MONTREAL PROTOCOL

ON SUBSTANCES THAT DEPLETE

THE OZONE LAYER

UNEP

2002 REPORT OF THE AEROSOLS, STERILANTS, MISCELLANEOUS USES AND CARBON TETRACHLORIDE TECHNICAL OPTIONS COMMITTEE

2002 Assessment

Montreal Protocol on Substances that Deplete the Ozone Layer

United Nations Environment Programme (UNEP)
2002 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)

There are no technical barriers for the transition to alternatives for aerosol products other than MDIs. However, some consumption of chlorofluorocarbons (CFCs) in aerosols still remains in Article 5(1) countries and countries with economies in transition (CEIT). The remaining main uses for CFCs in these countries have been identified as:

- Non-MDI medical aerosols such as local anaesthetics, throat sprays, nasal sprays, wound sprays, vaginal products and traditional Chinese medicines.
- Industrial/technical aerosols such as electronics cleaners, spinnerette sprays, anti-spatter sprays and tyre inflators.
- Personal hygiene products filled in small volume cans.
- Insecticide and disinfectant sprays for use aboard aircraft.

The Aerosols Technical Options Committee (ATOC) estimates that the consumption of CFCs in the non-MDI aerosol sector was approximately 4,300 tonnes in 2001 in Article 5(1) countries and CEIT. This represents less than 1 percent of the propellants used in aerosol products in 2001, and a 71 percent reduction in CFC consumption from 1997 (14,700 tonnes). For the first time, ATOC can report that CFC consumption in the non-MDI aerosol sector in Article 5(1) countries and CEIT has reduced to below that consumed for global CFC MDI manufacture.

The most progress has taken place in the Russian Federation where, as a result of the closure of CFC production facilities, use of CFCs in aerosol products, other than MDIs, has dropped from 7,800 tonnes in 1997 to 200 tonnes in 2001, representing a 97 percent reduction.

China and India have signed stepwise phase-out plans for CFC production, but the effect of these on the aerosol products sector is not yet apparent. In China the use of medical aerosols is increasing and new CFC-propelled products, including traditional Chinese medicines, continue to be developed. Lack of locally produced alternative pharmaceutical-grade propellants impedes their reformulation.

Comprehensive CFC consumption data for aerosol products is difficult to obtain. An estimation showing a regional break down of CFC consumption for 2001 is as presented in Table ES-1:

Table ES-1: CFC consumption in non-MDI aerosols in 2001 (tonnes)

ASEAN Countries*	700
China	1,800
South Asian Countries**	400
Latin America	400
Middle East, Africa	400
Russian Federation	200
Other CEIT and CIS***	400
Total	4,300

* Brunei, Cambodia, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailand, Vietnam
** Bangladesh, Bhutan, India, Nepal, Pakistan, Sri Lanka
*** CIS: Successor States of the former Soviet Union

Specific actions from governments and their national ozone officers will be needed to achieve final phase-out. The reformulation of the non-MDI medical aerosol products and industrial/technical aerosols may require technical and financial assistance. In the case of medical aerosols approval by national health and drug authorities will be required, after pharmacological and toxicity tests and clinical trials. Currently, more expensive products result if the new replacement products require the use of HFCs.

HFCs should be used in applications where either pharmaceutical or non-flammable propellants are required, but their high price and high global warming potential will limit their usage in aerosol products.

Hydrocarbons are the principal substitutes for CFCs used in aerosols. Suitable mixtures of *n*-butane, *iso*-butane, and propane are called hydrocarbon aerosol propellants (HAPs). Hydrocarbons are highly flammable and care is required during storage, transfer and filling. Where HAPs supplies were available at reasonable cost, transition out of CFCs has already taken place.

It is important to stress that in the process of replacing CFCs in the aerosol industry of Article 5(1) countries and CEIT, every effort should be directed to ensure that safety standards at the manufacturing plant and at the consumer level are maintained.

The declining trend in the use of CFCs in aerosols has accelerated. There still remain the following problem areas: HAPs availability; conversion of small and very small CFC users; industrial/technical aerosols; and non-MDI pharmaceutical products.

ES.2 Metered dose inhalers

Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic diseases of the air passages (airways or bronchi) of the lung and are estimated to affect over 300 million people worldwide. These illnesses account for high health care expenditure, cause significant loss of time from work and school and COPD in particular, is responsible for premature death. There are two main categories of treatment for asthma and COPD: bronchodilators (also called acute relievers) and anti-inflammatory medication (also called controllers or preventers).

A metered dose inhaler (MDI) is a complex system designed to provide a fine mist of medicament for inhalation directly to the lungs. MDIs contain either CFCs or more recently HFCs as propellants. Total reported use of CFCs for non-Article 5(1) countries manufacturing MDIs for asthma and COPD has fallen by 33 percent from a peak of 8,906 tonnes in 1997 to 5,983 tonnes in 2001. ATOC estimates that a total of 7,500 tonnes of CFCs were used worldwide for MDI manufacture in 2001, including an estimated 1,500 tonnes used in Article 5(1) countries.

The major alternative methods to CFC MDIs for drug delivery include:

- *HFC MDIs* – At least one HFC MDI is available in over 60 countries, and 30 countries have both bronchodilator and preventative drugs approved and used in that country. The number of HFC MDIs used worldwide has increased from 10 million in 1998 to an estimated 110 million in 2002.

- *Dry powder inhalers (DPIs)* – DPIs have been successfully formulated for most inhaled therapies, and are widely available. They are easy to use and are preferred by many patients. Their use has increased to 27 percent of inhaler units worldwide as new devices and formulations are introduced in new markets.

CFC transition

The rate of transition from CFC MDIs to CFC-free products has varied from country to country. Even when new products have been introduced, the rate of their uptake has varied. This has occurred for a number of reasons including price considerations, differences in medical practice and patient preferences. Brand-by-brand transition has generally occurred at comparable prices but its success is influenced by the above factors. In the European Union, the ratio of CFC MDIs to HFC MDIs to DPIs was approximately 1:1:1 in 2001.

It is clear that the development of HFC MDIs and their registration and launch into the market is only partially effective in transition. Parties may wish to consider official action (e.g. a target and timetable approach) to achieve CFC MDI phase-out.

There has been a lack of awareness by healthcare providers regarding the need for change from CFC to CFC-free inhalers. In developed countries already advanced in their transition process, multinational pharmaceutical companies have been more effective than governments and NGOs in educating healthcare providers. This may also prove to be the case in developing countries and CEIT.

In several countries there is a large proportion of generic or locally produced CFC MDIs that are priced significantly lower than the brand name CFC MDIs and HFC alternatives. Since payors (patients, purchasers, health authorities, insurance companies etc.) will continue to favour lower priced medicines, countries will have to address the means to have payors accept the CFC-free alternatives.

CFC manufacture

There are currently three producers of pharmaceutical-grade CFC-11/12 in the European Union. One important producer in the Netherlands will be allowed to continue CFC manufacture until 2005, and a second producer of CFC-11/12 in the European Union is currently modifying its CFC production to enable the manufacture of pharmaceutical-grade CFCs for supply to the United States. At the current time, no CFC production has been approved as pharmaceutical-grade from CFC manufacture in Article 5(1) countries.

Future CFC requirements are difficult to predict and there are a number of uncertainties in projecting CFC volume requirements:

- When CFC-free reformulation programmes will be completed;
- The introduction and uptake of CFC-free alternatives;
- The national determinations of non-essentiality;
- The dynamics of the market share between remaining CFC products and alternatives; and
- The role of existing CFC stockpiles and their transfer between MDI manufacturers.

The further into the future that a company projects its CFC requirements, the greater is the uncertainty. The ATOC believes that where possible, just in

time production should be continued. If final campaign production is required, the Decision to initiate should be taken as late as possible, compatible with guaranteed supply (see *UNEP, Report of the Technology and Economic Assessment Panel, April 2002, Volume 1* for further discussion of the timing of campaign production).

Although the satisfactory storage of pharmaceutical-grade CFCs for extended periods, e.g. 3-5 years under controlled conditions appears possible, it is not clear that some product would not be lost. Nevertheless, it is not unreasonable to assume that up to 3000 tonnes of CFCs could be the total needed to meet the cumulative United States' requirements for MDI production after 2005. As MDI producers in the United States held an inventory of close to 2000 tonnes at the end of 2001 and other storage facilities exist, storage of this size should not pose great operational problems. Similar considerations may hold for other regions/countries. (Refer to the *UNEP, Report of the Technology and Economic Assessment Panel Task Force on Collection, Recovery and Storage 2002* for further information).

Article 5(1) countries and CEIT

Multinational pharmaceutical producers provide the vast majority of MDIs in most Article 5(1) countries and CEIT. In some countries (e.g. Brazil, Mexico), local manufacture accounts for some MDIs, while the majority comes from multinational producers. In a few countries (e.g. People's Republic of China, Cuba and India), local manufacture, including that of multinational plants operating in these countries, supplies the majority of MDIs to the market. Continued provision of MDIs in Article 5(1) countries 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) countries and will overlap with the importation of CFC-free MDIs by multinational companies (the introduction of the latter will require approval by regulatory authorities).

It is important that countries collect accurate basic data on inhaler use if effective transition plans are to be developed. If such data already exist, the ATOC is not aware of them. Since price is such an important factor, the price of CFC alternatives will be a major barrier to transition, unless they are no more expensive than comparable CFC products.

Those countries with CFC MDI manufacture by local companies will require an interventionist transition policy. This may require assistance with the development of alternative formulations, modification of manufacturing plant and fulfilling of regulatory obligations for marketing. This assistance may vary, depending on whether local manufacture is undertaken independently, or under a licensing agreement. As has been the case in developed countries, an

evaluation of whether reformulation of a specific drug is technically feasible may be needed. This and similar aspects of transition policy will require input by appropriate pharmaceutical and technical experts in order to ensure optimal use of any development funding.

Most countries do not have local manufacture of CFC MDIs and supply of MDIs is wholly or largely by import. In those countries, national transition policies may be less interventionist, as in many developed countries. Experience in developed countries, where the supply of CFC MDIs comes from import by multinational companies, is that CFC alternatives can be introduced promptly where it is feasible within the regulatory framework of a country (e.g. Canada).

In Article 5(1) countries, this transition is occurring as a part of the overall phase-out of CFCs (with a 50 percent reduction from baseline levels in CFC consumption for basic domestic needs in 2005). Competition for supply of CFC between all uses may compromise supply of CFCs for MDIs. Therefore, ATOC strongly recommends that in order to protect patient health, MDI transition strategies be developed now, especially by those countries with local MDI manufacture. The development of transition policies could be facilitated by a series of regional workshops.

ES.3 Sterilants

Use of EO/CFC blends for sterilisation has been successfully phased out in most non-Article 5(1) countries and in some Article 5(1) countries. Although it is difficult to estimate, it is believed that the global total use of CFCs in 2001 for this application is less than 500 metric tonnes. Remaining worldwide use can be easily substituted, as there are a number of viable alternatives.

EO/HCFC mixtures that replace EO/CFCs are mostly used in the United States and in countries that allow venting of HCFCs to the atmosphere. The European Union has legislation restricting the use of HCFCs in emissive applications such as sterilisation. In 2001, the estimated use of HCFC replacement mixtures is thought to be less than 1,700 metric tonnes (some 50 ODP tonnes). Use has been reduced to almost one half of 1998 figures by using less mix per steriliser load, and by hospital conversion to other technologies.

Hospital units are now used more efficiently due to hospital consolidation. When several hospital sites become part of a single institution, they shut down their under-utilised sterilisers, and concentrate EO/HCFC sterilisation in one hospital. Alternative technologies to which hospitals have converted include: use of more steam-sterilisable devices; more single-use devices; pure ethylene oxide sterilisers; and other methods that will sterilise or disinfect some of the

low temperature devices used in hospitals. These other low temperature processes are vapour phase hydrogen peroxide-plasma, steam-formaldehyde (in parts of Europe and South America), and liquid phase peracetic acid.

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 with a great diversity of items. Process requirements for these two settings are very different.

Quality health care is dependent upon sterility 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. The nature and size of items to be sterilised will vary according to the user. Some items are more robust than others with regard to temperature and radiation. Thus, a number of different processes can be used, and each will offer specific advantages.

ES.4 Miscellaneous uses

Ozone depleting substances have a number of miscellaneous uses of which tobacco expansion is the most significant. China is believed to be the only remaining country to use significant quantities of CFC-11 for tobacco expansion, using about 1,000 ODP tonnes per year. According to decisions taken by the Executive Committee, a stepwise phase-out is planned by about 2007. Based on this and the planned installation of alternative carbon dioxide technology in China, declining use in this country can be expected.

Most remaining miscellaneous uses are believed to represent only small amounts of CFC use. Miscellaneous uses are difficult to identify and to obtain good data on volume and use patterns. 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.

ES.5 Laboratory and analytical uses

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.

Essential uses for 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 ODS be collected, recycled and/or destroyed. Other relevant Decisions include: Decision VII/11, Decision VIII/9(4), Decision IX/17, Decision X/19 and Decision XI/15. This latter Decision eliminated three uses from the global exemption: the testing of oil, grease and total petroleum hydrocarbons in water; testing of tar in road-paving materials; and forensic fingerprinting. Three Parties required an emergency exemption for the testing of oil, grease and total petroleum hydrocarbons in water for the year 2002.

A number of Parties have now reported on the use of controlled substances for analytical and laboratory uses. The European Community, 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.

Although only few data are available for laboratory and analytical uses, it can be estimated that the total global use of controlled substances for these applications in non-Article 5(1) countries 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) countries. An estimate for global use of controlled substances for laboratory and analytical uses is 1,500 metric tonnes. This will reduce as the major uses are phased out through the implementation of Decision XI/15.

In its April 2002 Report (Volume 1), the Technology and Economic Assessment Panel (TEAP) recommended a workshop on the elimination of controlled substances in laboratory and analytical uses. Such a workshop could assemble and document the methods that have enabled the phase-out of uses under Decision XI/15 and identify remaining uses and their potential substitutes.

ES.6 Carbon tetrachloride

Carbon tetrachloride (CTC) remains a widely available and used chemical. The main uses are:

- as a feedstock for the production of other chemicals, primarily CFC-11 and CFC-12;
- as a process agent (uses are detailed in the *UNEP, Report of the Technology and Economic Assessment Panel Process Agent Task Force, 2001*);
- as a solvent;
- as a laboratory or analytical chemical; and
- in miscellaneous applications.

The primary source of atmospheric emissions of CTC is manufacturing plants that use CTC as a feedstock to produce CFCs. These will decline in line with the phase-out of CFC production. Substantial reductions have been achieved recently through closures of CFC production facilities in Brazil and the Russian Federation. Significant emissions result from process agent, other uses, and inadvertent emissions.

CTC consumption in Article 5(1) Parties has been reported to the United Nations Environment Programme (UNEP) as 22,934 ODP tonnes in 1999 and 15,487 ODP tonnes in 2000. CTC consumption in non-Article 5(1) Parties has been reported to UNEP as 2,040 ODP tonnes in 1999, rising to 4,205 ODP tonnes in 2000. These data exclude reports by Parties of negative consumption, which originate where a Party destroys CTC or uses it as a feedstock and do not include data for 2000 from China.

CTC consumption for process agents and other uses in non-Article 5(1) Parties is low. Decision X/14 limits the 'make-up or consumption' of CTC to 4,501 tonnes and emissions to 220.9 tonnes. CTC consumption for process agents in Article 5 (1) Parties has proved very difficult to estimate. In particular, a number of different applications for CTC have been reported without conclusive evidence to determine whether these applications are indeed process agents. The TEAP, in its Assessment of the Funding Requirement for the Replenishment of the Multilateral Fund for the Period 2003-2005, assumed that around 8,000 ODP tonnes are used as process agents in uses approved by Decision X/14, but acknowledged that several thousand tonnes could be used in China in uses not approved by Decision X/14.

The estimate of consumption from laboratory and analytical uses of 1,500 tonnes in previous reports remains valid.

If the limit for non-Article 5(1) Parties, and the data reported to UNEP for CTC consumption are used, then the global CTC consumption/"make-up" for process agent, laboratory and analytical and other uses can be estimated as a maximum of 25,000 tonnes. These estimates should improve as a result of studies taking place in India and China to identify and quantify CTC use as a process agent.

1. Introduction

1.1 The Montreal Protocol including issues related to the Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee

In 1981, in response to the growing scientific consensus that chlorofluorocarbons (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, as well as the European Community, the developing countries Egypt, Ghana, Kenya, Mexico, Panama, Senegal, Togo and Venezuela, 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 at their Second Meeting in London, the Parties to the Montreal Protocol (Parties are nations that have ratified the Protocol) considered assessment reports on science and technology, prepared in response to Article 6 of the Protocol. The Parties agreed to Protocol adjustments requiring more stringent controls on the CFCs and halons than those 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 at the Fourth Meeting in 1992. 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. At this Meeting Parties were requested to nominate uses considered essential for the Sixth Meeting of the Parties in 1994.

At their Fifth Meeting in 1993, 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 Sixth Meeting in 1994, Parties decided levels of production or consumption necessary for 1996 and 1997 to satisfy essential uses of CFCs and 1,1,1-trichloroethane including for metered dose inhalers for the treatment of asthma and chronic obstructive pulmonary disease. Special conditions were applied to a global essential use exemption for laboratory and analytical uses of ozone-depleting substances.

At their Seventh Meeting in 1995, Parties considered the Panel 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 agreed for non-Article 5(1) Parties as well as a control schedule 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 for consideration in 1999.

At their Eighth Meeting in 1996, Parties agreed to updated terms of reference for the Technology and Economic Assessment Panel (TEAP) (compared to the original 1989 terms of reference). A number of measures were also agreed to facilitate a transition from CFC-based metered dose inhalers in non-Article 5(1) Parties. The Ninth Meeting of the Parties in 1997, which commemorated the tenth anniversary of the Montreal Protocol, Parties agreed to a phase-out schedule for developed and developing countries for methyl bromide.

At the Tenth Meeting, Parties agreed to extend the conditional global laboratory and analytical essential use exemption until the end of 2005.

At their Eleventh Meeting in Beijing, Parties agreed to a phase-out of bromochloromethane by January 2002. Parties also decided to eliminate certain uses from the global exemption for laboratory and analytical uses for controlled substances, from the year 2002, that is: testing of oil, grease and total petroleum hydrocarbon in water; testing of tar in road-paving materials; and forensic finger-printing.

At the Twelfth Meeting, the Parties agreed to a further set of measures to facilitate the transition from CFC-based metered dose inhalers in both non-Article 5(1) and Article 5(1) Parties, such as the development of national or regional transition strategies by all Parties. A report on issues related to the campaign production of CFCs for CFC metered dose inhalers was requested of the TEAP.

At the subsequent Thirteenth Meeting, the Executive Committee was requested to prepare guidelines for the presentation of projects involving the development of strategies and investment projects to enable the transition from CFC-based metered dose inhalers. A further TEAP study of campaign production of CFCs for metered dose inhalers was also requested.

1.2 The Technology and Economic Assessment Panel

Four Assessment Panels were defined in the original 1987 Montreal Protocol, that is, 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 in London to the Technology and Economic Assessment Panel. The TEAP has six standing Technical Options Committees (TOCs) (apart from other temporary subsidiary bodies).

1) **Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride** 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

1.3 The TEAP Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee and the 2002 Assessment

This report is part of the fifth assessment under Article 6 of the Montreal Protocol. The first assessment report was prepared in 1989, and updated in 1991, 1994 and 1998. This report is in response to Decision XI/17 of the

Parties to the Montreal Protocol, which requested an assessment to be undertaken for completion in 2002 for consideration by the Parties in 2003.

Article 6 specifically directs Parties 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. The assessment reports assist with this review.

This report 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, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee (ATOC) is made up of experts from industry, government, scientific, research and academic institutions. In 2002, there were 32 members of ATOC from 18 countries – Australia, Brazil, China, France, Germany, India, Indonesia, Japan, Malaysia, Mexico, Pakistan, Poland, Russia, Spain, Sweden, United Kingdom, the United States and Venezuela. The Committee met in April 2002 and undertook extensive written communication in the preparation of this report.

The Committee for 2002 was comprised of the following individuals who contributed to the preparation of this report.

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2. Aerosols

2.1 Worldwide use of CFCs in aerosol products (other than metered dose inhalers)

More than 10 billion aerosol products were used worldwide in 2001, the largest amount on record for this industry. Commercial use of aerosols developed after the Second World War based on the unique properties offered by CFC propellants. However, their use has been phased out so successfully that less than 1 percent of the 2001 production still used CFCs.

All of the controlled CFCs (CFC-11, -12, -113, -114, -115), and 1,1,1-trichloroethane (methyl chloroform or MCF) and carbon tetrachloride (CTC) can be used in aerosol products.

CFCs in aerosol products accounted for 60 percent of the total use of CFC-11 and CFC-12 in the mid-1970s. In the late 1970s and early 1980s the use of CFCs as propellants was banned in the United States, Sweden and Norway, with some exemptions. Later reductions in other countries led to a substantial cut back in the use of CFCs as propellants in aerosol products.

In 1996 most non-Article 5 (1) countries ceased the use of CFCs. Many conversions to phase out the use of CFCs have already taken place in Article 5 (1) countries and CEIT. Conversions can be characterised as being of 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). In the aerosol sector, some self-conversions take place when good quality hydrocarbon propellant is available. Where financial considerations are important, assistance is required from the MLF or GEF.

There are no technical barriers for the transition to alternatives for aerosol products other than metered dose inhalers (MDIs) (see Chapter 3 – *Metered Dose Inhalers*). However, some consumption of CFCs in aerosols still remains in Article 5(1) countries and CEIT. The main residual uses for CFCs in these countries have been identified as:

- Non-MDI medical aerosols such as local anaesthetics, throat sprays, nasal sprays, wound sprays, vaginal products and traditional Chinese medicine;
- Industrial / technical aerosols such as electronics cleaners, spinnerette sprays, anti-spatter sprays and tyre inflators;
- Personal products filled in small volume cans; and

- Insecticide and disinfectant sprays for use aboard aircraft.

The ATOC estimates that the consumption of CFCs in the non-MDI aerosol sector was approximately 4,300 metric tonnes in 2001 in Article 5(1) countries and CEIT. This represents a 71 percent reduction in CFC consumption from 1997 (14,700 tonnes). CFC consumption in the non-MDI aerosol products sector in Article 5(1) countries and CEIT has reduced to below that consumed for global CFC MDI manufacture.

The closure of CFC production facilities in the Russian Federation has resulted in considerable CFC reduction in the aerosol products sector. China and India have signed stepwise phase-out plans for CFC production, but the effect of these on the aerosol products sector is not yet apparent. These and many other Article 5(1) countries and CEIT continue to use CFCs for the remaining applications stated above and others. These products can either be reformulated to use non-CFC propellants or replaced by not-in-kind substitutes.

The most progress has taken place in the Russian Federation and other CEIT. In the Russian Federation, CFC consumption has reduced from 7,800 tonnes in 1997 to 200 tonnes in 2001, representing a 97 percent reduction. The CFC phase-out in the Russian Federation has resulted either from independent conversions or from conversions partially funded by the Global Environment Facility.

In China, slightly less than 2,000 metric tonnes of CFCs are still used for the production of medical aerosols, which include traditional Chinese medicines, as well as for industrial/technical products and aircraft disinfectants. The use of aerosols is increasing and new pharmaceutical products with CFCs continue to be developed. Local efforts to begin the reformulation of these products are underway and progressing, but this is being impeded by a lack of locally produced pharmaceutical-grade propellants, both hydrofluorocarbons (HFCs) and hydrocarbon aerosol propellants (HAPs).

India still has over 300 tonnes of remaining CFC consumption in aerosol products. The United Nations Development Programme is currently assisting the Ozone Cell of the Ministry of Environment and Forests in preparing a Terminal Umbrella Project. This project is expected to be presented this year for approval to the Executive Committee of the Montreal Protocol, and should result in the elimination of the remaining CFC consumption during 2003 and 2004.

The situation in other Article 5(1) countries and CEIT remains similar to that which was reported previously. Several Latin American countries still use CFCs in some of their industrial and pharmaceutical aerosol products; for

instance, Mexico is believed to have used about 200 tonnes in 2001. The remaining usage of CFCs in aerosols is small, distributed in many countries and difficult to identify. Specific actions from governments and their national ozone offices will be needed to achieve final phase-out.

The reformulation of medical aerosol products (other than MDIs) and industrial/technical aerosols may require technical and financial assistance. In the case of medical aerosols, approval by national health and drug authorities will be required, after pharmacological and toxicity tests and clinical trials. Currently, more expensive products result if the new replacement products require the use of HFCs.

Comprehensive CFC consumption data for aerosol products is difficult to obtain. An estimation showing a regional break down of CFC consumption for 2001 is as presented in Table 2-1:

Table 2-1: CFC consumption in non-MDI aerosols in 2001 (tonnes)

ASEAN Countries*	700
China	1,800
South Asian Countries**	400
Latin America	400
Middle East, Africa	400
Russian Federation	200
Other CEIT and CIS***	400
Total	4,300

* Brunei, Cambodia, Indonesia, Laos, Malaysia, Philippines, Singapore, Thailand, Vietnam
** Bangladesh, Bhutan, India, Nepal Pakistan, Sri Lanka
*** CIS: Successor States of the former Soviet Union

2.2 Alternatives to CFCs in aerosols

2.2.1 Currently available alternatives

CFCs can be used in aerosol products either as propellants or as solvents. There is a wide range of alternatives available for substituting CFCs in aerosol products. These include:

1. Alternative propellants (in order of use):

- HAPs – blends of hydrocarbons (propane, *n*-butane, *iso*-butane)
- dimethyl ether (DME)

- compressed gases (compressed air, CO_2, N_2, N_2O)
- HFC-152a
- HFC-134a
- HFC-227ea
- HCFC-22 (only in those countries where its use in aerosol products is not forbidden)

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, methylal, glycols, etc.
- HFC-43-10mee, HFC-245fa, volatile silicones, or hydrofluoro-ethers.
- HCFC-141b, which has an ozone depletion potential (ODP), can be used in those countries where its use is not prohibited.

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)
- barrier packs.

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.

2.2.2 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 (un-saturates), are called hydrocarbon aerosol propellants (HAPs).

Hydrocarbons are highly flammable and care is required during storage, transfer and filling. They are significantly heavier than air, and settle on the floor or in low spots, where they may concentrate. HAPs are refined to have virtually no odour in the gaseous form, and thus there is great danger that they may reach explosive concentrations – approximately 2 percent in air – without being noticed. Should this happen, any ignition source will cause an accident. Attention must therefore be paid to the following issues.

- Filling plant and storage facilities must be suitably sited to comply with local planning and legal requirements. The storage facilities for bulk propellant must be designed and equipped with emergency facilities (for example, fire detection system, 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 will depend on local laws.

- 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 leaking aerosol products and defective filled containers might be a potential source of dangerous HAPs and should be handled accordingly.

- Transportation of the odourless HAPs generally follows the norms of transporting LPG, but extra care should be taken because there is no warning of leakage due to the lack of odour. Another area of general concern is that some governments will not permit the transport of de-stenched or low odour hydrocarbons from suppliers to user locations for safety reasons. This forces each user to install expensive purification columns.

- 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 the requirements of insurers.

- Aerosol products should always be used in accordance with labelling directions, for example, “do not spray near open flame or hot surfaces”.

Where HAPs supplies were available at reasonable cost, transition out of CFCs has already taken place.

2.2.2.1 Costs of retrofit

There are wide variations in the cost of retrofit. The costs of converting filling facilities to hydrocarbon propellants increase dramatically if a new building, filling house or location is necessary. Thus, the decision to relocate is the largest single cost factor in conversion.

In several developing countries, there are small and very small “cottage industry” aerosol fillers, which may be in residential areas or in inappropriate areas that cannot safely be converted to a flammable propellant because of their location. If there are local contract fillers available, the most economical solution is contract filling. Contract fillers do not exist everywhere, and sometimes they are unacceptable for competitive reasons. Where the owners wish to relocate to continue their own filling, it is recommended that funding be sought to assist in the installation of safety equipment and sometimes filling equipment for the new locale.

In some countries the filler must also install equipment to deodorise locally available propane and butane gases of various compositions. This can also be a significant cost factor.

In many cases, the filling equipment has proved inadequate for conversion. There is still some electrical equipment that cannot be used with HAPs. In all cases where the machinery is dangerous, either by design or because of its deteriorated state, the recommendation is to replace the machinery.

A few small companies with ample land and relatively new equipment have been able to convert very inexpensively. In this case, total conversion costs can be less than USD $30,000.

Consultants to the implementing agencies have recommended assistance in the order of USD $50,000 to $350,000 for each facility to be converted, although there have been cases where large volume fillers required 1 million dollars or more in assistance.

2.2.2.2 Regulatory actions in developed countries

CFCs have been prohibited for aerosol use in developed countries since 1996.

In order to deal with air quality issues, some states of the United States have issued regulations that force 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.

In Europe, reformulation of consumer products to reduce emissions of VOCs is also underway. VOC regulations have a strong impact on the formulation of aerosol products, but have not impeded the phase-out of CFCs.

2.2.3 Dimethyl ether

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 United States to reduce VOC content in aerosol product formulations.

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.

2.2.4 Hydrochlorofluorocarbons and hydrofluorocarbons

Hydrochlorofluorocarbons (HCFCs) are controlled under the Montreal Protocol and must be phased out by 2020 in non-Article 5(1) countries and by 2040 in Article 5(1) countries. HCFCs have already been prohibited for aerosol use in several non-Article 5 (1) countries. Even where not prohibited, HCFCs should not be used unless absolutely necessary.

HCFC-22 and HCFC-142b, which were once considered replacements for CFCs, have minimal use today in aerosol production.

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.

All hydrofluorocarbons (HFCs) have ODPs of zero. HFCs that have been or are being commercialised include HFC-152a, HFC-134a, HFC-227ea, HFC-43-10mee, and HFC-245fa.

HFC-152a is slightly flammable, has a medium vapour pressure, relatively moderate global warming potential (GWP) (compared with CFC-12), and is not a VOC; and is gaining favour as a propellant in the United States. This propellant makes excellent quality mousses. It is being made in the United States, European Union, China and the Russian Federation.

HFC-134a and HFC-227ea are non-flammable fluorinated propellants. Commercial production of HFC-134a exists in the United States, Japan, Europe, China, and Brazil. Commercial production of HFC-227ea exists in Germany, the United States, and the Russian Federation. HFC-134a is replacing CFC-12 in MDIs. It is also the main non-flammable propellent in certain industrial products. HFC-227ea is currently being used for MDIs. HFC-43-10mee and HFC-245fa are used as solvent replacements for CFC-113.

The usage of all HFCs in aerosols is projected to be very modest because of their relatively high price and environmental concerns. Due to their high GWP, HFCs should not be used unless absolutely necessary. Their main applications will be those where either pharmaceutical or non-flammable propellants are required.

2.2.5 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, N_2, CO_2 and N_2O can be used for some aerosol products. They are injected into the can in gaseous phase. These naturally occurring substances have slightly increased their share as propellants due to their environmental acceptability.

From a technical perspective, compressed gases are not very good propellants. Their main limitation is the wet spray that results when the pressure in the aerosol product decreases. This is due to the propellant expansion that occurs while the can is emptied.

Technological advances have been made to compensate for the effects of pressure drops through novel valve designs, selection of adequate solvents, and compensation for pressure variations. While effective in improving the spray characteristics of compressed gas aerosols, the high cost of these speciality items does not allow their use in mainstream products.

Compressed air, CO_2, N_2O, and N_2 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. Due to high quality control requirements and innate technical limitations, compressed gas propellants will probably not be widely used in developing countries. Compressed gases are presently used in about 5-9 percent of all aerosol products.

2.2.6 Solvent reformulation

1,1,1-Trichloroethane (methyl chloroform or MCF), CFC-113 and CTC have all been used as solvents in aerosol formulations and they are still used in some Article 5(1) countries 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, evaporate rapidly, have high density, low viscosity and surface tension. They are widely available at relatively low cost. Their solvency power varies from very high in the case of CCl_4 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. CCl_4 is a chemical that is a probable human carcinogen and should not be used in aerosols for this reason alone.

It is possible to replace these solvents with non-ODS alternatives, although this is often complicated by VOC regulations.

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 to determine which characteristics are more desirable.

2.2.7 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.

Conditioning of finger or trigger pump products requires that the right amount of liquid be 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.

There are many more alternatives. Another well-known example of a non-spray dispenser is the solid stick dispenser for deodorant or antiperspirant. 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. These are often called “barrier packs.” 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.

2.3 Applications with potential challenges in reformulation

Phase-out of ODS in aerosol products is technically feasible for almost all products. In some Article 5(1) countries and CEIT where HAPs are available, some residual uses of ODS in aerosol products remain. They usually relate to the following applications.

2.3.1 Pharmaceutical products (other than MDIs)

Within the category of aerosol products, pharmaceutical products are the last to substitute. There are many pharmaceutical aerosol products apart from MDIs. Substantial reductions have been made within this category as CFCs are generally only used where no satisfactory alternatives are available.

Pharmaceutical aerosol products where CFCs are still used 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, nitrogen, or HFC-134a. 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. Such an approval can take several years.

2.3.2 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. Products in this category include electronic cleaners, dusters, fault detectors, mould releases, aircraft disinfection, weld anti-spatter, polyurethane foam, spinerette sprays, tyre inflators, and aerosol horns.

The majority of these products can be converted using HAPs or DME if flammability is not an insurmountable 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 slightly flammable and very difficult to ignite.

Some products have been the most problematic to reformulate, especially those that use CFC-113 because of its inert characteristics. However, reformulation efforts are ongoing, and have been aided by the availability of HCFC-141b, and more recently, by HFC-43-10mee, HFC-245fa, 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.

2.4 Issues for Article 5(1) countries and CEIT

Sources of purified 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 Article 5 (1) countries and CEIT, 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 process, filling, 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.

The declining trend in the use of CFCs in aerosols in Article 5(1) countries and CEIT has accelerated. Despite increased progress, there still remain the following problem areas: HAPs availability; conversion of small and very small CFC users; industrial/technical aerosols; and non-MDI pharmaceutical products. The sooner that these areas are addressed, the faster that total phase-out in non-MDI aerosols will be accomplished.

3. Metered dose inhalers

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

Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic diseases of the air passages (airways or bronchi) of the lung and are estimated to affect over 300 million people worldwide. These illnesses account for high health care expenditure, cause significant loss of time from work and school and COPD, in particular, is responsible for premature death.

Treatment of these conditions most commonly involves inhalation of aerosol medication, which is deposited into the airways of the lung (bronchi). This allows maximal local effect in the airways where it is needed and minimum side effects of drug elsewhere in the body.

3.1.1 Asthma

3.1.1.1 Description

Asthma is a chronic condition with two main components, airway inflammation and bronchoconstriction. In the majority of cases it may cause few symptoms for weeks or months. Attacks occur intermittently, during which cough and wheeze develop and the airways narrow, making it very difficult to breathe.

Attacks of asthma may occur spontaneously or be triggered by many environmental factors such as viral infections (colds), inhaled allergens (e.g. pollens), exercise, occupational dusts and fumes, medication (including aspirin) and others. Attacks of asthma usually require urgent additional medication and medical attention. They sometimes require hospitalisation. Such exacerbations can be fatal, although this is unusual.

Asthma most often starts in childhood. There is 50 percent chance of improvement or remission from asthma in early adult years if the condition has been mild. It may however persist or even start in adult life. In such cases it is often persistent and may cause frequent attacks, chronic ill health and incapacity.

3.1.1.2 The size of the problem

Asthma causes considerable morbidity, and mortality, and affects all races. A recent international study of asthma in childhood has shown a prevalence of asthma that varies from approximately 1 percent in some countries such as

Indonesia to over 30 percent in the United Kingdom, New Zealand, and Australia.

While there are large differences in prevalence between affluent and less affluent countries, asthma has been increasing worldwide over the last two decades. This increasing prevalence is likely to be due to multiple factors including "westernisation", changes in house design, greater exposure to house dust mite, 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.

3.1.2 Chronic obstructive pulmonary disease

3.1.2.1 Description

COPD is a condition of narrowing and inflammation of the airways in conjunction with damage to the lung tissue (emphysema). COPD is caused primarily by cigarette smoking, but may result in part, from inhalation of certain occupational dusts or environmental air pollution. Once present, COPD is persistent and usually progresses at an increasing rate if the patient continues to smoke. Even after smoking is ceased, continued deterioration of lung capacity occurs. This contrasts with asthma, in which regular treatment can generally maintain normal lung function and minimise the frequency of acute attacks. Deterioration of lung function in COPD ultimately leads to permanent disability.

Attacks or exacerbations of COPD may occur and are often associated with acute infections. Due to the already impaired lung function, exacerbations of COPD frequently require hospitalisation.

3.1.2.2 The size of the problem

The prevalence of COPD in many developed countries is around 4-17 percent in the adult population aged over 40 years. Data are less certain in less developed countries but figures as high as 26 percent have been quoted. Rates in men are generally higher than women and reflect smoking prevalence.

Smoking is beginning to decline in some developed countries, but trends in developing countries indicate that both smoking and the prevalence of COPD are of increasing concern.

The 1996 Global Burden of Disease Study compared the leading causes of disability in 1990 and those projected for 2020. In 1990 COPD was ranked 12, and it is projected to rank 5 in 2020, behind ischaemic heart disease, major depression, traffic accidents and cerebrovascular disease.

In 1998 COPD was the fourth most common cause of death in the United States, behind heart disease, cancer and stroke. In most developed countries the male death rate from COPD has been declining. In contrast, the female death rate is increasing and it is expected that death rates amongst females will overtake men in around 2005.

3.1.3 Treatment

Primary prevention of asthma is not yet feasible. Primary prevention of COPD entails not commencing tobacco smoking.

Treatment of the conditions once they have been established depend on avoiding environmental trigger factors, if possible, and use of regular medications to control the condition.

Avoidance of asthma trigger factors is only possible for some factors. Most trigger factors, such as viral infection, pollution, changes in weather etc., are impossible to avoid. In patients with COPD smoking cessation is crucial to minimising the progress of the condition. Medication to help patients cease smoking is available but is not associated with aerosols and will not be discussed further.

The preferred method of drug therapy for asthma and COPD is by medications that are delivered to the airways by means of a hand held inhaler device. This has the advantage that the medication is delivered directly to the site of the problem, minimising the dose of drug needed and the risk of potential systemic side effects. It also permits a more rapid onset of action than administration by tablets. Drug therapy for asthma is usually highly effective. Drug therapy of COPD is far less effective but has a role in minimising symptoms and frequency of exacerbations.

There are two main categories of inhaled treatment for asthma and COPD: bronchodilators (also called acute relievers) and anti-inflammatory medication (also called controllers or preventers).

3.1.3.1 Bronchodilators (acute reliever medication)

Bronchodilators reduce muscle tightening that contributes to the narrowing in the airways.

Virtually all patients with asthma and COPD require short acting bronchodilators. They are the key treatment for acute attacks and are lifesaving in severe attacks. In intervals between attacks, they may be needed frequently through the day; particularly in children for whom exercise induced

asthma is common. Bronchial muscle tightening is a greater feature of asthma than COPD, hence the greater effect of the drugs in asthma than COPD.

Bronchodilators fall into three classes:

- *Beta-agonists* – These are the mainstay of therapy for asthma and COPD. *Short acting beta-agonists* include albuterol/salbutamol (e.g. Ventolin™), terbutaline (Bricanyl™), and fenoterol (Berotec™). They act within a few minutes, and have an effect lasting approximately 4 hours. *Long acting beta-agonists* (salmeterol (Serevent™), formoterol (Oxis™)) may take longer to start working, but their effect may last for up to 12 hours. Due to their prolonged duration of action they are often included in the "preventer" or "controller" category, but they are not anti-inflammatory in action.

- *Anti-cholinergics* (e.g. ipratropium bromide (Atrovent®)) – These are commonly used as first line reliever therapy in COPD.

- *Methylxanthines* (e.g. theophylline/ aminophylline) – These are inexpensive oral medications but not particularly effective. They have a high rate of side effects. Inadvertent excess dosage can cause serious, potentially fatal side effects. These are oral medications and will not be mentioned further.

3.1.3.2 Anti-inflammatory medication (controllers or preventers)

Inflammation of the airways is a fundamental part of asthma, and suppression of this inflammation is recommended in all but those with mild infrequent symptoms. Anti-inflammatory treatment stabilises lung function and prevents acute exacerbations of asthma if used regularly, hence the term "preventer". Preventers are commonly used in COPD, but are not as effective in this condition. Preventers are usually one of three classes of drug:

- *Inhaled glucocorticosteroids (or inhaled steroids)* (e.g. beclomethasone, budesonide, flunisolide, fluticasone or triamcinolone) – These are the mainstay of preventer medication for asthma and COPD.

- *Cromoglycate-like drugs* (e.g. sodium cromoglycate or nedocromil sodium) – These are less effective than inhaled glucocorticosteroids, less tolerated by patients and rapidly falling from favour.

- A number of other oral medications have anti-inflammatory effects and have specific roles is asthma management. These include: *Leukotriene modifying drugs* (montelukast, zafirlukast, zileuton) and *Oral*

glucocorticosteroids (dexamethasone, prednisolone). These are oral medications and will not be discussed further.

3.1.3.3 Methods of aerosol administration

Aerosol medication is most conveniently administered with hand held inhaler devices. The most commonly used and convenient devices are the metered dose inhaler (MDI) and the dry powder inhaler (DPI).

The MDI generates an aerosol of liquid particles of specified diameter, containing medication, propellant (and any other excipients). The MDI is usually used alone, but may be used with a chamber (or spacer) device, which improves coordination and the deposition of aerosol particles in the lung, and which may permit certain patients to use an MDI who might otherwise not have the coordination to use one alone.

The DPI delivers powdered medication (and sometimes excipients) of specific particle size. Coordination is not required since these devices are breath-actuated.

Nebulisers are generally plastic devices, into which several millilitres of liquid medication are loaded, and an aerosol is generated by a flow of compressed air. There are two basic types – air driven and ultrasonic nebulisers. Pumps that generate the compressed air are usually electrically powered, not particularly convenient, but still portable. Due to cost and inconvenience, nebulisers are not the preferred method for routine administration of asthma medications.

A number of other hand held inhaler devices are under development and near to marketing, offering improved portability and/or functional performance. Some may be used for targeting deposition of drugs deep into the lungs allowing absorption into the blood stream. Many will be of more relevance to other diseases, such as diabetes, since the absorbed medication may be a substitute for injections.

3.1.3.4 Limitations of inhaled therapy

A number of devices have been developed for delivery of aerosol medication to the lungs since no single device is likely to be effective for all users.

Inhaler devices are only effective if used correctly. Many patients are not able to correctly coordinate actuation and inhalation of an MDI. Patients will often be able to use one device correctly but not another (e.g. a DPI but not an MDI). Incorrect use of inhalers is most common in young children, older

adults, those with certain manual disabilities and those who have not been instructed correctly. A choice of devices is needed.

Hand-held devices may be less effective during an acute attack of asthma, where inhalation may be impaired, and when respiratory distress may lead to panic. In addition, higher than usual doses of inhaled medication may be needed to treat attacks of asthma. Patients require training in management of acute asthma, over and above routine use of an inhaler device. In some cases either nebulised or injected medication is needed.

3.2 Metered dose inhalers

3.2.1 What is a metered dose inhaler?

An MDI is a complex system designed to provide a fine mist of medicament, generally with an aerodynamic particle size less than 5 microns, for inhalation directly to the airways for the treatment of respiratory diseases such as asthma and COPD.

The main components of all MDIs are:

- the active ingredient
- formulation excipients e.g. solubilising agents, suspending agents, lubricants
- the propellant(s) (a liquefied gas)
- a metering valve
- a canister
- an actuator

The active ingredient (the drug) may be either dissolved in the propellant or a co-solvent (e.g. ethanol) or suspended in the propellant. A surface-active agent may be included to ensure that the drug is well suspended and to help lubricate the metering valve.

The metering valve is the key to measuring and presenting a consistent and accurate dose to the patient, and is made up of a number of precision-made plastic or metal components. The valve is crimped onto the canister, which is ordinarily 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 (mouthpiece) 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.

MDIs contain either CFCs or more recently HFCs as propellants. CFC-containing MDIs contain CFC-12 and CFC-11, and sometimes CFC- 114. 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.

3.2.2 Trends in CFC consumption

The following trends in CFC use for MDIs have been drawn from reporting accounting frameworks submitted by non-Article 5(1) countries manufacturing CFC MDIs in response to Decision VIII/9, in which quantities of ODS produced and consumed under essential use exemptions granted in previous years are to be reported annually. Other sources have been used to estimate consumption in Article 5(1) countries.

Total reported use of CFCs for non-Article 5(1) countries manufacturing MDIs for asthma and COPD has fallen by 33 percent from a peak of 8,906 tonnes in 1997 to 5,983 tonnes in 2001 (Figure 3-1). ATOC estimates that a total of 7,500 tonnes of CFCs were used worldwide for MDI manufacture in 2001, including an estimated 1,500 tonnes used in Article 5(1) countries.

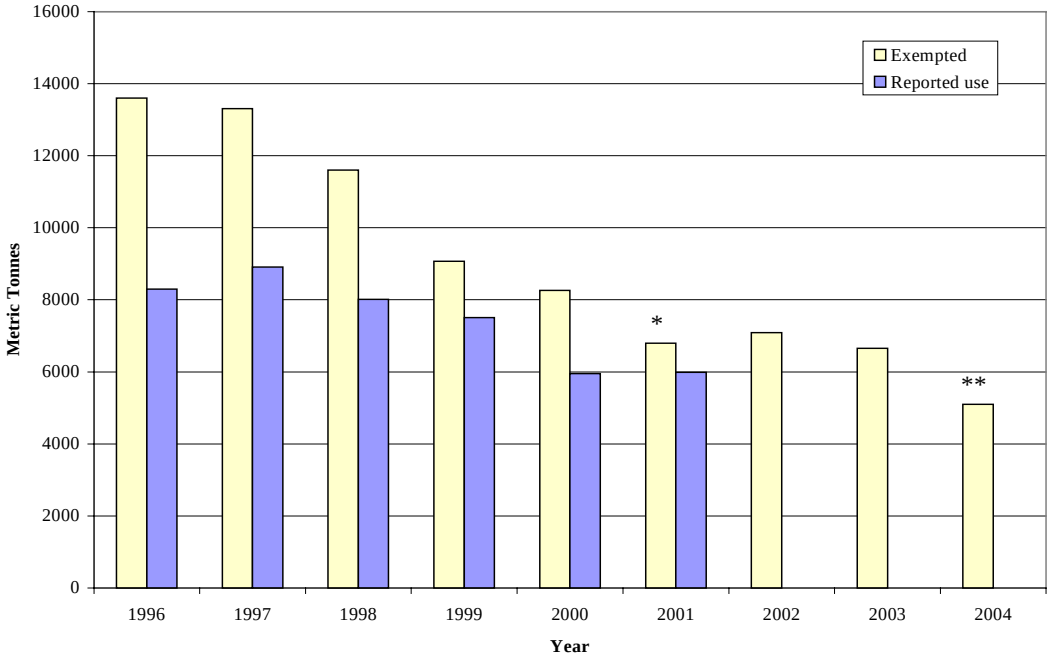

Figure 3-1: Total amounts of CFCs exempted and used (as reported by Parties) for essential uses for MDIs 1996-2004

* Year 2001 quantities do not include data for the Russian Federation. In 2001, the Russian Federation did not have an essential use exemption. Year 2002 and 2003 indicates quantities exempted by the Parties, which in these years includes the Russian Federation.
** Year 2004 indicates quantities nominated but not yet exempted by Parties. This excludes the Russian Federation and the Ukraine, which in 2002 had not yet submitted nominations for 2004.

Two Parties, the European Community and the United States, account for 95 percent of total CFC used for MDI manufacture in non-Article 5(1) countries for 2001. In the European Community, use has declined by 41 percent from a peak of 5,592 tonnes in 1997 to 3,322 tonnes in 2001, although there has been an increase in the year 2001 from the 3,090 tonnes reported in 2000. In the United States, CFC use between 1996 and 2001 is relatively unchanged (2,368 tonnes to 2,375 tonnes respectively), having increased to a peak of 2645 tonnes in 1999 and subsequently declined by 10 percent to 2,375 tonnes in 2001 (Table 3-1 and Figure 3-2). It should be noted that a significant proportion of European Community consumption of CFCs is for manufacture of MDIs for export.

Table 3-1: Reported amounts of CFCs used by Parties with essential use exemptions

Year	1996	1997	1998	1999	2000	2001
Australia	244.9	291.1	259.87	135.58	97.21	46.43
Canada	126	132.3	11	12	12	
Czech Republic	41.8					
EC	4822	5592	4660.4	4418	3089.3	3322.413
Hungary	11.6	4.9	3.2	0.932	0.949	0.46
Israel	7					
Japan	142.1	133.6	122.4	103.1	84.67	60.16
Poland	526.6	314.2	245.72	187.46	171.41	178.56
Russian Fed.		181.92	285.5			
Switzerland	0.75	0.75	0.52			
Ukraine						
USA	2368	2255	2425.5	2644.6	2492.5	2375
Total	8291	8906	8014	7502	5948	5983

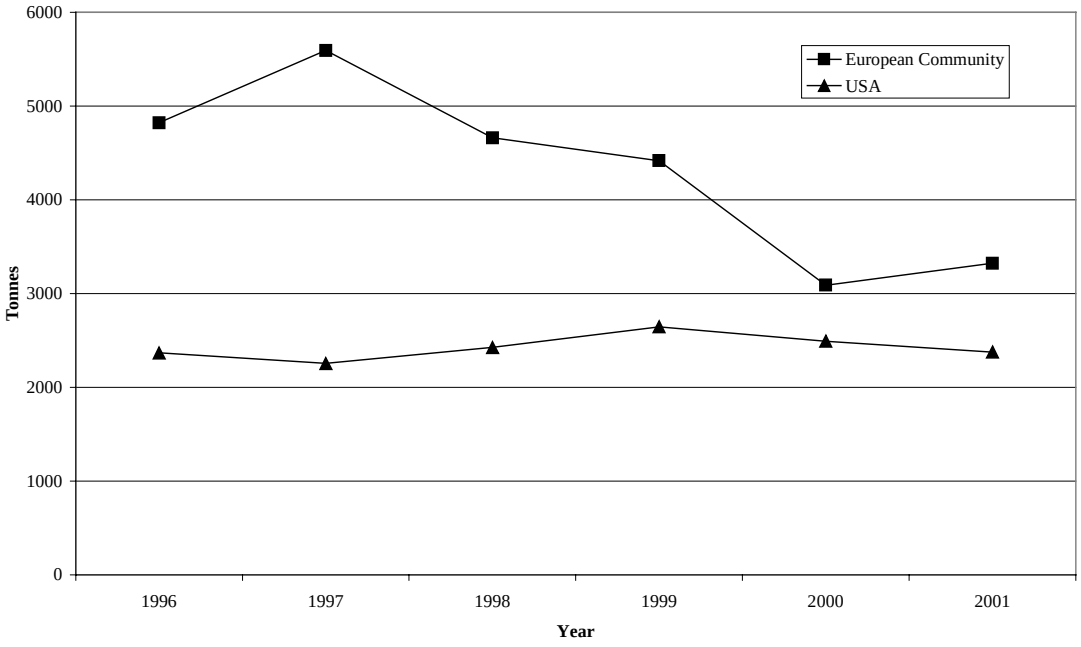

Figure 3-2: Total reported amounts of CFCs used by the European Community and the United States for essential uses for MDIs 1996-2001

Overall reductions reflect the fact that alternatives continue to be introduced around the world. For example, of the estimated 450 million MDIs

manufactured worldwide in 2001, approximately 350 million were CFC MDIs and 100 million HFC MDIs (up from an estimated 70 million in 1999). In some countries (e.g. Japan and the United States) there has been a recent increase in the sale of DPIs. This should further reduce the need for CFC MDIs.

In some cases upward trends may reflect regional changes in production, such as relocating some of the CFC MDI manufacturing from Canada and the European Community to the United States, or other factors. However, overall there is a clear global downward trend in CFC use, at the same time as prevalence in asthma and COPD has been increasing.

3.3 Alternatives to CFC MDIs

Whilst much effort has been focussed on developing in-kind replacements for CFC MDIs (i.e. HFC-based MDIs) there are other methods of delivering drugs to the lung. Alternative methods to CFC MDIs for drug delivery include:

- HFC MDIs and other non-CFC propellants;
- DPIs (single or multi-dose); and
- nebulisers (hand held or stationary).

Although the use of inhaled medicine is the preferred route for administering treatments for respiratory diseases like asthma and COPD, there are other types of administration that are used to treat these diseases and further such treatments are under development. These include:

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

At this point, it does not appear that the oral and parenteral therapies can be expected to generally replace inhaled therapies as the preferred manner of treatment.

3.3.1 MDI products using HFCs and other non-CFC propellants

The process of reformulating MDIs with HFCs began over a decade and a half ago when HFC-134a and HFC-227ea were proposed as alternatives to CFCs. These gases then underwent extensive toxicological testing on their own and were deemed to be safe for human use. Since that time, individual pharmaceutical companies have been working on reformulating their MDI product(s) to replace CFCs with the appropriate HFC. This has been difficult since the most common surfactants used in CFC-based inhalation aerosols

(e.g. lecithin, Span 85) are not soluble in HFCs and new formulation strategies have had to be developed. In addition, the valve elastomers used on CFC valves are not always compatible with HFCs. Thus companies have been innovative in their reformulations and each product has been treated as a completely new development.

3.3.1.1 Preclinical requirements

HFC-134a and -227ea are novel pharmaceutical propellants developed for widespread and long-term use as replacements for CFCs in MDIs. The propellants in MDIs comprise the large majority of the formulation, often in excess of 98 percent, and since the patient population using these drugs are particularly vulnerable to airway irritation or toxicities these HFCs have undergone the same toxicological testing required for any new chemical drug substance. The testing programs took over 5 years (during the late 1980s and early 1990s) and consisted of a wide range of studies, dictated by the overlapping regulatory requirements of health authorities from around the world.

3.3.1.2 HFC-134a

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.

3.3.1.3 HFC-227ea

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.

3.3.1.4 The technical development of HFC MDIs

Both propellents HFC-134a and -227ea are now being widely used to formulate drugs in MDIs. There are several products whose reformulation is essentially complete and their registration has taken place globally (e.g. products containing salbutamol, or inhaled corticosteroids). Other products are proving more difficult to reformulate and it is likely to be several more years before the existing CFC MDIs that are actively being reformulated are fully developed. Several products (usually older drug moieties or generic products) may never be reformulated due to technical challenges, economic considerations or changes in medical practice.

All the HFC MDIs under development contain the same physical components as the CFC MDI products (e.g. drug, propellant, canister, metering valve and actuator) but the very different physical properties of the HFC propellants has meant that significant changes have had to be made to the technology in these components. Although the active ingredient remains the same in most cases, whereas almost all CFC MDIs were presented as suspensions, there are now a growing number of HFC-propelled MDIs that have the drug in solution. Some formulations contain a co-solvent such as ethanol to help dissolve the surfactant or drug. 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 usually have had to be changed to accommodate the HFCs (and in some cases the actuator has also been modified), this may not be noticeable to the patient. While the HFC MDI as used by the patient may superficially look the same as the CFC MDI, the HFC products often have a different taste and mouth feel.

3.3.2 Dry powder inhalers

The first DPI became available in 1968 and like all DPIs until the late 1980s, consisted of single pre-measured doses stored in gelatine capsules (single dose products). New single-dose products are still being introduced today, along with new multi-dose formulations.

DPIs have been formulated successfully for most anti-asthma drugs and are now widely available. These inhalers represent currently available alternatives for a large proportion of patients. DPIs are preferred by some patients because of their ease of use, but, at present, they are not an alternative to the pressurised MDIs for all patients or for all drugs. However, in some countries, DPIs are the delivery system of choice for the treatment of asthma and COPD.

Some dry powder formulations contain the active drug alone while others have a carrier powder such as lactose. The drug particles must be of sufficiently small aerodynamic diameter to reach and be deposited in the airways. Micronised dry powder can be inhaled and deposited effectively in patients with adequate breathing capacity. However, for some children, and some patients with severe asthma or severe COPD (particularly the elderly), there may not always be adequate inspiratory flow to ensure optimal medication delivery from 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 handle and use their DPIs properly, for example in hot humid climates where excessive aggregation otherwise might impair its efficacy.

3.3.2.1 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 must be discarded after use and a new capsule inserted for the next dose.

Several introductions of single dose DPIs have occurred over the last few years (mainly Aerolizer™ for formoterol from Novartis). Their use, where launched, has not been significant to the overall uptake of DPIs. However, in some developing countries, these devices may have a role because they can provide the opportunity to purchase a small number of doses at an affordable cost.

3.3.2.2 Multi-dose powder inhalers

Multi-dose powder inhalers can deliver many doses without need to refill the device after each inhalation. They typically either have drug in a blister or contain drug that is metered from a drug reservoir. Current products vary from four to up to two hundred doses. There is an increasing use of the multi-dose DPI and this is likely to accelerate with the more widespread availability of commonly prescribed products as new multiple dose devices.

3.3.2.3 Dry powder inhaler usage

In 1998 DPI usage was estimated to be about 17 percent of all inhaled medication globally (in unit terms). In Europe the DPI was widely accepted but only a limited number of products were available in the United States and no DPI had been approved in Japan.

While the global use of DPIs has increased to 27 percent of inhaler units, the use of DPIs in Europe in absolute unit numbers has now grown to over 50 million units per annum and is comparable to HFC MDI use in Europe. This increase in use is mainly due to expansion of established products and the launch of new products, such as corticosteroid/long-acting beta-agonist combinations in established DPIs. In addition, there is increased availability of generic drug substances in novel multi-dose DPIs.

Acceptance of DPIs varies considerably between countries in Europe. The use relative to other inhalers is particularly high in the Scandinavian countries and

in Holland (greater than 65 percent in all cases) and is reported to be growing in Germany and France.

In the United States a number of DPI products have been introduced in the last year (the GlaxoSmithKline combination of salmeterol and fluticasone in the Diskus™ and Novartis' formoterol Aerolizer™, both in the spring of 2001). The use of newly available DPIs in the United States has increased markedly reaching 14 percent of the total market share by June 2002, supporting the acceptability of modern DPIs.

Since 1998 a limited number of multi-dose DPI products have entered the Japanese market. GlaxoSmithKline's fluticasone Diskhaler™ was introduced in late1998 and more recently AstraZeneca's budesonide Turbuhaler™ and GlaxoSmithKline's fluticasone Diskus™. Thus there are now three DPI products of two drug substances available in Japan. DPI usage is estimated at more than 30 percent of the Japanese market in 2001.

3.3.2.4 Development efforts

Substantial development efforts are being pursued in the DPI segment by a number of pharmaceutical 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; few have yet reached the market.

Devices where drug substance de-aggregation is independent of patient's inhalation are reported to be in early development. Such devices would be more suitable also for patients with very low inspiratory flow, e.g. small children and the elderly. The introduction of new and improved DPI products is likely to further stimulate the expansion of this treatment alternative over the next decade.

3.3.2.5 Cost

In general, prices of DPIs and branded MDIs of the same drug are similar in cost per dose. However, in some countries there is a significant price difference between DPIs and generic MDIs of the same drug. This is related to national pricing policies and local market considerations.

3.3.3 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. Until now nebulisers have generally not been

considered as alternatives to MDIs and have been 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.

Small portable devices that produce aerosols of respirable diameter, from aqueous formulations, are under development. These aerosols can be deposited deeply into the lungs and serve as a means of drug absorption. These devices are mostly targeting systemic delivery of drugs that would otherwise require injections, rather than treatment of asthma and COPD. A small hand-held nebuliser, which is pocket sized and as flexible and as easy to use as the MDI, has entered the registration process in Europe in 2001.

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 require either a battery or external power source, tend to be expensive and cannot be used for all drug formulations.

3.3.4 Oral medication

The optimum method of administration is determined by the drug's mechanism of action, pharmacokinetics, metabolism and therapeutic index. Oral medications, including tablets, capsules and oral liquids, have been the standard form of therapy for most diseases for many years. However, chronic administration of drugs by the inhaled route has been favoured for COPD and asthma because of the superior therapeutic index for some medications (e.g. beta-agonists and corticosteroids).

Oral medication is taken by mouth, swallowed and absorbed in the gastrointestinal tract. The active moiety circulates throughout the body and contacts many tissues (including the respiratory tract). Oral administration has the advantage of delivering therapeutic concentrations of medication to areas of lung or small airways not reachable by inhaled drugs. The higher circulating concentrations that are required for efficacy of oral administration (versus inhaled therapy) may lead to unwanted systemic effects. These may be

due to either side effects of the drug itself, or due to interactions with other drugs.

Typical 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
- appropriate pharmacokinetics and metabolism essential.

For the same medication delivered orally and by the inhaled route:

- higher doses are needed by oral route
- usually more side effects than inhaled medication
- some medication effective by one or other route only.

Recently a new class of oral medication, leukotriene (LTR) modifiers, has been approved for the treatment of asthma. This class is of value to some asthmatic patients, and LTR modifiers have been included in international asthma treatment guidelines.

Oral medications, including tablets, capsules and oral liquids, have been the standard form of therapy for most diseases for many years. Administration of drugs by the inhaled route is favoured for COPD and asthma because of superior local effects and fewer side effects. Present treatment guidelines recommend that the mainstay of asthma and COPD treatment for the majority of patients is inhaled therapy.

It is considered unlikely that any novel oral medication presently under development would, if approved in the next five years, significantly change these guidelines for the treatment of asthma or COPD.

3.3.5 Injectable therapy

Some drugs used for the treatment of asthma and COPD are also available for administration parenterally and are used in a hospital setting. However, regular injections (i.e. daily) are neither justifiable, nor feasible for general use in ambulatory patients. Even during life threatening asthma in hospital a

successful outcome is usually achieved, and with greater comfort for the patient, by delivery of appropriate medication by the oral or inhaled route.

A number of biological response modifiers are under development and may prove to have utility in the treatment of asthma. These are often delivered by injection, but may require only weekly or monthly administration. Should one or more of these be approved in the next five years, it is likely that inhaled therapy will remain as important treatment in international guidelines.

3.3.6 Commercial availability of HFC MDIs

At least one HFC MDI is now available in over 60 countries. In addition, over 30 countries have both a bronchodilator and an inhaled corticosteroid available.

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

Aventis – Azmacort™, a corticosteroid marketed in the United States with CFC propellant has been reformulated with HFC propellent; a New Drug Application is pending at the FDA and in 1996, the company received an approvable letter. Intal™ and Tilade™ cromolyns that are marketed worldwide have also been reformulated. HFC versions of these products have been approved in 19 countries and are available for sale in 15 markets. An allergic rhinitis therapy has also been reformulated with HFC propellant and approved in Canada and an approvable letter received from the United States Food and Drug Administration.
Boehringer Ingelheim – Boehringer Ingelheim has three MDI products, Berotec™, Berodual™ and, most recently, Atrovent™ available in HFC formulations in at least one European country. As of June 2002 no Boehringer Ingelheim HFC product had reached the United States market.
Cheisi has approval in four countries for their beclomethasone HFC MDI.

GlaxoSmithKline – GlaxoSmithKline has 49 percent of its MDI franchise in HFC MDIs. This is predominantly Ventolin™ (salbutamol) and Flixotide™ (fluticasone). GlaxoSmithKline has HFC MDI products approved in over 95 markets and is committed to ensuring markets launch the HFC product and to phase-out the CFC product in a timely manner as agreed with the relevant stakeholders in each country.

Ivax (Norton Healthcare) has two major MDI products formulated in HFCs. They currently have approvals for their Beclomethasone HFC product in 19 countries including 17 where they also have their breath-operated inhaler (Easi-Breathe™) also approved. In addition they have 23 countries where a salbutamol HFC MDI is approved, including 21 where the Easi-Breathe™ is also approved for salbutamol.

3M Health Care – Salbutamol HFC MDIs developed and manufactured by 3M Health Care are now available in over 60 countries throughout the globe. Beclomethasone dipropionate HFC MDIs developed and manufactured by 3M Health Care are now available in over 50 countries throughout the globe. In the majority of markets, the beclomethasone dipropionate HFC MDI is available for use in both adult and paediatric patients, with the US FDA granting approval for paediatric use in May 2002.

In addition a well-known pharmaceutical manufacturer, Cipla, has a range of HFC MDIs available on the Indian sub-continent.

3.3.7 Clinical and regulatory requirements

The European Community (Committee for Proprietary Medicinal Products) issued final guidelines and guidance is available in the United States (FDA) for the clinical studies needed for the replacement products.

The United States and European Community 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 CFC-free MDIs have to be large enough to detect a difference between the two products, if one exists (usually several hundred patients)

- post-marketing surveillance data from the patient population as a whole in normal use.

3.4 Transition to alternatives to CFC MDIs

3.4.1 Overview

It is now over 8 years since the first introduction of an HFC MDI for the short acting beta-agonist salbutamol in the United Kingdom. Today there are over 60 countries where there is at least one salbutamol (short acting beta-agonist) HFC MDI approved and marketed. Further product introductions are planned in the coming years. In addition, it is reported that some pharmaceutical companies are effectively switching their CFC products by introducing the HFC MDI, quickly evaluating its acceptance in the market place and then stopping supply of the corresponding CFC product. It is estimated that at least 25 percent of salbutamol MDIs marketed around the world today contain HFC as a propellant.

In addition to the introduction of beta-agonist HFC MDIs there are now a growing number of controller medications available as HFC MDIs. These include beclomethasone, fluticasone, sodium cromoglycate and nedocromil sodium.

After some early concerns about the taste and feel of HFC MDIs (they differ from CFC MDIs in these respects) as well as technical issues surrounding actuator blockage (which have all been resolved by ensuring patients adhere to good cleaning techniques) the uptake of HFC MDIs globally is gathering speed. The number of HFC MDIs used globally has increased from less than 10 million in 1998 to an estimated 110 million in 2002.

As anticipated, there have been no major product incidents during this period. This has been accomplished by the use of widespread education campaigns (primarily conducted by the pharmaceutical industry) to both healthcare professionals and patients on why the MDI needs to change and what the changes entail.

It is however very clear that the development of HFC MDIs and their registration and launch into the market is only partially effective in transition.

There is also a need for an additional step; for MDI companies to cease supplying the CFC MDIs. This has been done by some pharmaceutical companies, but not others. These other companies, which have not developed CFC free MDIs, will continue to produce CFC MDIs for as long as they are allowed. Increasingly it may be necessary for national governments to identify, adopt, and implement policies to ensure that the transition is completed in the next few years when there are sufficient, safe CFC-free alternatives available.

In the past decade, as well as the introduction of HFC MDIs, there has been a rapid increase in the introduction and acceptance of multi-dose DPIs . This has been partly fuelled by the availability today of state-of-the-art therapy options (a combination of long-acting beta-agonists and inhaled corticosteroids) in at least two widely accepted powder inhalers.

These alternative products are now being widely used in a number of countries in the developed world. It is estimated that during 2001 over 100 million HFC-containing MDIs were used globally. In addition it is estimated that approximately 65 million multi-dose DPIs were used on a global basis during 2001.

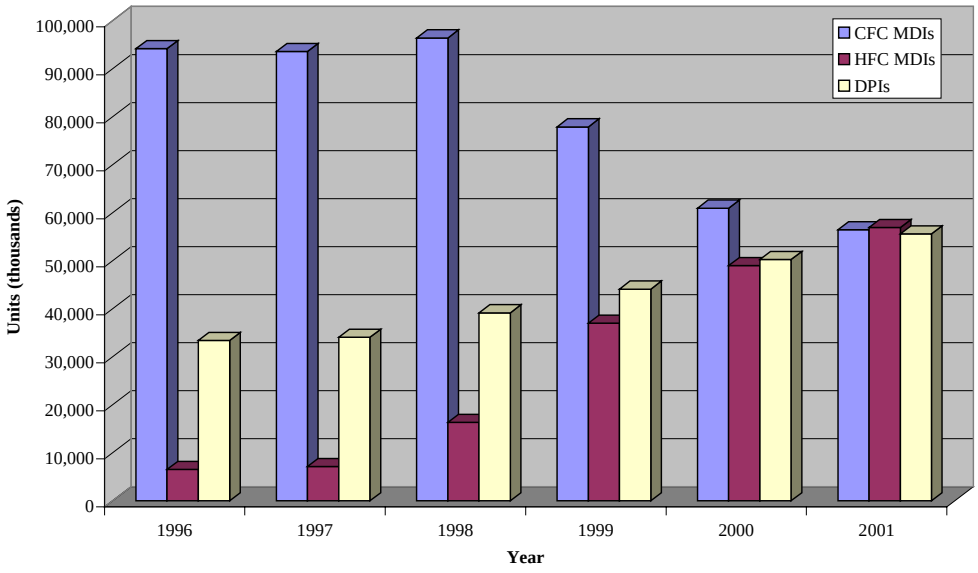

Figure 3-3: Progress of transition in the European Union for International Pharmaceutical Aerosol Consortium companies only*

*Member companies: Armstrong Pharmaceuticals, AstraZeneca, Aventis Pharmaceuticals, Boehringer Ingelheim, Chiesi Farmaceuticals, GlaxoSmithKline, IVAX.

3.4.2 Transition strategies

Starting in 1997, various non-Article 5 (1) countries have developed and published a range of transition strategies depending on their market circumstances and the way that asthma/COPD is treated in that country.

By 31 January 2002, 8 out of 43 non-Article 5(1) Parties had submitted interim or final transition strategies. Recently, the Ozone Secretariat also received transition policies from Poland and from the Hong Kong Special Administrative Region of the People's Republic of China. The United States also issued its final transition policy in July 2002. A number of other Parties have indicated they will shortly submit or update strategies.

Initial strategies based on a therapeutic approach to CFC MDI phase-out have given way to the phase-out of individual drug substances. The European Community has indicated it will declare short acting beta-agonist CFC MDIs non-essential during 2002. Canada also has targeted phase-out of this category during 2002.

These transition strategies generally fall into four major categories:

- brand-by-brand
- drug-by-drug
- category-by-category
- targets and timetables

The most effective management of the transition (i.e. phase-out of CFC MDIs) has been through the co-operation of industry and government in working towards a common goal of having target dates for the cessation of sale of certain CFC MDI products. This appears to have been successfully accomplished in Australia and more recently Canada. The more diverse market needs of, for example, the European Union, mean that this may not be achievable as market requirements and product mixes differ across the Member States. In addition, although transition strategies can manage MDI consumption within the nominating party, it is increasingly evident that export of MDIs (primarily to Article 5 countries) will need to be managed carefully for those Parties with export markets (e.g. European Community, Australia).

In the final analysis it is likely that increased regulatory involvement is now needed as the transition reaches the phase were there will be a few CFC MDI products remaining. These will either be technically very challenging to reformulate or low volume products that cannot justify resources to support reformulation. As such, pharmaceutical companies will need to indicate their

intentions as to how they plan to serve the needs of patients who currently take these medicines.

3.4.3 Experiences in transition

The rate of transition from CFC MDIs to CFC-free products has varied from country to country. Even when new products have been introduced, the rate of their uptake has varied. This has occurred for a number of reasons including price considerations, differences in medical practice and patient preferences. Brand-by-brand transition has generally occurred at comparable prices, but its success is influenced by the above factors.

In several countries (e.g. the United States) there is a large proportion of generic CFC MDIs that are priced significantly lower than the brand name CFC MDIs and HFC alternatives. Since payors (purchasers, health authorities, insurance companies etc.) will continue to favour lower priced medicines, countries will have to address the means to have payors accept the CFC-free alternatives. For example in New Zealand, PHARMAC (the government pharmaceutical purchasing organisation) has in July 2002 approved for purchase a new CFC MDI Beclomethasone on the basis of relative cost, when a HFC MDI has already been on the market for a number of years.

Trends in the reduction of the use of CFC MDIs have been mirrored by the uptake of HFC MDIs and, in some countries, by the very successful launch of DPIs. The introduction of an HFC MDI does not necessarily lead to a successful transition. Experience in some countries indicates that transition can only be achieved by regulatory policies that phase-out corresponding CFC products on a drug-by-drug or category-by-category basis once alternatives are widely available.

Despite widespread educational initiatives, transition does not appear to be a high priority amongst most healthcare providers, many of whom have taken a passive approach to transition. Pharmaceutical companies' educational and marketing endeavours have been the main driving force in the uptake of alternatives.

Reviewing all possible methods of transition (e.g. drug-by-drug, brand-by-brand, category-by-category, targets and timetables) it is clear that action by patient organisations, health professional organisations and the pharmaceutical industry will not alone drive the transition. Parties may wish to consider official action (e.g. a target and timetable approach or combining drug-by-drug with a subsequent category-by-category approach) to achieve CFC MDI phase-out.

Several countries have developed and implemented effective transition processes. Japan is a good example of such a country and is expected to phase out CFC MDIs by 2005. This has been accomplished by the collaboration of the various pharmaceutical companies and the relevant government authorities. It is important that Parties, in particular Article 5(1) countries, collect accurate basic data on inhaler use. This will aid the development of effective transition plans.

It is believed that Article 5(1) countries and CEIT can be divided into two broad categories: those with manufacture of MDIs by local companies and those without. Those countries with CFC MDI manufacture by local companies will require an interventional transition policy. This may require assistance with the development of alternative formulations, modification of manufacturing plant and fulfilling of regulatory obligations for marketing. This assistance may vary, depending on whether local manufacture is undertaken independently, or under a licensing agreement. As has been the case in developed countries, an evaluation of whether reformulation of a specific drug is technically or economically feasible may be needed. This and similar aspects of transition policy will require input by appropriate pharmaceutical and technical experts in order to ensure optimal use of any development funding.

Most countries do not have local manufacture of CFC MDIs and supply of MDIs is wholly or largely by import. In those countries, national transition policies may be less interventional, as in many developed countries. Experience in developed countries, where the supply of CFC MDIs comes from import by multinational companies, is that CFC alternatives can be introduced promptly where it is feasible within the regulatory framework of a country (e.g. Canada).

The CFC MDI transition has proven to be complicated, as it is influenced by medical, technical, economic and regulatory factors. In Article 5 (1) countries, this transition is occurring as a part of the overall phase-out of CFCs. Competition for supply of CFC between all uses may compromise supply of CFCs for MDIs. Therefore, ATOC strongly recommends that in order to protect patient health, MDI transition strategies be developed now, especially for those countries with local MDI manufacture.

3.4.4 Anticipated phase-out

In the non-Article 5(1) countries transition is underway and likely will be complete in the next few years. However Article 5 (1) countries still have much to do. Under the Protocol, complete phase-out of overall CFC consumption is mandated by 2010 for Article 5 (1) countries. In 2005, there will be a 50 percent reduction from baseline levels in CFC consumption for

basic domestic needs in developing countries. This will include consumption for MDI production, which will then compete with other uses of CFCs within the 50 percent cap.

Multi-national pharmaceutical producers provide the majority of MDIs in most Article 5(1) countries and CEIT. In some countries (e.g. Brazil, Mexico) local manufacturing accounts for a small volume of MDIs. In others (e.g. China, Cuba and India), local manufacture accounts for a significant proportion of production. Each of these patterns of CFC use to produce MDIs will have a different impact on the development of transition plans.

Although CFC-free inhalers are already available in at least 30 Article 5(1) countries, uptake has been very low. However some countries (e.g. the Philippines) have begun transition and have made good progress. In contrast, India has a local manufacturer producing the majority of the MDIs used in that country. Whilst this manufacturer has introduced at least three CFC-free MDIs, this introduction alone has not been sufficient to drive transition to these products. This is similar to the experience in developed countries.

3.4.5 Potential barriers to CFC MDI phase-out

3.4.5.1 Education and dialogue

Current experience is that transition plans will only be successfully implemented if there are frank discussion among the major stakeholders, that is, MDI producers, health and environmental agencies. In addition, there will be a need to involve national medical professional organisations. International organisations or programs, for example, Global Initiative for Asthma (GINA), Global Initiative on Obstructive Lung Disease (GOLD), International Union Against Tuberculosis and Lung Disease (IUATLD) and World Health Organization (WHO), also may have roles to play.

There has been a lack of awareness by healthcare providers regarding the need for change from CFC to CFC-free inhalers. In developed countries already advanced in their transition process, multinational pharmaceutical companies have been more effective than governments and NGOs in educating healthcare providers. This may also prove to be the case in developing countries and CEIT. Countries should consider this likelihood in developing their transition strategies.

3.4.5.2 Costs

It is acknowledged that there are major concerns over the cost and/or availability of healthcare in all countries, particularly in Article 5(1) countries and CEIT. Notably, inhaled therapies are usually more expensive than

commonly available oral medications that are less effective and maybe more hazardous. For the purpose of this document, ATOC has limited its comments to CFC MDI transition issues. Since price (which really means acquisition cost for the patients who use the medicines or governments who partly or wholly assume responsibility for the cost of medicine) is such an important factor in the use of inhaled therapy, the price of CFC alternatives will be a major barrier to transition, unless they are no more expensive than comparable CFC products.

3.4.5.3 Intellectual property

The technology covering the HFC formulations that have been developed is in some cases covered by Intellectual property rights owned by multinational pharmaceutical companies. This has been cited as a barrier to transition although in reality there is a growing number of examples where cross licensing of technologies has been agreed. This trend is likely to continue and indeed as the competitive landscape becomes more crowded and more products appear, the desire for cross licensing will increase.

3.4.6 Education and training

To facilitate patient and physician utilisation of the reformulated products, global education and training are required. Options in current use include:

- Professional associations through medical journals, medical symposia, reports and newsletters.
- Treatment guidelines issued by the country's medical authority that 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 many have been published since 1994, some of them written by members of the ATOC.

- 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 involves increasing awareness of DPIs as well as the reformulated MDI products. As more alternatives become available a more active patient strategy has developed. This involves concerted effort that has been led 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 countries without patient support associations it is possible that the NHLBI/WHO Global Initiative (GINA) have suitable material available (http://www.ginasthma.com).

Professional bodies and patient associations have been most active in addressing this issue when governments have taken a lead in highlighting the importance of the subject. However, educational efforts in advance of the availability of a suitable range of alternatives have been ineffective. So far, the main drive to transition has been by individual companies educational efforts in support of a brand-by-brand switch for one of their own products. At the time that an individual Party mandates transition, the health authorities will need to provide public education, both to support and justify this policy.

3.5 Managing the phase-out of CFC manufacturing

3.5.1 CFC production for CFC MDI manufacture

There are currently three producers of pharmaceutical-grade CFC-11/12 in the European Union. During the period in which Decision XIII/10 was taken by the Parties, there was uncertainty as to how long the facility operated by Honeywell at Weert in the Netherlands, which is currently a critical supplier of CFC-11/12 for MDI manufacture, and the only supply of this CFC type currently approved for MDI manufacture in the United States, would continue to operate.

This uncertainty has now been clarified. In October 2001, the Dutch Minister of Housing, Spatial Planning and the Environment stated that CFC production for essential uses would be allowed to continue until 31 December 2005, not withstanding commercial considerations. Furthermore, a second producer of CFC-11/12 in the European Union is currently modifying its CFC production to enable the manufacture of pharmaceutical-grade CFCs for supply to the United States. At the present time, the acceptability of the CFCs from this source for MDI manufacture in the United States is being determined.

There are two producers of pharmaceutical-grade CFC-114 in non-Article 5(1) countries. One of these sources recently announced that it would cease production. For the near term, the remaining supplier is reportedly committed to its continuing production.

At the current time, no CFC production has been approved by a regulatory authority in a non-Article 5(1) country as pharmaceutical-grade from CFC manufacture in Article 5(1) countries.

3.5.2 Future CFC requirements

Future CFC requirements are difficult to predict. Trends in CFC use for MDIs are presented in Figures 3.1 and 3.2.

Total CFC use for non-Article 5(1) countries manufacturing MDIs has fallen by about 28 percent from 8,290 tonnes in 1996 to an estimated 5,983 tonnes in 2001 with an estimated total of 7500 tonnes of CFCs used world wide, including an estimated 1,500 tonnes used in Article 5(1) countries for local manufacture of CFC MDIs. Reductions reflect the fact that alternatives continue to be introduced around the world.

However, there are a number of uncertainties in projecting CFC volume requirements:

- When CFC-free reformulation programmes will be completed;
- The introduction and uptake of CFC-free alternatives;
- The national determinations of non-essentiality;
- The dynamics of the market share between remaining CFC products and alternatives; and
- The role of existing CFC stockpiles and their transfer between MDI manufacturers.

The further into the future that a company projects its CFC requirements, the greater is the uncertainty. The ATOC believes that where possible, "just in time" production is the preferable option. However, if final campaign production is required, the Decision to initiate should be taken as late as possible, compatible with guaranteed supply (see *UNEP, Report of the Technology and Economic Assessment Panel, April 2002, Volume 1* for further discussion of the timing of campaign production).

3.5.3 Use of recycled CFCs

An intensive study on the possibility of using recycled CFCs in MDIs was carried out on behalf of the International Pharmaceutical Aerosol Consortium (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."

No further work has been reported on this issue.

3.5.4 Stockpiling 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; and

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 European

Union will remain operational for the next several years to meet the basic domestic needs of Article 5(1) countries and for MDI manufacture.

Since July 1999 levels of CFC production and consumption in Article 5(1) countries have been frozen. Some CFC manufacturing facilities now operating in Article 5(1) countries have closed as a result of initiatives undertaken under the Multilateral Fund to reduce global CFC production. This is resulting in CFC manufacture consolidating on a few producers and should result in sufficient supplies of medical grade CFCs during the transition.

Although the satisfactory storage of pharmaceutical-grade CFCs for extended periods, e.g. 3-5 years under controlled conditions appears possible, it is not clear that some product would not be lost.

Stockpiles of CFCs are currently being held by a number of pharmaceutical companies, and some of these companies have been using some stockpiled material. The material from the stockpiles for use has generally met specification and been suitable for use. However, there have been a number of exceptions to this, which longer-term storage may only exacerbate.

Problems include:

Odour – This is one of the most persistent storage problems for pharmaceutical CFCs, particularly for CFC-12, which can develop a strong odour on storage. This makes it unsuitable for use in MDIs. There have been instances where substantial quantities of CFC-12 have 'gone off' in this way. It is sometimes possible to remove such odour by 'polishing' it out with adsorbents, but the approach is not reliable, and material 'reworked' in this way may not be acceptable in countries with exacting pharmaceutical standards.

Related impurities – CFCs are chemically stable, and are unlikely to undergo significant chemical change on storage. In recent years, analytical methods (Gas Chromatography) have been developed to a very high level and are currently 'state of the art'. There have been previous instances of CFC stockpiles effectively becoming out of specification on impurity content during storage. This has been attributed to the improvements in analytical techniques over the duration of the storage period and not to any change in the material.

If a final production campaign is needed, the necessary storage capacity will depend on the cumulative requirements expected beyond 2005.

For example, it seems likely that by 2005 the United States requirements for pharmaceutical-grade CFC may be less than 1,000 tonnes per year. It is less certain for how long after 2005 CFCs will be required in the United States and the rate at which their use will decline. It is not unreasonable to assume that up to 3000 tonnes of CFCs could be the total needed to meet the cumulative United States' requirements for MDI production after 2005. However, this figure could be an over estimate. As MDI producers in the United States held an inventory of close to 2000 tonnes at the end of 2001 and other storage facilities exist, storage of this size should not pose great operational problems. Similar considerations may hold for other regions/countries. (Refer to the *UNEP, Report of the Technology and Economic Assessment Panel Task Force on Collection, Recovery and Storage, 2002* for further information).

3.6 Issues for Article 5(1) countries and CEIT

The first control measure on the total consumption of CFCs in Parties operating under paragraph 1 of Article 5 of the Montreal Protocol started on 1 July 1999, with a freeze at an average of 1995-7 levels. It is expected that a 50 percent reduction from baseline levels will be achieved by 2005. A complete phase-out of overall CFC consumption by Article 5(1) countries is mandated by 2010.

3.6.1 Current situation in Article 5(1) countries and CEIT

The sources of MDIs in a country will have a major impact on the development of its plans for transition to CFC-free alternatives.

Multinational pharmaceutical producers provide the vast majority of MDIs in most Article 5(1) countries and CEIT. In a few countries (e.g. Brazil, Mexico), local manufacture accounts for some MDIs, while the majority comes from multinational producers. In other countries (e.g. People's Republic of China, Cuba and India), local manufacture supplies the majority of MDIs to the market.

Local production alone is unlikely to be the single element driving transition to CFC-free MDIs. Although CFC-free inhalers are already available in at least 30 Article 5(1) countries, uptake has been very low. India, for instance, has a local manufacturer producing the majority of the MDIs used in that country. Whilst this manufacturer has introduced at least three CFC-free MDIs, this introduction alone has not been sufficient to drive transition to these products. This is similar to the experience in developed countries. Transition to CFC-free MDIs can however be achieved provided a good transition policy is in place. The ATOC is aware that the Philippines (an importing country) has achieved more than 50 percent transition to CFC-free MDIs.

Table 3-2: MDI units used (not produced) in some Article 5(1) countries in 2001 (data are approximate)

Country	Total number of MDIs used (Millions)	Number of HFC MDIs used (Millions)	MDI produced and imported by multinationals (%)
Argentina	3.34	0	87
Brazil	6.13	0	99
People's Republic of China	20.00	0	30
Mexico	1.88	0	98
Pakistan	2.20	0	100
Philippines	1.20	0.68 (1)	94
India (2)	15.00	0 (2)	20
South Africa	1.95	0.025	53
Turkey	2.47	0	95

(1) Over 60 percent of MDIs used are HFC MDIs.

(2) Vast majority of MDIs in India are manufactured by Cipla, which has launched a salbutamol HFC MDI. This was not included in the analysis.

The prevalence of asthma and COPD has been increasing in both developed and developing countries (Article 5(1) and CEIT) over the last two decades.

The population of Russia is approximately 150 million and an estimated minimum of 4 million people have significant airways diseases and it is suggested that approximately only 10 percent of these utilise modern inhaled therapy. There is local production of MDIs in Russia and the Ukraine but most MDIs are imported.

There is potential for a rapid and dramatic increase in MDI use, as illustrated by an intervention in Moscow where, following patient and health professional education, children's MDI use increased by 50 to 60 percent.

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 majority of MDIs used in Brazil are imported, but there is some local production. Local MDI production is by multinational companies that currently sell 5 million CFC MDIs every year.

In the People's Republic of China, where there is a population of 1.3 billion people, there are an estimated 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. Consumption of CFCs for use in MDIs in 2001 totalled 430

tonnes. Three multinational companies import and produce locally (accounting for 25 percent of China's production and 30 percent of total use) and there are over 60 pharmaceutical aerosol producers. In 2001, industrial MDI production in China was seventeen million units and there was an additional production of 0.1 million units in hospitals. CFC-based MDI products from multinational companies (either produced locally, or imported) are approximately 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 has 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 20 percent of India's use) and five domestic companies have facilities for MDI production. At the present time, 15 million MDI units are sold locally with an additional 7 million being exported by one, large Indian company to other Article 5(1) countries. Locally manufactured products are said to retail at approximately the same price as those produced by the multinational companies.

Pakistan has a population of 140 million people. There are no firm epidemiological data regarding the prevalence of COPD, but an estimated 10 percent of children have asthma. Forty percent of adult males smoke and the prevalence of smoking-related airway disease is expected to rise. Fewer than 10 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. Overall annual sales of MDIs in the year 2001 were over 2.2 million units. There is a large market for oral beta-agonists in Pakistan and in the year 2001 over 8 million units were sold in the country. As acceptance of MDIs by the patient increases, sales are likely to increase in the next few years. There are no known locally owned producers.

In many countries such as those cited above, there is reported to be a lack of awareness of CFC transition issues in both the general population, as well as amongst health professionals. Since it is anticipated that in most Article 5(1) countries 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.

3.6.2 Manufacturing issues – CFC production and MDI production

A number of factors will be crucial in the process of transition to CFC-free MDIs in Article 5(1) countries and CEIT.

Both continued availability and cost of pharmaceutical grade CFCs after 2005 may be major issues.

MDIs are usually made with pharmaceutical grade propellants, which have more stringent specifications than technical grade propellants and command a higher price. Several Article 5(1) manufacturers of MDIs import pharmaceutical grade CFCs from Europe and will be affected by the announced closure by 2005 of the Honeywell plant in Netherlands.

If CFC availability falls and final campaign production and storage are to be undertaken for the final stages of transition, then reliable estimates of CFC requirements by Article 5(1) countries and CEIT will be necessary. Safe transition to alternative inhalers will require continued availability of supply of MDIs for medical purposes. At present, data on the prevalence of airways diseases and future needs for MDIs are not readily available for many countries. Reliable data and estimates are needed.

The cost of CFCs may increase as final phase-out approaches, if supply falls and if final campaign production and storage facilities are required. MDI manufacturers in Article 5(1) countries will be competing for CFC supply with other CFC users such as the foam and refrigeration industries under the Montreal Protocol phase-out schedule. Such competition could add significantly to the price of propellants. As a result, the price differences between traditional (less expensive) CFC-based MDIs and the newer (more expensive) CFC-free alternatives may narrow. However, as of 2002, prices of CFCs remain low.

3.6.3 Technology transfer, local production and costs

Continued provision of MDIs in Article 5(1) countries 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) countries 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, whether 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. Local production of CFC-free inhalers will thus involve capital costs and either multiple year or one-off licensing arrangements. 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. Multinational companies operating in Article 5(1) countries should be encouraged to undertake this technology transfer as soon as possible.

The cost of CFC-free inhalers (whether imported or produced locally) is likely to be similar for branded products. Therefore, the costs of transition, to any one Party, will be dependent upon its use of branded versus generic MDIs.

3.6.4 Conclusions

It is acknowledged that there are major concerns over the cost and/or availability of healthcare in all countries, particularly in Article 5(1) countries and CEIT. Notably, inhaled therapies are usually more expensive than commonly available oral medications that are less effective and maybe more hazardous. For the purpose of this document, ATOC has limited its comments to CFC MDI transition issues.

It is important that countries collect accurate basic data on inhaler use if effective transition plans are to be developed. If such data already exist, the ATOC is not aware of them.

Current experience is that transition plans will only be successfully implemented if there are frank discussions among the major stakeholders, that is, MDI producers, health and environmental agencies. In addition, there will be a need to involve national medical professional organisations. International organisations or programs, for example, Global Initiative for Asthma (GINA), Global Initiative on Obstructive Lung Disease (GOLD), International Union Against Tuberculosis and Lung Disease (IUATLD) and World Health Organization (WHO), also may have roles to play. This is relevant for all Article 5(1) countries and CEIT, irrespective of whether they have local manufacturing or not.

Since price is such an important factor in the use of inhaled therapy, the price of CFC alternatives will be a major barrier to transition, unless they are no more expensive than comparable CFC products.

There has been a lack of awareness by healthcare providers regarding the need for change from CFC to CFC-free inhalers. In developed countries already advanced in their transition process, multinational pharmaceutical companies have been more effective than governments and NGOs in educating healthcare providers. This may also prove to be the case in Article 5(1) countries and CEIT. Countries should consider this likelihood in developing their transition strategies.

For the purposes of considering funding, Article 5(1) countries and CEIT can be divided into two broad categories: those with manufacture of MDIs by local companies and those without.

Those countries with CFC MDI manufacture by local companies will require an interventionist transition policy. This may require assistance with the development of alternative formulations, modification of manufacturing plant and fulfilling of regulatory obligations for marketing. This assistance may vary, depending on whether local manufacture is undertaken independently, or under a licensing agreement. As has been the case in developed countries, an evaluation of whether reformulation of a specific drug is technically feasible may be needed. This and similar aspects of transition policy will require input by appropriate pharmaceutical and technical experts in order to ensure optimal use of any development funding.

Most countries do not have local manufacture of CFC MDIs and supply of MDIs is wholly or largely by import. In those countries, national transition policies may be less interventionist, as in many developed countries. Experience in developed countries, where the supply of CFC MDIs comes from import by multinational companies, is that CFC alternatives can be introduced promptly where it is feasible within the regulatory framework of a country (e.g. Canada).

Experience in developed countries has been that education has largely been provided by MDI manufacturers, supplemented by information from health authorities and patient support groups. Support for educational efforts in Article 5(1) countries may be needed to facilitate transition, dependent on local circumstances.

The CFC MDI transition has proved to be complicated, as it is influenced by medical, technical, economic and regulatory factors. In Article 5(1) countries, this transition is occurring as a part of the overall phase-out of CFCs (with a 50 percent reduction from baseline levels in CFC consumption for basic domestic needs in Article 5(1) countries in 2005). Competition for supply of CFC between all uses may compromise supply of CFCs for MDIs. Therefore, ATOC strongly recommends that in order to protect patient health, MDI transition strategies be developed now, especially by those countries with local MDI manufacture, notwithstanding the date of 31 January 2005 (by which time Article 5(1) Parties are encouraged to develop MDI transition strategies. The development of transition policies could be facilitated by a series of regional workshops.

4. Sterilants

4.1 Introduction

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. 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.

There is a range of sterilisation methods; including steam, radiation, ethylene oxide (EO), formaldehyde, chlorine dioxide and ionised gas plasma.

EO is a sterilant of medical/surgical equipment and devices. 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 has the ability to penetrate packaging materials, destroy microorganisms and diffuse away from the package leaving almost no residues after sufficient aeration.

EO is toxic, mutagenic, a suspected carcinogen, flammable and explosive. Great efforts have been made to replace EO, particularly in hospitals where personnel exposure is of great concern. The fact that EO is still used as a sterilant is evidence that in numerous applications the benefits of its use outweigh these disadvantages.

EO can be used as a sterilant either alone or diluted with other gases (such as CFC-12, blends of HCFCs or carbon dioxide (CO_2) to make non-flammable mixtures. A 12 percent by weight EO and 88 percent CFC-12 has been used for this purpose.

Many hospitals continue to rely on non-flammable EO/HCFC blends and have added new sterilisers for this purpose. These new units are used more efficiently than the previous EO/CFC units. One way efficiency has increased is by hospital consolidation. When several hospital sites become part of a single institution, they shut down their under utilised sterilisers and concentrate EO/HCFC sterilisation in one hospital. By loading the remaining sterilisers more fully, the institution uses less sterilant per cubic feet of devices sterilised. Also, new techniques have been validated to use up to 25 percent less sterilant per load. In the United States, the control systems for these techniques await regulatory approval.

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) countries and in some Article 5(1) countries. Although it is difficult to estimate, it is believed that the global total use of CFCs in 2001 for this application was less than 500 metric tonnes.

HCFC mixtures that replace EO/CFCs are used mostly in the United States and in countries that allow venting of HCFCs to the atmosphere. These mixtures are virtual drop-in replacements for 12/88. The European Union has legislation restricting the use of HCFCs in emissive applications such as sterilisation. HCFCs were introduced as transitional products for sterilisation in those countries that previously employed 12/88 extensively. Estimated use of HCFC replacement mixtures in 2001 is thought to be less than 1,700 metric tonnes (some 50 ODP tonnes). Use has almost reduced to one half of 1998 figures by using less mix per steriliser load and by hospital conversion to other technologies.

Alternative technologies to which hospitals have converted include: use of more steam-sterilisable devices, more single-use devices, pure ethylene oxide sterilisers and other methods that will sterilise or disinfect some of the low temperature devices used in hospitals. These other low temperature processes include vapour phase hydrogen peroxide-plasma, steam-formaldehyde (in parts of Europe and South America), and liquid phase peracetic acid.

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 regulations on fire protection, occupational safety, validation of results, liability considerations, availability of sterilisation equipment and materials, and medical practices.

Quality health care is dependent upon sterility 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. The nature and size of items to be sterilised will vary according to the user. Some items are more robust than others with regard to temperature and radiation. Thus, a number of different processes can be used, and each will offer specific advantages.

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

Steam Sterilisation – This process is non-toxic, economical, and relatively safe. Devices treated must be able to withstand a temperature greater than 113ºC (235ºF) and very high moisture levels.

Formaldehyde – Used mainly in Europe and parts of South America for materials that are able to withstand temperatures of 80-85ºC (176-185ºF), although uses at 60-65ºC (140-149ºF) 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 ranges from large industrial units to small canister units used in hospitals.

Blends of EO and CO_2 – Carbon dioxide is used to produce flammable and non-flammable mixtures with EO. Those containing more than 8.5 wt.% EO are flammable. Usually, EO/CO_2 mixes are not used to replace the non-flammable mixes. Operating pressures are about ten times higher than for 12/88. Use of EO/CO_2 blends has other disadvantages, such as composition changes during the use of a single tank or cylinder, increased polymerisation, and compatibility and corrosion problems caused by the acidity of CO_2.

Blends of HCFCs and EO – These HCFC-124 containing blends are virtual drop-in replacements for 12/88, although more costly. These gas mixtures have been validated for different applications and compatibility with the products and their packaging established. They have been used for the last eight years and allow continued use of expensive sterilisers with minor control adjustments.

Blends of HFCs and EO – These have been tested and validated by at least one hospital and one medical device manufacturer. Both used existing sterilisation equipment, changing only process controls. Also, EO/HFC blends have been validated to replace EO/methyl bromide blends to fumigate archives and antiquities. Several agencies will need to give regulatory approval before new HFC blends are broadly used worldwide. This process is expected to take several years, at the end of which time it is expected that the EO/HFC blends will replace the EO/HCFC mixes.

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; for this reason radiation sterilisation is not generally acceptable for hospitals. Not all materials are compatible with radiation. Facilities using gamma radiation need to dispose of spent isotopes.

Ionised Gas Plasma – Two processes were 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 with peracetic acid. Many units of these different processes have been sold worldwide, mostly to hospitals. The peracetic acid process, which had not received FDA approval for this application, was associated with patient injuries when ophthalmic surgical instruments sterilised with this system were used. A global recall of this particular ionised gas process was mandated. The hydrogen peroxide/plasma system continues to be used extensively.

Chlorine Dioxide – A system for sterilising medical devices using chlorine dioxide has been developed. Typically it operates at 25-30^{o}C and at a relative humidity of 70-90 percent. Chlorine dioxide is generated *in situ* from sodium chlorite and chlorine gas in a nitrogen carrier. Gaseous chlorine dioxide is drawn into an evacuated chamber to achieve a concentration in the range 10-50 mgl^{-1} and these conditions are maintained for a pre-determined time, generally less than 2 hours.

Liquid Peracetic Acid – This is an effective sterilant, although applications of this wet process are limited. Available equipment uses cassettes where items to be sterilised such as endoscopes are placed. The cassette is designed to provide a chamber for exposure to the peracetic acid solution, flushing out, rinsing with a neutralizing agent, rinsing with sterile, filtered water, and final drying.

4.4 Conclusions

CFC-12 use in the sterilisation sector has been phased out in most non-Article 5(1) countries. Remaining worldwide use can be easily substituted, as there are a number of viable alternatives. EO/HCFC blends have a small ODP (0.03) and should not be promoted in countries that have not been major 12/88 users.

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 the health of patients unnecessarily at risk.

5. Miscellaneous uses

Below is described a selection of miscellaneous uses. Most 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 to obtain accurate data on volume and use patterns. Any new information would be gratefully received by 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 accurately estimate the 2002 worldwide consumption of CFC-11 to expand tobacco due to declining use. China is believed to be the only remaining country to use significant quantities of CFCs for this purpose, using about 1,000 ODP per year. According to decisions taken by the Executive Committee, a stepwise phase-out is planned. Based on the planned installation of alternative carbon dioxide technology in China, declining use in this country is expected.

Most countries have converted plants to cease the use of CFCs to expand tobacco:

- By the end of 1998, Mexico and the Philippines were expected to have carbon dioxide plants on line that would eliminate the use of CFCs in those countries. In the past, 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 United States, 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 was planning 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 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.

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. As 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, which has been successfully used as an expansion agent for approximately twenty years and is now the most widely used process;
- Propane, which is being successfully used by one company in Germany, with another facility being installed in the United Kingdom in 1998;
- Nitrogen, which is a high pressure process system being used in France; and
- *Iso*-pentane, which 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 have been phased out. This process impregnates tobacco with liquid CO_2 under pressure. This combination of tobacco/CO_2 is then passed into a heated air stream (less than 800°F). This heat causes the CO_2 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.

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. As the propane process requires a pressurised system, it may require additional safeguards for employees, is highly flammable, and may be explosive. 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 process is being used commercially in at least two locations.

5.1.2.3 Nitrogen

Nitrogen expansion requires special equipment due to the extremely high pressures in the expansion vessel. While this process is used in France, the extremely high pressures have prevented further marketing of this process.

5.1.3 Costs

The estimated costs for each alternative are 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. Further information on costs of conversion is available in the *UNEP, Assessment Report of the Aerosols Technical Options Committee, 1998.*

5.1.4 Developing country perspective

The principal 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 was 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.

5.3 Leak detection

CFCs, HCFCs and HFCs can be used to locate leaks in underground, pressurised pipes. ODSs 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 include HCFC-22 and HFC-134a. Detection equipment is specific to, or can be calibrated according to, the fluorocarbon being used. Dyes, such as those visible in the ultraviolet range, are also used to detect leaks using light sources.

Helium, in conjunction with a helium-actuated detection device, is another available alternative.

Other alternatives include sulfur hexafluoride, although its potency as a greenhouse gas is likely to limit its use.

Dyes can also be used to check for cracks in large tanks, mostly in welding joints, where the surface is cleaned, a penetrant dye is applied, and a developer coat applied. Any fissures can be easily spotted. A variation is to use ultrasonic vibration to concentrate and highlight the dye in the cracks.

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 is available 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 SF_6.

5.7 Thermostats and thermometers

CFCs 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 waveguides. 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 waveguide transmission 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 and 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 and 2002, 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. SF_6 is used in power supplies and in Van de Graaf units, because of its excellent dielectric properties and its non-toxicity. SF_6 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 marketed globally 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) countries using ODS inventory produced before 1996, or from Article 5(1) countries.

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."

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.

The Parties at their 10th Meeting extended the global exemption for laboratory and analytical uses until 31 December 2005 (Decision X/19(1)). The TEAP were requested to report annually on the development and availability of laboratory and analytical procedures that can be performed without using the controlled substances in Annexes A and B of the Protocol.

It was also decided (Decision X/19(3) that:

"That the Meeting of the Parties shall each year, on the basis of information reported by the Technology and Economic Assessment Panel in accordance with paragraph 2 above, decide on any uses of controlled substances which should no longer be eligible under the exemption for laboratory and analytical uses and the date from which any such restriction should apply;"

The Secretariat were requested to make available to Parties each year a "*consolidated list of laboratory and analytical uses that the Parties have agreed should no longer be eligible for production and consumption of controlled ozone-depleting substances under the global exemption."*

It was specifically noted in Decision X/19(5) that:

"any Decision taken to remove the global exemption should not prevent a Party from nominating a specific use for an exemption under the essential uses procedure set out in Decision IV/25."

The Parties at their 11th Meeting decided in Decision XI/15 to eliminate, for the first time, a number of uses of controlled substances from the global exemption for laboratory and analytical uses, which had been previously approved in Decision X/19. This took effect from the year 2002. The uses were:

(a) Testing of oil, grease and total petroleum hydrocarbons in water;
(b) Testing of tar in road-paving materials; and
(c) Forensic fingerprinting.

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 were detailed in the *UNEP, Assessment Report of the Aerosols Technical Options Committee, 1998*.

6.2.1 Estimated use of ODS for laboratory and analytical use

Although only few data are available for laboratory and analytical uses, it can be estimated that the total global use of controlled substances for these

applications in non-Article 5(1) countries will not exceed a maximum of 500 metric tonnes. Use in CEIT is unlikely to be more than a few hundred metric tonnes. Estimated use in India of 150 metric tonnes of CTC as a laboratory reagent would indicate that up to 500 metric tonnes could be used for analytical and laboratory uses in Article 5(1) countries. An estimate for global use of controlled substances for laboratory and analytical uses is 1,500 metric tonnes. This will reduce as the major uses are phased out through the implementation of Decision XI/15.

6.2.2 Analysis of oil, grease and total hydrocarbons in water

In Decision XI/15, the Parties decided to eliminate the use of ozone-depleting substances for the 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.

This Decision was taken on the grounds that readily available cost-effective alternatives for these applications had already been implemented in many countries.

Three Parties, the European Community, Poland and Norway requested, and were granted, emergency exemptions for the year 2002 in order to continue the use of ODS for the testing of oil, grease and total petroleum hydrocarbons in water. Both Parties are in the process of changing over from using ODS analytical procedures to the use of non-ODS procedures. The European Community noted that full implementation is dependent mainly upon the adoption of the standards by competent authorities operating in all Member States, competent authority validation of the detection limit of the new procedures compared to those that used ODS and, in some Member States, adjustment of waste water discharge permits and monitoring programmes by reference to non-ODS methods.

The European Community requested 37.5 metric tonnes of CTC and 35 metric tonnes of CFC-113. Norway requested 2.0 metric tonnes of CFC-113. Poland requested 0.01 tonnes of CFC-113 and 2.0 tonnes of CTC.

The United States Environmental Protection Agency issued a final rule in February 2002 that extended the general exemption for controlled “Class 1 ozone depleting substances” for use in essential laboratory and analytical applications through 2005 as consistent with the Montreal Protocol. It also clarified that use of these substances for the testing of oil and grease” and “total petroleum” in water, testing of tar in road paving materials, and forensic fingerprinting are not considered essential under the exemption.

US EPA Method 1664 to extract oil and grease from water. The following listings can be found on the Internet at http://www.epa.gov/ost/methods/oil.html:

1. Analytical Method Guidance for EPA Method 1664A Implementation and Use (40CFR part 136 in the Federal Register).

2. Method 1664, Revision A: N-Hexane Extractable Material (HEM; Oil and Grease) and Silica Gel Treated N-Hexane Extractable Material (SGT-HEM; Non-polar Material) by Extraction and Gravimetry.

3. Approval of EPA Methods 1664, Revision A, and 9071B for Determination of Oil and Grease and Non-polar Material in EPA's Wastewater and Hazardous Waste Programs.

The 1999 US Federal Register lists the final rule that approved Method 1664 under 40 CFR Parts 136 and 260: Guidelines Establishing Test Procedures for the Analysis of Oil and Grease and Non-Polar Material Under the Clean Water Act and Resource Conservation and Recovery Act--Final Rule.

This notice is located at http://www.access.gpo.gov/su_docs/aces/aces140.html. From this page, click on the 1999 Federal Register; enter the release date as 05/14/1999, and search for "Oil, Grease, and Water."

Appendix 1 to this report details some methodologies for the analysis of oils, greases, waxes etc.

6.2.3 A new methodology

A new method has been published for the analysis of oil/grease in water by B. Minty, E.D. Ramsay and I. Davies, "Development of an automated method for determining oil in water by direct aqueous supercritical fluid extraction coupled on-line with infra-red spectroscopy", *Analyst*, 2000, 12, pp. 2356-2263. This has been demonstrated to produce comparable results to the traditional infrared method.

6.2.4 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 and 1998 Assessment Reports of the Aerosols Technical Options Committee. Specific applications of carbon tetrachloride have been investigated in the 1995 Reports of the TEAP Process Agents Working Group and were further elaborated by the TEAP Process Agents Task Force in 1997 and 2001; review can also be found in the 1995 Report of the TEAP Laboratory and Analytical Uses Working Group. Inadvertent Emissions and Process Losses were discussed in the *UNEP, Report of the Technology and Economic Assessment Panel, 1994*.

The April 2000 Report of the TEAP reviewed the emissions of CTC from its use as feedstock, including estimating future emissions of CTC from this application. Using the same methodology to that used in the *UNEP, Assessment Report of the Aerosols Technical Options Committee, 1998*, emissions of CTC used to manufacture CFCs in 1998 were estimated to be 26,378 metric tonnes (-25 percent, +50 percent).

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 *UNEP, Report of the TEAP Process Agents Task Force (PATF), 1997* 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 *UNEP, Report of the TEAP Process Agents Task Force (PATF), 1997* 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 as 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 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) countries. 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.

The Montreal Protocol mandates an 85 percent reduction of CTC production and consumption effective January 1, 2005 for Article 5(1) Parties. The base level is the average of 1998-2000 figures.

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 have enabled the collection of much clearer data on CTC consumption, although these data do not allow a more detailed analysis of CTC applications. These data are, at present, being supplemented by on-going studies to evaluate the use of CTC in countries that are undertaking country phase-out programmes, such studies will enable a considerably more detailed analysis of the remaining uses of CTC. The ATOC will prepare a further analysis of atmospheric emissions when these data are available.

By using data provided by UNEP, estimates have been made of the CTC required for the manufacture of CFCs (Tables 7-2, 7-3 and 7-4). The calculated level of CTC required for global CFC manufacture of 128,127 ODP tonnes is 178,084 ODP tonnes.

India has increasing consumption of CTC for non-CFC feedstock use in the production of DV Acid Chloride, which is an intermediate for the production of cypermethrin or synthetic pyrethroids. It is estimated for the year 2000 that this application used 7,700-8,000 metric tonnes. CTC is also used as a feedstock for the production of many other substances, but the volumes required are much smaller than those needed for CFC production.

A number of conclusions can be drawn:

- CTC remains a widely available and used chemical. The primary source of atmospheric emissions of CTC are those from point sources which are present on manufacturing plants that use CTC as a feedstock to produce CFCs. These will decline in line with the phase-out of CFC production. Substantial reductions have been achieved recently through closures of CFC production facilities in Brazil and the Russian Federation. Significant emissions result from process agent, other uses and inadvertent emissions.

- There is considerable trade in CTC. India and China meet demand with domestic production and importation. India imports between 17,000-20,000 metric tonnes per annum to meet the shortfall in local production.

- CTC consumption in Article 5(1) Parties has been reported to UNEP as 22,934 ODP tonnes in 1999 and 15,487 ODP tonnes in 2000. CTC consumption in non-Article 5(1) Parties has been reported to UNEP as 2,040 ODP tonnes in 1999, rising to 4,205 ODP tonnes in 2000. These data exclude reports by Parties of negative consumption that originate where a Party destroys CTC or uses it as a feedstock and do not include data for 2000 from China.

- CTC consumption for process agent and other uses in non-Article 5(1) countries is low. Decision X/14 limits the "make-up or consumption" of CTC to 4,501 tonnes and emissions to 220.9 tonnes for non-Article 5(1) Parties.

- CTC consumption for process agents in Article 5 (1) Parties has proved very difficult to estimate. In particular, a number of different applications for CTC have been reported without conclusive evidence to determine whether these applications are indeed process agents. In its Assessment of the Funding Requirement for the Replenishment of the Multilateral Fund for the Period 2003-2005, the TEAP assumed that around 8,000 ODP tonnes are used as process agents in uses approved by Decision X/14, but acknowledged that several thousand tonnes could be used in China in uses not approved under Decision X/14.

- The estimate of consumption from laboratory and analytical uses of 1,500 tonnes in previous reports remains valid.

If the limit for non-Article 5(1) Parties, and the data reported to UNEP for CTC consumption are used, then the global CTC consumption/"make-up" for

for process agent, laboratory and analytical and other uses can be estimated as a maximum of 25,000 tonnes. These estimates should improve as a result of studies taking place in India and China to identify and quantify CTC use as a process agent.

7.3 Atmospheric measurements

The 2002 Scientific Assessment has noted that the global lifetime of carbon tetrachloride is currently estimated to be 26 (23-42) yr, or about 25 percent shorter than in the previous Assessment. This shorter lifetime stems from widespread observations of substantial under-saturation of carbon tetrachloride in surface waters of the ocean (Yvon-Lewis and Butler, in press, 2002). Emissions inferred from this shorter lifetime and measured trends during the 1990s are generally higher than those estimated from 1996 industry production data. Global emissions of carbon tetrachloride, as inferred from measured trends, did not decrease significantly during 1995-2000.

Global surface mixing ratios (tropospheric concentrations) of carbon tetrachloride have decreased since about 1990; mixing ratios in 2000 were between 95 and 100 ppt (Simmonds *et al*., Global trends and emissions estimates of CCl_4 from in-situ background observations from July 1978 to June 1996, *J. Geophys. Res., 103,* 16017-16027, 1998; Montzka *et al*., Decline in the tropospheric abundance of halogen from halocarbons: Implications for stratospheric ozone depletion, *Science, 272,* 1318-1322, 1996; Present and future trends in the atmospheric burden of ozone-depleting halogens, *Nature, 398,* 690-694, 1999; Prinn *et al*., A history of chemically and radiatively important gases in air deduced from ALE/GAGE/AGAGE, *J. Geophys. Res., 105,* 17751-17792, 2000 – see reproduction of data in Table 7-1 below). The observed rates of change have remained fairly constant since 1993 at about -1% yr^{-1} or -1 ppt yr^{-1}. The inter-hemispheric ratio has also been fairly constant at about 2 percent since 1993 and suggests that significant emissions of carbon tetrachloride remain. Calibration differences between the National Oceanic and Atmospheric Administration (NOAA), the University of California Irvine and the Advanced Global Atmospheric Gases Experiment (AGAGE) are of the order of 3 percent.

These data demonstrate the necessity of collecting accurate production and consumption data for CTC in order to better understand the levels of CTC measured in the atmosphere and to pinpoint their origins.

Table 7-1: Mixing ratios and growth rates of CTC

Concentration (ppt) Year			Growth (1999-2000)		Laboratory, Method
1996	1998	2000	ppt yr^{-1}	% yr^{-1}	
100.5	98.2	96.1	-0.94	-0.97	AGAGE, *in situ*
103.2	101.9	99.6	-0.95	-0.95	NOAA, *in situ*

7.4 Production and consumption of carbon tetrachloride and production of CFCs in 2000

Source: UNEP *Production and Consumption of Ozone Depleting Substances*

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

Table 7-2: Article 5(1) Parties (2000) (ODP tonnes)

	Reported CFC production to UNEP	Calculated CTC requirement for CFC production	Reported CTC production to UNEP	Reported CTC consumption to UNEP
Argentina	3,027	4,238	0	413
Brazil	0	0	7,013	767
China	36,200*	50,700	0	0
India	20,404	28,565	12,147	12,147
Korea, Dem. of	77	108	1,045	1,045
Korea, Rep. of	7,000**	9,800	NR	NR
Mexico	7,546	10,564	0	0
Romania	0	0	-150	-150
South Africa	0	0	0	0
Venezuela	2,281	3,193	0	0
Total***	76,535	107,168	20,205	14,372

NR – not reported

* Estimate based on country CFC phase-out programme

** Estimate

*** Total only for countries listed

Table 7-3: Western Europe and others (2000) (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	0	0	0
Canada	0		1	0
European Union	27,051	35,166	1824	-550
Japan	0	0	23	23
USA	-7	0	2	-18,660
Total	27,051	35,166	1,850	23

Table 7-4: Eastern Europe (2000) (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	5	7	-81.4	-81
Russian Federation	25,536	35,750	0	4,124
Poland	0	0	27.9	30.7
Ukraine	0	0	0	0
Total	24,541	35,750	27.9	4,155

7.4.1 Notes for reported production and consumption data in Tables 7-2 to 7-4

Negative consumption data in Tables 7-2, 7-3 and 7-4 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 7-2 to 7-4. The fact that reported CTC consumption exceeds production by far 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 *UNEP, Assessment Report of the Aerosols Technical Options Committee, 1994*, 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 7-3) and 1.4 for the Article 5(1) countries and Eastern Europe (Tables 7-2 and 7-4) were used here.

A1 Appendix 1

Methodologies for the analysis of oils, greases and waxes

The methodology used is determined by the analysis that is required. This can be decided by a number of questions:

1. Is the method needed for analysis of total hydrocarbons in water, sediment, or soil?

2. Is it required to finger print oils, as diesel, vegetable oil, petrol, kerosene?

3. Is a quantification of individual hydrocarbons in a sample of water, oil or soil/sediment the goal?

If Q1 is relevant, the method that is probably being used is a solvent extraction with CTC followed by quantification using infrared spectroscopy using the C-H stretch. CTC is the best solvent here as it is fully chlorinated. The other solvents mentioned as suitable are 1,1,2-trichloroethane, 1,2,2-trifluoroethane. The limit of detection for this method is 0.06mg/kg.

Reference: SCA, The determination of hydrocarbon oils in water by solvent extraction, infra red adsorption and gravimetry 1983, HMSO ISBN 0 11751728 3

Where Q2 is relevant, that is for the finger printing of oils, a number of solvents are mentioned depending on the sensitivity required. These are as follows:

- Toluene or diethyl ether for low resolution Gas Chromatography.

- Toluene or redistilled dichloromethane. Solvent extraction and distillation method followed by high resolution Gas Chromatography.

- Dichloromethane liquid-liquid extraction followed by solvent reduction and high resolution Gas Chromatography. (River water analysis general organic screen)

- Dichloromethane is used in pollution control laboratories where rapid screening for pollutants is carried out.

Reference: SCA, Gas chromatographic and associated methods for the characterisation of oils, fats, waxes and tars. 1982 HMSO. ISBN 0 11 751677 5

Where Q3 is relevant and there is a need to determine the concentrations of individual hydrocarbons, pentane is used as the main extraction solvent, but re-distilled dichloromethane is used as part of the sample clean-up procedure. Samples are then analysed by high resolution capillary Gas Chromatography with a flame ionisation detector. The range of the application is 0-20 microgram/litre.

Reference: SCA. Determination of very low concentrations of hydrocarbons and halogenated hydrocarbons in water. 1985 HMSO. ISBN 0 11 752004 7.

Other solvents that have been used to extract organic compounds from sediments and water are:

- CFC-113 for polyaromatic hydrocarbons (1991), ethyl acetate;
- dichloromethane for benzo(a)pyrene, nitrophenols and nitroaniline (USEPA CLP method 1990);
- *n*-hexane for organochlorine pesticides.

Generally in water analysis there has been a move away from liquid-liquid extraction in favour of solid phase extraction using disks or small C18 columns, which are then eluted with methanol. There is also an increase in the use of purge and trap methods.