospheric ozone.

Ozone ( $O_3$ ) is formed in the atmosphere when an oxygen molecule combines with a free oxygen atom, and acts as a screen to filter much of the ultraviolet radiation reaching the earth from the sun. Ozone is destroyed by active free radicals including chlorine, which catalyses the conversion of ozone to molecular oxygen. Remarkably, a single atom of chlorine can destroy up to 100,000 molecules of ozone [5]. It is important to distinguish between "hard" CFCs (including 11, 12 and 114 with lifetimes of 75, 111 and 185 yrs, respectively), which remain in the atmosphere for prolonged periods, and the much shorter-lived "soft" CFCs which have a much reduced potential for ozone depletion. Because of their long lifetimes in the atmosphere, ozone depletion lags behind hard CFC emission, and hence ozone would continue to be destroyed even if hard CFC emissions were halted immediately. In the mid 1970s, the environmental effects of hard CFCs were not treated with the seriousness that, with hindsight, they deserved; nevertheless, in 1978, CFCs as aerosol propellants were banned for non-medical purposes in North America and in some Nordic countries, and there was a voluntary EEC agreement to decrease the use of spray cans by 30% from 1976 levels [5].

Worldwide, however, CFC levels in the atmosphere were increasing by 5% per annum [19], but matters did not come to a head until the 1980s with the discovery of an ozone "hole" over Antarctica, *i.e.* a reduction of about 50% in the springtime ozone levels compared to those in the early 1970s. The reason why this ozone depletion takes the form of a hole is incompletely understood, but it appears to be related to trapping of high concentrations of chlorine by air currents over Antarctic regions [20]. It was also realized that CFCs are, together with carbon dioxide, methane and other substances, "greenhouse" gases, and that their presence in the atmosphere will contribute to its anthropogenic warming in the coming decades, with unpredictable consequences for climate throughout the world. Damage to the ozone layer can be caused not only by CFCs, but also by carbon tetrachloride, methyl-chloroform and bromines released from some fire extinguishers [19].

The adverse effects upon health from depletion of the ozone layer include an increase in the incidence of skin cancers [20]. Calculations by the US Environmental Protection Agency have suggested that a 1% decrease in stratospheric ozone leads to increases in the incidence of basal-cell carcinoma, squamous-cell carcinoma and malignant melanoma of 1 to 3% [19]. It is also possible

that reduction in the ozone layer might reduce crop yields and cause disturbances in aquatic food chains [5].

In September 1987, 27 nations agreed in Montreal upon a 50% cut in hard CFC consumption by 1999; in fact this was quickly seen to be inadequate, since calculations suggest that only an immediate 85% cut in emissions could limit environmental damage to its present level. Data which became available after the Montreal Agreement indicated that the situation was worse than anticipated, with a deepening of the Antarctic ozone "hole", evidence of a possible smaller and shallower hole over the Arctic, and indications of depleted global levels of ozone. In commendable response to this situation, representatives of over 80 nations, meeting in Helsinki in May 1989, agreed in principle to eliminate hard CFCs by the end of the century.

### Implications for MDIs

It is important to get into context the damage that aerosol sprays in general, and pressurized MDIs in particular, are causing. In 1987, world production of CFCs was around 1,000,000 tonnes per annum with uses divided approximately equally between: a) extrusion moulding for fast food packaging and insulation; b) refrigerators and air conditioning systems; c) solvents used in the electronics industry; and d) aerosol propellants. There are significant regional variations in use, *e.g.* CFCs 11 and 12 as aerosol propellants contribute <10% of the total use in the US, but about 30% amongst countries reporting to the Chemical Manufacturers' Association [5]. The biggest single use of CFCs in the UK has been as aerosol propellants, but there now seems to be a rapid move away from CFC-containing aerosols in response to consumer pressure. Medical aerosol inhalers utilize only 5,000 tonnes per annum (0.5% of worldwide consumption) and thus make only a very small contribution to the overall environmental problem.

The implications for asthma inhalers appear to be twofold: a) the phasing out of hard CFCs as propellants in MDIs and their replacement with safer alternatives; and b) the increased use of new inhalers that do not use CFCs at all. Major manufacturers of CFCs have been reported to favour drastic cutbacks in the production of hard CFCs [3], and it will be difficult for the pharmaceutical industry to obtain further supplies. Hydrofluorocarbon (HFC) 134a is a possible "ozone-friendly" replacement for CFC 12, but in general it is hard to find non-chlorine-containing compounds with the correct thermodynamic properties, which are also non-toxic and non-inflammable. Thus the change to ozone-friendly propellants in MDIs is unlikely before the mid-1990s.

Fortunately, alternatives to the MDI do exist. Nebulizers can be used to deliver aqueous solutions and suspensions of bronchodilators and corticosteroids. However, dry powder inhalers are more portable than nebulizers. Spinhaler (Fisons) and Rotahaler (Allen and Hanbury) were introduced more than ten years ago, for delivery of single metered doses of sodium cromoglycate, salbutamol or beclomethasone

dipropionate in powder form, with the energy required to disperse the powder being derived from the patient's own inspiratory effort. These have proved especially useful for those patients who cannot use an MDI correctly because of co-ordination problems, and they do not contain CFCs.

Spinhaler and Rotahaler are, however, rather inconvenient because it is necessary to load a gelatine capsule containing the drug powder, into the device immediately prior to use. Recently, however, two new multidose dry powder inhalers have been introduced. One of these was Diskhaler (Allen and Hanbury) which contains eight doses of either salbutamol or beclomethasone dipropionate (two days' supply at normal dosing levels) in blisters around the periphery of a small disk [21]. Even more interesting is Turbuhaler (Astra), which contains 200 metered doses of the bronchodilator terbutaline sulphate in the manner of a pressurized MDI, but without additives of any kind [22]. The corticosteroid budesonide is available from Turbuhaler in some countries. Turbuhaler [23] and Diskhaler [21] are easy to use and are readily accepted by patients. Turbuhaler delivers a similar percentage of the drug dose to the lungs compared to that from a correctly used MDI [24] and has an equivalent efficacy [25]. We may well see a gradual shift in emphasis towards these multidose powder inhalers over the next few years, because of their ease of use, convenience and environmental advantages. In the Turbuhaler, Diskhaler and their successors, we may be looking at the shape of asthma inhalers to come.

**Acknowledgement:** The author wishes to thank Dr F. Morén and Dr. I. Kökeritz for their many helpful comments and suggestions regarding this manuscript.

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