

**MONTREAL PROTOCOL
ON SUBSTANCES THAT DEplete
THE OZONE LAYER**



UNEP

**1998 REPORT OF THE
AEROSOLS, STERILANTS, MISCELLANEOUS USES AND
CARBON TETRACHLORIDE
TECHNICAL OPTIONS COMMITTEE**

1998 Assessment

Montreal Protocol on Substances that Deplete the Ozone Layer

United Nations Environment Programme (UNEP) 1998 Report of the Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee.

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ES Executive summary

ES.1 Aerosol products (other than MDIs)

For aerosol products, other than metered dose inhalers (MDIs), there are no technical barriers to global transition to alternatives. The major issue remaining is the use of CFCs in Article 5(1) Parties and CEIT. Some significant reductions have been achieved in recent years, and further reductions can be expected in the near future. Conversions can be characterised as three types: (1) self-conversions, (2) conversions assisted by the Multilateral Fund (MLF) of the Montreal Protocol, and (3) conversions assisted by the Global Environment Facility (GEF). Self-conversions have occurred when good quality hydrocarbon propellant was available at reasonable cost. Where capital outlay is necessary assistance is generally required from the MLF or GEF. The former assists aerosol fillers in Article 5(1) Parties, while the latter may assist Parties that are not eligible for MLF financing.

The ATOC estimates that 1997 CFC consumption in the aerosol sector was less than 15,000 tonnes in Article 5(1) Parties and some CEIT, excluding MDI use. The ATOC estimate of regional break down of quantities for 1997 is as follows:

1997 CFC Consumption in non-MDI Aerosols (metric tonnes)

ASEAN and Indian Subcontinent Countries*	1,500
China	2,400
Indonesia	700
Latin America	600
Middle East, Africa	700
Russian Federation	7,800
Ukraine	800
Other CEIT and CIS**	200
Total	14,700

* South Asia: India, Pakistan, Sri Lanka, Bangladesh, Nepal and Bhutan

** CIS: Successor States of the former Soviet Union

Since the 1997 Report, significant reductions have occurred due to the diminishing use of CFCs in China, where only a few pharmaceutical and industrial/technical aerosols remain to be converted. A slight reduction in CFC use in aerosols in the Russian Federation was due to reductions in three

of the eight domestic chemical enterprises. CFC usage in Ukraine has reduced, as export of CFC-based products is no longer allowed.

Poor economic conditions in South East Asia were responsible for a significant decrease in all aerosol production, including aerosols with CFCs. Additional reductions will occur upon completion of ongoing phase-out projects in several countries such as Jordan, India, Indonesia, Malaysia, Thailand, Tunisia, and Vietnam.

The remaining use of CFCs in most countries – especially Latin America and South East Asia Pacific (SEAP) – is concentrated in the industrial/technical aerosols (principally electronics contact cleaners) and in non-MDI pharmaceutical products. In China, remaining consumption is mostly in non-MDI pharmaceuticals. It is necessary to address the needs of these two sub-sectors to achieve total phase-out in aerosols.

The specific problems of the industrial/technical aerosols and pharmaceutical products require technical assistance in reformulation. Contact cleaners can be reformulated by using different new products such as HFC-43-10mee, volatile silicones or hydrofluoro-ethers. In the case of pharmaceutical products, many topical sprays can use hydrocarbon aerosol propellants (HAPs) or DME, while HFC-134a is a more costly alternative.

Hydrocarbons are the preferred substitutes for CFCs used in aerosols. The phase-out of the remaining CFCs in the aerosol sector is dependent upon the availability of HAPs. Where HAPs supplies were available at reasonable cost, transition out of CFCs has already taken place. Lack of ready availability of HAPs or any good quality hydrocarbon propellant is the main factor impeding the elimination of CFCs in India and SEAP, and an important factor in the Russian Federation.

A HAPs plant may be a simple facility that consists of storage tanks for crude and purified propane and butane and several towers with molecular sieves. Alternatively, it could also be a much more complicated facility that uses the petrochemical process of hydrogenation to saturate undesired olefin molecules. The type of process required depends entirely upon the quality of feedstock available. Transport and safety equipment is also needed.

Construction of suitable HAPs plants under the MLF is contingent on a corresponding volume reduction in CFC production. Usually the HAPs supplier is neither a CFC manufacturer nor an aerosol producer. Furthermore, there is no link between aerosol product manufacturers and CFC producers. Neither the HAPs manufacturer nor the aerosol manufacturer is in a position to guarantee the reductions in CFC production that the MLF is requesting as a prerequisite to fund HAPs projects. Consequently although there are no

technical barriers to transition, it is difficult to predict when total phase-out in the aerosol sector will occur.

The financial cost of retrofitting to handle flammable propellants is another factor constraining transition. This becomes especially important considering the proliferation of small and very small fillers that either continue to use CFCs, or that are using commercial LPG (fuel grade mixtures of butane and propane) in an unsafe manner. Haphazard conversions to hydrocarbons makes it obligatory for governments to develop suitable monitoring procedures to ensure safe practices including proper design, management and use of prescribed filling equipment, hydrocarbon storage and handling facilities. When considering the conversion of CFCs to hydrocarbons, the problems facing small aerosol fillers operating in congested areas in Article 5(1) Parties need to be resolved.

A test project is underway in India to evaluate hand-powered production filling equipment. Should this test prove positive, it will facilitate the conversion of very small aerosol industries, by providing an inexpensive and safe alternative that uses HAPs.

CFC use in aerosols is declining, but the pace is slow. However, it could be accelerated if the specific problems of (1) HAPs availability, (2) industrial/technical aerosols, and non-MDI pharmaceutical products, and (3) conversion of small and very small CFC users, were resolved.

ES.2 Metered dose inhalers

CFC-containing metered dose inhalers (MDIs) are reliable and effective therapy for respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). MDIs generally use CFC-12 as a propellant and most use CFC-11 and CFC-114 either alone or in a mixture to suspend or dissolve medication. HFC-134a and HFC-227ea have been approved as propellants in MDIs.

The prevalence of asthma and COPD is increasing worldwide. There are estimated to be 300 million patients with asthma and COPD worldwide. Evidence now confirms that asthma prevalence is increasing as urbanisation of developing countries continues. Currently, approximately 500 million MDIs are used annually worldwide, using approximately 10,000 tonnes of CFC. Non-Article 5(1) Parties that requested essential use nominations for MDIs are reported to have used 7,893 tonnes of CFCs in 1996.

There is international consensus that primary treatment of these diseases should be by the inhaled route. Inhalation permits fast and efficient delivery of treatment to the airways, with minimal risk of adverse reactions. Therapy

necessitates regular treatment, often with more than one drug. MDIs remain the dominant inhaled delivery system in most countries and for all categories of drugs.

Overall use of inhaled medication is increasing because of increased disease prevalence. World Health Organisation/US National Heart, Lung and Blood Institute (WHO/NHLBI-GINA) Guidelines in asthma management also encourage the inhaled route as the preferred method of administering medicine. The mainstay of therapy for asthma/COPD is likely to remain therapy administered by the inhaled route.

An MDI is a complex system designed to provide a fine mist of medicament for inhalation directly to the lungs for the treatment of respiratory diseases such as asthma and COPD. The active ingredient may be dissolved in the propellant but is more often presented as a suspension of particles, the majority of which are less than 5 micrometers in diameter. A surface-active agent may be included to ensure that the drug is well suspended and to help lubricate the metering valve. When a patient uses an MDI, the drug/propellant mixture in the metering chamber of the valve is expelled by the vapour pressure of the propellant through the exit orifice in the actuator. As droplets of drug in propellant leave the spray nozzle the propellant gases expand, with very rapid evaporation, resulting in a fine aerosol cloud of drug particles.

Currently available alternatives to CFC-based MDIs are primarily CFC-free MDIs, dry powder inhalers (DPIs) (single or multi-dose), nebulisers (hand held or stationary), orally administered drugs (tablets, capsules or oral liquids) and injectable drugs.

All the CFC-free MDIs under development contain the same components as the CFC products, but the very different physical properties of the HFC propellants have meant that significant changes have had to be made. CFC-free MDIs will contain the new propellants HFC-134a or HFC-227ea, and some products may contain both. The HFCs have very different properties to the CFCs, which have resulted in new formulations being developed. The CFC-free MDI may superficially look the same as the CFC MDI but will have a different taste and mouth feel that will be obvious to the user.

In the future alternatives are likely to include non-CFC MDIs, new DPIs, new nebulisers, novel non-inhaled treatments, and new propellant-free inhalation devices. Some of these are already in the market, and many others are in the late stage of development or under regulatory evaluation and will reach the market place in the next few years.

DPIs have been formulated successfully for most anti-asthma drugs. These inhalers are an immediately available alternative for a large proportion of

patients, but they may not represent a satisfactory alternative to the pressurised MDIs for all patients or for all drugs.

Currently available DPIs are lightweight and portable like MDIs; they require less co-ordination to use than most MDIs; they have the potential to use pure drug without additives; they are difficult for patients with very low inspiratory flow – e.g. small children and the elderly; they may require special packaging for use in humid climates; some require special handling during use; the cost compared with MDIs varies between products and countries; patient acceptability is not uniform. In some countries, over 85 percent of inhalers used are DPIs.

There is an increasing use of the multi-dose dry powder inhaler and this is likely to accelerate as new multiple dose devices are produced, particularly as they may be more suitable for young children with sufficient inspiratory flow.

DPI usage globally as a percentage of all inhaled medication is estimated to be around 17 percent. This figure varies considerably from country to country, e.g. currently from 85 percent in Sweden to less than 2 percent in the USA and there are no DPIs yet available in Japan. It seems unlikely that the uptake of DPIs in most countries will be at the levels seen in Scandinavian countries.

Nebulisers are devices, which are filled with drug dissolved or suspended in aqueous solution, which is converted to inhalable droplets using compressed air or ultrasonic waves. Nebulisers are generally not considered to be alternatives to MDIs but are restricted mainly to the treatment of infants and severely ill patients where patient co-operation is minimal or to situations when larger doses of drug and/or prolonged administration times are desired.

Oral medications include tablets, capsules, and oral liquids and have been the standard form of therapy for most diseases for many years. For existing products such as steroids and bronchodilators, tablet therapies involve higher doses and greater risk of side effects.

Regulatory authorities in some countries have recently approved four novel oral compounds (leukotriene modifiers) for the treatment of asthma. These may be of value to a certain number of those with asthma, but it is unlikely that these will be a full substitute for the current inhaled preventive therapy.

Some drugs used for the treatment of asthma and COPD are also available in injection form. However, this is not practical for general use in ambulatory patients and is therefore reserved for the treatment of hospitalised patients.

A number of pharmaceutical companies have introduced or plan to introduce a number of CFC-free MDIs. The most recent details for each of the major manufacturers are listed below.

3M Pharmaceuticals has approvals for and is currently marketing salbutamol (a bronchodilator) HFC MDI in over 40 countries. In the USA, salbutamol HFC MDI has been licensed to Schering Plough. 3M's beclomethasone (an anti-inflammatory steroid) HFC MDI has been submitted for approval in several countries with the first introduction anticipated during the second half of 1998. Under a further licence agreement, Hoechst Marion Roussell and 3M Pharmaceuticals have entered into a strategic marketing alliance to co-promote some of 3M's HFC MDI products. Glaxo Wellcome has filed registration applications for both salbutamol HFC MDI and fluticasone propionate (an anti-inflammatory steroid) HFC MDI (125/250 mcg) in over 30 countries worldwide. Further product launches are anticipated in the coming year. Rhone-Poulenc Rorer has filed applications for triamcinolone (an anti-inflammatory steroid) HFC MDI in the USA and Canada. Filings for disodium cromoglycate (a non-steroidal anti-inflammatory) HFC MDI have been made in 21 European countries and in Japan. Boehringer Ingelheim's first submissions for reformulated products are scheduled during 1998. Ivax (Norton Healthcare) launched its first HFC MDI, beclomethasone dipropionate (an anti-inflammatory steroid) in Ireland in January 1998. The same product range is also approved in France and further international approvals are pending. Norton also expects to receive its first regulatory approvals for salbutamol (a bronchodilator) HFC MDI before the end of 1998.

In the ATOC 1997 Update Report, graphical representations were included for projected timetables for the launches of HFC MDI products in both the European Union and the USA. These were based on an industry survey of International Pharmaceutical Aerosol Consortium (IPAC) members. More recent company specific data are available that indicate that a number of companies are well advanced with their reformulation programs. However, it would appear that the projected IPAC "best case" scenario is now not possible due to technical and regulatory delays.

However, the schedule for the safe introduction of new propellants and reformulated products, which was suggested in the 1994 ATOC report and confirmed in the 1996 and 1997 reports, remains on target. It is likely that a wide range of reformulated products will be available in many developed nations and transition will be making good progress by the year 2000. Minimal need for CFCs for MDIs is envisaged by the year 2005 in non-Article 5(1) Parties. Remaining technical, patent, safety and regulatory issues for some commonly used drugs still make it difficult to predict the schedule for full phase-out with precision.

The ATOC does not believe that a rigid global transition strategy is appropriate in view of the widely differing circumstances of individual Parties. However, the Parties could consider the benefits of a “Global Transition Framework” which would underpin national strategies and ensure that they are complementary. Because the phase-out of CFC-containing MDIs in non-Article 5(1) Parties is anticipated in the next few years, the Parties may wish to recommend that Article 5(1) Parties and CEIT start work on preparing their national transition strategies.

The essential use assessment process has allowed a better understanding of CFC requirements for MDI manufacture. Overall greater than 90 percent of the CFCs required each year for MDIs are filled into the product used by patients. The manufacture and on-line testing of MDIs result in some CFC being released to the environment. Pharmaceutical companies have made substantial investments to minimise emissions.

An intensive study on the possibility of using recycled CFCs was carried out on behalf of IPAC in 1993. The study analysed materials recovered from refrigeration plants and concluded that both recovered and reclaimed CFCs are complex mixtures. To be used in MDIs recovered CFCs would have to meet the same rigorous specifications as applied to virgin materials (i.e. free of toxic impurities). Because of the very complex nature of the contaminants and their number, it is impractical to develop commercial facilities to purify used CFCs to pharmaceutical standards.

At present continued supply of newly produced material remains necessary since stockpiling can only be viewed as a short term measure to provide buffer stock of CFCs. Stockpiled CFCs cannot be seen as a complete replacement for the annual essential use allowance in non-Article 5(1) Parties.

Strategic CFC stockpiles of reasonable size are prudent to safeguard public health needs. Stockpile size will vary according to country and company specific situations. However, excessive stockpiles could be utilised to prolong CFC MDI manufacture against the spirit of the Montreal Protocol, and act as an impediment to the transition to CFC-free alternatives.

Strategic CFC stockpiles can safeguard manufacturing supplies against unforeseen production contingencies and other uncertainties. Pharmaceutical manufacturers advocate the maintenance of reserves of CFCs to protect against supply disruptions. Maintaining a strategic stockpile for a period of time, e.g. up to 12 months, is not unreasonable. However, these levels may be adjusted depending on special circumstances.

The ATOC has considered the implications of the transition for patient subgroups that may have compelling medical needs.

Some patients may have a personal preference for CFC MDIs. This matter is likely to be overcome by education and should not be the basis for a continuing essential use nomination. Many patients can convert to DPIs. DPIs are continuing to be introduced by a number of companies into many countries. There is good evidence that the previously noted trend of increased DPI usage continues but since overall inhaled therapy has increased further, they have not reduced the sales of MDIs.

A second subgroup which may have a compelling need for CFC products well into the phase-out is low income patients (whether in Article 5(1) or non-Article 5(1) Parties) who rely on less expensive generic or locally branded products for control of their diseases. This issue has less to do with HFC MDIs versus CFC MDIs than it does with branded versus generic product price differentials, since it does not appear that HFC MDIs will be more expensive than their branded CFC counterparts.

In Article 5(1) Parties, the first control measure on the total consumption of CFCs commences in the year beginning 1 July 1999. Controls on CFCs make no allowance to permit exemptions for essential uses prior to the phase-out date of 2010. This will mean that MDI manufacturers in Article 5(1) Parties will be competing for CFC supply in their local markets with other users of CFCs.

Parties may wish to consider the procedure by which non-Article 5(1) Parties that no longer need CFCs for their own use can continue to produce CFC MDIs for export for a limited period, as necessary. Some CFC supply will be needed by multinational companies in, for example, the EU to enable them to service the continuing need of some Article 5(1) Parties for CFC MDIs.

Communication with experts in a number of developing countries including India, Pakistan, China, and Brazil has revealed some similarities, but there are some country specific issues. In all of these countries, the limited available information suggests that the airway diseases of asthma and COPD are common and increasing in prevalence. Local manufacture by multinational firms and/or local firms is reported in these countries, with local products sometimes cheaper than those manufactured by multinational firms. In China sixteen million CFC MDIs were produced in 1996 and consumption of CFCs for use in MDIs totalled 400 tonnes. In India, 6 million MDI units are sold annually with an additional 3 million being exported by one Indian company to other Article 5(1) Parties. In each of these countries, there is reported to be poor awareness of CFC and transition issues in general, as well as a lack of health professional awareness. Also, since it is anticipated that in most Article 5(1) Parties and some CEIT there will be an increasing number of patients

newly receiving MDI therapies, it would be preferable for them to start on CFC-free products.

Continued provision of MDIs in Article 5(1) Parties and CEIT will depend either upon import of products, or local production. The local production of CFC MDIs is likely to continue for some time after cessation of their use in non-Article 5(1) Parties and will overlap with the importation and local production of CFC-free MDIs by multinational and national companies. Local production of CFC-free MDIs by a local producer, a multinational company, or by a local producer in collaboration with a multinational company will require the transfer of new technologies and may require new licensing arrangements and transfer of intellectual property. The costs of such local production of CFC-free inhalers will involve capital costs and licensing arrangements. Multinational companies operating in Article 5(1) Parties should be encouraged to make the technology transfer as soon as possible. One company is already committing resources to install manufacturing capacity in Latin America (Brazil) and Eastern Europe (Poland) to manufacture HFC MDIs. These plants will be operational in the next couple of years and will serve local and regional market needs.

In relation to Article 5(1) Parties, the ATOC suggests that Parties may wish to consider:

- the importance of maintaining adequate supplies of the necessary range of inhaled medications during transition in non-Article 5(1) Parties
- encouraging the introduction of CFC-free technologies into these countries
- encouraging these Parties to start work on preparing their national transition strategies.

To facilitate patient and physician utilisation of the reformulated products, global education and training are required. Options currently employed and planned include:

- *Professional associations* – through medical journals, medical symposia, reports and newsletters.
- *Treatment guidelines* issued by the country's medical authority which document the advantages and drawbacks of different forms of therapy and recommend specific forms of care for specific patient groups.
- *Promotional material and media coverage* – Advertising and promotional material placed in medical journals and circulated to physicians by pharmaceutical companies.

- *Pharmaceutical industry* – Education of the medical profession, support of medical symposia, reprint of pertinent articles and reports and information sheets to patients are strategies to help to inform both professionals and the public of developments and alternatives.
- *Medical literature* – Articles appearing in the medical journals inform professionals of developments, and several have been published since 1994, many written by members of the ATOC, with further major editorials to be published in 1998.
- *Support groups* that provide information, seminars, and programs aimed at both the general community and through schools, sporting groups etc.

The amount of educational activity being undertaken varies from country to country and should involve increasing awareness of DPIs as well as the reformulated MDI products. As more alternatives become available it is essential that a more active patient strategy is developed. This will involve concerted effort by the industry, health professional associations and national health authorities working together with patient support associations (e.g. National Asthma Campaigns and Asthma Foundations). For Parties without patient support associations, the NHLBI/WHO Global Initiative (GINA) may be able to provide suitable literature for copying in the same way as they do with their current patient booklet, or add transition information to the GINA page on the Internet (<http://www.ginasthma.com>).

Professional bodies and patient associations are most likely to address this issue if governments take a lead in highlighting the importance of the subject. These educational activities are likely to require funding. Responsibility for and sources of adequate funding need to be identified if a successful transition is to occur.

Increasing numbers of medical symposia are scheduled for 1998/9, including the World Asthma Meeting in December 1998. This is supported by the major world respiratory organisations (European Respiratory Society, European Society for Asthma, Allergy and Immunology, American Thoracic Society, Asia-Pacific Society of Respiriology, American Academy for Asthma, Allergy and Immunology, International Union Against Tuberculosis and Infectious Disease and GINA). This meeting will highlight issues surrounding the safe transition to non-CFC treatments. UNEP is a co-sponsor of the World Asthma Meeting.

ES.3 Sterilants

By the beginning of 1997, CFC-12 use in non-Article 5(1) Parties for 12/88, a sterilant gas based on ethylene oxide (EO), had virtually disappeared, as final

inventories were depleted. There remain no technical barriers to the phase-out of CFCs in sterilisation, but in some Article 5(1) Parties there are indications of increased use of CFC-12 as a sterilant gas diluent. Some manufacturers of surgical equipment may even be shipping products from non-Article 5(1) Parties to be sterilised in Article 5(1) Parties.

In non-Article 5(1) Parties, low temperature medical device sterilisation is being met by HCFC-diluent replacement sterilant gas and 8.5/91.5 EO/CO₂, both of which are non-flammable. Pure EO can also be used, but since it is a flammable/explosive gas precautionary measures are necessary to use it safely. In some European countries formaldehyde is also used. There are a variety of not-in-kind substitutes, but some of these substitutes may either have materials compatibility problems or may be less robust processes with serious quality implications. Not-in-kind substitutes include radiation (gamma and electron beam), plasma systems, and liquid chemical systems. In other instances medical devices compatible with the steam process have been developed.

Global consumption of CFC-12 in this sector is very difficult to estimate since it is basically located in Article 5(1) Parties; it is estimated to be less than 1,500 tonnes. Estimated use of substitute HCFC replacement is thought to be less than 3,000 tonnes (some 90 ODP tonnes). CEIT and Article 5(1) Parties could convert to EO/HCFC-124 sterilant gas rapidly with reasonable cost and no changes in operating procedures.

HCFCs remain important as transitional products for sterilisation technology. Quality health care is dependent upon sterility assurance of medical devices. A new non-HCFC/EO sterilant blend has been tried, but has not been successful due to low sterilisation efficacy, high pressure limitations, and high cost. This alternative was developed in reaction to the EU ban on HCFC emissive uses in new equipment.

ES.4 Miscellaneous uses

CFCs have a number of miscellaneous uses of which tobacco expansion is the most significant. It is difficult to estimate the 1998 worldwide use of CFC-11 to expand tobacco. Most countries have stopped or will shortly stop the use of CFCs to expand tobacco. After 1998, China may be the only remaining country to use significant quantities of CFCs for this purpose. In 1996, 4050 tonnes were used in China compared with 900 tonnes in 1992. Based on the recent and planned installation of alternative carbon dioxide technology in China, declining use in this country is expected.

The CFC-11 tobacco expansion process is a patented, physical process that uses CFC-11 to restore cured, aged tobacco to its original field volume. In this process tobacco is impregnated with CFC-11 in a stainless steel vessel

maintained at 50 C (120°F) and pressurised at 20 to 75 psig. The tobacco is then contacted with hot air (up to 165 C, 330°F) which causes the tobacco to regain its original volume. The CFC-11 is vaporised and recovered by cooling and compressing, hence most of the CFC-11 is continually recovered and recycled.

Expanded tobacco is used in tobacco blends and cigarettes to improve the smoking characteristics of cigarettes and keep “tar” and nicotine levels within reduced ranges.

Carbon dioxide is an alternative expansion agent used in many countries. Others used less commonly are nitrogen, propane, and *iso*-pentane.

The principal difficulty for Article 5(1) Parties is the high capital cost of conversion to alternative technologies. Most are converting to carbon dioxide expansion technologies.

ES.5 Laboratory and analytical uses

Typical uses include: equipment calibration; extraction solvents, diluents, or carriers for specific chemical analyses; inducing chemical specific health effects for biochemical research; as a carrier for laboratory chemicals. Other uses are for critical applications in research and development where substitutes are not readily available, or where standards set by agencies require specific use of the controlled substances.

Essential uses of ODS for laboratory and analytical uses were authorised by the Parties to the Montreal Protocol, Decision VI/9(3). Manufacture as highly pure chemicals for final marketing in small, labelled containers was to discourage non-essential use. The Decision by the Parties allows marketing in blends including blends with more than one controlled substance.

Decision VI/9(3) also requires that Parties report on each controlled substance and that used or surplus substances be collected, recycled, and/or destroyed. Other relevant decisions include Decision VII/11, Decision VIII/9(4), and Decision IX/17.

A number of Parties have now reported on the use of controlled substances for analytical and laboratory uses. The European Union, Australia, the Czech Republic, and the United States have adopted licensing systems in order to manage supplies into these applications. Registration of the many thousands of small users in this sector is generally impracticable. Therefore, supplies are usually licensed to the distributors of controlled substances for analytical and laboratory uses.

It has been estimated that the total global use of controlled substances for these applications in non-Article 5(1) Parties will not exceed a maximum of 500 metric tonnes. Use in CEIT is unlikely to be more than a few hundred metric tonnes. Additionally, up to 500 metric tonnes could be used in Article 5(1) Parties for an estimated global consumption of 1,500 tonnes of controlled substances for laboratory and analytical uses.

TEAP has learned that the following specific uses have identified alternatives and substitutes and therefore do not require the use of ODS:

- testing of oil, grease, and total petroleum hydrocarbons in surface and saline waters and industrial and domestic aqueous wastes including the testing of water which is separated from oil and discharged from offshore drilling and production platforms
- testing of tar in road paving materials by dissolving tar and separating it from aggregate
- forensic fingerprinting.

The Standard of Purity recommended by TEAP and decided by Parties was based on international and/or national standards such as the International Standards Organisation (ISO) or Japanese Industrial Standards (JIS). High purity ODS and mixtures containing ODS shall be supplied only in clearly marked containers that belong to one of the following: containers equipped with closures; high pressure cylinders smaller than three litres; and 10 millilitre or smaller glass ampoules.

ES.6 Carbon tetrachloride

CTC can be used:

- As a feedstock for the production of other chemicals. The 1997 Report of the Process Agents Task Force (PATF), offered the following definition of feedstock:

“A controlled substance that undergoes transformation in a process in which it is converted from its original composition except for insignificant trace emissions as allowed by Decision IV/12.”

- Used as a process agent. The 1997 Report of the PATF offered the following definition of process agent:

“A controlled substance that because of its unique chemical and/or physical properties, facilitates an intended chemical reaction and/or inhibits an unintended chemical reaction.”

Note 1: Refrigerants, solvent & cleaning agents, sterilisation, aerosol propellants and fire-fighting, are not process agents according to this definition.

Note 2: Parties need not consider use of ODS for foam blowing, tobacco puffing, caffeine extraction, or fumigation because these uses are already covered in other Decisions and/or by Technical Options Committee Reports.”

- As a solvent. This includes simple solvent extraction such as caffeine extraction and palm oil extraction, and cleaning applications such as metal degreasing and textile spotting. Substitutes are commercially available and economic and, thus, these uses should be discontinued to protect the ozone layer as well as to safeguard the health and safety of people now using CTC.
- In miscellaneous applications such as fire extinguishers, as grain insecticide fumigant, and in an anti-helminthic agent (especially for the treatment of liver fluke in sheep). These uses also should be discontinued for the same reasons stated above.
- As a laboratory chemical.

Data on both CTC production and consumption have, in the past, been difficult to obtain. The new UNEP data reporting formats will enable the collection of much clearer data and a more detailed analysis of CTC applications. Indeed, total CTC production data including production for feedstock use is well known for 1996 and was reported to UNEP as 203,820 ODP tonnes.

ATOC has estimated atmospheric emissions of CTC to be 41,000 tonnes (-25 percent, +50 percent) for 1996. The primary source of atmospheric emissions of CTC are from the use as a feedstock to produce CFCs. This has been estimated to be between 27,500 and 29,100 tonnes for 1996 (67-71 percent of total emissions). The majority of the emissions from feedstock use originate from CFC production in Article 5(1) Parties and CEIT (25,700 to 27,300 tonnes, 64-67 percent of total emissions).

Whilst CTC atmospheric levels have reduced as a result of the phase-out of CFC consumption in the majority of non-Article 5(1) Parties, they will only fall significantly in the near future if the use of CFC and CTC in Article 5(1) Parties is phased out at a faster pace than required by the Montreal Protocol. Otherwise use of CFC and CTC will remain frozen until 1 January 2005 and CTC emissions will remain unchanged until that time.

There are a number of measures that could lead to reductions in CTC emissions to the environment:

- Closure of CFC manufacturing facilities in Article 5(1) Parties and CEIT with accelerated introduction of alternatives.
- Conversion of facilities using CTC as process agents in Article 5(1) Parties to alternatives.
- Use of improved emission control technology in CTC and CFC manufacturing facilities in Article 5(1) Parties and CEIT.
- Use of improved containment and emission control technology in Article 5(1) Parties and CEIT manufacturing facilities using CTC as process agents.
- The ATOC wishes to point out that projects to phase out solvent uses of CTC are eligible for financing under the Multilateral Fund. The ATOC further believes that in some cases eligible solvent uses have been presented to the Multilateral Fund incorrectly as process agent uses and, as a result, have not been funded.

1. Introduction

1.1 Montreal Protocol developments

In 1981, in response to the growing scientific consensus that CFCs and halons would deplete the ozone layer, the United Nations Environment Programme (UNEP) began negotiations to develop multilateral protection of the ozone layer. These negotiations resulted in the Vienna Convention for the Protection of the Ozone Layer, adopted in March 1985. The Convention provided a framework for international co-operation in research, environmental monitoring and information exchange.

In September 1987, 24 nations, including the United States, Japan, the Soviet Union, certain country members of the European Community, the developing countries Egypt, Ghana, Kenya, Mexico, Panama, Senegal, Togo and Venezuela, as well as the European Community, had signed the Montreal Protocol on Substances that Deplete the Ozone Layer.

The Montreal Protocol entered into force on January 1, 1989. This international environmental agreement originally limited production of specified CFCs to 50 per cent of the 1986 levels by the year 1998 and called for a freeze in production of specified halons at 1986 levels starting in 1992.

Shortly after the 1987 Protocol was negotiated, new scientific evidence conclusively linked CFCs to depletion of the ozone layer and indicated that depletion had already occurred. Consequently, many countries called for further actions to protect the ozone layer by expanding and strengthening the control provisions of the 1987 Montreal Protocol.

In June 1990, the Parties to the Montreal Protocol met in London to consider assessment reports on science and technology. The Parties agreed to Protocol adjustments requiring more stringent controls on the CFCs and halons specified in the original agreement, and amendments placing controls on other ozone depleting substances including carbon tetrachloride and 1,1,1-trichloroethane. At this Meeting, Parties also agreed that a new science and technology assessment should be conducted, for completion in 1991 and consideration in 1992.

In April 1991, the National Aeronautics and space Administration (NASA) concluded that depletion of the ozone layer had occurred at a faster rate over the past decade than was previously estimated.

Further reductions in the production of ozone depleting substances were agreed to in 1992 in Copenhagen. Methyl bromide and hydrochlorofluorocarbons (HCFCs) were also included as controlled

substances under the Protocol and controls agreed. A further assessment of science, technology and economics was requested for completion in 1994 and consideration in 1995. With the mandated phase-out of production and consumption of CFCs, carbon tetrachloride, 1,1,1-trichloroethane and other fully halogenated controlled substances by January 1 1996, Parties also agreed to a set of criteria and a procedure for assessing an essential use that would allow for exemptions for production and consumption. This Meeting requested Parties to nominate uses considered essential for the sixth Meeting of the Parties in 1994.

At their fifth Meeting in 1993, the Parties agreed that the feasibility of control schedules for HCFCs in Article 5(1) Parties should be investigated. Studies were also requested on the relative effects of accelerated HCFC and methyl bromide control schedules for non-Article 5(1) Parties.

At their seventh Meeting in 1995, Parties considered the assessment reports and focused on the progress made in phasing out ozone depleting substances and the difficulties experienced by countries with economies in transition (CEIT), in particular several successor states to the former Soviet Union. More stringent controls on HCFCs were decided for non-Article 5(1) Parties and a control schedule agreed upon for Article 5(1) Parties. Decision VII/34 of this Meeting requested a new assessment to be carried out by the Assessment Panels in the year 1998.

At their eighth Meeting in 1996, Parties agreed to updated terms of reference for the Technology and Economic Assessment Panel (compared to the original 1989 terms of reference). The ninth Meeting of the Parties in 1997 commemorated the tenth anniversary of the Montreal Protocol. A phase-out schedule for developed and developing countries for methyl bromide was agreed. Strengthening of controls for HCFCs were considered but no further changes to HCFC controls were decided.

As of October 1998 165 countries have ratified the Montreal Protocol.

1.2 The UNEP Technology and Economic Assessment Panel

Four Assessment Panels were defined in the original 1987 Montreal Protocol, i.e. Assessment Panels for Science, Environmental Effects, Technology and Economics. The Panels were established in 1988-89.

The Technical and Economics Assessment Panels were merged after the 1990 Meeting of Parties to the Montreal Protocol in London to the Technology and Economic Assessment Panel. Since 1993, the UNEP Technology and Economic Assessment Panel (TEAP) has had 7 standing Technical Options Committees (TOCs) (apart from other temporary subsidiary bodies).

- 1) **Aerosols, Sterilants, and Miscellaneous Uses** Technical Options Committee
- 2) **Foams** Technical Options Committee
- 3) **Halons** Technical Options Committee
- 4) **Methyl Bromide** Technical Options Committee
- 5) **Refrigeration, AC and Heat Pumps** Technical Options Committee
- 6) **Solvents, Coatings and Adhesives** Technical Options Committee
- 7) **Economics** Options Committee

1.3 The UNEP Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee and the 1998 Assessment

This report is part of the fourth UNEP assessment under Article 6 of the Montreal Protocol. The first assessment report was written in 1989, updated in 1991 and again in 1994. This report is in response to Decision VII/34 of the Parties to the Montreal Protocol, which requested an assessment to be undertaken for completion in 1998 and consideration by the Parties in 1999. Article 6 specifically directs Parties (nations that have ratified the Protocol) to assess whether the control measures, as provided for in Article 2 of the Protocol, are sufficient to meet the goals for reducing ozone depletion based on a review of the current state of knowledge on technical, scientific, environmental, and economic issues related to stratospheric ozone protection.

This Technical Options Report on Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride re-examines the use of, phase-out and alternatives to ozone depleting substances in aerosols, sterilants, miscellaneous uses including laboratory and analytical uses and carbon tetrachloride. This report has undergone a peer review among experts from organisations and companies globally. The report will be distributed internationally by UNEP.

The Aerosols, Sterilants and Miscellaneous Uses Technical Options Committee (ATOC) is made up of experts from industry, government, scientific, research and academic institutions and the medical community. In 1997/1998, there were 35 members of the Aerosols, Sterilants and Miscellaneous Uses Technical Options Committee from 18 countries – Australia, Brazil, China, Germany, India, Indonesia, Japan, Malaysia, Mexico, Pakistan, Poland, Russia, Singapore, Spain, Sweden, United Kingdom, USA and Venezuela. The Committee met in March 1998 and undertook extensive written communication in the preparation of this report.

The Committee for 1997/1998 was comprised of the following individuals who contributed to the preparation of this report.

Name	Affiliation, Country
Co-Chairs	
Jose Pons Pons	Spray Quimica C.A., Venezuela
Helen Tope	Environment Protection Authority Victoria, Australia
Ashley Woodcock	University Hospital of South Manchester, United Kingdom
Members	
D D Arora	Tata Energy Research Institute, India
Paul Atkins	Glaxo Wellcome PLC, United Kingdom
Olga Blinova	Russian Scientific Center “Applied Chemistry”, Russia
Nick Campbell	ICI Klea, United Kingdom
Hisbello Campos	Ministry of Health, Brazil
Christer Carling	Astra Draco, Sweden
Francis Cuss	Schering Plough Research Institute, USA
Chandra Effendy	Candi Swadaya Sentosa, Indonesia
Carmen Flasch	Boehringer Ingelheim Pharma KG, Germany
Charles Hancock	Charles O. Hancock Associates, USA
Eamonn Hoxey	Medical Devices Agency, United Kingdom
Javaid Khan	The Aga Khan University, Pakistan
P Kumarasamy	Aerosol Manufacturing Sdn Bhd, Malaysia
Rob Layet	Ensign Laboratories, Australia
Robert Meyer	Food and Drug Administration, USA
Robert Morrisey	Johnson & Johnson, USA
Geno Nardini	Instituto Internacional Del Aerosol, Mexico
Dick Nusbaum	Penna Engineering, USA
Tunde Otulana	Aradigm Corporation, USA
Martyn Partridge	Whipps Cross Hospital, United Kingdom
Fernando Peregrin	AMSCO/FINN-AQUA, S.A., Spain
Jacek Rozmiarek	POLFA POZNAN S.A., Poland
Abe Rubinfeld	Royal Melbourne Hospital, Australia
Daisaku Sato	Ministry of Health and Welfare, Japan
Albert Sheffer	Brigham and Women’s Hospital, USA
Greg Simpson	CSIRO Molecular Science, Australia
Robert Suber	RJR-Nabisco, USA
Ian Tansey	3M Health Care, United Kingdom
David Townley	Boehringer Ingelheim International, Singapore
Adam Wanner	University Miami, USA
You Yizhong	Journal of Aerosol Communication, China
Hua Zhangxi	China National Council of Light Industry, China

2. Aerosols

2.1 Reasons to use CFCs in aerosol products

Aerosol products have unique features that make them a preferred packaging method. These features include controlled release, avoidance of spills, product integrity and recyclability of the empty container. CFCs are non-flammable and easy to use, and therefore are ideal propellants that facilitated the growth of the aerosol industry. CFCs can also be used as solvents in aerosol products, and in isolated instances, as the product itself.

All of the controlled CFCs (CFC-11, -12, -113, -114, -115), 1,1,1-trichloroethane (methyl chloroform, MCF) and carbon tetrachloride (CTC) can be used in aerosol products. On a world scale CFC-11 and -12 are the most commonly used CFCs, followed by CFC-113 and -114 for specialised areas.

The aerosol product applications of 1,1,1-trichloroethane are dealt with in the UNEP Technical Options Report on Solvents, Coatings and Adhesives.

2.2 Worldwide use of CFCs in aerosol products – historical trends

CFCs in aerosol products have accounted for a substantial part of the total use of CFCs worldwide. In the mid-1970s they accounted for about 60 percent of the total use of CFC-11 and -12. In the late 1970s and early 1980s the use of CFCs as propellants was banned in USA, Sweden and Norway, with some exemptions. In Canada they were banned as propellants in cosmetic and hygiene products. Countries belonging to the European Union (EU) decided on a voluntary 30 percent reduction of the use of CFC-11 and -12 in aerosol products. This led to a substantial cut back in the use of CFCs as propellants in aerosol products. At the same time the use of CFCs in other applications such as foams, refrigerants, and solvents, continued to grow.

For aerosol products, other than metered dose inhalers (MDIs), there are no technical barriers to global transition to alternatives. In 1996 developed countries covered by Article 2 of the Montreal Protocol ceased the use of CFCs. Therefore, the major issue remaining for Parties to address is the use of CFCs in Article 5(1) Parties and CEIT. Some significant reductions have been achieved in recent years, and further reductions can be expected in the near future. Conversions can be characterised as three types: (1) self-conversions, (2) conversions assisted by the Multilateral Fund (MLF) of the Montreal Protocol, and (3) conversions assisted by the Global Environment Facility (GEF). Some self-conversions take place almost everywhere when good quality hydrocarbon propellant is available. Where financial considerations are important, assistance is required from the MLF or GEF. The former

assists aerosol fillers in Article 5(1) Parties, while the latter may assist in countries that are not eligible for MLF financing.

The TOC believes that 1997 CFC consumption in the aerosol sector was less than 15,000 metric tonnes in Article 5(1) Parties and CEIT excluding MDI use. Comprehensive CFC consumption data for aerosol products is difficult to obtain. However the best estimate of regional break down of quantities for 1997 is as follows:

1997 CFC Consumption in non-MDI Aerosols (metric tonnes)

ASEAN and Indian Subcontinent Countries*	1,500
China	2,400
Indonesia	700
Latin America	600
Middle East, Africa	700
Russian Federation	7,800
Ukraine	800
Other CEIT and CIS**	200
Total	14,700

* South Asia: India, Pakistan, Sri Lanka, Bangladesh, Nepal and Bhutan

** CIS: Successor States of the former Soviet Union

Since the 1997 ATOC Report, significant reductions have occurred due to the diminishing use of CFCs in China, where only a few pharmaceutical and industrial/technical aerosols remain to convert. A slight reduction in the use of CFCs in aerosols in the Russian Federation was due to reductions in three of the eight domestic chemicals enterprises. CFC usage in Ukraine is down, as they can no longer export CFC-based products.

Economic conditions in South East Asia were responsible for a significant decrease in all aerosol production, including aerosols with CFCs. Additional reductions will materialise upon completion of ongoing phase-out projects in several countries, such as Jordan, India, Indonesia, Malaysia, Thailand, Tunisia and Vietnam.

The remaining use of CFCs in most countries – especially Latin America and South East Asia Pacific (SEAP) – is concentrated in the industrial/technical aerosols (principally electronics contact cleaners) and in non-MDI pharmaceutical products. In China, remaining consumption is mostly in non-MDI pharmaceuticals. It is necessary to address the needs of these two sub-sectors to achieve total phase-out in aerosols.

The specific problems of the industrial/technical aerosols and pharmaceutical products require technical assistance in reformulation. Contact cleaners can be reformulated by using different new products such as HFC-43-10mee, volatile silicones or hydrofluoro-ethers. In the case of pharmaceutical products, many topical sprays can use hydrocarbon aerosol propellants (HAPs) or DME, while HFC-134a is a more costly alternative.

2.3 Alternatives for reducing or replacing CFCs

2.3.1 Currently available alternatives

There is a wide range of alternatives available for substituting CFCs in aerosol products. These include:

1. Alternative propellants (in order of use):

- hydrocarbons (HAPs) – blends of hydrocarbons (propane, *n*-butane, *iso*-butane)
- dimethyl ether (DME)
- compressed gases (compressed air, CO₂, N₂, N₂O)
- HFC-152a
- HFC-134a
- HFC-227ea
- HCFC-22

2. Alternative solvents, for example:

- water
- certain alcohols (ethanol, *iso*-propanol, *n*-propanol)
- certain chlorinated solvents (methylene chloride, trichloroethylene, perchloroethylene)
- pentane, hexane, white spirits, acetone, methyl ethyl ketone, methyl *iso*-butyl ketone, glycols, etc.
- HCFC-141b, HFC-43-10mee, volatile silicones, or hydrofluoro-ethers

3. Alternative delivery systems:

- finger pumps and trigger pumps
- sticks (deodorants and antiperspirants, insect repellents)
- roller, brush, cloth, etc.
- powder inhalers and nebuliser systems (pharmaceutical products).
- bag-in-can systems and piston-can systems

The suitability of each alternative depends upon the product in which it is used. Each of the alternatives has its own physical, chemical and economic characteristics that make it an optimal choice for the product in question and are discussed in more detail below. Table 2.1 shows comparative data on some propellants and solvents.

Table 2.1 Comparative data on some propellants and solvents

Substance	Structural Formula	Boiling Point (oC)	ODP	GWP	Atmospheric life (years)	Typical Occupational Exposure Level (8hr TWA)	Flammability Range (% volume in air)
HCFC							
HCFC-22	CHClF ₂	-40.8	0.04	1500	13.3	1000 ppm	non-flammable
HCFC-123	CHCl ₂ CF ₃	27.9	0.014	90	1.4	10 ppm	non-flammable
HCFC-124	CHClF ₂ CF ₃	-12	0.03	470	5.9	500 ppm	non-flammable
HCFC-141b	CH ₃ CCl ₂ F	32	0.10	600	9.4	500 ppm	5.6 to 17.7
HCFC-142b	CH ₃ CClF ₂	-9.2	0.05	1800	19.5	1000 ppm	9.0 to 14.8
HCFC-225ca	CHCl ₂ CF ₂ CF ₃	51.1	0.02	170	2.5	n.a.	non-flammable
HCFC-225cb	CClF ₂ CF ₂ CHClF	56.1	0.02	530	6.6	n.a.	non-flammable
HFC							
HFC-23	CHF ₃	-78.4	<4x10 ⁻⁴	11700	264	1000 ppm	non-flammable
HFC-32	CH ₂ F ₂	-51.6	-	650	5.6	1000 ppm	14.6 (lower limit)
HFC-125	CF ₃ CHF ₂	-49	<3x10 ⁻⁵	2800	32.6	1000 ppm	non-flammable
HFC-134a	CF ₃ CH ₂ F	-26.5	<1.5x10 ⁻⁵	1300	14.6	1000 ppm	non-flammable
HFC-143a	CF ₃ CH ₃	-47.3	-	3800	48.3	1000 ppm	7.1 (lower limit)
HFC-152a	CHF ₃ CH ₃	-24.7	-	140	1.5	1000 ppm	3.7 (lower limit)
HFC-227ea	CF ₃ CHFCF ₃	-17.0	-	2900	36.5	1000 ppm	non-flammable
For Comparison							
CFC-12	CCl ₂ F ₂	-29.8	0.82	8100	102	1000 ppm	non-flammable
CFC-11	CCl ₃ F	23.8	1.0	3800	50(+/-5)	1000 ppm	non-flammable
1,1,1-Tri-chloroethane	CCl ₃ CH ₃	74.1	0.12	100	5.4(+/-0.4)	350 ppm	7.5 to 12.5
Dimethyl ether	CH ₃ OCH ₃	-24.8	0	-	-	1000 ppm	flammable
Propane	C ₃ H ₈	-42.1	0	11	-	simple asphyxiant	flammable
Butane	C ₄ H ₁₀	-0.5	0	11	-	simple asphyxiant	flammable
Isobutane	C ₄ H ₁₀	-11.7	0	11	-	simple asphyxiant	flammable
Compressed Gases							
Carbon dioxide	CO ₂	-78.5	-	1	variable	5000 ppm	non-flammable
Nitrous Oxide	N ₂ O	-89.5	n.a.	310	120	50 ppm	non-flammable
Nitrogen	N ₂	-195.8	-	-	-	-	non-flammable
Comp. Air			-	-	-		-

“n.a.” – not available at time of printing

References: Intergovernmental Panel on Climate Change, 1990; *Climate Change 1995: The Science of Climate Change*, Intergovernmental Panel on Climate Change, 1996; *1994 UNEP Scientific Assessment of Ozone Depletion*, World Meteorological Organisation, Global Ozone Research and Monitoring Project – Report No. 37.

2.3.2 Hydrocarbons

Hydrocarbons are the principal substitutes for CFCs used in aerosols. Suitable mixtures of *n*-butane, *iso*-butane, and propane, with constant pressure, low odour and low olefin levels (unsaturates), are called “hydrocarbon aerosol propellants,” or HAPs. A HAPs plant may be a simple facility that consists of storage tanks for crude and purified propane and butane, and several towers with molecular sieves; or it may be a much more complicated facility that uses the petrochemical process of hydrogenation to saturate undesired olefin molecules. The type of process required depends entirely upon the quality of feedstock available.

Construction of suitable HAPs plants under the MLF is contingent on a corresponding volume reduction in CFC production. Usually the HAPs supplier is neither a CFC manufacturer nor an aerosol producer. Furthermore, there is no link between aerosol product manufacturers and CFC producers. Neither the HAPs manufacturer nor the aerosol manufacturer is in a position to guarantee the reductions in CFC production that the MLF is requesting to fund HAPs projects.

Hydrocarbons are highly flammable and care during storage, transfer and filling is required. Attention must also be paid to the following issues.

- Filling plant and storage facilities must be suitably sited to comply with local planning and legislative requirements. If the plant is located in a populated area, the amount of flammable substances to be stored may be limited. The storage facilities for bulk propellant must be designed and equipped with emergency facilities (for example, fire detection, sprinklers, shut-off valves etc).
- The aerosol filling station should be located in an explosion-tolerant filling house, preferably located outside the main plant building and fitted with a blow-out wall, grounded equipment and explosion-proof electrical systems. Additional requirements, depending on local legislation, can include standard and emergency ventilation at floor level, gas detection equipment, explosion suppression systems and electro-protective interlock systems that will react to emergency situations. For plants located in suitably warm climates, outside filling of propellants may be appropriate. Ventilation must be assured in these open areas. Attention should be paid to explosion proof electrical equipment and the elimination of ignition sources. It should be kept in mind that faulty aerosol products and defective batches of goods might be a potential source of dangerous HAPs and should be handled accordingly.

- All employees in filling plants handling flammable propellants must be well trained and must adhere to high safety standards. Good management and safety controls must be maintained and plants must be equipped to comply with local regulations and requirements of insurers.
- Hydrocarbon-containing aerosol products should be used in accordance with labeling directions, for example, do not spray near open flame or hot surfaces.

The phase-out of the remaining CFCs in the aerosol sector is dependent upon the availability of hydrocarbon propellants (HAPs). Where HAPs supplies were available at reasonable cost, transition out of CFCs has already taken place. Lack of ready availability of HAPs or any good quality hydrocarbon propellant is the main factor impeding the elimination of CFCs in India, and SEAP, and an important factor in the Russian Federation.

2.3.2.1 Costs of retrofit

The costs of converting filling facilities to hydrocarbon propellants depend on whether the plant facilities are already designed for flammable gas filling or need to be retrofitted. In some cases a new building, filling house or location is necessary. In some countries the filler must also install equipment to deodorise locally available propane and butane gases of various compositions. The conversion costs for a one hundred cans per minute line (capable of 10,000,000 cans per year on a one-shift basis) can run from around \$150,000 to \$1,750,000 USD, depending on the amount of retrofitting and/or relocation needed. Maintenance costs will also increase.

The cost of the hydrocarbons is, however, generally lower than that of CFCs. In most cases a conversion to hydrocarbons will result in a net gain for the producer and a cheaper product for the consumer.

The lower cost of the hydrocarbons is especially important for developing countries with a shortage of hard currency. As the price of CFCs rises due to market scarcity, factories using CFCs will be increasingly less competitive.

There are wide variations in the cost of retrofit due largely to the following variables:

- actual location and space availability within the plant
- type and condition of the filling machinery
- volume to be produced

- availability or not of local contract fillers
- type of filling (enclosed or open air) to be done, and
- requirement for permanent storage tanks for HAPs.

In several places (India, Indonesia) there are small and very small “cottage industry” aerosol fillers which may be in residential areas or in very congested industrial areas that cannot be converted to a flammable propellant because of their location. If there are local contract fillers available, the most economical solution is contract filling.

This is of course not always possible, either because contract fillers do not exist or because they are unacceptable for competitive reasons. Where the owners wish to relocate to continue their own filling (there are several cases in India), it has been recommended that funding be sought to assist in the installation of safety equipment for the new locale.

In many cases, the filling equipment has proved inadequate for conversion. There is still some electrical equipment that cannot be used with HAPs. In India there is a local brand of burette type filler that contains about 10 litres of gas, far too much to be safe in case of catastrophic failure. A test project is underway in India to evaluate hand-powered production filling equipment. Should this test prove positive, it will facilitate the conversion of very small aerosol industries, by providing an inexpensive and safe alternative that uses HAPs. The largest problem has been with semi-automatic filling machines in very poor condition. The recommendation in this case is to replace the machine.

Consultants to the implementing agencies have recommended assistance in the order of 50,000USD to 350,000 USD for each facility to be converted, although there are cases where large volume fillers would require up to 1 million dollars USD in assistance.

Some companies will probably make a profit on their conversion to HAPs, and these profits would be deducted from a grant according to the formula used by the Multilateral Fund.

2.3.2.2 Regulatory Actions in Developed Countries

Some states in the USA in order to deal with air quality issues are forcing consumer products including aerosol products to reduce their emissions of volatile organic compounds (VOCs). VOCs are substances such as hydrocarbons that react in the presence of sunlight and other pollutants to form ground level ozone and photochemical smog. Efforts to comply with these regulations have required significant changes in formulations. These

new formulations try to maximise the use of non-VOCs such as water, HFC-152a, chlorinated solvents, silicones etc. The definition of VOCs probably will have to be modified to take into account the different contribution that different substances make to ground level ozone. In Europe, reformulations of consumer products to reduce emissions of VOCs are also underway. VOC regulations have a strong impact on aerosol products, but have not impeded the phase-out.

Another area of general concern is that some governments for safety reasons will not permit the transport of unstenched (or low odour) hydrocarbons from suppliers to user locations. This forces each user to install redundant yet expensive purification equipment.

2.3.3 Dimethyl ether (DME)

Dimethyl ether (DME) is a flammable liquefied propellant with excellent solvency and water compatibility. It has found substantial use particularly in some European countries where it has been used as a combination propellant/solvent replacement. DME use has increased in the USA to reduce VOC content in aerosol product formulations.

DME can generally be used in filling facilities equipped to handle a flammable propellant. With minor modifications the solvency of the propellant can be accommodated. In the USA there are some additional safety requirements for the electrical equipment.

Aerosol paints and hairsprays often use DME for its excellent solubility characteristics. DME is the only available propellant that is soluble in water, which presents interesting possibilities for the aerosol formulator.

2.3.4 Hydrofluorocarbons (HFCs) and hydrochlorofluorocarbons (HCFCs)

HFCs that are being commercialised now include HFC-152a, -134a, HFC-227ea and HFC-43-10mee.

HFC-152a is flammable, has a medium vapour pressure, no ODP, relatively moderate GWP (compared with CFC-12), and is not a VOC; and is gaining favour as a propellant in the USA. This propellant makes excellent quality mousses.

HFC-134a and HFC-227ea are non-flammable fluorinated propellants. HFC-134a and -227ea have negligible ozone depletion potentials (ODPs). Commercial production of HFC-134a exists in the USA, Japan, Europe, and Brazil. Commercial production of HFC-227ea exists in Germany and the USA. HFC-134a is replacing CFC-12 in MDIs. It is also the main non-

flammable propellant in certain industrial products. HFC-134a usage in these segments is projected to be very modest because of its relatively high price, and because of a high GWP its use should be avoided whenever possible.

HFC-227ea is currently being evaluated specifically for MDIs. HFC-43-10mee is used as a solvent replacement for CFC-113.

HCFC-22 and -142b were once considered replacements for CFCs in personal care products, however their use in this category is minimal today.

HCFC-141b, which is flammable and has an ODP of 0.10, is a low pressure HCFC once viewed as a potential replacement for CFC-113. In practice, its high solvency has limited its usage for this purpose. Its use as a substitute of methyl chloroform should be discouraged since these substances have about the same ODP.

2.3.5 Compressed gases

All of the previously mentioned propellants are in the liquid state inside the aerosol can (liquefied propellants). Compressed gases such as compressed air, N₂, CO₂ and N₂O can be used for some aerosol products. They normally produce coarser spray patterns unless special valves are used. Their main limitation for many products is the wet spray and pressure decrease as they expand while the can is emptied with the attendant lowering of the spray pattern quality.

Technological advances have been made to compensate for the effects of pressure drops through novel valve designs, selection of adequate solvents, and compensation for leakage and/or misuse. The filling technology and quality control with compressed gases is much more demanding than with liquefied propellants. Compressed gases are presently used in about 5-9 percent of all aerosol products.

Compressed air, CO₂ and N₂ are non-flammable and do not require the use of explosion-proof gassing equipment. Accurate controlled compressed gas charge is imperative for performance and safety. Because of high quality control requirements and innate technical limitations, compressed gas propellants will probably not be widely used in developing countries.

2.3.6 Solvent reformulation

1,1,1-Trichloroethane (Methyl chloroform, or MCF), CFC-113 and carbon tetrachloride (CCl₄) have all been used as solvents in aerosol formulations and they are still used in some Article 5(1) Parties and CEIT. The selection of a solvent for an aerosol formulation has to take into account several parameters:

- solvency power
- flammability
- evaporation rate
- density
- viscosity and surface tension (wetting power)
- environmental acceptability
- cost
- local availability.

The controlled substances mentioned above are all non-flammable, have large evaporation rates, high density, low viscosity and surface tension, and are reasonably low cost and widely available. Their solvency power varies from very high in the case of CCl₄ and MCF, to very low in the case of CFC-113. CFC-113 has generally been considered safe for most uses, MCF has much lower exposure levels and should be used only in well-ventilated places. CCl₄ is a well-known carcinogen that should not be used in aerosols for this reason alone.

It is possible to replace these solvents with non-ODS alternatives. However, in developed countries, particularly in some parts of the United States of America, VOC regulations made this substitution more difficult by limiting the amount of VOCs that could be used in each product category.

The two properties that are most difficult to duplicate simultaneously are high evaporation rate and non-flammability. Where VOC regulations do not limit available options, formulators can usually use mixtures of chlorinated solvents, such as non-ozone depleting methylene chloride and perchloroethylene, with alcohols, ketones, and aliphatic and/or aromatic hydrocarbons. In other cases it may be possible to replace the ODS solvent with a mixture of DME and water.

The multiplicity of aerosol products dictates that each formulation has to be carefully analysed in each case to determine which characteristics are more desirable.

2.3.7 Alternative non-aerosol methods

Finger pumps and trigger pumps are mechanical dispensing devices that have captured market share due to improved design. Modern pumps are capable of dispensing fine mists of low viscosity products at any angle of operation. The disadvantages of pump sprays are that they produce larger droplets, and the spray penetrates less than that produced by aerosol products.

However, aerosol products still offer some unique advantages over these mechanical devices such as total enclosure that prevents tampering with the product or oxidation due to air intake (in pumps, air is admitted to replace the liquid that is dispensed).

Conditioning of finger or trigger pump products requires that the right amount of liquid is filled into the bottle and that at a second stage the pump is fixed to it. To keep the pace of modern filling equipment, this second operation requires an automatic capper whose price depends on the ability to handle single or multiple pump types and sizes.

Total investment will be lower than for a similar throughput aerosol facility. The cost of the package for pumps is highly dependent on the style of the bottle and pump, degree of construction, order quantity, local supply and economics. However, in most cases pumps will be at least as expensive as the aerosol products, and probably more so.

A well-known example of a non-spray dispenser is the solid stick dispenser for deodorant or antiperspirant. Filling solid sticks is expensive. Pack costs for solid sticks will vary with the degree of package sophistication and will, in some cases, exceed an aerosol can and valve price. However, the finished product will also last longer than an aerosol product. Stick products are usually filled as hot liquids and cooled down to their solid state. Capital costs for filling and assembling roll-on dispensers are lower than those for an aerosol line of similar capacity (typically half the investment cost).

Application by other means has also been suggested, such as brushing or dipping.

Two compartment aerosol (or “pressurised”) products separate the concentrate and propellant inside the aerosol package either by use of a piston, by an inner bag containing the product, or by an expanding bag containing propellant. The propellant will only be released to the atmosphere if the system is broken but only small amounts are required – hydrocarbon or compressed gas may be used. There are a number of available systems, some of which have been commercialised for a long time. Designed originally for dispensing viscous products (gels, pastes, cheese spreads etc) they can be used with liquids to

provide a propellant free spray. The spray quality will generally be similar to that of a pump but it can be continuous, used at any angle, will not permit air ingress and is tamper proof. A two compartment pressurised can costs about double of what a normal aerosol product costs. Special filling machines are needed for these systems. These machines are more expensive than normal aerosol fillers.

2.4 Applications with potential problems

Phase-out of ODS in aerosol products is technically feasible for all products but the metered dose inhalers for asthma and chronic obstructive pulmonary disease (COPD). In some Article 5(1) Parties and CEIT where HAPs are available, some residual uses of ODS in aerosol products remain. They usually relate to the following applications.

2.4.1 Pharmaceutical products

Within the category of aerosol products, pharmaceutical products are the last to substitute. However, substantial reductions have been made within this category as CFCs are generally only used where no satisfactory alternatives are available.

The major proportion of CFCs used in this category is for MDIs for the treatment of asthma and COPD. The use of CFCs in MDIs is discussed in the following section.

Other CFC-propelled medical aerosol products include nasal preparations, local anaesthetics, wound sprays, antibiotics, antiseptics and ancillary products. These products do not require the aerodynamic properties considered necessary for oral inhalers. In the case of pharmaceutical products, many topical sprays can use HAPs, DME, or nitrogen, while in some cases HFC-134a is a more costly alternative. Therefore, pharmaceutical products can be reformulated through the use of these alternative propellants, or by using mechanical pump sprays or powders, liquids and creams.

Any new formulation requires time for toxicological tests and approval by regulatory agencies for therapeutic use. The time for such an approval may vary among countries. Typically this can take several years.

2.4.2 Industrial and technical specialities

There are a number of industrial technical aerosol products that relied upon the non-flammable and inert characteristics of the CFCs and which, therefore, could not easily be reformulated. Products in this category include electronic

cleaners, dusters, fault detectors, mould releases, aircraft disinfection, weld anti-spatter, polyurethane foam and aerosol horns.

The majority of these products can be converted using HAPs or DME if flammability is not an issue. Where flammability is a concern, HFC-134a is close to being a direct substitute for CFC-12. It is a slightly poorer solvent, which must be taken into account. HFC-152a can also be used in some instances – it is very slightly flammable and very difficult to ignite.

Some products, especially those which use CFC-113 due to its inert characteristics have been the most problematical to reformulate. However, reformulation efforts are ongoing, and have been aided by the availability of HCFC-141b, and more recently, by HFC-43-10mee, volatile silicones, and hydrofluoro-ethers. Many countries provided domestic CFC use exemptions through legislation for these product segments. However, it is now possible to reformulate all of them adequately.

It should be noted that alternatives to replace CFCs are not limited to the use of another propellant or solvent but can also include using totally different products or techniques to achieve the required result.

2.5 Article 5(1) Parties' perspective

In summary, the following issues are of importance in Article 5(1) Parties. Sources of hydrocarbons must be developed in each country still using CFCs. Financial assistance must be provided to aerosol fillers to cover the cost of conversion where conversion is otherwise not possible. It is important to stress that in the process of replacing CFCs in the aerosol industry of developing countries, every effort should be directed to ensure that safety standards at the manufacturing plant and at the consumer level are maintained. To meet this goal, information on the following items should be made available and distributed as widely as possible:

- proper installation guidelines
- source of suitable processing filling equipment and auxiliary equipment
- list of suppliers of safety equipment
- good manufacturing practices and specific manufacturing practice codes
- technical information on new propellants, propellant systems and solvents that do not deplete the ozone layer.

Whereas there is a declining trend in the use of CFCs in aerosols in Article 5(1) Parties, the pace of reduction is slow and is likely to slow further unless the specific problems of (1) HAPs availability, (2) conversion of small and very small CFC users, (3) industrial/technical aerosols and non MDI pharmaceutical products are resolved.

3. Metered dose inhalers

3.1 Introduction to lung diseases, epidemiology, treatment options and medical trends

Diseases of the lungs may conveniently be considered as either predominantly affecting the airways (obstructive diseases), or as predominantly affecting the lung tissue (restrictive diseases). Diseases of the airways are the commonest and the most likely to necessitate treatment which is inhaled directly onto the airway surface. Inhaled drugs are also occasionally used in the treatment of infections (e.g. nebulised antibiotics in cystic fibrosis and preventive aerosolised treatment for those with HIV/AIDS).

Some generalised diseases are relatively uncommon (for example, conditions such as obliterative bronchiolitis, cystic fibrosis and bronchiectasis) but two are very common, asthma and chronic obstructive pulmonary disease (COPD). These affect a significant proportion of the world's population. There are estimated to be 300 million patients with asthma and COPD worldwide. Latest studies show up to 20 percent of children having asthma in some countries. For adults, 5-6 percent of the population may have asthma. A similar percentage of adults may have COPD, but this figure may be even higher in some countries where there are historically high levels of tobacco consumption.

3.1.1 Asthma

3.1.1.1 Description

Asthma is an inflammatory disorder of the airways associated with generalised airway hyper-responsiveness. This may lead to airway narrowing which varies in severity over short periods of time, either spontaneously or as a result of treatment. One of the major features is that the sufferer has more irritable airways than normal and this irritability is associated with an underlying airway inflammation which is often present even when the patient is free of symptoms. As a result of the airway irritability, contact with a variety of trigger factors, varying from exercise to infections and allergens to laughter, gives rise to the symptoms of coughing, chest tightness, wheezing and shortness of breath.

The tendency to have asthma is probably inherited and many people with asthma are affected first in childhood. Often there is an improvement in the condition during teenage years and in some the condition disappears. In others, the condition varies in severity and recurs in later life or first develops over the age of 21 years.

3.1.1.2 The size of the problem

Determining the prevalence of asthma worldwide is difficult and the data are often confusing. A change in prevalence sometimes reflects changes in diagnostic habit as much as true change in the number suffering from the condition. Confusion arises when some talk of the number of people with asthma at a point in time (point prevalence), whilst others refer to figures for cumulative prevalence (the number who have ever had asthma). Figures also vary according to the method of disease assessment and the criteria for making a diagnosis of asthma, and may be very high if a criterion of “have you ever wheezed?” is adopted. Despite these provisos most authorities are now convinced that the prevalence is increasing worldwide.

Asthma affects all races. More reliable figures are available for the prevalence of the condition in developed countries. The highest prevalence is to be found in Australians where 11 percent of 8-11 year old children may currently have asthma, 23.5 percent have previously been diagnosed as having the condition and a third of the population report previous wheeze. Whilst the rates may be the highest in Australia they are only a little lower in England, Wales and Denmark. There are, however, large differences in prevalence between affluent and less affluent countries (e.g. 1.9 percent prevalence in Chinese children) and the reasons for this are not clear. The rise in prevalence of asthma over the last two decades that has been reported in affluent countries appears to be followed by an increase in the less affluent. It may reflect “Westernisation”, for example, an increased prevalence in Papua New Guinea following the introduction of blankets which may harbour the house dust mite or changes in house design, maternal smoking, diet, or the rate of infections in early life. There may also be a synergistic action of air pollution and/or tobacco smoking.

3.1.1.3 Treatment of asthma

The preferred treatment of asthma includes drugs that are delivered to the airways by means of some form of inhaler device. This has the advantage that the medication is delivered directly to the site of action, reducing the size of the dose needed and thus reducing the risk of adverse systemic effect. It often also permits a more rapid onset of action than administration by tablet. The trend towards greater use of regular anti-inflammatory medication and the greater use of inhaled therapy has been advocated in guidelines on treatment produced by several countries, by the International Consensus Report on the Management of Asthma and by the WHO/NHBLI-GINA Global Strategy for Asthma Management and Prevention.

There are two main categories of treatment for asthma: relievers and preventers.

Relievers:

Relieving (airway opening) bronchodilator treatments are required for the relief of sudden symptoms of breathlessness experienced by all patients with asthma and some of these bronchodilators are also taken regularly.

Treatments falling into the class of short-acting relieving treatments include the beta-agonist agents, such as salbutamol (albuterol), terbutaline, rimiterol or fenoterol, or anti-cholinergic agents such as ipratropium bromide. There are also long-acting beta-agonist inhalers, such as salmeterol or formoterol.

Preventers:

The underlying inflammation of the airways, which is such a fundamental part of asthma, needs treatment in all but those with the mildest infrequent symptoms. Such regular anti-inflammatory treatment is accomplished with either cromoglycate-like drugs (sodium cromoglycate or nedocromil sodium) or inhaled glucocorticosteroids (for example, beclomethasone, budesonide, fluticasone or triamcinolone).

3.1.1.4 Methods of administration

Both relieving and regular preventive medication can be given to those with asthma via inhaler devices. These devices include the metered dose inhaler (MDI) (with or without an attached chamber (spacer) device, and with either a mouthpiece or mask), and the dry powder inhaler (DPI) device, which may be either single or multiple dose in type. Less commonly, the patients may need their drug administered to the airways via a nebuliser. This is commonly used for bronchodilator treatment of an acute attack of asthma and much less commonly as a means of administering regular preventive treatments (see section 3.3.2). Due to their need for an external power source and their bulkiness, nebulisers are not a preferred method for routine use in delivering asthma medications.

3.1.1.5 Patient choice and patient education

It is important that the inhaler device is carefully selected for a given patient and that the patient feels comfortable using it. Both the patient and parent must receive adequate instruction in its correct use and with children especially it is important that the child is able to use the device when breathless and when symptom free.

At the present time, published guidelines on the treatment of asthma stress that children and those on the higher doses of inhaled steroid treatments should use chamber (spacer) devices with their metered dose inhalers to reduce

difficulties in the co-ordination of actuation and inhalation and in the case of steroids to reduce oro-pharyngeal deposition with its resulting side effects and to reduce the swallowing and potential adsorption of the steroid. Spacers are currently not available for use with dry powder inhalers.

3.1.2 Chronic obstructive pulmonary disease (COPD)

3.1.2.1 Description

Chronic obstructive pulmonary disease (COPD) is also known by the alternative terms of chronic airflow limitation or chronic bronchitis and emphysema. These diseases are characterised pathologically by the presence of increased size and number of mucus glands within the airways resulting in a cough and excess sputum production. The sputum also obstructs the lumen of the airway reducing its calibre, and the flow of air into and out of the lung is further impaired by a marked increase in the size of the wall of the airway. Emphysema, a lung condition in which there is destruction and distortion of the airway sacs, may also be present to varying degrees. This interferes with the ability of the sufferer to pass oxygen from air to the bloodstream, and the exhaust gas carbon dioxide, in the reverse direction. The damage to the air sacs also causes a loss of lung elasticity and this further impedes the airway calibre.

COPD may result, in part, from certain occupations and certain adverse environmental conditions, but it is primarily associated with cigarette smoking.

3.1.2.2 The size of the problem

In most developed countries the prevalence of COPD in men is around 5-8 percent with a slightly lower rate for females. Figures for less affluent countries are more difficult to obtain but while smoking may be beginning to decline in some developed countries, trends in developing countries indicate that COPD is going to be of increasing concern.

3.1.2.3 Treatment of COPD

The pathological changes described above, once present, are predominantly irreversible and the scope for major therapeutic effect is much less than for asthma. Nevertheless, for the breathless patient with severe airway narrowing, even a 5-10 percent improvement in lung function is worth having and the majority of these patients benefit from the same airway opening drugs as do asthmatics. While most will benefit from beta agonist bronchodilating therapy, some treatment guidelines recommend that patients be treated with anti-cholinergic bronchodilators either as first line or as combination therapy.

Such drugs are administered from the same range of inhaler devices described previously.

After some promising initial studies, there are now several large European and US trials evaluating whether the use of inhaled steroids may slow the progression of COPD. Results of the first suggest a small beneficial effect and if confirmed, it is likely that in the future a larger number of patients with COPD might use up to three inhaled medications on a regular basis.

3.2 Metered dose inhalers

A metered dose inhaler (MDI) is a complex system designed to provide a fine mist of medicament for inhalation directly to the lungs for the treatment of respiratory diseases such as asthma and COPD.

The main components of all MDIs are:

- the active ingredient
- the propellant (a liquefied gas)
- a metering valve
- a canister
- an actuator/mouthpiece

The active ingredient may be dissolved in the propellant but is more often presented as a suspension of particles, the majority of which are less than 5 micrometers in diameter. A surface-active agent may be included to ensure that the drug is well suspended and to help lubricate the metering valve.

All existing CFC containing MDIs contain CFC-12 and CFC-11. CFC-114 is included in some products to modify the pressure, density and solvency properties of the formulation. It is essential that the propellant is a liquefied gas as the vapour pressure of the liquid provides a constant pressure throughout the life of the MDI.

The metering valve, which is the key to developing and presenting an accurate dose to the patient, is made up of seven or more precision-made plastic or metal components. The valve is crimped onto a canister, which is almost always made of aluminium. Finally there is the actuator which holds the canister and through which the patient inhales the dose.

When a patient uses an MDI the drug/propellant mixture in the metering chamber of the valve is expelled by the vapour pressure of the propellant

through the exit orifice in the actuator. As droplets of drug in propellant leave the spray nozzle the propellant gases expand, with very rapid evaporation, resulting in a fine aerosol cloud of drug particles.

Currently, approximately 500 million MDIs are used annually worldwide, using approximately 10,000 tonnes of CFC. Non-Article 5(1) Parties that requested essential use nominations for MDIs are reported to have used 7,893 tonnes of CFCs in 1996.

3.2.1 The CFC-free MDI

All the CFC-free MDIs under development contain the same components as the CFC products but the very different physical properties of the HFC propellants have meant that significant changes have had to be made.

The active ingredient remains the same but whereas almost all CFC MDIs are presented as suspensions, there will be at least one HFC propelled MDI which has the drug in solution.

CFC-free MDIs will contain the new propellants HFC-134a or HFC-227ea, and some products may contain both. The HFCs have very different properties to the CFCs, which have resulted in new formulations being developed, some of which contain a co-solvent such as ethanol to help dissolve the surfactant. There are also products on the market that do not contain a surfactant, simply being a suspension of micronised drug in propellant.

Although the elastomeric components of the metering valve have had to be changed to accommodate the HFCs (and in some cases the actuator has also been modified), this will not be obvious to the patient who will still be presented with an MDI that utilises a metering valve.

The CFC-free MDI as used by the patient may superficially look the same as the CFC MDI but the HFC products will have a different taste and mouth feel which will be obvious to the user.

3.3 Alternatives

In addition to the restricted number of reformulated MDIs, the currently available alternatives to CFC based MDIs are primarily:

- dry powder inhalers (single or multi-dose)
- nebulisers (hand held or stationary)

- orally administered drugs (tablets, capsules or oral liquids)
- injectable drugs.

In the future alternatives are likely to include:

- further non-CFC MDIs
- new nebulisers
- new DPIs
- pocket sized small volume nebulisers
- novel non-inhaled treatments
- soft mist inhalers – multi-dose, propellant-free inhalation devices.

The regulatory issues raised by the development of any new inhaler are substantial, since alteration of an inhalation device or excipient (e.g. propellant) requires extensive pharmaceutical, pre-clinical and clinical studies as a basis for a submission in each country. Development lead times are of the order of 5-7 years. Regulatory approval, which may take in excess of 2 years in each country, is then required before the product can be marketed. Some of the alternatives mentioned above are already in the market, and many others are in the late stage of development or under regulatory evaluation and will reach the market place in the next few years.

3.3.1 Dry powder inhalers

Dry powder inhalers (DPIs) have been formulated successfully for most anti-asthma drugs. These inhalers are an immediately available alternative for a large proportion of patients, but they may not represent a satisfactory alternative to the pressurised MDIs for all patients or for all drugs.

The first DPI became available in 1968 and like all DPIs, until the late 1980's, consisted of single pre-measured doses stored in gelatin capsules. At present DPI alternatives are available for most major inhalation products in a large number of countries.

Some dry powder formulations contain the active drug alone while others have a carrier powder such as lactose. The particles must be of sufficiently small aerodynamic diameter to penetrate the airways. Micronised dry powder can be inhaled and deposited in the airways as effectively from DPIs as from MDIs by patients with adequate breathing capacity. However, for some children, patients with severe asthma and other mainly elderly COPD patients and

patients experiencing acute airways obstruction, there may not always be adequate inspiratory flow to ensure optimal function of all DPIs.

Powdered drug particles tend to aggregate, thus delivery devices usually contain a mechanism to ensure adequate de-aggregation of the drug powder or separation of drug powder and carrier (where the product contains carrier) so that the drug particles are sufficiently small to be inhaled deep into the lungs. It is essential that patients use their DPIs properly. Excessive aggregation may further be a problem in some countries (for example, hot humid climates) or if patients exhale through the device.

Features of currently available dry powder inhalers:

- as lightweight and portable as MDIs
- require less co-ordination than most MDIs
- potential to use pure drug without additives
- difficult for patients with very low inspiratory flow – e.g. small children and the elderly
- may require special packaging for use in humid climates
- some require special handling during use
- the cost compared with MDIs varies between products and countries
- patient acceptability is not uniform
- in some countries, greater than 85 percent of inhaler use is DPI.

3.3.1.1 Single-dose powder inhalers

Single-dose powder inhalers are devices in which a powder-containing capsule is placed in a holder. The capsule is opened within the device and the powder is inhaled. The capsule residue must be discarded after use and a new capsule inserted for the next dose. In some developing countries these devices may have a role because they provide the opportunity to purchase a small number of doses.

3.3.1.2 Multi-dose powder inhalers

Multi-dose powder inhalers can deliver many doses without need to refill the device after each inhalation. Current products vary from four to up to two hundred doses.

There is an increasing use of the multi-dose dry powder inhaler and this is likely to accelerate as new multiple dose devices are produced, particularly as they may be more suitable for young children with sufficient inspiratory flow.

DPI usage globally as a percentage of all inhaled medication is estimated to be around 17 percent. This figure varies considerably from country to country, e.g. currently from 85 percent in Sweden to less than 2 percent in the USA and there are no DPIs yet available in Japan. A number of reasons exist for this variability including availability of the formulation, cost of DPI versus MDIs and reluctance to change. Worthwhile advances in the uptake of currently available DPIs have been made in the past few years. It seems unlikely that the uptake of DPIs in most countries will be at the levels seen in Scandinavian countries.

Astra Draco's Turbuhaler for budesonide was granted approval for marketing in the USA in 1997, as was Glaxo Wellcome's salmeterol Diskus (a long-acting beta-agonist) multi-dose device and Glaxo Wellcome's fluticasone in the Rotadisk for use with the Diskhaler. Whilst the potential exists for the introduction of multi-dose powder inhalers for other molecules, including the short acting beta-agonists (terbutaline; albuterol/salbutamol) and formoterol, a long acting beta-agonist, it is too early to assess the rate at which this will impact on CFC-MDI sales in the US.

In recent years some further multi-dose DPIs, Easyhaler from Orion, Clickhaler from Medeva have been made available in some countries. The introduction of these products has however not yet increased total use of DPIs substantially in these countries.

3.3.1.3 Development efforts

The DPI segment is subject to further substantial development efforts by a number of pharmaceutical companies and technology based device companies. This includes the development of new devices as well as formulation of new products in established DPI systems. A number of devices, mainly multiple-dose, are reported to be in late phase of clinical evaluation or subject to regulatory approval. The introduction of new and improved DPI products is likely to further stimulate the expansion of this treatment alternative, over the next decade.

3.3.1.4 Cost

In general prices of DPIs and branded MDIs of the same drug are similar. However, in some countries there is a significant price difference between

some DPIs and generic MDIs of the same drug. This is related to national pricing policies and local market considerations.

3.3.2 Nebulisers

Nebulisers are devices that are filled with drug dissolved or suspended in aqueous solution, which is converted to inhalable droplets using compressed air or ultrasonic waves. Nebulisers are generally not considered to be alternatives to MDIs but are restricted mainly to the treatment of infants and severely ill patients where patient cooperation is minimal or to situations when larger doses of drug and/or prolonged administration times are desired.

Air jet nebulisers use a source of compressed air to provide the energy to break up the liquid into small droplets. Established systems are not readily portable, are powered by compressed gas or electricity, and largely restricted to home or hospital use. Some portable systems have been recently introduced in their first markets. They are, however, still dependent on external power supply and thus restricted in their use. Hand-held nebulisers utilising modern technology however are under development.

Ultrasonic nebulisers utilise a vibrating crystal at the bottom of a nebulising chamber. The crystal vibration causes droplets to form on the surface of the liquid. These can be entrained in a stream of air created either by a fan or by the patient inhaling. Ultrasonic nebulisers are efficient but cannot be used for all drug formulations.

Features of nebulisers:

- most require a source of electricity or compressed gas and are very bulky and complicated to set up and use;
- dose reproducibility is relatively variable;
- electric nebulisers require 5-20 minutes to deliver a dose;
- do not require patient coordination;
- currently treatment cost is generally higher than for MDIs.

3.3.1.5 Development efforts

The development of small hand-held nebulisers is of particular interest as it aims at pocket sized devices which are as flexible and easy to use as the MDIs. Most development programs are however at an early stage and will probably need some more years to be finalised.

3.3.2 Oral medication

Oral medications include tablets, capsules and oral liquids and have been the standard form of therapy for most diseases for many years. Taken by mouth the active ingredient is absorbed from the gut, then circulated by the blood stream throughout the body (including the lungs). For existing products such as steroids and bronchodilators, tablet therapies involve higher doses and greater risk of side effects. For this reason treatment guidelines have favoured the inhaled route for the treatment of airway disease.

Features of oral products:

- simple technology which is widely available;
- convenient and easily transportable;
- easy to administer;
- better patient compliance than with more complex devices;
- higher doses needed than inhaled medication;
- usually more side effects than inhaled medication;
- some drugs effective by inhalation are not effective as oral therapy.

3.3.2.1 New oral therapy

Regulatory authorities in some countries have recently approved four novel oral compounds (leukotriene modifiers) for the treatment of asthma. These may be of value to a certain number of those with asthma, but it is unlikely that these will be a full substitute for the current inhaled preventive therapy. Where these new drugs will fit into international Asthma Treatment Guidelines is not clear, but it appears they may be most appropriate after failure to obtain a satisfactory response to current inhaled therapy. The mainstay of therapy for asthma and COPD is likely to remain therapy administered by the inhaled route.

3.3.3 Injectable therapy

Some drugs used for the treatment of asthma and COPD are also available in injection form. However, this is not practical for general use in ambulatory patients and is therefore reserved for the treatment of hospitalised patients.

3.4 Development of MDI products using HFC-134a and HFC-227ea

The process of reformulating MDIs with HFCs began in late 1988 when HFC-134a was proposed as an alternative to CFCs. Work on HFC-227ea began approximately 18 months later. Since that time, individual companies have been working on reformulating their own products to replace CFCs with the appropriate HFC. This has been difficult since the three most common surfactants used in CFC-based inhalation aerosols are not soluble in HFCs and the valve elastomers used on CFC valves are not all compatible with HFCs. Thus companies have been innovative in their reformulations and each product has been treated as a completely separate case. No two products have exactly the same qualitative and quantitative formulation ingredients.

The easier products to reformulate could not have been forecast from existing knowledge, but there are several products whose reformulation is essentially complete and their registration is now taking place around the world. There are also other products that are proving very difficult to reformulate and it is likely to be several years before all existing CFC MDIs have been successfully reformulated. It is only after successful reformulation that product stability testing and extensive clinical studies can commence.

3.4.1 Preclinical requirements

HFC-134a and -227ea are novel pharmaceutical excipients (inactive ingredients) proposed for widespread and long-term use. They therefore have undergone the same toxicological testing required for any new chemical drug substance.

The testing programs consisted of a wide range of studies, dictated by the overlapping regulatory requirements of health authorities from around the world. They were in the following general categories:

- single dose toxicity
- repeat dose toxicity
- reproduction studies
- mutagenic potential
- carcinogenic potential
- safety pharmacology
- toxicokinetics

3.4.2 Clinical and regulatory requirements

Final guidelines were issued by the European Union (Committee for Proprietary Medicinal Products) and a guidance is available in the USA (FDA) for the clinical studies needed for the replacement products.

The US and European Union guidelines both indicate that in addition to full laboratory characterisation of the delivery characteristics of the reformulated product, both clinical efficacy and safety determinations are necessary.

Regulatory authorities will require the following:

- initial tolerability and dose ranging studies (occurring in small numbers of subjects)
- efficacy data
 - acute dosing studies (e.g. bronchodilators)
 - chronic dosing, bronchial challenge (anti-inflammatories)
- safety data
 - short term (acute toxicity)
 - long term clinical experience (large populations)
- separate studies are generally required for adults and children
- expectations for the design of clinical trials may differ between regulatory authorities
- large scale efficacy and safety studies (up to 12 months) then proceed in parallel to reflect the general patient population, e.g., age groups and different degrees of disease severity
- studies designed to compare the CFC and non-CFC MDIs have to be large enough to detect a difference between the two products, if one exists (usually several hundred patients)

3.4.3 Current status

In order to minimise the use of HFCs and the number of animals needed for toxicity testing, the pharmaceutical industry formed two consortia, IPACT I and II which undertook the required toxicity testing on HFC-134a and HFC-227ea respectively.

The IPACT I and II testing programs were established in May and December 1990 respectively. The consortia were formed to fund and manage extensive toxicology testing programs designed to ensure the safety of HFC-134a and HFC-227ea as CFC replacements for use in MDIs. The consortia consisted of major European and North American manufacturers and distributors of MDIs. Each company has been and will be responsible for the toxicity testing of each of their HFC formulations. These data will be combined with the Consortia generated data to provide the toxicological package for submission to government agencies.

3.4.3.1 HFC-134a

A full set of preclinical safety data on HFC134a has been completed through IPACT I, a CFC producers consortium PAFT (Program for Alternative Fluorocarbon Toxicity Testing) and one MDI manufacturer who performed its own independent program of toxicology testing on HFC-134a. These programs included two-year carcinogenicity studies in rats and mice. No toxicity or oncogenicity associated with HFC-134a was reported from this testing.

The European regulatory authorities (CPMP) approved the IPACT I toxicology data for HFC-134a as suitable for MDI use in July 1994. The Drug Master File (DMF) for HFC-134a was submitted to the USA FDA in September 1992 and subsequently was reviewed as part of the marketing approval of the first salbutamol HFC MDI in September 1996.

3.4.3.2 HFC-227ea

The complete set of preclinical safety data on HFC-227ea has been completed through IPACT II.

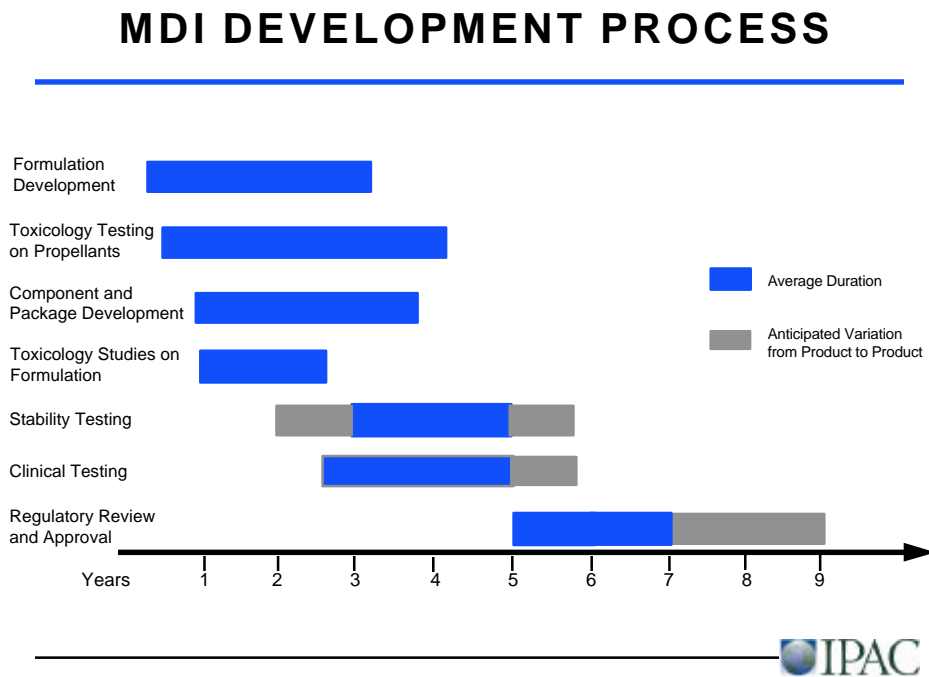
No toxicity or oncogenicity associated with HFC-227ea was reported from this testing.

The European regulatory authorities (CPMP) approved the IPACT II toxicology data for HFC-227ea as suitable for MDI use in September 1995. The Drug Master File (DMF) for HFC-227ea was submitted to the USA FDA in July 1993.

3.4.4 Timetable from development to approval

In the ATOC 1997 Update Report, graphical representations were included for projected timetables for the launches of HFC MDI products in both the European Union and the USA. These were based on an industry survey of IPAC members. More recent company specific data is available that indicate that a number of companies are well advanced with their reformulation programs. However, it would appear that the projected “best case” scenario is now not possible due to technical and regulatory delays.

Table 3.2 *Timetable for Completing Development of CFC-free MDIs in the United States (Courtesy of IPAC)*



The most recent details for each of the major manufacturers are listed below.

3M Pharmaceuticals has approvals for and is currently marketing salbutamol HFC MDI in over 40 countries. In the USA, salbutamol HFC MDI has been licensed to Schering Plough. 3M's beclomethasone HFC MDI has been submitted for approval in several countries with the first introduction anticipated during second half of 1998. Under a further licence agreement, Hoechst Marion Roussell and 3M Pharmaceuticals have entered into a strategic marketing alliance to co-promote some of 3M's HFC MDI products.

Glaxo Wellcome has filed registration applications for both salbutamol HFC MDI and fluticasone propionate HFC MDI (125/250 mcg) in over 30 countries worldwide. A number of product approvals have been received and products launched in many countries in Europe including Austria, Denmark, France, Germany, Greece, Holland, Norway, Spain, Switzerland and the United Kingdom. Further product launches outside of Europe are anticipated in the coming year.

Rhone-Poulenc Rorer has filed applications for triamcinolone HFC MDI in the USA and Canada. Filings for di-sodium cromoglycate HFC MDI have been made in 21 European countries, in the United States and in Japan.

Boehringer Ingelheim first submissions for reformulated products are scheduled during 1998.

Ivax (Norton Healthcare) launched its first HFC MDI, beclomethasone dipropionate in Ireland in January 1998. The same product range is also approved in France and further international approvals are pending. Norton also expects to receive its first regulatory approvals for salbutamol HFC MDI before the end of 1998.

3.5 Transition to alternatives

The schedule for the safe introduction of new propellants and reformulated products, which was suggested in the 1994 ATOC report and confirmed in the 1996 and 1997 reports, remains on target. It is likely that a wide range of reformulated products will be available in many developed nations and transition will be making good progress by the year 2000. Minimal need for CFCs for MDIs is envisaged by the year 2005 in non-Article 5(1) Parties. Remaining technical, patent, safety and regulatory issues for some commonly used drugs still make it difficult to predict the schedule for full phase-out with precision.

The ATOC does not believe that a rigid global transition strategy is appropriate in view of the widely differing circumstances of individual Parties. However, the Parties could consider the benefits of a "Global Transition Framework" which would underpin national strategies and ensure that they are complementary. Because the phase-out of CFC containing MDIs in non-Article 5(1) Parties is anticipated in the next few years, the Parties may wish to recommend that Article 5(1) Parties and CEIT start work on preparing their national transition strategies.

3.5.1 Patient subgroups

The ATOC has considered the implications of the transition for patient subgroups which may have compelling medical needs.

Some patients may have a personal preference for CFC MDIs. This matter is likely to be overcome by educational endeavours and should not be the basis for a continuing essential use nomination. Many patients can convert to DPIs. DPIs are continuing to be introduced by a number of companies into many countries. There is good evidence that the previously noted trend of increased DPI usage continues but since overall inhaled therapy has increased further, they have not reduced the sales of MDIs.

A second subgroup which may have a compelling need for CFC products well into the phase-out is low income patients (whether in Article 5(1) or non-Article 5(1) Parties) who rely on less expensive generic or locally branded products for control of their diseases. This issue has less to do with HFC MDIs versus CFC MDIs than it does with branded versus generic product price differentials, since it does not appear that HFC MDIs will be more expensive than their branded CFC counterparts.

3.5.2 Education and training

To facilitate patient and physician utilisation of the reformulated products, global education and training are required. Options currently employed and planned include:

- *Professional associations* – through medical journals, medical symposia, reports and newsletters.
- *Treatment guidelines* issued by the country's medical authority which document the advantages and drawbacks of different forms of therapy and recommend specific forms of care for specific patient groups.
- *Promotional material and media coverage* – Advertising and promotional material placed in medical journals and circulated to physicians by pharmaceutical companies.
- *Pharmaceutical industry* – Education of the medical profession, support of medical symposia, reprint of pertinent articles and reports and information sheets to patients are strategies to help to inform both professionals and the public of developments and alternatives.
- *Medical literature* – Articles appearing in the medical journals inform professionals of developments, and several have been published since

1994, many written by members of the ATOC, with further major editorials due to be published in 1998.

- *Support groups* that provide information, seminars and programs aimed at both the general community and through schools, sporting groups etc.

The amount of educational activity being undertaken varies from country to country and should involve increasing awareness of DPIs as well as the reformulated MDI products. As more alternatives become available it is essential that a more active patient strategy is developed. This will involve concerted effort by the industry, and by health professional associations and national health authorities working together with patient support associations (e.g. National Asthma Campaigns and Asthma Foundations). For Parties without patient support associations it is possible that the NHLBI/WHO Global Initiative (GINA) may be able to have available suitable literature for copying in the same way as they do with their current patient booklet, or add transition information to the GINA page on the Internet (<http://www.ginasthma.com>).

Professional bodies and patient associations are most likely to address this issue if governments take a lead in highlighting the importance of the subject. These educational activities are likely to require funding. Responsibility for and sources of adequate funding need to be identified if a successful transition is to occur.

Increasing numbers of medical symposia are scheduled for 1998/9, including the World Asthma Meeting in December 1998. This is supported by the major world respiratory organisations (European Respiratory Society, European Society for Asthma, Allergy and Immunology, American Thoracic Society, Asia-Pacific Society of Respiriology, American Academy for Asthma, Allergy and Immunology, International Union Against Tuberculosis and Infectious Disease and GINA). This meeting will highlight issues surrounding the safe transition to non-CFC treatments. UNEP is a co-sponsor of the World Asthma Meeting.

The ATOC has reported to the Parties on issues surrounding transition strategies in response to Decisions VII/34, VIII/12 and IX/19 in the TEAP reports of 1996, 1997 and 1998. New information can be included in annual updates provided by the TEAP but has not been further elaborated in this Assessment Report.

3.6 Use of CFCs during the manufacture of MDIs

The first stage of the process is the delivery of propellants to the manufacturing facility where the materials are transferred from the delivery vehicle to large storage tanks. Transfer is very efficient and very little material is lost during the process.

There are two manufacturing processes used to make MDIs, cold filling and pressure filling, both of which require the preparation of a concentrate comprising active ingredient, some CFC-11 and surfactant. This operation is conducted in chilled or pressurised tanks from which the blend is pumped to the filling line. The concentrate preparation is carried out in carefully controlled conditions and because CFC-11 boils at 23°C, losses are minimal.

Can-filling is carried out by cold or pressure filling. In the former the concentrate is mixed with propellants chilled far below their boiling points and the entire blend is metered into cans. As the chilled formulation at -60°C comes into contact with cans at room temperature, the first part of the liquid to make contact is vaporised. The amount lost is small as the can is then immediately sealed with a metering valve.

With pressure filling the concentrate is added to the can which is immediately sealed with a metering valve. The remaining propellant is then injected via the valve stem using a pressure of 300-400 psi. As the gassing adaptor releases and moves from the valve stem, a small puff of CFC is released into the atmosphere.

On a per can basis the two filling processes consume an approximately equivalent amount of CFCs. It is very difficult to capture the 0.1 to 0.2 ml of CFC lost at the point of filling each container as the use of any extraction equipment will affect the precise environmental conditions at the filling head.

Each MDI canister is actuated three or four times after it is filled and sealed to ensure that the metering valve functions in accordance with the specification. This constitutes the largest single source of CFC emissions during the manufacturing process. The product released is captured and vented to the outside atmosphere and it is impossible to recycle the CFCs due to the presence of active medicament and excipients.

CFC-11 is used by valve suppliers to leach out extractables from the elastomeric seals used in the MDI metering valve. This is a critical process and is carried out in an enclosed recirculating system. Most of the CFC-11 is re-used but some is retained in the contaminant slurry that is the waste product from the extraction. This slurry is sealed in waste containers and taken by a specialist company for destruction.

Overall greater than 90 percent of the CFCs required each year for MDIs are filled into the product used by patients. The manufacture and on-line testing of MDIs results in some CFC being released to the environment. Current technology does not permit the collection of this material. Additionally, of the order of 1 percent of all MDIs manufactured are rejected because the weight of contents lies outside the strict limits agreed with regulatory authorities. Most major MDI manufacturers now use a process that has been developed which permits the collection of CFCs from those rejected MDIs for recycling for other applications.

3.6.1 CFC minimisation efforts during manufacture and testing

3.6.1.1 Test firings

One manufacturer has introduced equipment that for certain formulations reduces the number of mandatory test firings from four to two. The first firing is in fact a priming shot that emits virtually no propellant. The second shot is automatically checked for spray characteristics and quantity during the manufacturing process.

In addition to testing during manufacture, the Quality Assurance laboratory fires to exhaustion ten cans from every batch resulting in further emissions.

3.6.1.2 Propellant recovery process

As mentioned above, technology is now available to recover CFCs from reject aerosols. A simple system for propellant extraction has been devised and allows cleaning of the propellant of all contaminants leaving a mixture of CFC-11 and -12 acceptable for reconstitution into CFCs and HCFCs for use in other sectors.

The equipment is also used to clean the liquid bulk CFC-11 used to flush the aerosol filling lines. The process yields exceptionally clean material that is also returned to the manufacturer for reprocessing.

3.7 Use of recycled CFCs

An intensive study on the possibility of using recycled CFCs was carried out on behalf of IPAC in 1993. The study analysed materials recovered from refrigeration plants and concluded that both recovered and reclaimed CFCs are complex mixtures. The predominant contaminants are straight chain, aromatic and polycyclic hydrocarbons but there are hundreds of other compounds present in smaller amounts. Even when concentrating on the more abundant

components of the mixture it was evident that no two samples were alike in either composition or concentration.

To be used in MDIs recovered CFCs would have to meet the same rigorous specifications as applied to virgin materials (i.e. free of toxic impurities). Because of the very complex nature of the contaminants and their number, it is impractical to develop commercial facilities to purify used CFCs to pharmaceutical standards.

A conclusion of the IPAC report was "...in view of the special risks involved in exposing millions of highly sensitive asthmatics to material already used for commercial and industrial purposes...authorities would be concerned about the possibility of unknown impurities that escaped detection in the manufacturing process."

3.8 Stockpiling CFCs for future production of MDIs

Stockpiled CFCs cannot be seen as a complete replacement for the annual essential use allowance for the production and consumption of virgin CFCs in non-Article 5(1) Parties. At present, stockpiling can only be viewed as a short-term measure to provide buffer stock of CFCs.

The purpose of maintaining a reasonable strategic reserve or buffer stock of CFC can be broadly summarised as:

- a) in order to guard against supply interruption
- b) provide ability to cope with unexpected demands.

The reasonable quantity must be sufficient to adequately achieve (a) and (b) above whilst ensuring that over-stocking does not act as an impediment to transition. In view of the risks inherent in the supply of bulk CFCs, the observed increasing demand volatility and the role that inhaled medicines play in asthma therapy, strategic reserves need careful and possibly region specific approaches.

Pharmaceutical MDI manufacturers have concerns over the viability of the CFC supply base and have taken the operational decision to create storage facilities for strategic reserves of CFC in Europe and North America. On the other hand, CFC suppliers have indicated that CFC plants in the EU will remain operational for the next several years to meet the basic domestic needs of Article 5(1) Parties and for MDI manufacture.

After July 1999 levels of CFC production and consumption in Article 5(1) Parties will be frozen. It is expected that some CFC manufacturing facilities

now operating in Article 5(1) Parties might be closed as a result of initiatives undertaken under the Multilateral Fund to reduce global CFC production. If these assumptions are correct, and CFC manufacture is consolidated on a few producers, this should result in sufficient supplies of medical grade CFCs during the transition.

However, as a prudent step to ensure medical grade CFCs are available as long as Essential Use Allowances continue, attempts are being made to qualify suitable pharmaceutical quality CFC plants in China and India. However both feedstock and process quality have yet to meet the specifications for the production of CFCs for MDIs in non-Article 5(1) Parties. This process might take several years to complete.

It is critical that secure supplies of CFCs for MDI manufacture be maintained for the full transition period. Extended supply routes that may be subject to unforeseen circumstances underpin the need to have adequate stockpiles.

3.8.1 Demand analysis

MDI volume demand continues to grow throughout much of the world. This is driven by higher disease diagnosis and effective treatment using MDIs. In many markets MDIs will remain the device of choice for inhaled therapy for the foreseeable future. As large volume CFC MDI products such as salbutamol and beclomethasone decline in developed markets (e.g. Europe and N. America), this is currently being offset by the rapid and difficult to forecast growth in the rest of the world

For example, in 1997 one company experienced quality problems for CFC manufactured in Latin America. This generated an unforecast demand for the manufacture of over 4 million CFC MDIs in Europe for use in Latin America. This illustrates that demand volatility or supply interruptions anywhere in the world can directly impact European MDI production, where according to a recent survey of IPAC members, approximately two thirds of the world's MDI requirements are currently produced.

Lack of predictability of regulatory approvals of HFC MDIs has also made accurate forecasting of CFC requirement very difficult.

3.8.2 CFC stock levels

The factors highlighted above, i.e. CFC supply interruption and demand volatility, taken together with the consequence of any CFC MDI product supply interruption, are the factors routinely used when assessing appropriate stock levels.

As an example, experience gained with two common excipients used in the manufacture of inhaled products leads to the following stock holding:

- lactose (excipient in dry powder inhalation devices) – 12 months
- lecithin (surfactant used in CFC MDIs) – 15 months

Given levels of supply interruption risk, difficulty of qualifying new supply sources, demand volatility and consequence of product shortage, CFC supply policies should be adopted that are consistent with these other critical raw materials.

At present, given the nature of the supply base and demand pattern, a stock of up to 12 months of forward demand seems prudent. However, these levels may be adjusted depending on special circumstances.

3.9 Article 5(1) Parties and CEIT

In 1997 the Parties requested a further report on the impact of the CFC phase-out in Article 5(1) Parties and CEIT. The current protocol provisions regarding Article 5(1) Parties are as follows:

The first control measure on the total consumption of CFCs in Parties operating under paragraph 1 of Article 5 of the Montreal Protocol commences in the year beginning 1 July 1999, with a freeze at an average of 1995-7 levels. This is followed by reductions in consumption of 50 percent in 2005 and 85 percent in 2007, with phase-out in the year beginning 1 January 2010.

These controls on CFCs make no allowance to permit exemptions for essential uses prior to the phase-out date of 2010. This will mean that MDI manufacturers in Article 5(1) Parties will be competing for CFC supply in their local markets with other users of CFCs, such as the foam and refrigeration industries. Such competition could lead to rises in the price of propellants and therefore make CFC-free MDIs more economically attractive.

3.9.1 The manufacture of CFC MDIs for export to Article 5(1) and non-Article 5(1) Parties

Paragraph 1(a)(ii) of Decision IV/25: Essential Uses states

“ that a use of a controlled substance should qualify as ‘essential’ only if:

- a) it is necessary for the health, safety or is critical for the functioning of society (encompassing cultural and intellectual aspects); and*

- b) *there are no available technically and economically feasible alternatives or substitutes that are acceptable from the standpoint of environment and health;*”

A strict interpretation of the above paragraph would indicate that once CFC-free MDIs were available in a specific Party, then no further exemption for CFC use should be permitted for that Party. Such an interpretation would mean that CFC-use for the manufacture of MDIs in non-Article 5(1) Parties for export to other non-Article 5(1) or Article 5(1) Parties would not be permitted.

In many countries, the process of regulatory approval for a new treatment can take a number of years and the consequences of the above interpretation could lead to severe concerns over compromise of patient care. A number of Parties have previously expressed such concerns regarding patient care in Article 5(1) Parties during the MDI transition in non-Article 5(1) Parties. This led to Decision VIII/12 (5) which requested the Technology and Economic Assessment Panel to provide a report to the Tenth Meeting of the Parties “...on issues surrounding a transition to non-CFC treatments of asthma and chronic obstructive pulmonary disease in Parties not operating under Article 5(1) that is fully protective of public health.” Items to be considered included the following:

“(b) The impact on the right and ability of patients in Parties operating under Article 5(1), in countries with economies in transition, in Parties not operating under Article 5(1) with large disadvantaged communities and in importing countries to receive CFC-based MDIs where medically acceptable and affordable alternatives are not available due to reductions in essential-use exemptions in Parties not operating under Article 5(1) for CFC-based MDIs;...”

Parties may wish to consider the procedure by which non-Article 5(1) Parties which no longer need CFCs for their own use can continue to produce CFC MDIs for export for a limited period, as necessary. Some CFC supply will be needed by multinational companies in, for example, the EU to enable them to service the continuing need of some Article 5(1) Parties for CFC MDIs.

3.9.2 Current situation in Article 5(1) Parties and CEIT

Communication with experts in a number of countries including India, Pakistan, China, Brazil and Russia has revealed a similar situation in most, but there are some country specific issues. In all countries, the limited information that is available suggests that the airway diseases of asthma and chronic obstructive pulmonary disease (COPD) are common and increasing in prevalence. A new validated questionnaire survey of children (aged 6 to 7 and

13 to 14) has been undertaken in 34 countries so far and reported results show that the prevalence of symptoms suggestive of recent asthma vary from 2 to 35 percent amongst 13 to 14 year olds (*ISAAC – International Study of Asthma and Allergies in Children*). Data have not yet been reported from all of the relevant countries. Whilst it is likely that rates in some Article 5(1) Parties may not be as high as in non-Article 5(1) Parties, high prevalence rates are likely in India, Pakistan and Brazil, with slightly lower rates in China.

The Russian population is approximately 150 million people. There are higher rates of COPD reported than for asthma, reflecting heavy use of tobacco products. However, there is also likely to be some under-diagnosis of asthma. Estimates suggest a minimum of 4 million people with significant airways diseases and it is suggested that in that country, only approximately 10 percent of these patients utilise modern inhaled therapy from MDIs. The impact of patient and health professional education upon these figures can be shown by an intervention in Moscow where following education, the number of children using MDIs increased by 50-60 percent and the number of MDIs used by these children with asthma increased 5 to 7 times. There is local production of MDIs in Russia and the Ukraine but most MDIs are imported.

Brazil has a population of 180 million people and an estimated asthma prevalence of 10 percent. Exact prevalence figures for COPD are not available. The major proportion of MDIs is imported, but there is some local production. MDI production is by multinational companies that currently sell 5 million CFC MDIs every year.

In China, where there is a population of 1.2 billion people, there are 16 million people with asthma and 65 million with COPD. There are many CFC aerosol products used for medicinal purposes and CFC usage is not currently confined to MDIs for the treatment of airway diseases. Three multinational companies import and produce locally (accounting for 20 percent of China's production) and there are over 60 pharmaceutical aerosol producers. In 1996, such companies produced fifteen million CFC MDIs and there was further production of 1 million units in hospitals. Consumption of CFCs for use in MDIs in 1996 totalled 400 tonnes. Products from multinational companies (either produced locally, or imported) are six times more expensive than local Chinese products.

In India, a country of approximately 920 million people, it is estimated that 10 percent of the population have airway diseases. For various economic, cultural and health delivery reasons, only 1 percent of these people are currently treated with MDIs. Two multinational companies produce locally (accounting for 25 percent of India's use) and four domestic companies have facilities for MDI production. At the present time, 6 million MDI units are sold annually with an additional 3 million being exported by one, large Indian

company to other Article 5(1) Parties. Local manufactured products are said to retail at approximately the same price as those produced by the multinational companies.

Pakistan has a current estimated population of 150 million people. There are no firm epidemiological data regarding the prevalence of asthma and COPD, but it is thought that 10 percent of the population have asthma. Forty percent of adult males smoke and the prevalence of smoking-related airway disease is expected to rise. Fewer than 5 percent of patients with airway diseases are using MDIs, but this number is expected to rise with the introduction of new national asthma guidelines and as availability of inhalers increases. MDIs are imported and also produced locally by multinational companies and annual sales currently total 1.7 million units. There are no known locally owned producers.

In each of these countries, there is reported to be poor awareness of CFC and transition issues in general, as well as a lack of health professional awareness. Also, since it is anticipated that in most Article 5(1) Parties and CEIT there will be an increasing number of patients newly receiving MDI therapies, it would be preferable for them to start on CFC-free products to the greatest extent possible.

3.9.3 Technology transfer, local production and costs

Continued provision of MDIs in Article 5(1) Parties and CEIT will depend either upon import of products, or local production. The local production of CFC MDIs is likely to continue for some time after cessation of their use in non-Article 5(1) Parties and will overlap with the importation of CFC-free MDIs by multinational companies (the introduction of the latter will require approval by regulatory authorities).

Local production of CFC-free MDIs by a local producer, a multinational company, or by a local producer in collaboration with a multinational company will require the transfer of new technologies and may require new licensing arrangements and transfer of intellectual property. The costs of such local production of CFC-free inhalers will thus involve capital costs and either multiple year or one off licensing arrangements. Multinational companies operating in Article 5(1) Parties should be encouraged to make the technology transfer as soon as possible. Even if satisfactory arrangements can be made, the work involved in introducing the new technology into a large number of production facilities is likely to take some time. The costs of the new inhalers (whether imported or produced locally) is likely to be similar for branded products. Therefore, the cost implications to any one Party, whether non-Article 5(1) or Article 5(1) of the transition will be dependent upon what

proportion of their previous use comprised of locally branded and generic MDIs compared with branded products (either domestic or imported).

3.9.4 Transition strategies – Article 5(1) Parties and CEIT

Because the phase-out of CFC containing MDIs in non-Article 5(1) Parties is anticipated in the next few years, the Parties may wish to recommend that Article 5(1) Parties and CEIT start work on preparing their national transition strategies. Such strategies should include educational programs for health care professionals, and awareness that such transition could increase health care costs. Along with the CFC transition issues, such planning should include efforts to increase the proportion of populations receiving modern therapy as outlined in international guidelines. Increasing the percentage of patients with airway diseases who receive modern therapy from the current figures of less than 10 percent in many countries is likely to require concerted government action.

3.9.5 Conclusions

Regarding Article 5(1) Parties and CEIT, Parties may therefore wish to consider:

- the paramount importance of maintaining adequate supplies of the necessary range of inhaled medications during transition in non-Article 5(1) Parties
- the circumstances and process by which non-Article 5(1) Parties which no longer need CFCs for their own use can continue to provide CFC MDIs for export for a limited period of time
- how to encourage the introduction of CFC-free technologies into these countries
- encouraging these countries to start work on preparing their national transition strategies
- how to ensure that transition strategies do not impede the introduction of modern inhaled therapies in these countries.

4. Sterilants

4.1 Introduction

CFC-12 can be mixed with ethylene oxide to make non-flammable mixtures. Typically a 12 percent by weight EO and 88 percent CFC-12 is used. EO is a sterilant of medical/surgical equipment and devices. It has the ability to penetrate packaging materials, destroy microorganisms and diffuse away from the package leaving almost no residues after sufficient aeration. Medical authorities have established standards for acceptable levels of these residuals after processing.

Sterilisation with EO is used preferably to treat heat and moisture sensitive products which are wrapped in materials that maintain sterility once the product is removed from the sterilisation chamber. EO is toxic, mutagenic, a suspected carcinogen, flammable and explosive. Great efforts have been made to replace EO as a sterilant, particularly in hospitals where personnel exposure is of great concern. The fact that EO is still widely used as a sterilant is evidence that in numerous applications, the benefits of its use outweigh these disadvantages.

There is a range of sterilisation methods, of them some use EO while others do not. EO can be used as a sterilant either alone or diluted with other gases such as CFC-12, blends of HCFCs or carbon dioxide (CO₂). Methods that do not rely on EO include steam sterilisation, dry heat, formaldehyde, radiation and ionised gas plasma.

Sterilisation of medical devices can be performed in industrial settings with large outputs of the same item (such as manufacturers of syringes and droppers) and in hospitals with much smaller outputs, but great diversity of items. Process requirements for these two settings are very different.

4.2 CFC and HCFC use for sterilisation worldwide

Use of EO/CFC blends for sterilisation has been successfully phased out in most non-Article 5(1) Parties. In Article 5(1) Parties some use of EO/ CFC blends remains. Although it is difficult to estimate, it is believed that the global total use in 1998 is less than 1500 metric tonnes. Consumption patterns are very different, thus while no use of 12/88 mixtures is reported for China, consumption of 12/88 has been reported in more than 40 other Article 5(1) Parties. There are indications of increased use of CFC-12 as a sterilant gas diluent in some Article 5(1) Parties. Some manufacturers of surgical equipment may even be shipping products from non-Article 5(1) Parties to be sterilised in Article 5(1) Parties.

HCFC replacement mixtures are used mostly in the USA and in some European countries. The EU has legislation restricting the use of HCFCs in emissive applications such as sterilisation. HCFCs are virtual drop in replacements for 12/88. The new gas mixtures require validation for the particular application and compatibility with the product and its packaging needs to be established. As such, HCFCs remain important as transitional products in sterilisation in those countries that previously employed 12/88 extensively. Estimated use of HCFC replacement mixtures in 1998 is thought to be less than 3000 metric tonnes (some 90 ODP tonnes). CEIT and Article 5(1) Parties that are using 12/88 can convert to these HCFC mixtures with reasonable cost and no changes in operating procedures.

4.3 Available options for replacing CFC-12

Methods for sterilisation of medical / surgical equipment and devices developed differently in each country, due to the respective codes and regulations on fire protection, occupational safety, validation of results, liability considerations, availability of sterilisation equipment and materials, and medical practices.

There are many types of sterilisation technologies available and they have applications for particular products. Quality health care is dependent upon sterility assurance of medical devices. Validation of processes for the intended application is important to avoid either materials compatibility problems or deficiencies in the level of sterility. Not every process/sterilant will be compatible with all products. But once a technology is validated for a specific application it becomes a viable alternative for that application.

A brief list of alternatives currently available to reduce or phase out the use of ODS follows. More detailed descriptions were included in the 1994 Report of this Technical Options Committee.

Steam Sterilisation: This process is non-toxic, economical, and relatively safe and it is well established. Devices treated must withstand a temperature of 113 C (235 F) at least and very high moisture levels.

Formaldehyde: Used mainly in Europe for materials that can withstand temperatures of 80-85 C (176-185 F), although uses at 60-65 C (140-149 F) have also been reported. Formaldehyde is toxic and a suspected carcinogen.

100 percent EO: EO can be used as a flammable gas if proper safety requirements are met. Equipment has to be designed according to user needs. These range from large industrial units to small hospitals that use small canisters of 157g EO. As mentioned before EO is toxic, mutagenic and a

suspected carcinogen, but a well-proven sterilant for heat sensitive materials and devices.

Blends of EO and CO₂ : Carbon dioxide can be used to produce non-flammable mixtures with EO. A common ratio is 8.5 percent EO and 91.5 percent CO₂. Operating pressures are about ten times higher than for 12 / 88; use of blends of EO and CO₂ has other disadvantages, such as composition changes while a single tank or cylinder is used, increased polymerisation, and compatibility and corrosion problems caused by the acidity of CO₂. Flammable mixtures of EO and CO₂ are also used in some countries; these mixtures should be handled with the same precaution as 100 percent EO.

Blends of HCFCs and EO: These HCFC-124 containing blends are virtual drop in replacements for 12/88. The new gas mixture requires validation for the particular application and compatibility with the product and its packaging needs to be established. They have been used for the last four years and allow continued use of expensive sterilisers with minor control adjustments. Their use in some European countries is restricted by regulations on emissions of HCFCs and can be used only in existing equipment. As mentioned above, these are important transitional products in those countries that previously employed 12/88 extensively. CEIT and Article 5(1) Parties that are using 12/88 can convert to these HCFC mixtures with reasonable cost and minimal changes in operating procedures. Estimated use of HCFC replacement mixtures in 1998 is thought to be less than 3000 metric tonnes (some 90 ODP tonnes)

Radiation: There are two different processes, one based on gamma radiation and the other on electron beam. Both processes are well established, and usually used in large facilities. Not all materials are compatible with radiation. Facilities using gamma radiation need to dispose of spent isotopes and are not acceptable for hospitals.

Ionised Gas Plasma: Several processes have been commercialised. They have significant technical differences, for instance in one case the plasma is produced in a hydrogen peroxide atmosphere, while in another it is generated in a peracetic acid environment. Many units of these different processes have been sold worldwide in the last four years, mostly to hospitals. One of these processes, which had not received FDA approval for this application, was recently associated with patient injuries when ophthalmic surgical instruments sterilised with this system were used. The cause of the problem appears to be the formation of toxic salts when the device is used on surgical tools made of copper, brass or zinc. A global recall of this particular ionised gas process was mandated.

4.4 Conclusions

CFC-12 use in the sterilisation sector has been phased out in most non-Article 5(1) Parties. Use that remains worldwide can be substituted easily, at minimum equipment replacement cost, by using drop in HCFC blends. These blends have a small ODP (0.03) and should not be promoted in countries that have not been major 12/88 users. Alternatively, other sterilisation options can be considered for uses where the technology has been proven effective and appropriate.

Sterilisation is an important step for good quality health services. It is also a delicate process that requires strict quality assurance, reliability, and long term materials compatibility. Therefore, any alternative to the use of ODS needs to be well proven and tested to avoid putting unnecessarily at risk the health of patients.

5. Miscellaneous uses

Noted below is a selection of miscellaneous uses. Most of them are believed to represent only small amounts of CFCs. There could be other small applications of CFCs, varying from country to country. These uses are difficult to identify and obtain good data on volume and use patterns. Any new information would be gratefully received by the ATOC for future reports. With the phase-out of CFCs in developed countries for non-essential uses, the use of CFCs in miscellaneous uses in, for example, leak detection or solar panels, is most likely almost non-existent.

5.1 Tobacco expansion

It is difficult to estimate the 1998 worldwide use of CFC-11 to expand tobacco due to declining use. After 1998, China may be the only remaining country to use significant quantities of CFCs for this purpose. In 1996, 4050 tonnes were used in China compared with 900 tonnes in 1992. Based on the recent and planned installation of alternative carbon dioxide technology in China, declining use in this country is expected.

Most countries have stopped or will shortly stop the use of CFCs to expand tobacco:

- By the end of 1998, Mexico and the Philippines should have carbon dioxide plants on line that will eliminate the use of CFCs in those countries. Mexico has used approximately 300 tonnes.
- Most major tobacco companies in Indonesia and Malaysia have converted to carbon dioxide expansion. It is less clear what the situation is for smaller companies but the cost of using CFCs may be prohibitively high.
- Korea, the USA, Japan, Brazil, Singapore, Canada, Australia and New Zealand have converted to alternative carbon dioxide technologies.
- One company in France has converted to nitrogen expansion technology.
- One company in Germany has converted to propane and a company in the United Kingdom expects to use propane by the end of 1998.
- One company in the United Kingdom has converted to *iso*-pentane.
- Finland no longer operates any expansion process for tobacco.

5.1.1 Background

The expansion process originated in the USA and has also been used by European and Asian cigarette manufacturers. The CFC-11 tobacco expansion process is a patented, physical process that uses CFC-11 to restore cured, aged tobacco to its original field volume. The process is an effective and non-hazardous method of expanding tobacco and has been widely used to increase tobacco volume so that finished cigarettes will use less weight of tobacco, thereby reducing tar and nicotine, and reducing cost.

In this process tobacco is impregnated with CFC-11 in a stainless steel vessel maintained at 50 C (120°F) and pressurised at 20 to 75 psig. The tobacco is then contacted with hot air (up to 165 C, 330°F) which causes the tobacco to regain its original volume. The CFC-11 is vaporised and recovered by cooling and compressing, hence most of the CFC-11 is continually recovered and recycled.

Expanded tobacco is used in tobacco blends and cigarettes to improve the smoking characteristics of cigarettes and keep “tar” and nicotine levels within the reduced ranges preferred by smokers and recommended by various governmental regulatory authorities. Because less tobacco is used, raw material costs decrease, although there is an added processing cost.

5.1.2 Alternative expansion

Carbon dioxide is an alternative expansion agent used in many countries. Others used less commonly are nitrogen, propane and *iso*-pentane.

Current alternatives are:

- Carbon dioxide that has been successfully used as an expansion agent for approximately twenty years and is now the most widely used process. The US National Cancer Institute (DHEW Publication NIH 76 - 1111, 1975) evaluated the expanded tobacco.
- Propane that is being successfully used by one company in Germany and a propane expansion facility is being installed in the United Kingdom.
- Nitrogen that is a high pressure process system being used in France.
- *Iso*-pentane that is being used by one company in the United Kingdom.

5.1.2.1 Carbon dioxide

Carbon dioxide has been used to expand tobacco for approximately twenty years and installed expansion capacity has increased significantly as CFCs are being phased out. This process impregnates tobacco with liquid CO₂ under pressure. This combination of tobacco/CO₂ is then passed into a heated air stream (less than 800°F). This heat causes the CO₂ to be volatilised and expands the cellulosic structure of the tobacco. Carbon dioxide is non-toxic, but is an asphyxiant at high levels, is non-flammable and has zero ODP.

Although carbon dioxide is a greenhouse gas, increased use of CO₂ for tobacco expansion should not contribute to global warming. The CO₂ can be captured from a stream of gas that otherwise would be emitted into ambient air. Additionally, CO₂ recycling equipment is available however, is expensive.

The US National Cancer Institute evaluated the potential effects of the CO₂ and CFC-11 process on tobacco expansion. No adverse effects were reported in chemistry, genotoxicity, nor dermal tumorigenicity assays (DHEW Publication NIH 76 - 1111, 1975).

The CO₂ technology is currently commercially available. It takes approximately 18 to 24 months to build and start up a processing facility.

5.1.2.2 Propane

Propane is a colourless gas that is non-toxic. It is considered an asphyxiant at high levels. This is a patented process which requires liquid propane contact with tobacco at pressures of 1500 psig or greater and at a temperature of at least 124°C. The technology to conduct this process and recycle the propane has been developed (US patent No 4, 531,529).

The toxicology and chemistry studies on propane expanded tobacco began in early 1994. The propane process requires a pressurised system, which may require additional safeguards for employees, is highly flammable, and may be explosive.

This process is being used in Germany and will be available in the United Kingdom in late 1998 or early 1999.

5.1.2.3 Nitrogen

Nitrogen expansion requires special equipment due to the extremely high pressures in the expansion vessel. These extremely high pressures have prevented further marketing of this process.

5.1.3 Costs

The estimated costs for each alternative is greatly increased above the costs for CFC-11. This is partially due to the fact that many countries invested capital monies to implement the CFC-11 process. The estimated costs are 0.37 USD per pound of tobacco per year or 3.0 million USD per year for an 8 million pound per year plant (725 kg/hour).

The CO₂ process requires a new processing facility that takes approximately 18 to 24 months to construct. This results in a total capital cost of approximately 8 million USD to build an 8 million pound per year (725 kg/hour) processing plant. The smallest CO₂ expansion production facility is currently 2.5 million pounds of tobacco when operated 24 hours/day, 5 days per week. The most common facility is expected to produce approximately 8 million pounds of expanded tobacco per year. The operational costs including patent royalties is approximately 0.80 USD per pound or 6.4 million USD per year for an 8 million pound per year plant.

Propane expansion would also require a new manufacturing facility. The capital costs for such a facility would be approximately 25 percent less than a comparable CO₂ facility. A propane expansion facility with a recovery/recycling unit would cost approximately 5.2 million USD for an 8 million pound per year facility. Without the recovery/recycling unit, the capital costs would be approximately 2.6 million USD for an 8 million pound per year (725 kg/hour) facility.

The propane can be recycled and re-used in the process with the available recovery unit or could be used to fuel boilers or incinerators if the expansion unit were not equipped with a recovery unit. The operating costs of the units are also dependent upon the use of a recovery unit. If a recovery/recycling unit is not used, the operating costs are much higher due to the costs of replacement propane.

The operating costs, including potential royalties of a propane expansion unit with a recovery system is approximately 0.70 USD per pound, and approximately 0.82 USD per pound without the recovery unit using United States labour costs of 0.36 USD per pound of expanded tobacco. This equates to annual operating costs of 5.6 million USD for an 8 million pound per year facility with a recovery unit or 6.6 million USD for a similar unit without a recovery system. These operating costs are approximately 15 percent less for the propane facility with a recovery unit than a comparable CO₂ facility. The operating costs of a propane facility without a recovery unit are approximately the same as a comparable CO₂ unit. The propane process may also result in additional monetary savings since the more optimal operating conditions of

the propane technology will not result in as much tobacco destruction as the CO₂ process.

5.1.4 Developing country perspective

The principle difficulty for developing countries is the high capital cost of conversion to alternative technologies. Most developing countries are converting to carbon dioxide expansion technologies.

5.2 Food freezants

The technology to use CFC-12 as a freezant was first presented in 1967 and has been called the "Liquid Freon Freezant" method, abbreviated to LFF. The LFF method is based on direct contact of food particles with liquid CFC-12 at atmospheric pressure. At this pressure CFC-12 boils at -30°C. Food particles are dropped into a pan filled with liquid CFC-12, causing intensive evaporation at their surface. The generated vapours are recondensed on refrigerating coils situated above the pan.

CFC consumption has been totally eliminated using currently available alternative freezing methods, primarily the cryogenic techniques (LIN), which use liquid nitrogen, and air blast freezing. This process is not thought to be used at all in developing countries.

The consumption of CFC-12 for food freezing in 1986, worldwide, was estimated to be about 3,400 tonnes, used in some 30 units. The major part of this consumption (about 3,000 tonnes) was located in the USA. The process, called "Liquid Freon Freezant (LFF)", was used primarily to freeze seafood, corn-on-the-cob and raspberries (with a CFC consumption of about 1,500 tonnes for each product). CFC consumption (emissions) for LFF units had been reduced to 1,000 tonnes in 1991 for the USA and 300 tonnes for Europe.

5.3 Leak detection

CFCs and HCFCs can be used to locate leaks in underground, pressurised pipes. CFC-12 can be readily detected in low concentrations by means of a halide leak detector. Mixtures of CFC-12 and air were therefore used for leak testing pressure vessels of all types. This practice is not confined to the refrigeration industry, but is common throughout the engineering industry.

Suitable alternatives e.g. HCFC-22 and HFC-134a can be used for this purpose with calibration changes made to detection equipment being required. Equipment designed specifically to detect these alternative fluorocarbon alternatives is available. A helium-actuated device may also be available.

5.4 Repair of piping

CFCs can be used to create ice plugs in piping (every half metre) in order to facilitate repair. The pipe fitter can thereby change defected parts without emptying the whole system.

Alternatives to the use of CFC-12 are HCFC-22, HFC-134a or HFC-125. There is ongoing concern regarding the safety of this method where used in confined spaces regardless of which substance is used.

5.5 Solar tracking systems

CFC-12 can be used in solar tracking systems. The CFC is sealed within tubing that is attached to two opposite sides of the solar panel linked via a capillary tube. When radiation from the sun strikes the frame, the CFC expands. If both sides of the frame do not receive the same level of radiation then the CFC will be forced to the side that receives less radiation. The movement of CFC causes the frame to tilt. When equilibrium is reached, the panel will be at right angles to incoming radiation. Depending on the panel, there can be approximately 3 to 8 kilograms of CFC-12 in each unit.

HCFC-22 is being used as an alternative. HFC-134a is also technically suitable although no information was received on its use in this application.

Mechanically driven solar tracking systems are also available as an alternative. They may be suitable in many situations although they are more prone to damage from high winds. Energy is required to drive the tracking motor, making them less suitable where energy supply is a factor.

5.6 Wind tunnels

The velocity of sound in CFCs is approximately half that velocity of sound in air. CFC-12 has been used in wind tunnels to create supersonic conditions at very much lower circulation rates through the wind tunnel. Alternatives for this application include HFC-134a and SF6.

5.7 Thermostats and thermometers

CFC-11, -12, -113, -114 and -115 can be used in thermostats and thermometers. The thermostats are typically those used in domestic refrigerators and also room thermostats for controlling central heating. The thermostat consists of a bulb, capillary and bellows, with the bulb attached to the point at which it is desired to measure temperature. The pressure generated by the CFC in the sealed assembly activates the bellows, usually to

operate an on/off switch. The amount of CFC used is in the range of 1-10 g per unit.

Similarly the vapour pressure developed by CFCs at different temperatures can be converted into a rotary motion to indicate temperature on a dial thermometer.

HFC alternatives are suitable for this application.

5.8 Linear accelerators

Modern medical therapy uses radio frequent energy to accelerate electrons for cancer radiation treatment. The equipment for such therapy may use CFC-12 as a dielectric medium in transmission wave-guides. Radio frequent radiation for cancer treatment is increasingly used and gradually replacing methods using isotope machines with Cobalt 60.

Linear accelerators utilise a dielectric gas in the pressurised wave guide transmission system. The dielectric gas is supplied in containers attached to the waveguide system. The purpose of CFC-12 in the accelerators is to provide an atmosphere that does not affect microwave transmission while at the same time suppressing any electrical arcing inside the waveguide from the high microwave energy required for radiation. Some CFC-12 leaks out of the system. CFC-12 therefore has to be replaced periodically. The emissions depend on the age of the accelerators. Experience from a Swedish hospital indicates emissions not exceeding 25 kg/year for three middle-aged machines.

In 1998 no new information was received on the continued use of CFCs in this application. In 1994, less than 2 tonnes per annum were used annually to supply the initial charge of CFC-12 to newly manufactured linear accelerators and to maintain the dielectric gas in the installed equipment.

Sulfur hexafluoride is likely to be used as an acceptable alternative. It is used in a variety of similar research and industrial purpose accelerators such as particle, E-beam and tandem units. SF₆ is used in power supplies and in Van de Graaf units, because of its excellent dielectric properties and its non-toxicity. SF₆ is used extensively in the world as an insulating gas in heavy electrical equipment, including circuit breakers, substations and waveguides.

5.9 Other miscellaneous uses

It is likely that many devices are globally marketed which contain small quantities of ozone depleting substances. Such devices are from inventory (especially as spare parts of old equipment), manufactured in non-Article 5(1)

Parties using ODS inventory produced before 1996, or from Article 5(1) Parties.

Common devices containing ODS include: expansion bellows used to open sky lights and vents in office buildings and greenhouses, sealed switch gear (typical on electric trains), electronic controllers, and other electronic devices. These devices, may be just one component in a complex piece of equipment.

6. Laboratory and analytical uses

6.1 Introduction

Typical laboratory and analytical uses include: equipment calibration; extraction solvents, diluents, or carriers for specific chemical analyses; inducing chemical-specific health effects for biochemical research; as a carrier for laboratory chemicals; and for other critical purposes in research and development where substitutes are not readily available or where standards set by national and international agencies require specific use of the controlled substances.

The Parties to the Montreal Protocol granted at their 1994 6th Meeting (Decision VI/9(3)).

“That for 1996 and 1997, for Parties not operating under paragraph 1 of Article 5 of the Protocol, production or consumption necessary to satisfy essential uses of ozone depleting substances for laboratory and analytical uses are authorised as specified in Annex II to the Report of the Sixth Meeting of the Parties;”

The “standard-of-purity” applied to the exemption for laboratory and analytical uses are detailed in a later section of this report. The reason to require manufacture as highly pure chemicals for final marketing by manufacturers, agents, or distributors in small, labelled containers was to discourage non-essential use through the high price and inconvenience of small containers for high volume uses. Because laboratory chemicals often contain stabilisers or are sold at a particular concentration as reference materials, the Decision by Parties allows marketing in blends (including blends containing more than one controlled substance).

The conditions for continuous use under the Global Exemption as specified in Decision VI/9(3), Annex II (See Section 2.5 of the Handbook for the International Treaties for the Protection of the Ozone Layer (1996)), include requirements that:

“Parties shall annually report on each controlled substance produced: the purity; the quantity; the application, specific test standard, or procedure requiring its uses; and the status of efforts to eliminate its use in each application. Parties shall also submit copies of published instructions, standard specifications, and regulations requiring the use of the controlled substance.”

“... used or surplus substances should be collected and recycled, if practical. The material should be destroyed if recycling is not practical or destroy the material if recycling is not practical.”

In order to elaborate on laboratory uses and to assist the collection of data, the Parties adopted at their 7th Meeting (Decision VII/11), a non-exhaustive list of “Categories and examples of laboratory uses (Appendix II, Handbook for the International Treaties for the protection of the Ozone Layer (1996)). Furthermore, Decision VII/11(2):

“...urges Parties to organise National Consultative Committees to review and identify alternatives to laboratory and analytical uses and to encourage the sharing of information concerning alternatives and their wider use;

To encourage national standards organisations to identify and review those standards which mandate the use of ozone-depleting substances in order to adopt where possible ODS-free solvents and technologies;

To urge Parties to develop an international labelling scheme and encourage its adoption to stimulate awareness of the issue;”

Decision VII/11(8) continues:

“To urge Parties operating under Article 2 to provide funding within their countries and on a bilateral basis for Parties operating under Article 5 to undertake research and development and activities aimed at ODS alternatives for laboratory and analytical uses.”

The Parties at their 8th Meeting extended the global exemption for laboratory and analytical uses to include 1998 (Decision VIII/9(4)). At the meeting it was noted that Parties had not provided information concerning either the quantities of controlled substances used for laboratory and analytical uses or the efforts made by the Parties to eliminate specific uses.

The 9th Meeting of the Parties extended the exemption to include 1999, reinforced the reporting requirements in Decision IX/17 and clarified that essential use exemptions for laboratory and analytical uses of controlled substances shall continue to exclude the production of products made with or containing such substances.

6.2 The use of controlled substances for laboratory and analytical uses

A number of Parties have now reported on the use of controlled substances for analytical and laboratory uses. The European Union, Australia, the Czech Republic and the United States have adopted licensing systems in order to

manage supplies into these applications. These systems license supplies to the distributors of controlled substances into the laboratory and analytical sector. Registration of the many of thousands of small users in this sector is generally impracticable.

These systems are detailed below.

6.2.1 United States

Regulations in the United States require companies to follow very specific procedures to ensure compliance with obligations under the Montreal Protocol's global laboratory and analytical essential-use exemption. Laboratories that purchase high purity controlled substances in accordance with Annex II of the Decision VI/9(3) must certify to a distributor that the substance will only be used for laboratory applications and will not be resold or used in manufacturing.

Companies that distribute laboratory supplies are required to meet restrictions in Annex II of Decision VI/9 regarding purity, size and labelling. In order to receive quantities of controlled substances from producers or importers, companies that distribute laboratory supplies must certify that substances purchased under the global laboratory and analytical essential-use exemption are for sale solely to laboratory customers who certify the substances will be used for laboratory applications and will not be resold or used in manufacturing. Companies that distribute controlled substances to laboratories must report quarterly the quantities they receive from producers and importers and report quarterly the quantities they sell to laboratories.

6.2.2 European Union

In the European Union, companies that distribute analytical supplies are required on an annual basis to request from the European Commission a quota to enable them to sell, within Europe, controlled substances for use under the laboratory and analytical essential-use exemption. The quota permits the laboratory supplier to obtain from a bonafide producer or importer production or importation of the controlled substance.

The Management Committee under the European Regulation on Substances that Deplete the Ozone Layer carries out allocation of the essential-use quotas. Member States of the European Union are requested to investigate the requests for quotas by those companies that distribute analytical supplies in order to that they meet the requirements to sell the controlled substances.

Companies that distribute analytical supplies and those manufacturing and importing controlled substances against the quotas issued by the European

Commission are required to request a licence prior to obtaining production or importation. They are also required to make annual reports to the Commission detailing respectively their sales and production or importation. Companies distributing analytical supplies are required to keep information detailing the actual customers to whom the controlled substances were sold. These records are available for audit by the Commission.

The European Commission has published the quantities of controlled substances that it has licensed in 1995 and 1996 in its Official Journal. These data give an indication of the levels requested by the distributors and do not demonstrate the actual levels used. In a number of cases distributors may be building stocks for future sales or have not actually purchased controlled substances against their licences due to a lack of demand in the sector.

6.2.3 Australia

Australia has a licence system for companies that distribute analytical supplies for the import of controlled substances for laboratory and analytical uses. End use declarations are required from all purchasers of the products imported to ensure that they are being used for essential uses.

6.2.4 Czech Republic

Manufacturing and/or imports of regulated substances are subject to the licences issued by the Ministry of the Environment according to the Act on the Protection of the Ozone Layer of the Earth passed in 1995.

The products imported and produced in the Czech Republic were for special analytical usage, and to a very limited extent for laboratory research. They were of high purity. For example, CFC-113 was used, above all, for the analytical determination of water quality.

6.2.5 Laboratory and analytical uses by country (tonnes)

Year	1996			1997		
	Party	CFCs	CTC	MCF	CFCs	CTC
Australia (1)	(6)	(6)	(6)	0.07	0.41	0.09
Czech Republic (2)	6.90	0.10	-	(6)	(6)	(6)
European Union (3)	157.00	1.70	19.50	66.6	96.4	31.1
USA (4)	4.00(7)	10.00	5.00	(6)	(6)	(6)
Hungary (5)	0.00	0.00	0.00	0.00	0.00	0.00
United Kingdom (5)	0.00	0.00	0.00	0.00	0.00	0.00

MCF 1,1,1-Trichloroethane

- (1) Quantities imported
- (2) Quantities produced or imported
- (3) Licenses required
- (4) Quantities supplied
- (5) No production for laboratory/analytical uses
- (6) Not yet reported
- (7) Specified as CFC-113

6.2.6 Other data

Although data are only available for laboratory and analytical uses in Australia, the Czech Republic, the European Union, Hungary, United Kingdom, and the United States, it can be estimated that the total global use of controlled substances for these applications in non-Article 5(1) Parties will not exceed a maximum of 500 metric tonnes. Use in CEIT is unlikely to be more than a few hundred metric tonnes. An estimate of Indian use of CTC of 150 metric tonnes as a laboratory reagent would indicate that up to 500 metric tonnes could be used for analytical and laboratory uses in Article 5(1) Parties. An estimate for global use of controlled substances for laboratory and analytical uses is 1,500 metric tonnes.

6.2.7 Standards requiring the use of ODS

The United States has provided a list of institutions that develop laboratory standards, procedures, instructions and regulations requiring the use of ODSs, and those institutions investigating, researching or developing alternative laboratory procedures that do not require ODSs. The latter group comprises 20 committees and the former 13. A list of 80 standard laboratory procedures has been compiled and submitted along with the respective documents detailing the procedures.

6.2.8 Currently available alternatives

The following specific uses have identified alternatives and substitutes and therefore do not require the use of ODS:

- testing of oil, grease, and total petroleum hydrocarbons in surface and saline waters and industrial and domestic aqueous wastes including the testing of water which is separated from oil and discharged from offshore drilling and production platforms
- testing of tar in road paving materials by dissolving tar and separating it from aggregate
- forensic fingerprinting.

Readily available cost-effective alternatives for these applications have been implemented in many countries.

6.2.9 Standard-of-Purity and required containers

The Standard-of-Purity recommended by TEAP and decided by Parties was based on international and/or national standards such as the International Standards Organisation (ISO) or Japanese Industrial Standards (JIS).

ODS	Standard of Purity
CTC (reagent grade)	99.5
1,1,1-trichloroethane	99.0
CFC-11	99.5
CFC-13	99.5
CFC-12	99.5
CFC-113	99.5
CFC-114	99.5
Other (B.P.>20C)	99.5
Other (B.P.<20C)	99.0

These pure, controlled substances can be subsequently mixed by manufacturers, agents, or distributors with other chemicals controlled or not controlled by the Montreal Protocol as is customary for laboratory and analytical uses.

High purity ozone depleting substances and mixtures containing controlled substances shall be supplied only in:

- containers equipped with closures, or
- high pressure cylinders smaller than three litres, or in
- 10 millilitre or smaller glass ampoules.

Containers, cylinders and ampoules must be marked clearly as containing substances that deplete the ozone layer.

7. Carbon tetrachloride

7.1 Introduction

Carbon tetrachloride (CTC) is a heavy, colourless liquid at normal temperature and pressure (boiling point 77 C). It is non-flammable, miscible with most organic liquids and is a powerful solvent. CTC is the most toxic of the chloromethanes (10 ppm by volume in air threshold limit as a maximum safe concentration for daily 8-hour exposure). It is harmful if swallowed, inhaled or absorbed through the skin and its vapour decomposes on contact with flame or very hot surfaces to give off phosgene and other toxic products. CTC vapour or mist is irritating to the skin, eyes, mucous membranes and upper respiratory tract. Exposure can cause stomach pains, vomiting, diarrhoea, nausea, dizziness and headaches, and damage to the eyes, liver and kidneys.

CTC is an easily manufactured chemical that is widely available. Because of its relevance to ozone depletion, CTC has been extensively reviewed in the 1994 Report of the Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee. Specific applications of carbon tetrachloride have been investigated in the 1995 Reports of the Process Agents Working Group and were further elaborated by the Process Agents Task Force (PATF) in 1997; review can also be found in the 1995 Report of the Laboratory and Analytical Uses Working Group. Inadvertent Emissions and Process Losses were discussed in the 1994 Report of the Technology and Economic Assessment Panel (TEAP).

This large number of studies reflects the multiple nature of CTC uses. To better understand the role of this chemical it is important to keep in mind that CTC can be:

- Used as a feedstock for other chemicals. In the 1997 Report of the Process Agents Task Force (PATF), feedstock is defined as:

“A controlled substance that undergoes transformation in a process in which it is converted from its original composition except for insignificant trace emissions as allowed by Decision IV/12.”

- Used as a process agent. The 1997 Report of the PATF recommends that Parties consider process agent to be defined as:

“A controlled substance that because of its unique chemical and/or physical properties, facilitates an intended chemical reaction and/or inhibits an unintended chemical reaction.”

Controlled substances are typically used in chemical processes as process agents for at least two of the following unique chemical and/or physical properties:

1. *Chemically inert during a chemical reaction*
2. *Physical properties, e.g.*
 - *boiling point*
 - *vapour pressure*
 - *specific solvency*
3. *To act as a chain transfer agent*
4. *To control the desired physical properties of a process, e.g.,*
 - *molecular weight*
 - *viscosity*
5. *To increase plant yield*
6. *Non-flammable/non-explosive*
7. *To minimise undesirable by-product formation*

Note 1: Refrigeration, solvent cleaning, sterilisation, aerosol propellants and fire-fighting are not process agents according to this definition.

Note 2: Parties need not consider use of ODS for foam blowing, tobacco puffing, caffeine extraction, or fumigation because these uses are already covered in other Decisions and/or by Technical Options Committee Reports.”

- Used as a solvent. This includes simple solvent extraction such as caffeine extraction and palm oil extraction, and cleaning applications such as metal degreasing and textile spotting. These uses should be discontinued to protect the ozone layer as well as to safeguard the health and safety of people using CTC.
- Used in miscellaneous applications such as fire extinguishers, as grain insecticide fumigants, and in an anti-helminthic agent (especially for the treatment of liver fluke in sheep). These uses also should be discontinued for the same reasons stated above.
- Used as a laboratory chemical.

The distinction between these uses is not always clear cut and therefore this makes it difficult to provide global data on both CTC production and consumption.

7.2 Atmospheric emissions of CTC

Recent atmospheric measurements (Simmonds *et al.*, JER, 1998) have described levels of CTC at five remote surface locations from 1978 to 1996. They have concluded the following:

- Atmospheric concentrations of CTC maximised in 1989/1990 at 104.4 (+/-3.1) ppt and have decreased at 0.7 (+/-0.1) ppt/year since that time.
- Assuming an atmospheric lifetime of 42 (+/-12) years, atmospheric emissions of CTC have been estimated at 94 (-11, +22) thousand tonnes for 1979 to 1988 and 49 (-13, +26) thousand tonnes from 1991 to 1995.
- The reductions in emissions in 1989/1990 occurred coincidentally with the substantial decrease in global production of CFCs.

There are a number of possible reasons for this reduction:

- Reduction in the use of CTC as a feedstock to produce CFC-11 and CFC-12 in non-Article 5(1) Parties and CEIT resulting in a reduction in emissions during the manufacturing processes.
- Improvements in containment technologies in process agent applications in non-Article 5(1) Parties.
- Reductions in the use of CTC in process agent and other applications in CEIT.

These reductions could be partially offset by increased use and emissions of CTC in some Article 5(1) Parties. The degree of CTC emissions varies significantly from country to country depending on the type of process, use and emission control techniques.

7.3 CTC production and consumption

CTC is normally produced by the high temperature chlorination of propylene or methanes, known as chlorinolysis. Other starting materials have been used. Most production facilities to manufacture CTC alone have closed in non-Article 5(1) Parties. Some facilities can produce CTC and perchloroethylene as joint products – these latter facilities can usually be tuned to produce either 100 percent perchloroethylene or 100 percent CTC by recycling within the plant.

Data on both CTC production and consumption have, in the past, been difficult to obtain. This has been mainly due to the confusion existing over

the reporting of feedstock uses, confusion between feedstock applications and process agent uses, and a lack of detailed knowledge on other, unspecified uses of CTC. A number of countries have reported CTC data as consumption when the CTC has been used for CFC production.

The new UNEP data reporting formats will enable the collection of much clearer data and a more detailed analysis of CTC applications. Indeed, total CTC production data including production for feedstock use is well known for 1996 and was reported to UNEP as 203,820 ODP tonnes.

By using data provided by UNEP, Production and Consumption of Ozone Depleting Substances 1986-1995, September 1997, estimates have been made of the CTC required for the manufacture of CFCs (Appendix 1). The calculated level of CTC required for global CFC manufacture of 333,800 ODP tonnes is 6 percent greater than that calculated in the April 1997 Report of the Technology and Economic Assessment Panel as it reflects the operation of manufacturing facilities particularly in Article 5(1) Parties and CEIT, where greater quantities are used per tonne of CFC production primarily due to the plants being able to produce both CFCs and HCFCs.

Using similar methodology to that reported by Simmonds, atmospheric emissions of CTC in 1996 are estimated as 41,000 tonnes (-25 percent, +50 percent). The rationale used in the analysis is explained in Appendix 2. The main conclusions that have been drawn are detailed below:

- CTC remains a widely available and used chemical. The primary source of atmospheric emissions of CTC are those from the use as a feedstock to produce CFCs. This has been estimated to be between 27,500 and 29,100 tonnes in 1996 or 67 to 71 percent (+/-10 percent) of total CTC atmospheric emissions (Appendix 2). The majority of the emissions from feedstock use originate from CFC production in Article 5(1) Parties and CEIT (25,700 to 27,300 tonnes, or 64 to 67 percent of estimated total global CTC emissions from all sources). The remaining emissions (11,500 to 12,400 tonnes) result from process agent, other uses and inadvertent emissions. See Table 1.1 for breakdown of percentage contributions to CTC atmospheric emissions.

Table 1.1 Contribution to CTC atmospheric emissions

Emission source	%	tonnes
Non-Article 5(1) Feedstock	5	<2000
Article 5(1) Feedstock	54-58	22,200-23,600
CEIT Feedstock	9-10	3,500-3,700
Non-Article 5(1) non-Feedstock	3-5	1,200-2,000
CEIT and Article 5(1) non-Feedstock	25	10,300-10,400

- CTC consumption for process agent and other uses in non-Article 5(1) Parties is low and has primarily involved the use of existing stocks rather than new production. It is unlikely to exceed 500 tonnes now. This figure is estimated to further decline to less than 100 tonnes by the year 2000. The estimate of emissions from laboratory and analytical uses and process agents in previous reports remain valid.
- CTC consumption in Article 5(1) Parties has been estimated at 11,500 ODP tonnes or 10,500 (+/- 25 percent) tonnes from the 1995 UNEP data. This estimate includes applications such as process agents and laboratory uses, the former application is now considered by the Parties as feedstock and the latter as an essential use. Significant use has been reported for India (3,112 tonnes); it is estimated that 60 percent of this will be used in the manufacture of pesticides, pharmaceutical and chlorinated rubber (some considered as process agent uses), with the remainder for cleaning (equipment, metals and textiles) and aerosol use. Process agent and other uses are also reported in the 1997 PATF Report.
- The global use of CTC as process agents and other uses other than feedstock is estimated by the TOC to be between 11,500 and 12,400 tonnes.

The TOC note that the analysis of the UNEP data on production and consumption of CTC and the atmospheric measurements described in Simmonds *et al.* clearly indicate that the larger source of CTC emissions to the atmosphere is from the use of CTC as a feedstock to manufacture CFCs (estimated to be between 27,500 and 29,100 tonnes in 1996, 67 to 71 percent of the total global emission of CTC). Whilst CTC atmospheric levels have reduced as a result of the phase-out of CFC consumption in the majority of non-Article 5(1) Parties, they will only fall significantly in the near future if the use of CFC and CTC in Article 5(1) Parties is phased out at a faster pace than required by the Montreal Protocol. Otherwise use of CFC and CTC will remain frozen until 1 January 2005 and CTC emissions will remain unchanged until that time.

There are a number of measures that could lead to reductions in CTC emissions to the environment:

- Closure of CFC manufacturing facilities in Article 5(1) Parties and CEIT with accelerated introduction of alternatives.
- Conversion of facilities using CTC as process agents in Article 5(1) Parties to alternatives.
- Use of improved emission control technology in CTC and CFC manufacturing facilities in all countries.
- Use of improved emission control technology in manufacturing facilities using CTC as process agents.

Due to the complexity of the industries using CTC, the TOC recommends that these options be considered on a case by case basis taking into account technical, economic and environmental considerations.

Other uses of CTC, such as metal and textile cleaning and fumigants have been described in previous reports of the Aerosols, Sterilants, Miscellaneous Uses and CTC TOC (1991, 1994). Alternatives exist for the majority of these uses, and are widely available as discussed in the 1994 Report of the UNEP Solvents, Coatings and Adhesives TOC.

The ATOC wish to point out that solvent uses of CTC should be phased out and that projects to this effect will be eligible for Multilateral Funding. The TOC further believe that in some cases solvent uses have been presented incorrectly as process agent uses and as a result have not been approved for funding.

A1 Appendix 1

Production and consumption of carbon tetrachloride and production of CFCs in 1995

Source: UNEP *Production and Consumption of Ozone Depleting Substances 1986-1995*, September 1997

In the following Tables, production and consumption should not include feedstock use, however the TOC believes that in some cases feedstock uses were included.

Table 1.1: Article 5(1) Parties (1995) (ODP tonnes)

	Reported CFC production to UNEP	Calculated CTC requirement for CFC production	Reported CTC production to UNEP	Reported CTC consumption to UNEP
Argentina				
Brazil	9,071	12,700	11,462	933
China	46,655	65,300	35,413	63,379
India	21,780	30,500	-21,788	3,112
Korea, Rep. of	9,746	13,600	3,772	15,795
Mexico	15,737	22,000	12,077	21,965
Romania	22		4,665	-1,584
South Africa	1,627	2,300	4,931	0
Venezuela	4,285	6,000	0	1,708
Total	108,923	152,400	72,320	106,892

Table 1.2: Western Europe and others (1995) (ODP tonnes)

	Reported CFC production to UNEP	Calculated CTC requirement for CFC production	Reported CTC production to UNEP	Reported CTC consumption to UNEP
Australia	3,850	5,000		0
Canada	0		2,553	-908
European Union	28,509	37,100	359	-4,030
Japan	29,757	38,700	2,463	255
USA	34,728	45,100	8,932	-17,922
Total	96,844	125,900	14,307	255

Table 1.3: Eastern Europe (1995) (ODP tonnes)

	Reported CFC production to UNEP	Calculated CTC requirement for CFC production	Reported CTC production to UNEP	Reported CTC consumption to UNEP
Czech Republic	320	400	1	2
Russian Federation	39,322	55,100	2,735	0
Ukraine			9,865	0
Total	39,642	55,500	12,601	2

Table 1.4: Totals (1995) (ODP tonnes)

	Reported CFC production to UNEP	Calculated CTC requirement for CFC production	Reported CTC production to UNEP	Reported CTC consumption to UNEP
Non-A5 Producers	136,486	181,400	26,908	257
Non-A5 non-Producers				139
A5 Producers	108,923	152,400	72,320	106,892
A5 non-Producers				1,834
Total	245,409	333,800	99,228	109,122

Notes for tables

Negative consumption data in Tables 1.1 and 1.2 result from reductions in existing stocks for feedstock use or for export. They are not negative use. All negative consumption data have been omitted from the totals calculated in Tables 1.1 to 1.4. The fact that reported CTC consumption exceeds by far production can be explained by the reduction of stocks and by the misreporting of feedstock uses

CTC requirements have been calculated by multiplying the CFC production by a factor that converts CFC ODP tonnes to CTC ODP tonnes. This factor is 10 percent greater than the one that would be used to calculate the amount of CTC needed to produce a tonne of CFC. In the 1994 ATOC Report, the values of 1.14 and 1.3 were given for CFC-11 and -12 respectively. Therefore factors of 1.3 for the "Western Europe and Others" group (Table 1.2) and 1.4 for the Article 5(1) Parties and Eastern Europe (Tables 1.1 and 1.3) were used here.

Table 1.5: 1996 CTC production data including production for feedstock use (ODP tonnes)

	Reported CFC production to UNEP	Calculated CTC requirement for CFC production	Reported CTC production to UNEP
Non-A5 Parties	55,899	72,700	113,329
A5(1) Parties	109,000	152,600	90,491
Total	164,899	225,300	203,820

Source: UNEP

CFC requirements have been calculated by multiplying the CFC production by 1.3 for the “Western Europe and Others” group and 1.4 for the Article 5(1) Parties and Eastern Europe. Figures for 1996 CTC production include all CTC uses either feedstock or process agent and other uses.

A2 Appendix 2

A2.1 Identification and quantification of emission sources of CTC

A2.1.1 Methodology

In order to identify and quantify the major sources of emissions of CTC for 1995 and 1996 a calculation has been carried out. This has entailed using estimates of CTC requirements to produce the quantities of CFC reported to UNEP for 1995 and 1996. Estimates of consumption of CTC from process agent and other uses have been made for 1995, based on UNEP reported data. These consumption estimates were subtracted from the global emissions data reported by Simmonds *et al.* to calculate the contribution of feedstock use to the global CTC emission measurements.

Using the data reported by Simmonds *et al.* for the emissions of CTC due to CFC manufacture in non-Article 5(1) Parties the contribution to the global emissions of CTC from this source could be calculated. The remainder from the total reported by Simmonds *et al.* can be attributed to CTC emissions from CFC manufacture in Article 5(1) Parties and CEIT.

A2.1.2 Calculation

The total requirement of CTC for feedstock use for CFC production in 1995 has been calculated from UNEP data as 333,800 ODP tonnes.

A2.1.3 Process agent and other uses of CTC

An estimate of process agent and other uses in Article 5(1) Parties is made through subtracting from the total CTC consumption in Article 5(1) Parties (106,892 tonnes in 1995) the CTC consumption quantities reported by CFC producer countries where it is likely that they have been used for feedstock purposes, but have been reported as consumption. CTC consumption data from China, Korea, and Mexico (63,379 tonnes, 15,795 tonnes and 21,965 tonnes respectively) have been subtracted. The remaining data are estimated to be process agent and other uses of CTC (5,753 tonnes). Since some consumption other than feedstock must be considered for China, Korea and Mexico this figure is increased to 9,700 tonnes. In order to obtain the total for all Article 5(1) Parties this is added to the data reported by non-CFC producers in Article 5(1) Parties (1,834 tonnes). See Table 1.4.

Total CTC consumption in Article 5(1) Parties is estimated as approximately 11,500 ODP tonnes.

Using the data reported to UNEP and shown in Table 1.4, CTC consumption in non-Article 5(1) Parties is 396 ODP tonnes. Inadvertent losses in non-Article 5(1) Parties may add some 700 ODP tonnes.

This would allow an estimate of 12,600 ODP tonnes or 11,500 tonnes to be made for process agent and other uses of CTC in all countries.

A2.2 Calculation of feedstock emissions

Simmonds *et al.* have estimated CTC atmospheric emissions in 1995 to be 49,000 tonnes (-13,000 tonnes, +26,000 tonnes). In their report they stated that the global emission of CTC from countries which report CFC production annually (primarily included in the “Western Europe and Others” group) are estimated to have declined from 11 percent in 1972 to 4 percent of total emission in 1995.

The calculated CTC requirement for CFC production from the “Western European and Others” group in 1995 (Table 1.2) is 125,900 ODP tonnes or 114,455 tonnes. Using Simmonds methodology this would translate to CTC emissions of approximately 5,000 tonnes.

Feedstock emissions for Article 5(1) Parties and CEIT can then be calculated by subtracting the global process agent and other uses (11,500 tonnes) and the Western European feedstock emissions (5,000 tonnes) from the estimate of CTC atmospheric emissions by Simmonds (49,000 tonnes).

Feedstock emissions for Article 5(1) Parties and CEIT can therefore be estimated as 32,500 tonnes in 1995. Note that an error estimate using Simmonds data can be carried out. This would make an upper estimate of 59,000 tonnes and a lower estimate of 20,000 tonnes.

This allows an estimate of emissions as a function of production to be made for Article 5(1) Parties and CEIT. Given that CTC required for production in Article 5(1) Parties was 152,400 ODP tonnes and in CEIT was 55,500 ODP tonnes, as shown in Tables 1.1 and 1.3, the feedstock emissions estimated as 32,500 tonnes represent 17 percent of total CTC used during the CFC and CTC production processes of Article 5(1) Parties and CEIT. This estimate will range from 31 percent to 11 percent of total CTC being used if the upper and lower figures of 59,000 and 20,000 tonnes respectively are used instead. By using the average estimate of Simmonds of 49,000 tonnes, an emission estimate of 17 percent of total CTC used in the manufacturing process can be calculated.

A2.3 Calculation of 1996 global emissions of CTC

Using the 1996 UNEP data (Table 1.5), CTC emissions from feedstock applications can be estimated by multiplying the calculated CTC requirements for the respective regions with the emission percentages calculated above. Figures drawn from Table 1.5 have to be divided by 1.1 to convert from ODP tonnes.

Western Europe and others	$(48,700/1.1) \times 0.04$	= 1,800 tonnes
CEIT	$(24,000/1.1) \times 0.17$	= 3,700 tonnes
Article 5(1) Parties	$(152,600/1.1) \times 0.17$	= 23,600 tonnes

Total CTC emissions from feedstock uses = 29,100 tonnes

To this number should be added the non-feedstock emissions of CTC. This is estimated to remain unchanged from that of 1995, which is 11,500 tonnes.

The estimated global emission of CTC for 1996 is 40,600 tonnes. In line with the errors quoted in Simmonds the accuracy in the calculation is -25 percent, +50 percent.

A second method of calculating 1996 CTC emissions would be to use the data reported in the 1997 Report of the Process Agent Task Force. This would indicate that 1995 emissions are:

Article 5(1) Parties Process Agent emissions	7,000 tonnes
Non-Article 5(1) Parties Process Agent emissions	1,100 tonnes

Other emissions estimated are:

Inadvertent emissions	1,000 tonnes
Laboratory and analytical uses	1,500 tonnes
Other uses	1,800 tonnes

Total 12,400 tonnes

This quantity is then subtracted from Simmonds estimate of 1995 global emissions (49,000 tonnes) to give the feedstock emissions of CTC which are 36,600 tonnes, of which 5,000 tonnes are estimated to originate from non-Article 5(1) Parties, leaving 31,000 tonnes from Article 5(1) Parties and CEIT. This calculates as 16 percent of the CTC requirement of Article 5(1) Parties and CEIT to manufacture CFCs.

This percentage is then used to calculate 1996 CTC emissions as follows:

Western Europe and others	$(48,700/1.1) \times 0.04$	= 1,800 tonnes
CEIT	$(24,000/1.1) \times 0.16$	= 3,500 tonnes
Article 5(1) Parties	$(152,600/1.1) \times 0.15$	= 22,200 tonnes

Total CTC emissions from feedstock uses = 27,500 tonnes

To this number should be added the non-feedstock emissions of CTC. This is estimated to remain unchanged from that of 1995, which is 12,400 tonnes.

The estimated global emission of CTC for 1996 is 39,900 tonnes, which is equivalent to the previous estimate based on the data reported to UNEP. In line with the errors quoted in Simmonds the accuracy in the calculation is -25 percent, +50 percent. In this case, the contribution of feedstock emissions from Article 5(1) Parties and CEIT is 64 percent of the estimated 1996 total global CTC emissions.