Medical and Chemicals Technical Options Committee

2018 Assessment Report

Montreal Protocol
on Substances
that Deplete the
Ozone Layer

UN environment
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MONTREAL PROTOCOL

ON SUBSTANCES THAT DEPLETE

THE OZONE LAYER

2018 REPORT OF THE
MEDICAL AND CHEMICAL TECHNICAL OPTIONS COMMITTEE

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ASSESSMENT REPORT

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Metered Dose Inhalers

Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic diseases of the respiratory tract. Inhalation therapy is the mainstay of treatment for asthma and COPD. There are two common types of inhalation devices for the delivery of respiratory drugs: (pressurised) metered dose inhaler (MDI) and the dry powder inhaler (DPI) in single- or multi-dose. In different markets, the proportion of MDIs to DPIs differs. These proportions vary for many reasons including prescribing practices, cost, availability, patient preference, and national government guidance. Other methods of delivering drugs to the lung include soft mist inhalers and nebulisers.

MDIs that use chlorofluorocarbons (CFCs) as a propellant were historically the inhaled-delivery device of choice as they were affordable, reliable and extremely effective. Under the Montreal Protocol, the manufacture of pharmaceutical grade CFCs for MDIs has been successfully phased out worldwide without significant adverse impact to human health. Pharmaceutical companies have replaced the CFC propellants in MDIs with hydrofluorocarbons (HFCs, namely HFC-134a and to a lesser extent HFC-227ea). Three low-GWP (global warming potential) chemicals are under development as potential propellants for MDIs (isobutane, HFC-152a, and a hydrofluoroolefin, HFO-1234ze(E)).

Following the Kigali Amendment to the Montreal Protocol, HFCs, including -134a, -152a, and -227ea, are now listed as controlled substances under Annex F. Approximately 800 million HFC MDIs are currently manufactured annually worldwide, using approximately 11,500 tonnes HFCs in 2018. HFC-134a makes up the major proportion of MDI manufacture (~10,600 tonnes in 2018), with HFC-227ea accounting for about 8 percent (~900 tonnes in 2018). This corresponds to direct emissions with a climate impact of approximately 18,000 ktCO$_2$-eq. For the year 2016, HFC propellant consumption for MDI manufacture corresponded to direct emissions that are estimated to be about 2 percent of global GWP-weighted total emissions of HFCs. The use of HFC MDIs is projected to increase, especially with increasing use of MDIs in developing countries.

Dry powder inhalers (DPIs) are devices that deliver powdered medication (active ingredient mixed with excipient) without the need for a propellant. Most commonly used respiratory drugs have been formulated successfully for DPIs and are now widely available. Almost all new drugs are being developed in the DPI format, often exclusively.

In many circumstances, DPIs are technically and economically feasible alternatives that could substantially reduce the use of HFC MDIs. Nebulisers and emerging technologies may also be technically feasible alternatives for avoiding the use of some HFC MDIs. The main exception is salbutamol, where salbutamol multi-dose DPIs are generally more expensive than salbutamol HFC MDIs, which remain an essential and affordable therapy. It is not yet technically or economically feasible to avoid HFC MDIs completely in this sector because, currently: for salbutamol, there are economic impediments in switching from some HFC MDIs to multi-dose DPIs; and some patients (young children and frail elderly) cannot use DPI alternatives to HFC MDIs.

By moving from CFC MDIs to HFC MDIs and DPIs, not only have emissions of ozone depleting substances been eliminated, but there have also been benefits for climate change. The carbon footprint of HFC MDIs is about one-eighth the carbon footprint of CFC MDIs. DPIs have an even lower comparative climate impact, about one-hundredth of the impact of CFC MDIs and less than one-tenth the impact of HFC MDIs. For a given dose, the carbon footprint of HFC inhalers can vary threefold. The carbon footprint of an HFC-152a MDI is projected to be about 90 percent less than an HFC-134a MDI. Aqueous mist inhalers also have much lower carbon footprints than current HFC MDIs.

The choice of the most suitable treatment method is a complex decision taken between the health care provider and the patient. MDIs, DPIs and other delivery systems all play an important role in the treatment of asthma and COPD, and no single delivery system is considered universally acceptable for all patients. Similarly, not all active ingredients are available equally as either an MDI or DPI. Healthcare professionals continue to consider that a range of therapeutic options is important. Complex considerations are necessary when patients and healthcare professionals make an informed choice about a patient's inhaled therapy, taking into account therapeutic options, patient history, patient preference, ability (e.g., dexterity, inspiratory flow, vision) and adherence, patient-borne costs, as well as environmental implications, with the overall goal of ensuring patient health.

While acknowledging these complex considerations, including patient health and broader public health implications, it is possible to minimise the carbon footprint of inhaled therapy use through certain choices. These choices include: minimising the use of MDIs containing the highest volumes of HFC-134a and those containing HFC-227ea; and giving preference to lower GWP propellants (if and when they become available, e.g. HFC-152a) and lower carbon footprint therapies (e.g. DPIs and aqueous mist inhalers). Patient choice may be enhanced with an increase in publicly available information about the environmental impact of different inhaler products. Healthcare professionals and their patients may benefit from this information in order to take environmental impact into account, among other important considerations, in their choice of inhaler.

Aerosols

Aerosols are used in a wide range of different applications. Aerosols incorporate propellants and solvents with the appropriate technical properties and characteristics in formulations designed to deliver a product for its intended purpose. Propellants include compressed gases (nitrogen, nitrous oxide, carbon dioxide), or liquefied gases, which are liquid inside the pressurized container; these liquefied gas propellants include chlorofluorocarbons (CFCs) (no longer used), hydrochlorofluorocarbons (HCFCs, e.g. HCFC-22) and hydrofluorocarbons (HFCs) (e.g. HFC-134a, HFC-152a), hydrofluoroolefins (HFOs, e.g. HFO-1234ze(E)), hydrocarbons, and dimethyl ether (DME). Some aerosol products also contain solvents, including HCFCs, HFCs, hydrofluoroethers, aliphatic and aromatic solvents, chlorinated solvents, esters, ethers, alcohols, ketones, and hydrochlorofluoroolefins (HCFOs, e.g. HCFO-1233zd(E)). CFC solvents are no longer used in aerosols.

Technically and economically feasible alternatives to ozone-depleting propellants and solvents (CFCs and HCFCs) are available for aerosol products. Small uses of HCFCs remain in a few countries (China and the Russian Federation) for specific medical aerosol products. A significant proportion of aerosol propellants have migrated to hydrocarbons and DME, which dominate in the consumer aerosol market. Hydrocarbons and DME are highly flammable propellants. Hydrocarbons and oxygenated hydrocarbons (such as DME) are volatile organic compounds (VOCs) that contribute to photochemical smog generation. In some jurisdictions, strict VOC controls can have an impact on the choice of propellant, where hydrocarbons are avoided. The use of compressed gases as propellants has increased as a result of VOC controls and the availability of better cans.

A smaller proportion of aerosols migrated to HFC propellants where: emissions of VOCs, such as hydrocarbons and DME, are controlled; a non-flammable propellant is needed; and/or a propellant is necessary that is safe to inhale, such as HFC-134a. HFC-134a is used more commonly as a propellant in technical and non-MDI medical aerosols where its non-flammable and inhalation safety properties have advantages. HFC-152a is used more commonly as a propellant in consumer aerosols. HFC-152a has moderate flammability, and is used alone, or in blends with hydrocarbons to meet VOC regulations. HFC-152a is also blended with HFC-134a to produce a propellant with lower GWP (than HFC-134a) and lower flammability (than HFC-152a). HFO-1234ze(E) is starting to be used as a propellant in technical and consumer aerosols where non-flammable and low-GWP properties are needed. HFO-1234ze is also used in jurisdictions that have VOC emission controls.

ODS solvents (CFC-113, methyl chloroform, HCFC-141b) used in aerosols have migrated to hydrofluorocarbons (HFC-43-10mee, -365mfc, -245fa), hydrofluoroethers (HFEs), aliphatic and aromatic solvents, chlorinated solvents, oxygenated organic chemicals, and low-GWP chemicals, such as hydrofluoroolefins and hydrochlorofluoroolefins, including methoxytridecafluoroheptene (MPHE) and HCFO-1233zd(E).

There are also not-in-kind (NIK) technologies that compete with aerosol products to perform the same or similar functions, including trigger sprays, finger pumps, squeeze bottles, roll-on liquid products (e.g., for deodorants), and non-sprayed products (e.g., for polishes and lubricating oils). NIK alternatives are sometimes not as easy to use or achieve lower performance for some applications.

HCFC use in China for medical aerosols for Traditional Chinese Medicines could be about 2,000-2,500 tonnes HFCF-22 or HCFC-22/HCFC-141b blend (HCFC-22: 1,500-2,000 tonnes and HCFC-141b: 500 tonnes). HCFC-22 is used as propellant, and HCFC-141b is used for its solvent properties. Flammability safety concerns with some economically feasible alternatives, such as DME or LPG, are currently a barrier to their use in this application. Other potential technical alternatives, such as HFC-134a, currently present an economic impediment in this particular application. In the Russian Federation, topical medical aerosol applications also use HCFC-22 and -141b as propellant and solvent, respectively, in quantities of around 20 tonnes per year. The products are aerosol foams used to provide local anti-inflammatory and antiseptic action, and to stimulate healing. Regarding the use of HCFC-141b in topical medical aerosols, it is worth noting that the National Institute for Occupational Safety and Health (NIOSH) have presented the immediately dangerous to life or health (IDLH) air concentration value for HCFC-141b to be 1,700 ppm (8,245 mg/m^3) on the basis of cardiac sensitization.

Global HFC demand in aerosols was estimated to be around 45,000 tonnes (~15,000 tonnes HFCs -134a; ~30,000 tonnes HFC-152a) in 2015. This corresponds to a warming impact from direct emissions of about 25,000 $ktCO_2$-eq. HFC propellant consumption for aerosol manufacture corresponds to direct emissions that are estimated to be about 3 percent of global total GWP-weighted emissions of HFCs. HFC demand in aerosols is dominated by the North American market, which consumes about 85 percent of the global total. The Asia and Asia-Pacific region is the next most significant, consuming around 10 percent of global total of HFCs in aerosols. Production is expected to expand in Article 5 parties.

HFC use is limited, either owing to cost, safety or regulatory reasons, or to applications where VOC controls might limit hydrocarbon use, or where a propellant with low flammability and/or proven safety is needed. HFC consumption in this sector is ranked as the third largest after the refrigeration and air conditioning and foams sectors, where aerosols are a totally emissive use. There would be environment benefits in promoting low-GWP and climate-friendly alternatives and by avoiding high-GWP propellants and solvents. In many cases, HFC propellants and solvents can be substituted with low-GWP options, and NIK alternatives are commercially available where they are suited for the purpose.

Sterilants

Sterilization is an important process in the provision of good quality healthcare services. Sterilization of medical devices can be performed in facilities ranging from industrial settings to smaller facilities including hospitals. It is also a process that requires strict application of the principles of quality management, reliability and long-term materials compatibility.

Ethylene oxide (EO) can be used as a sterilant either alone or diluted with other gases to make non-flammable mixtures. A mixture of 12 percent by weight EO and 88 percent dichlorodifluoromethane (CFC-12) (12/88) was once widely used for this purpose. CFC-12 use for sterilization has been successfully phased out in non-Article 5 Parties, and in most, if not all, Article 5 Parties, and only then from any remaining stockpile. Although it is difficult to be certain, global total use of CFCs for this application is believed to be zero.

EO/hydrochlorofluorocarbon (HCFC) mixtures (10 percent by weight EO in a mix of HCFC-124 and HCFC-22) were virtual drop-in replacements for the 12/88 mixture using CFC. They were introduced as transitional products for sterilization in those countries that employed 12/88 extensively. Estimated global use of HCFCs in sterilization is now considered less than 50 metric tonnes, which amounts to less than 2 ODP tonnes worldwide. EO/HCFC use has been significantly reduced by using less gas per sterilizer load, 100 percent ethylene oxide, and by hospital conversion to other technologies.

The complete phase-out of HCFCs in sterilization uses to meet the Montreal Protocol schedule is readily achievable. The useful lifetime of existing EO/HCFC sterilizers is about 20 years when well maintained. Therefore, by 2030 at the latest, any remaining sterilizers should be ready for replacement with available alternative technologies that do not use ozone-depleting substances. Hospital procurement should take the HCFC phase-out, and the coming redundancy of EO/HCFC sterilization equipment, into consideration in making future investment decisions.

There is a range of commercially available sterilization methods including: heat (moist heat or dry heat), ionizing radiation (gamma ray, electron beam, x-ray), alkylating processes (such as EO, formaldehyde) and oxidative processes (including hydrogen peroxide gas, gas plasma systems, liquid or gaseous peracetic acid, and ozone). Many of these alternative technologies provided significant advances, such as better safety profiles and turn-around times, and reduced cost per cycle. Further sterilization methods based on these and other chemical agents are under investigation for commercialization. Hydrofluorocarbons (HFCs) were investigated as alternative replacement diluents but were not widely adopted for technical reasons and the environmental impact of the use of HFCs. Any alternative to the use of ozone-depleting substances in sterilization needs to be well proven and tested to avoid putting the health of patients unnecessarily at risk. It is legal requirement in pharmaceutical and medical devices industries that any change in manufacturing processes, including sterilization, must be validated using appropriate guidelines before implementation.

Feedstocks

Ozone-depleting substances (ODS) feedstocks are chemical building blocks that allow the cost-effective commercial synthesis of other chemicals. The use of ODS as feedstocks, including carbon tetrachloride (CTC), 1,1,1-trichloroethane (TCA) (also referred to as methyl chloroform), chlorofluorocarbons (CFCs), hydrochlorofluorocarbons (HCFCs), allows incorporation of chlorine and fluorine atoms into molecule structures. The resulting products, such as refrigerants, blowing agents, solvents, polymers, pharmaceuticals and agricultural chemicals, find important uses that benefit society.

As raw materials, ODS feedstocks are converted to other products, except for *de minimus* residues and emissions of unconverted raw material. Emissions from the use of ODS feedstock consist of residual levels in the ultimate products, and fugitive leaks in the production, storage and/or transport processes. Significant investments and effort are spent to handle ODS feedstocks in a responsible, environmentally sensitive manner and, in most countries, are regulated through national pollution control measures.

In 2016, total ODS production for feedstock uses was 1,189,536 tonnes, representing a total of 438,712 ODP tonnes. Use of ODS as feedstock grew significantly between 1990 and 2011. Since 2011, use has been roughly constant, fluctuating around a mean total of 1,116,000 (±44,000) tonnes per year. The largest feedstock uses currently are HCFC-22 (45 percent of the total mass quantity), CTC (19 percent), and HCFC-142b (11 percent). CFCs, mainly CFC-113, have shown a long-term decline in use as feedstock.

The sophistication of the operating facility can heavily influence emission levels. Highly automated, tight and well-instrumented facilities with proper, closely observed, procedures can have ODS emission levels as low as 0.05 percent of the ODS amount used as feedstock. At the other extreme, batch processes of limited scale with less tight facilities, with less concern for operational excellence, could have emission levels up to 5 percent of the ODS amount used as feedstock. Producers can follow specifically defined responsible use practices, which, *inter alia*, define equipment to control processes, closed-loop loading and recovery, and thermal destruction of vapour emissions. When strictly followed, these responsible use practices can limit ODS emissions to about 0.1 percent of the ODS amount used as feedstock in continuous processes. Close cooperation between producers and regulators can continue to make these operations safe and environmentally sustainable.

Emissions are not reported by parties, and the estimation of ODS emissions is also inexact. The Intergovernmental Panel on Climate Change default emission factor of 0.5 percent for HFC production has been applied as a surrogate emission factor for ODS feedstock (and process agent) use. For guidance purposes only, estimated emissions associated with ODS feedstock (and process agent) uses in 2016 can be calculated as 5,948 tonnes, or 2,194 ODP tonnes.

Process agents

Process agents have been characterised as controlled substances that, because of their unique chemical and/or physical properties, facilitate an intended chemical reaction and/or inhibit an unintended (undesired) chemical reaction. Process agent uses can be differentiated from feedstock uses, where controlled substances undergo transformation in processes in which they are converted from their original compositions except for insignificant trace emissions.

Parties have made a range of decisions relating to the use of controlled substances as process agents. Decision X/14 established that: the term “process agents” should be understood to mean the use of controlled substances for applications listed in Table A in that decision; and to treat process agents in a manner similar to feedstock and not to include them in the calculation of production and consumption provided that emissions from these processes were reduced to insignificant levels, as defined by Table B. Subsequent decisions have updated Tables A and B with new information.

The process agent uses first defined in Table A included 25 applications of ozone-depleting substances (ODS), including carbon tetrachloride, trichlorotrifluoroethane (CFC-113), trichlorofluoromethane (CFC-11), and dichlorodifluoromethane (CFC-12), with total maximum emissions limits of about 200 tonnes for 4,500 tonnes of make-up or consumption. In subsequent decisions, Table A grew to more than 40 applications, adding halon 1011 (bromochloromethane, BCM) to the group of controlled substances used in these applications. Table B emissions reached a maximum of 511 tonnes in decision XXIII/7 in 2011. From 2010 onwards, Article 5 parties were included in the measures for process agent uses. By 2017, when Table A was last updated, the number of process agent applications had reduced to 11 across 4 parties.

Most of the process agent uses are long-standing processes, where the ODS are used as solvents to create unique yields, selectivity and/or resistance to harsh chemical environments, with the result that production is achieved with high efficiency. Legacy processes built around these properties make it difficult or impossible to convert to alternatives in a cost effective and timely manner, and only a few examples are known. In this regard, the process agent uses have much in common with feedstock uses.

Almost all of the removals of process agents from Table A have resulted from plant closures, rather than substitution of other substances for the ODS process agent. For some of the remaining applications, no alternatives are available to date. The lifetime of a chemical production plant could be as long as 50 years. If the product is important enough to warrant continued production, and the plant is maintained in good condition, then the large investment required to put into operation a new ODS-free process is unlikely to be justified.

There exists a suite of measures that can be applied to minimize make-up/consumption and emissions and each one needs to be considered by an operator. These measures include limiting make-up/consumption to the essential minimum, ensuring tight systems (no leaking valves and joints); evacuation and purging with recovery, prior to opening equipment; closed-loop transfer systems; proximity of production and use of the ODS; monitoring sensors at potential leak locations to provide alerts for prompt repair; use of absorbents such as activated charcoal on vents; and destruction of vent gases.

Solvents

The main applications of solvents are metal cleaning where metal working oil, grease, pitch wax, etc., are cleaned, electronics cleaning where flux is mainly cleaned, and precision cleaning where particulate or dust is mainly cleaned.

Among controlled substances, trichlorotrifluoroethane (CFC-113) and 1,1,1-trichloroethane (TCA) use as solvents has been phased out in both of Article-5 and non-Article 5 parties, with the exception being the use of CFC-113 as a cleaning solvent in aerospace applications until stockpiles are depleted.

Hydrochlorofluorocarbons (HCFCs) have been used in several different industries, for example in aerospace, micro-mechanical part manufacturing, plating, aerosol cleaners, circuit flushing, electronics defluxing/cleaning, oxygen service cleaning and the medical industry in deposition. The use of HCFC-141b and HCFC-225 for solvent cleaning has been largely phased out in non-Article 5 parties, with the exception of aerospace and military applications. In Article 5 parties, HCFC use for solvent cleaning has declined and will continue to reduce further as more critical uses of HCFCs, such as in refrigeration, are given priority and as available quantities decline under the HCFC phase-out schedule of the Montreal Protocol.

Many alternative solvents and technologies developed for chlorofluorocarbon (CFC) alternatives since 1980s are also the candidates for HCFC alternatives. These include not-in-kind technologies such as aqueous cleaning, semi-aqueous cleanings, hydrocarbon and alcoholic solvents, and in-kind solvents such as chlorinated, fluorinated and unsaturated solvents, including hydrofluorocarbons (HFCs) and low-GWP HCFO-1233zd(E) and hydrofluoroethers (HFEs), with various levels of acceptance. Alternatives to HCFCs are being used for automotive, aerospace, precision component and optical cleaning where high levels of cleanliness are required.

Each application has its own set of specific cleaning requirements and associated test procedures to ensure the cleaned parts are acceptable for use. The consequences of incomplete cleaning can include decreased product lifetime or performance in electronics cleaning, and even large potential safety concerns, such as when parts are cleaned for use in oxygen services. When transitioning, it is important to match cleaning requirements with the new solvent or cleaning system.

n-Propyl bromide is being used as a solvent in a range of applications. *n*-Propyl bromide is used as an electrical cleaning agent, degreaser or carrier solvent, as an intermediate in chemical manufacture, in spray adhesives, dry cleaning, insulation, and as a refrigerant flushing agent. *n*-Propyl bromide has also appeared in consumer aerosol cans as electronics cleaning and degreasing products, as adhesive products, as textile spot removers, and as paintable mould release agents.

n-Propyl bromide is not a controlled substance under the Montreal Protocol, however, due to the presence of bromine in the molecule, concerns have been expressed based both on its potential for ozone depletion and its toxicity. The relatively low workplace exposure standards indicate that use of *n*-propyl bromide in solvent applications is likely to be problematic, and its use will likely be limited to applications where worker exposure is controlled and will require significant emission control. Nevertheless, *n*-propyl bromide continues to appear as a marketed solvent at trade exhibitions with demand in a number of markets.

Other chemicals issues

Information is included about carbon tetrachloride (CTC), dichloromethane (DCM), dichloroethane (EDC), and trichlorofluoromethane (CFC-11) and their emissions, in response to scientific atmospheric observations and their analysis, and concerns about their potential for ozone depletion.

Regarding the reported discrepancy between emissions of CTC calculated from atmospheric observations and those estimated from industrial activity, experts under the auspices of Stratosphere-troposphere Processes And their Role in Climate (SPARC) concluded that some of the discrepancy could be explained by unreported emission sources, including from contaminated soils and industrial waste, and from chloromethanes production, and by revised estimates of partial CTC lifetimes (stratosphere, ocean, or soil). With the new total lifetime, the global top-down emissions calculation decreases to 40 (25-55) ktonnes per year. The new industrial bottom-up emissions estimate (including unreported emissions from chloromethanes plants, feedstock fugitive emissions, legacy emissions and unreported inadvertent emissions, for example from use of chlorine as disinfectant) could be up to 25 ktonnes per year.

The CTC discrepancy has been further reduced by recent estimates of uncontrolled CTC emissions from China, calculated using atmospheric measurements at Gosan Island, Korea, and giving a new source-based estimate of 36 ktonnes per year, consistent with SPARC's 40 ktonnes per year top-down estimate. These studies have almost closed the gap between top-down and bottom-up estimates of CTC emissions. However, much of the apportionment of sources is uncertain and subjective, and most of the emissions appear to arise from unregulated sources. Parties may wish to consider examining potential unregulated sources of CTC emissions with a view to increasing the understanding of those emissions and accuracy of emissions estimates.

DCM has widespread use as an industrial solvent, in applications such chemicals and pharmaceuticals production, and to a lesser extent as a food extraction solvent, and for metal cleaning and paint removal. It is also a component of special adhesives and has been used in polyurethane foam blowing, in aerosols, paint strippers and as a laboratory agent. Many of these uses are emissive. More recently, smaller quantities of DCM have been used as chemical feedstock to produce HFC-32 (CH_2F_2, difluoromethane), although this does not result in significant emission of DCM. The current level of DCM emissions, inferred from atmospheric measurements, is about 1.3 million tonnes per year, contributing less than 1 percent to the current total stratospheric chlorine loading (within the uncertainty of the total chlorine loading estimate).

Most of the global production of DCM is from chloromethanes plants that also make methyl chloride, chloroform and carbon tetrachloride. Carbon tetrachloride and chloroform are primarily used as feedstocks. More than 95 percent of chloroform is used as a chemical feedstock for HCFC-22 production. The ratio of DCM to chloroform can be changed from 60 percent DCM: 40 percent chloroform to 40 percent DCM: 60 percent chloroform. With current low demand for carbon tetrachloride, the resulting product mix contains relatively higher amounts of DCM, even if chloroform is the more commercially desirable product. Given the reductions in HCFC-22 production, and other trends in DCM usage, global DCM production and atmospheric concentrations are unlikely to increase significantly. The short atmospheric lifetime of DCM means that any reduction in emissions would have a very rapid impact in reducing atmospheric levels.

A recent scientific study contains scenarios with high growth rates in DCM emissions that would give rise to significant stratospheric ozone depletion. These scenarios are extrapolations of short-term sub-sets of historic measurements that are difficult to reconcile based on a commercial and technical analysis of the DCM market.

EDC is the principal raw material for the production of vinyl chloride, which is the monomer for polyvinylchloride (PVC). About 40 million tonnes per year of vinyl chloride is currently consumed, requiring about 65 million tonnes per year of EDC. EDC is also used as a chemical feedstock for ethylene diamines. Estimated fugitive global emissions of EDC from feedstock uses are 65,000 tonnes per year. EDC is a very short-lived substance, with a global average atmospheric lifetime of 65 days (range 41-555 days). Using the global average atmospheric lifetime, possible emission of 65,000 tonnes per year results in a calculated atmospheric burden of 11,000 tonnes, yielding an average global atmospheric concentration of less than 1 ppt (part per trillion). Reported observed concentrations in the remote atmosphere near 9 ppt are substantially higher. The discrepancy could be due to a number of uncertainties. Further investigation of these uncertainties is required to resolve this apparent discrepancy. Based on predicted growth rates for EDC consumption of about 6 percent per year, the background atmospheric concentration of EDC could double by 2030.

In a recent scientific study, measurements showed that, up until 2012, the atmospheric concentration of CFC-11 had declined at a rate consistent with the low emissions expected from a declining bank in equipment and zero production. However, since then, observations show that the rate of decline in concentration has slowed. Using atmospheric models, the study's authors infer that an additional 13,000 ± 5,000 tonnes per year of CFC-11 has been released into the atmosphere from 2014 to 2016, with the increase (from zero to this level) occurring over the course of a year. Using back trajectories of winds, the authors indicate that evidence strongly suggests increased CFC-11 emissions from eastern Asia after 2012.

Historically, CFC-11 was used primarily as a foam blowing agent (for flexible and polyurethane insulating foams) and as a refrigerant for air conditioners (centrifugal chillers, used in large commercial buildings), and in a range of other smaller or less common uses. Alternative products or technologies have replaced the use of CFC-11 in these uses. Nevertheless, a significant "bank" of CFC-11 remains in products and systems, particularly in foam insulation where the emission rate into the atmosphere from an installed foam is very low.

Commercial CFC-11 production installations consist most simply of a heated reaction vessel charged with a pentavalent antimony catalyst dissolved in partly fluorinated organic intermediates. The system is pressurised and totally enclosed. Anhydrous hydrogen fluoride and CTC are fed into a reactor, and simultaneously hydrogen chloride and the desired organic products (CCl_3F and CCl_2F_2, CFC-11 and CFC-12) are removed as the products of reaction. The relative proportions of CFC-12 and CFC-11 can be controlled by varying the operating conditions, with 100 percent CFC-12 achieved relatively easily and 100 percent CFC-11 more difficult to achieve but not impossible. Until around 1990, most processes were operated to achieve around 50:50 CFC-12 and CFC-11, with a comfortable operating range of 30:70 either way. Due to unpredictability and the potential for corrosive attack of the reaction vessel, operators are cautious about changing process conditions drastically. Nevertheless, it is possible to produce almost 100 percent CFC-11 in a detuned CFC-11/-12 plant. There would be limited scope to recycle any by-produced CFC-12 to extinction, implying use/disposal of any remaining CFC-12.

Losses of 13,000 tonnes per year of CFC-11 are not economical from a chemical production process. At the upper end of possible emission levels (5 percent losses) for an economically run process, this would equate to production of 260,000 tonnes CFC-11 per year. By comparison, CFC-11 production in the 1980s peaked between about 350,000-400,000 tonnes per year.

The fate of any CFC-12 produced as a by-product of CFC-11 production is not yet clear. Neither is it yet clear whether the observed unexplained increase in CFC-11 emissions is associated with CFC-11 production to supply emissive CFC-11 uses, or whether CFC-11 is being produced as a by-product of CFC-12 production for the purpose of supplying CFC-12 uses.

Montzka suggested that inadvertent CFC-11 production is possible from the fluorination of chlorinated methanes (for example, to produce HCFC-22). CFC-11 produced as a by-product in other chemical manufacturing pathways is unlikely for technical reasons. Under normal operating conditions, CFC-11 production as a by-product of HCFC-22 production is negligible (around 0.1

percent). Any CFC-11 produced in this manner is more likely to be captured and recycled or destroyed.

Any stockpile accumulated from ODS production is not reported under the Montreal Protocol. Consumption of CFC-11 stockpile after the production phase-out is not prohibited under the Montreal Protocol. However, there is not likely to be enough CFC-11 in the stockpile inventory to account for the total amount of unaccounted CFC-11 emissions.

Decision XXX/3 requests the Technology and Economic Assessment Panel (TEAP) to provide parties with information on potential sources of emissions of CFC-11 and related controlled substances from potential production and uses, as well as from banks, that may have resulted in emissions of CFC-11 in unexpected quantities. A preliminary report will be provided to the Open-ended Working Group at its 41st meeting and a final report to the 31st Meeting of the Parties.

Laboratory and analytical uses

Laboratory and analytical uses of controlled substances have included: 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.

At the 6th Meeting, parties authorised an essential use exemption for laboratory and analytical uses, according to conditions that authorise essential use production for laboratory and analytical purposes only if the controlled substances are manufactured to high purity and supplied in re-closable containers and in small quantities; this became known as the global essential use exemption. Various decisions have subsequently extended the global laboratory and analytical use exemption under these specified conditions, and/or excluded specific uses from the global exemption. Decision XXX/8 includes Annex C, group I, substances in the global laboratory and analytical use exemption.

In 2016, the global production of all reported controlled substances for laboratory and analytical uses was relatively small (151 tonnes). Carbon tetrachloride is the main controlled substance produced for these uses (more than 99.9 per cent); the production of other controlled substances is relatively very small. Reported total production in non-Article 5 parties was 21 tonnes (about 14 per cent of the reported global total) in 2016. Article 5 parties began reporting production data for laboratory and analytical uses in 2009, with a gradual overall decrease in reported production, from a peak of 257 tonnes in 2010 to 130 tonnes (about 86 per cent) in 2016.

Parties may wish to consider removing some additional listed procedures from the global exemption for laboratory and analytical uses of ozone-depleting substances (ODS), at a date to be determined by parties. Parties may also wish to consider establishing cooperation with standards organisations, to facilitate and accelerate the development or revision of standards for the replacement of ODS in analytical uses. Parties may also wish to consider providing: more comprehensive data (e.g. on consumption); sharing information on alternatives and on the revision of standards that use ODS; possible support for the development and/or revision of standards, and/or training, where needed.

Many standards still require the use of small quantities of ODS. There may come a point when the continued exclusion of specific laboratory and analytical uses on a case by case basis from the global exemption creates potential confusion for practitioners and regulators. Monitoring of, and adherence to, specific authorised uses of ODS in laboratory and analytical applications may become increasingly challenging as the exclusion list expands. At the 30th Meeting of the Parties, a number of parties noted the relatively insignificant quantities of ozone-depleting substances produced to supply laboratory and analytical uses, and the suggestion that excluding specific uses on a case by case basis could be confusing. In light of those considerations, parties discussed a proposal to take a fresh look at how to continue to reduce the use of ODS in laboratory and analytical procedures without sacrificing clarity or introducing excessively complicated measures for such as small quantity of ODS. Parties agreed to consider a draft decision on laboratory and analytical uses at the 41st meeting of the Open-ended Working Group.

Destruction technologies

Under the Montreal Protocol, the definition and data reporting requirements for production of controlled substances require parties to determine the quantity of ozone-depleting substances (ODS) destroyed in destruction facilities, in order to meet their reporting and compliance obligations. These definitions require parties to determine the quantity of ODS destroyed in destruction facilities, in order to meet their reporting and compliance obligations. The Montreal Protocol also allows remanufacture of ODS to replace a portion of ODS destroyed under specific conditions (within the same year as destruction, within the same group of substances, etc.). In practice, parties have not typically remanufactured ODS to offset quantities otherwise destroyed. In addition to these obligations, ODS destruction has been implemented to meet regulatory requirements and voluntary objectives to help protect stratospheric ozone and climate. In 2016, the Kigali Amendment to the Montreal Protocol included hydrofluorocarbons (HFCs) as controlled substances with obligations for their destruction.

Parties have taken a number of related subsequent decisions to approve destruction technologies for the purposes of Montreal Protocol requirements. Decision XXX/6 confirmed a range of approved destruction technologies for their applicability to HFCs and approved thermal decay for the destruction of methyl bromide.

Non-Article 5 parties generally have well established requirements to minimise emissions of ODS, including through the destruction of ODS. Recently, the Multi-lateral Fund of the Montreal Protocol (MLF) supported pilot destruction projects in Article 5 parties with an objective of overcoming some of the barriers to ODS destruction in those countries.

Cumulatively, over 300,000 tonnes of ODS have been destroyed since 1996, of which the majority was carbon tetrachloride (CTC) (70 percent). The amount of ODS, excluding CTC, potentially available for management and destruction has been projected to peak globally at 200,000 tonnes in 2016. Based on ODS (excluding CTC) destruction reported to the Ozone Secretariat, a global destruction rate of about 3 percent, of the total amount potentially available for destruction, was apparently achieved in 2016.

In 2015, the Executive Committee of the MLF reviewed a total of 15 approved ODS destruction demonstration projects approved in 2009, involving 12 countries, two regions, and one global project. The results of this review indicated that there were only two main approaches to destruction selected by countries, namely domestic destruction through local facilities and export of the ODS waste abroad for destruction in another country. In terms of the environmental performance of the destruction technologies evaluated in the MLF demonstration program, these were specific to the facility and the location. National standards/regulations impose emission limits for destruction facilities. However, destruction technologies were generally qualified for ODS destruction consistent with or similar to performance criteria used by the Technology and Economic Assessment Panel (TEAP) in assessing destruction technologies for the Montreal Protocol, which were sometimes more stringent than national standards.

Typically, waste HFCs are destroyed using the same processes that are used for ODS destruction. Many non-Article 5 parties already undertake and report on destruction of waste HFCs.

1 Background to the 2018 Assessment

1.1 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 (TEAP). Currently, TEAP has five standing Technical Options Committees (TOCs) (apart from other temporary subsidiary bodies).

1. Flexible and Rigid Foams Technical Options Committee
2. Halons Technical Options Committee
3. Medical and Chemical Technical Options Committee
4. Methyl Bromide Technical Options Committee
5. Refrigeration, Air Conditioning and Heat Pumps Technical Options Committee

1.2 The Medical and Chemical Technical Options Committee and the 2018 Assessment

This report is part of the ninth assessment under Article 6 of the Montreal Protocol. The first assessment reports were prepared in 1989, and subsequently updated in 1991, 1994, 1998, 2002, 2006, 2010, and 2014. This 2018 quadrennial report is in response to decision XXVII/6 of the Parties to the Montreal Protocol, which requested an assessment to be undertaken for completion by 31 December 2018 for consideration at the Open-Ended Working Group and by the 31st Meeting of the Parties in 2019.

Article 6 specifically directs parties to assess whether the control measures, as provided for in Article 2 of the Protocol, are sufficient based on a review of the current state of knowledge of technical, scientific, environmental, and economic issues related to stratospheric ozone protection. The assessment reports assist with this review.

Previously, the Aerosols, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee (ATOC) assessed, *inter alia*, medical aerosols, sterilants, laboratory and analytical uses, and carbon tetrachloride. ATOC was reconstituted in 2005 to form the Medical Technical Options Committee (MTOC) to assess medical applications of ozone-depleting substances (ODS), namely medical aerosols and sterilants.

Previously, the Solvents, Coatings and Adhesives Technical Options Committee (STOC) assessed solvent uses of ozone depleting substances. STOC was reconstituted in 2005 to form the Chemicals Technical Options Committee (CTOC) to assess non-medical aerosol products, carbon tetrachloride, feedstocks, laboratory and analytical uses, process agents, solvent uses, and destruction.

Since the 2014 assessment, CTOC and MTOC were reconstituted in 2016 to form the Medical and Chemical Technical Options Committee (MCTOC) to assess medical and chemicals related applications, namely, medical and non-medical aerosols, sterilants, carbon tetrachloride and other chemicals emissions, feedstocks, laboratory and analytical uses, process agents, solvent uses, and destruction.

MCTOC is made up of experts from industry, government, scientific, research and academic institutions. In 2018, there were 3 co-chairs, 34 members, and 4 consulting experts contributing to this assessment from 21 countries – Argentina, Australia, Bangladesh, Canada, China, Denmark, Finland, France, Germany, Ghana, India, Italy, Japan, Kuwait, Mauritius, the Netherlands, Pakistan, Russian Federation, United Kingdom, the United States and Venezuela.

This 2018 Assessment Report re-examines the current use of alternatives to controlled substances (ODS and HFCs) in a range of sectors. MCTOC undertook mainly written communication in the drafting of this report. The report has undergone a limited peer review among experts from a selection of relevant global organisations.

2 Metered Dose Inhalers

2.1 Asthma and COPD: prevalence, treatment options and medical trends

Asthma and chronic obstructive pulmonary disease (COPD) are the most common chronic diseases of the respiratory tract. Asthma increased rapidly in the second half of the 20th century and now affects over 300 million people worldwide. The World Health Organization (WHO) estimates that there will be an additional 100 million sufferers by 2025, with 428,000 deaths per annum by 2030.[1] COPD affects at least an equivalent number of patients, and its prevalence continues to rise with increasing tobacco consumption in developing countries. Both of these illnesses account for high healthcare expenditure, and COPD in particular is responsible for premature death. COPD is currently the fourth commonest cause of death worldwide, and by 2030[1] it will have advanced to third.

Inhalation therapy is the mainstay of treatment for asthma and COPD. Inhaled drugs are targeted to the airways, where they have maximal benefit with least side effects. This is achieved by modulating particle size through inhaler design, and by adjusting excipients and propellants.

Other diseases treated by the inhaled route include cystic fibrosis, bronchiectasis, pulmonary arterial hypertension and respiratory tract infections. These diseases require treatment with relatively high doses of drugs, which are often delivered by nebuliser rather than a portable inhaler. Delivery of drugs via the respiratory tract for systemic diseases (e.g. insulin for diabetes) is an area of increasing interest.

2.1.1 Asthma

Asthma is a chronic inflammatory condition of the airways. Its prevalence increased and then stabilised in developed countries in the late 20th century, but its prevalence continues to increase in developing countries. In some regions of Africa, especially in urban areas, the prevalence has been doubling every decade and now approaches that of developed countries. There remains a wide difference in prevalence between some countries, such as Indonesia where prevalence is about 1 percent, to the United Kingdom and New Zealand where it is approaching 20 percent. Some of these trends may relate to the proportion of patients that are accurately diagnosed.

Asthma can vary in severity from mild asthma with intermittent symptoms through to severe and/or chronic asthma requiring specialist support, frequent hospital admissions with extensive medication, and despite this, in some cases, death. WHO estimates that 80 percent of asthma deaths occur in low- and middle-income countries.

Asthma has two primary features, airway inflammation and bronchoconstriction, in which there is a muscular spasm of the airways. Controlling airway inflammation through the use of inhaled corticosteroids is the mainstay of asthma treatment. Globally, inhaled bronchodilators relieving the symptoms associated with bronchoconstriction are still the most widespread drug in asthma.

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[1] WHO Fact Sheet No. 307, 2008; WHO Fact Sheet No. 315, 2009; WHO projections of mortality and burden of disease, 2004-2030; Global surveillance, prevention and control of chronic respiratory diseases (WHO publication), 2007; WHO World Health Statistics, 2008. diseases (WHO publication), 2007; WHO World Health Statistics, 2008.

2.1.2 Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a condition of narrowing and inflammation of the airways (bronchiolitis) in conjunction with damage to the lung tissue (emphysema). The relative severity of these two features may vary from patient to patient, but they both contribute to progressive obstruction of the airways. The commonest single cause of COPD is cigarette smoking though exposure to biomass fuel smoke plays an important role in less developed countries[2] [3]. In some patients, occupational dusts, or environmental pollution (including household air pollution), or a small genetic component in patients with alpha 1-antitrypsin deficiency, may cause COPD. There is also increased evidence that factors early in life affecting growth of lungs and airways play a major role for subsequent risk of COPD. Patients become progressively and irreversibly disabled if they continue to smoke, and smoking cessation is a major individual, as well as general, public health issue.

The prevalence of COPD is hard to estimate, since it is not usually recognised until it is moderately advanced. However, it affects 5-15 percent of the population in developed countries, with mortality doubling in females in the last 20 years in the United States. Rates of COPD are increasing rapidly in developing countries, reflecting both an increase in air pollution and trends in cigarette consumption. The increase in cigarette consumption in China is a major reason why COPD will advance to the third highest cause of mortality by 2030.

COPD provides a substantial burden to healthcare systems worldwide with exacerbations frequently requiring expert support and hospital admission, accounting for between 50 and 75 percent of overall costs of COPD.

2.1.3 Treatment of asthma and COPD

Prevention of asthma remains impossible for the majority, until it is clearer what has driven the increased prevalence. This seems to be a cohort effect, with increased levels of asthma in children now leading to increased levels in adults. The pathology of asthma usually arises in early life, and even if a form of prevention were to be developed today, it seems likely that this would not impact significantly on the prevalence of asthma for many decades.

Prevention of COPD requires public health leadership so that rates of tobacco smoking decline. Controls on advertising and bans on smoking in public places have been associated with significant declines in tobacco consumption in developed countries, assisted in some countries by nicotine replacement therapies. However, increasing affordability of tobacco and lack of advertising controls are driving increasing prevalence of COPD in developing countries. The global increase in air pollution is also a major threat to future COPD and lung health in general. Reducing indoor pollution from cooking and heating sources inside homes is an important measure in developing countries. With global trends for increased longevity, increasing numbers of elderly will develop COPD in later life.

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[2] Vogelmeier, C.F., Criner, G.J., Martinez, F.J., et al., Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary, *Eur. Respir. J.,* 2017, **50** (1), pii: 1700671, doi: 10.1183/13993003.00671-2017.

[3] WHO, Household air pollution and health, Fact sheet N°292, Updated March 2014. http://www.who.int/mediacentre/factsheets/fs292/en. Accessed February 2015.

Inhaled therapy remains the mainstay of treatment for established asthma and COPD. Inhalers offer effective symptomatic benefit and control of disease, by delivering drugs directly to the airways, whilst minimising systemic side effects[4]. The particle size is a factor in targeting the drug to the lungs. If the particles are too large, then the drug is deposited in the mouth and throat and is ineffective. If the particles are too small, they are simply exhaled and wasted.

For both asthma and COPD, there are two main categories of inhaled treatment, bronchodilators (“relievers”) and anti-inflammatory medications (“preventers”). Inhaled salbutamol (a short-acting reliever) remains by far the most used treatment, mainly as inexpensive hydrofluorocarbon (HFC) metered dose inhalers (MDIs), but with an increasing amount of multi-dose dry powder inhalers (DPIs) used in developed countries, and single capsule DPIs used, e.g. in South Asia. Many different twice daily combinations of long-acting bronchodilators and inhaled corticosteroids (“LABA/ICS”) in a single inhaler have been successfully implemented in all developed countries. The first combination inhalers combining two different bronchodilators (long-acting bronchodilators and long-acting anti-muscarinic, “LABA/LAMA”) have recently been launched. Two new triple therapies (LABA/LAMA/ICS all in one inhaler) have been recently introduced, and these may become more significant for asthma, and potentially also for COPD, as more brands come to the market over the coming years, and prices come down. New once-daily DPI-delivered combination treatments have been introduced which are clinically effective in real world studies. Treatment regimens will continue to evolve over time, with regional and country variations.

Oral drugs are also prescribed for asthma. In developing countries, inexpensive methylxanthines (theophylline) are widely available, but these can have serious side effects (excess dosage can be fatal). In developed countries, and especially the United States, oral montelukast occupies a significant proportion of the market for preventive drugs although it is generally less effective than inhaled steroids. In developing countries, it is also a significant treatment; for example, oral montelukast is one of the most widely prescribed treatments for asthma in Bangladesh.

There are new developments in injectable drugs. The first injectable preventive therapy against Immunoglobulin E (IgE) is now marketed worldwide. However, it has very low uptake outside developed countries, and most often then in patients with severe asthma because of its cost (20-24 times the cost of an inhaled corticosteroid). Novel injectable biologic drugs have also been launched, targeting eosinophilic inflammation through the interleukin-5 pathway and others will likely be on the market in the next 2 years. These drugs are expensive and will likely be restricted mostly to patients with severe asthma. None of these developments will impact the continued need for inhaled therapies for the vast majority of patients with asthma and COPD worldwide.

2.1.4 Other disease areas

Whilst asthma and COPD will continue to dominate the use of inhaled therapies for the foreseeable future, there are other diseases that are treated this way.

- **Cystic fibrosis** results in thickening of the mucus in the airways, leading to a heightened susceptibility to airway infection, blocked airways and loss of lung function. This is normally treated with inhaled saline, antibiotics and DNA-ase alone or in combination,

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[4] Reddel, H.K., Bateman, E.D., Becker, A., et al., A summary of the new GINA strategy: a roadmap to asthma control, *Eur. Respir. J.*, 2015, **46**, 622-39.

most commonly delivered by nebuliser, although there are inhaled antibiotic DPI formulations as well.

- **Bronchiectasis**, resulting from persistent damage to the lungs (often from repeat infection) is often treated pharmacologically in the same manner as cystic fibrosis. There are several late stage clinical trials attempting to demonstrate the utility of inhaled antibiotics in this disease.

- **Pulmonary arterial hypertension**, whereby increased arterial blood pressure in the lungs leads to damage may be treated with nebulized prostacyclins.

- **Influenza** may be treated by attenuated live virus delivered by nasal spray, or a neuraminidase inhibitor delivered from a DPI.

- Other respiratory diseases where drugs delivered by inhalation are in clinical trials include idiopathic pulmonary fibrosis, pneumonia, respiratory syncytial virus infection, tuberculosis, lung transplantation and lung cancers.

- Various systemic therapies have been developed, but are yet to be commercialised in significant quantities (e.g. insulin delivered from a DPI for the treatment of **diabetes)**

2.2 Aerosol delivery

There are two common types of inhalation devices for the delivery of respiratory drugs: (pressurised) metered dose inhaler and the dry powder inhaler in single- or multi-dose. Other methods of delivering drugs to the lung include soft mist inhalers and nebulisers. The choice of the most suitable treatment method is a complex decision taken between the health care provider and the patient. It is not uncommon for patients to be prescribed a mix of medications in a range of devices.

The sections below briefly describe each main type of inhaler and their use. One feature generally common to the use of inhalers (MDIs and DPIs) is that patients need to use the correct technique, and this needs training and reinforcement, which unfortunately is rarely provided in routine practice. There is great variation in the quality of inhaler training by healthcare providers. As a result, a large proportion of patients who are prescribed inhaled medications do not use their inhalers correctly[5]. Studies have observed critical errors in the use of both MDIs and DPIs. On

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[5] It is important to understand how critical training, appropriate use, and patient choice are to adherence. Adherence is central to optimal disease control. The following are a selection of references on the topic:

National Asthma Council Australia, *Inhaler technique in adults with asthma or COPD*, Melbourne, National Asthma Council Australia, 2008. http://www.nationalasthma.org.au/publication/inhaler-technique-in-adults-with-asthma-or-copd. Accessed February 2015

Bjermer, L., The Importance of Continuity in Inhaler Device Choice for Asthma and Chronic Obstructive Pulmonary Disease, *Respiration*, 2014, 346-352.

Pritchard, J., and Nicholls, C., Emerging Technologies for Electronic Monitoring of Adherence, Inhaler Competence, and True Adherence, *J. Aerosol Med. Pulm. Drug Deliv*, 2015, **28**(2), 69-81.

Lavorini, F., et al., Effect of Incorrect Use of Dry Powder Inhalers on Management of Patients with Asthma and COPD, *Respir. Med.*, 2008 **102**(4), 593-604.

rare occasions, patients may also inhale foreign objects if the inhaler is not adequately cared for[6]. The patterns of prescribing suggest that the choice of inhalers is based on local custom and practice. Clinicians and patients have their own preferences based on their own experiences. In addition to the need for adequate training, clinicians should provide the device that the patient can most easily use and afford.

2.2.1 MDIs

An MDI is a complex device designed to produce a fine mist of medication for inhalation directly to the airways. These products were first developed over 60 years ago and are particularly suited to administration of therapy when respiratory function is compromised.

MDIs that use chlorofluorocarbons (CFCs) as a propellant were historically the inhaled-delivery device of choice as they were affordable, reliable and extremely effective. Under the Montreal Protocol, the manufacture of pharmaceutical grade CFCs for MDIs has been successfully phased out worldwide without significant adverse impact to human health.

The process of reformulating MDIs with HFCs began over 30 years ago when HFC-134a and HFC-227ea were proposed as alternatives to CFCs. These HFCs underwent extensive toxicological testing and were deemed to be safe for human use. Since 1994, pharmaceutical companies have gradually replaced the CFC propellants in MDIs with HFCs (HFC-134a and to a lesser extent HFC-227ea). This has been difficult because the components and formulations had to be substantially modified to use the HFC propellant. Furthermore, the absence of an acceptable HFC that is liquid at room temperature has meant the development of new manufacturing processes. Each new MDI product underwent extensive regulatory assessments of safety, efficacy and quality, much the same as for the development of any new drug product. Development costs for the transition of MDIs from CFCs to HFCs have been estimated to be well in excess of US$2 billion, and the phase-out of CFC MDIs took over 20 years to complete. The cost to research and develop a new medicine was recently estimated to be US$2.6 billion[7].

Following reformulation, the MDI remains popular, especially because it is inexpensive for the short-acting bronchodilator salbutamol, which is the predominant short-term relief or “rescue” treatment for acute symptoms in asthma/COPD worldwide. Many patients feel the cooling effect on the throat associated with evaporation of propellant as a positive signal for inhalation. The low cost of salbutamol MDIs to the patient has remained relatively constant over 50 years, even with

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Laube, B., et al., ERS ISAM Task Force Consensus Statement, *Eur. Respir. J.*, 2011, **37**(6), 1308-1331. http://erj.ersjournals.com/content/erj/early/2011/02/10/09031936.00166410.full.pdf.

Bosnic-Anticevich, S., Inhaler Device Handling: Have We Really Started to Address the Problem?, *Eur. Respir. J.*, 2017, **49**, 1700120. http://erj.ersjournals.com/content/erj/49/2/1700120.full.pdf.

[6] Medicines & Healthcare products Regulatory Agency, United Kingdom, *Pressurised metered dose inhalers (pMDI): risk of airway obstruction from aspiration of loose objects*, July 17, 2018. https://www.gov.uk/drug-safety-update/pressurised-metered-dose-inhalers-pmdi-risk-of-airway-obstruction-from-aspiration-of-loose-objects. Accessed December 2018.

[7] DiMasi, J.A., Grabowski, H.G., Hansen, R.W., Tufts Center for the Study of Drug Development, Costs Study, November 18, 2014. http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study. Accessed February 2015. The figure includes out of pocket costs of $1,395 million and time costs of $1,163 million (i.e., expected returns that investors forego while a drug is in development).

the new HFC re-formulation[8]. Accurate co-ordination of drug release and inhalation is required for correct use. Studies have shown that many patients do not use MDIs correctly. In routine clinical practice as many as 50 percent of patients fail to use an MDI correctly, mainly due to poor synchronisation of actuation with inhalation. A valved holding chamber, spacer device or breath-actuated inhaler can be used to overcome coordination issues. However, breath-actuated inhalers are more costly in many markets, and spacers are often quite large so less portable, which often results in the patient using the MDI without the spacer[9]. With information and training, poor inhaler technique can be improved, but this requires reinforcement, which is rarely provided on a regular basis in practice. MDIs with spacers provide a cost-effective option for patients with low inspiratory flow, such as patients with severe lung disease and very young children, and for severe asthma attacks (where nebulisers are the alternative) [10].

Some studies suggest a potential therapeutic benefit associated with extra-fine HFC MDIs, with some therapies, particularly corticosteroids, shown to be more effective when delivered as ultrafine HFC MDI aerosols than as DPI aerosols[11]. However, some Medical and Chemical Technical Options Committee (MCTOC) experts do not believe that the ultrafine HFC MDIs have shown a clinically significant advantage.

2.2.2 Dry powder inhalers

Dry powder inhalers (DPIs) are devices that deliver powdered medication (active ingredient mixed with excipient) without the need for a propellant. There are many different devices that deliver powder medication. Most devices are available exclusively from a single pharmaceutical company that has patented that device, although there are device developers who are offering their devices generically to the industry. Most commonly used respiratory drugs have been formulated successfully for DPIs and are now widely available.

Micronized dry powder can be inhaled and deposited effectively in the airways of patients with adequate breathing capacity. Some studies have indicated that DPIs can be easier for some patients to use than MDIs, because drug delivery is driven by the patient's inhalation, and they therefore do not require patient co-ordination. Some patients prefer DPIs because of their ease of use. In some countries DPIs are widely prescribed for the treatment of asthma and COPD. However, younger children and some patients with severe asthma or severe COPD (particularly the frail elderly) may not always be able to generate an adequate inspiratory flow to ensure optimal medication delivery from all DPIs. Studies have also shown that some patients do not use some DPIs correctly[12], and the variety of different DPI designs can lead to confusion in the

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[8] This may not be the case in some countries, in particular the United States.

[9] Laube, B.L., et al., What the pulmonary specialist should know about the new inhalation therapies, *Eur. Respir. J.*, 2011, **37**, 1308-1417.

[10] Burnham, T., Inhaler use technique and related interventions, an annotated bibliography, *National Electronic Library for Medicines*, Medicines Management Overview, August 2012. https://use-inhalers.com/sites/default/files/publicationpdf/Reference_Studies_Tom_Burnham.pdf. Accessed February 2015.

[11] van den Berge, M., ten Hacken, N. H. T., van der Wiel1, E., Postma, D. S., Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma, *Allergy*, 2013, **68**, 16–26; Cohen, J., Postma, D.S., Douma, W.R., Vonk, J.M., De Boer, A.H., ten Hacken, N.H.T., Particle size matters: diagnostics and treatment of small airways involvement in asthma, *Eur. Respir. J.*, 2011, **37**, 532–540.

[12] Lavorini, F. et al., Effect of incorrect use of dry powder inhalers on management of patients with asthma and COPD,

correct usage of each DPI. With information and training, and using the optimal device, poor inhaler technique can be improved, but this requires reinforcement, which is rarely provided on a regular basis in practice.[13]

Powdered drug particles tend to aggregate; therefore, 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 deeply into the lungs. It is essential that patients handle and use their DPIs properly, for example in humid conditions where excessive powder aggregation otherwise might impair their efficacy.

DPIs fall into two categories: single-dose and multi-dose.

Single-dose DPIs, which have been in use for more than 60 years, utilise a capsule, containing one dose, inserted into the device. 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. They are inexpensive but may be more susceptible to humidity than more recently developed multi-dose DPIs. Despite this, they are generally found to be effective. In developing countries, single-dose DPIs have a major role because they require simple manufacturing technology, and patients can purchase a small number of doses at an affordable cost. However, this purchasing behaviour, of a small number of doses, has the potential to undermine adherence to treatment for products that are required on a daily basis (e.g. corticosteroids or combination therapies), with adverse health outcomes. Correct training in the usage of single-dose DPIs is important (as for all inhalers). They can require a degree of manual dexterity that elderly patients with COPD do not have. As long as a decade ago, an FDA public health advisory was issued to highlight the correct use of Spiriva® HandiHaler® (tiotropium bromide inhalation powder) and Foradil® Aerolizer® (formoterol fumarate inhalation powder) capsules, where patients had swallowed the capsules instead of inhaling them from the device [14]. Patients may also be at risk of inhaling the capsule if the device is used incorrectly[15]. With information and training, misuse of single-dose DPIs can be minimised.

Multi-dose DPIs, which have been in use for almost 30 years, typically contain enough doses for at least one month's treatment. There are two types of multi-dose DPI, one with individual doses pre-metered during manufacture, and the second that loads a measured amount of medicine for inhalation from a reservoir in the device. Older reservoir multi-dose DPIs can suffer from water

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Respiratory Medicine, 2008, **102**, 593-604.

[13] Burnham, T., Inhaler use technique and related interventions, an annotated bibliography. *National Electronic Library for Medicines*, Medicines Management Overview, August 2012. https://use-inhalers.com/sites/default/files/publicationpdf/Reference_Studies_Tom_Burnham.pdf. Accessed February 2015.

[14] U.S. Food and Drug Administration, United States, *Public Health Advisory: Important Information on the Correct Use of Spiriva and Foradil Capsules*, 29th February 2008. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm051132.htm. Archived content accessed, February 2015.

[15] Medicines & Healthcare products Regulatory Agency, United Kingdom, *Braltus (tiotropium): risk of inhalation of capsule if placed in the mouthpiece of the inhaler - Drug Safety Update*, May 24, 2018. Available at: https://www.gov.uk/drug-safety-update/braltus-tiotropium-risk-of-inhalation-of-capsule-if-placed-in-the-mouthpiece-of-the-inhaler. Accessed December 2018.

ingress in high humidity environments that leads to aggregation of the powder formulation. These issues can be partially addressed by supplying the device in a foil pouch opened upon first use and disposed of within the month. Newer multi-dose DPIs have improved moisture protection and are approved in countries with humid climates, such as experienced in many developing countries.

Substantial development efforts are being pursued in the DPI segment by pharmaceutical companies. Most new chemical entities (drugs) for the last decade have been commercialised only in DPI formulations. The challenges and costs associated with the development of new DPI products are similar to those that were incurred for HFC MDIs developments. Multi-dose DPIs containing off-patent molecules have entered the European and North American markets in recent years (e.g. AirDuo Respiclick DPI, combination of Salmeterol/ Fluticasone Propionate; and ProAir Respiclick with salbutamol).

2.2.3 Nebulisers

Nebulisers are devices that are filled with drug dissolved or suspended in aqueous solution, which is converted to inhalable droplets using compressed air, ultrasonic waves or vibrating mesh. Historically, the situation has been different to that of MDIs or DPIs, in that pharmaceutical companies supply drug formulations but not the delivery device. Therefore, in principle, any drug formulation could be used with any nebuliser, with widely different outputs, and dose to the patient. In practice, this has been largely restricted to short-acting β-agonists, short-acting anti-muscarinics and corticosteroids. The differences in nebuliser performance have led to recommendations for the use of a particular formulation only with selected nebulisers, usually those with clinical data to support their use. More recent drug approvals for nebulized products in the United States have been cross-labelled to a specific nebulizer device. Therefore, nebulisers have generally not been considered as alternatives to MDIs and are now recommended mainly for the treatment of infants and severely ill patients, where patient assistance is not needed; or to situations when larger doses of drug and/or prolonged administration times are desired. A nebuliser takes 3-10 minutes to deliver its dose and is relatively inconvenient to maintain. Until recently, only short-acting bronchodilators, corticosteroids, antibiotics and DNA-ase have been widely available for nebulised use. However, there have been recent launches in the United States of nebulised formulations of long-acting β-agonists and anti-muscarinics, with further long-acting bronchodilators in late stage development.

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 introduced in their first markets. However, they are still dependent on external power supply and therefore restricted in their use.

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 more efficient than air jet nebulisers but require either a battery or external power source. They tend to be expensive and cannot be used for all drug formulations particularly suspensions, nor with drugs that are thermally labile due to heating of the medication during use.

The most recent development has been to vibrate a mesh containing micron-sized holes at ultrasonic frequencies in portable battery-powered devices. The vibration serves to pump liquid through the mesh creating a respirable spray. The use of electronics also allows introduction of more sophisticated features, such as triggering spray generation only during a portion of the inspiratory manoeuvre, thereby minimising waste and environmental discharge. The initial cost of these devices is substantially more than an MDI or DPI, and the relative lifetime cost will also depend on the cost of the drug/solution for nebulisation.

For patients with asthma and COPD, drug delivery via nebulised therapy is at least as efficacious as an MDI plus a valved holding chamber (“spacer”) but costs far more. However, in many countries nebuliser use is still seen as optimal treatment in the acute situation in hospital and for chronic severe patients at home. In China, it is often first-line therapy, and initiated at hospital out-patient clinics. Over time, nebuliser use for asthma treatment could largely be replaced by the use of an MDI plus spacer. In COPD, there may be a role for nebulisers in breathless patients with low inspiratory flow rates especially after hospital admission. Several companies are exploring particle engineering approaches that allow larger doses of drug to be dispensed with the energy available from the patient’s inspiratory manoeuvre; one such product is marketed in many countries to deliver an antibiotic in the treatment of cystic fibrosis[16]. This may also become an alternative to other nebulised treatments in the future.

2.2.4 Aqueous mist (soft mist) inhalers

Small portable devices that produce aerosols of respirable diameter from aqueous formulations have been under development for a number of years and one (Respimat™)[9] is now commercially available in a number of countries.

These new-generation devices produce an aerosol through mechanisms different from those described for nebulisers. The mechanisms include collision of two jets of liquid to produce an aerosol, or forcing liquid through tiny micron-sized holes, or vibrating mesh/plate, or other novel mechanisms (e.g. electro-hydrodynamic effects). They can be distinguished from nebulisers in that they endeavour to deliver a complete dose within one or two breaths. The combination of improved efficiency and smaller aerosol particle size from these devices ensure that the aerosol they generate can be deposited deeply into the lungs and therefore serve as local delivery for treating lung disease or for absorption for systemic delivery.

Boehringer Ingelheim’s Respimat™, utilises the collision of two liquid jets to generate an aerosol. This novel device took many years to develop and optimise but is now marketed with five different drug or drug combination formulations, although availability of each product may be restricted in certain countries.[17]

While some of the other devices in development may also serve as alternatives in the future, their contribution to asthma and COPD management is hard to predict. In particular, they rely upon the drug to be sufficiently potent and soluble that it can be concentrated within 300 μl to deliver within a few breaths, or 25-50 μl in order to deliver it within a single breath. These devices are currently more expensive than standard MDIs and DPIs.

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[16] VanDevanter, D.R., and Geller, D.E., Tobramycin administered by the TOBI® Podhaler® for persons with cystic fibrosis: a review. *Med Devices (Auckl)*, 2011, **4**, 179–188.

[17] https://www.respimat.com/hcp. Accessed July 2018.

The development and regulatory timescales for new aqueous inhaled delivery systems are lengthy and new technical breakthroughs are not common. Even with the same drug already approved in an MDI or DPI, an aqueous formulation will require full clinical trials to establish dose, safety and efficacy. As well as conforming to pharmaceutical regulations, novel devices are becoming regulated under device regulations; for example, the new EU Medical Device Regulations which will become fully implemented in May 2020. In addition, they can be regarded as drug-device combinations, which involves more regulations. There are hybrid approaches in development, whereby a portable mesh nebuliser can be combined with a formulation containing10s-100s μl dispensed from a bottle.

2.2.5 Novel devices

In recent years, there has been a development of devices that use heat to vaporize a formulation based around propylene glycol. These have been applied to the inhaled delivery of nicotine and flavourings for recreational and smoking replacement ("vaping"). These are not currently regulated as medicinal products, there is no mechanism to control the dose delivered, nor levels of quality control of performance applied in the way that an inhaler or nebuliser would be assessed. However, there are companies looking at whether the technology can be converted for application in the medical field.

In addition, there is a class of devices under development that vaporize an excipient-free drug to form a condensation aerosol that, when inhaled, allows for systemic drug delivery. The Staccato® device (Alexza) is approved for systemic administration of loxapine in the treatment of schizophrenia (marketed as Adasuve™ by Teva). This technology will only work with drugs that have relatively low boiling points and are thermally stable.

2.2.6 New propellants for MDIs

An inhalation propellant must be safe for human use and meet several other criteria relating to safety and efficacy. Traditionally the list would include: (i) liquefied gas, (ii) low toxicity, (iii) non-flammable, (iv) chemically inactive and stable, (v) acceptable to patients (in terms of taste and smell), (vi) appropriate solvency characteristics, and (vii) appropriate density. Not all of these requirements may be essential for an alternative propellant, but careful study and justification would be required to support any significant change. It is, however, extremely difficult to identify chemicals fulfilling all of these criteria, and which are also environmentally acceptable.

At the time of the introduction of the Montreal Protocol, extensive research had already identified the two currently used hydrofluorocarbons as alternative propellants – HFC-134a and HFC-227ea. Two international consortia (IPACT-I and IPACT-II) conducted toxicological testing to ensure that these propellants were safe for inhalation by humans. The direct cost of this testing was tens of millions of dollars. Once identified, the MDI industry reformulated the CFC MDIs so that they could use HFCs. The components and formulations were substantially modified to use the new HFC propellants.

MDIs are subject to extensive regulation by national health authorities to ensure product safety, product efficacy and product quality. The process for developing HFC MDIs was therefore essentially identical to the development of a wholly new drug product, involving full safety testing, stability testing and clinical trials for each reformulated MDI. Research and development for a new product is a lengthy, challenging, costly and resource-intensive process. A safety study for an entirely novel MDI propellant for asthma/COPD treatment requires at least 12 months clinical trial experience in hundreds[18] of patients, as well as lifetime studies in laboratory animals. In summary, the process of bringing a new product to market is time-consuming. While the first new products might reach the prescribing physician in as little as 6 years, significant market penetration may take 10 years or longer. For the CFC MDI phase-out, after identifying HFC propellants and developing safe products, the final step was to switch millions of patients to reformulated MDIs and other CFC-free products.[19] This led to an essential use process to supply adequate pharmaceutical grade CFCs during transition, which continued for over 20 years.

Three low-GWP (global warming potential) chemicals are under development as potential propellants for MDIs (isobutane, HFC-152a[20], and HFO-1234ze(E)[21]). Which of these, if any, would make it to the market, and the subsequent rate of uptake, is unpredictable. For a new propellant development programme, there is major risk, significant investment, and no guarantee of success. At this point, the pharmaceutical development of HFC-152a, and HFO-1234ze, are being largely supported by the chemical companies themselves. For existing products, it might be difficult for a pharmaceutical company to justify an investment in new propellants given the limited benefit to patients (i.e., the active ingredient will remain the same and the performance characteristics are likely to be comparable to current MDIs). On the other hand, companies may wish to be highly rated on the environmental indices, such as the Dow Jones Sustainability Index, which is difficult when the current propellants constitute a very substantial part of their company’s carbon footprint. The choices to reduce a company’s carbon footprint include new propellants in MDIs and/or DPI formulations.

2.2.6.1 Isobutane

Under an MLF-funded project, a company in Argentina (Pablo Cassara), undertook research and development to use isobutane as a propellant. The registration process for the isobutane-based salbutamol MDI was initiated and expected to complete in 2014. A planned launch of an isobutane salbutamol MDI has not yet taken place and no MDI products containing isobutane have appeared on the market by late 2018. Previous studies had reported toxicological concerns for isobutane used in combination with a beta-agonist[22]. Isobutane is flammable, with a lower flammable limit of 1.8 volume percent in air, and therefore its adoption would require MDI manufacturing to address safety[23]. Safety considerations for manufacturing with flammable chemicals requires significant engineering and investment.

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[18] The number of patients varies on the clinical trial and/or the country where the trial is conducted. Patient numbers can range from the low hundreds to more than a thousand.

[19] Metz, B., Kuijpers, L., Solomon, S., Andersen, S. O., Davidson, O., Pons, J., de Jager, D., Kestin, T., Manning, M., and Meyer, L. (eds.), IPCC/TEAP Special Report: Safeguarding the Ozone Layer and the Global Climate System: Issues Related to Hydrofluorocarbons and Perfluorocarbons, 2005, page 355.

[20] 1,1-difluoroethane

[21] *trans*-1,3,3,3-tetrafluoroprop-1-ene

[22] Final report of the Safety Assessment of isobutane, isopentane, n-butane, and propane. *Int. J. Toxicology*, 1; 4: 127-142, 1982.

[23] For flammability limits of isobutane see: *J Hazard Mater.,* 2007, **148**(3), 640-7. Epub 2007 Mar 12.

2.2.6.2 HFC-152a

One chemical company has recently reported research and development to investigate HFC- 152a as a possible MDI propellant with lower global warming potential than HFC-134a. HFC-152a is a colourless and odourless gas that is already manufactured in large volumes and widely used in a number of non-medical applications. It has shown some promising MDI formulation benefits in initial research. HFC-152a is flammable, with a lower flammable limit of 3.8 volume percent in air, and therefore its adoption would require MDI manufacturing to address safety. Safety considerations for manufacturing with flammable chemicals requires significant engineering and investment.

The toxicology of HFC-152a is well known as an industrial gas (similar to HFC-134a). Work to fill in gaps in the industrial toxicity was initiated in 2016 and is now successfully completed. This has to be repeated to GLP standards[24] and to medical protocols, and the whole sub-chronic toxicology programme is projected to be completed in 2019. The long-term toxicology testing on HFC-152a is expected to be completed in 2021 with the first clinical trials in humans scheduled for mid-2019.

The global warming potential[25] of HFC-152a is 124, compared with 1,430 for HFC-134a and 3,220 for HFC-227ea. A lifecycle carbon footprint study has shown that the carbon footprint of an HFC-152a MDI (1,800 g CO_2-eq./200 actuation inhaler) is reduced by greater than 90 percent compared to an HFC-134a MDI[26], and similar to the carbon footprint of a DPI[27]. Due to the lower the liquid density of HFC-152a (compared with HFC propellants), early indications are that less weight of propellant is used in MDIs resulting in additional savings.

Research and development on a range of HFC-152a MDI drug formulations is underway, with similar performance to current HFC-134a and HFC-227ea MDIs. Inhalation safety and toxicology studies are underway and, until these are completed, its potential is uncertain.

No pharmaceutical industry consortium has yet formed that might accelerate the development of HFC-152a drug combinations in a manner similar to that undertaken for HFCs.

2.2.6.3 Hydrofluoroolefins (HFOs)

HFOs are a new range of unsaturated HFCs, which have attractive chemical, physical and environmental properties for a range of applications. They have a very low-GWP (less for example than HFC-152a).

One chemical company has started research and development to investigate HFO-1234ze(E) as a possible propellant for use in MDIs. HFO-1234ze(E) is a colourless and odourless gas, with a

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[24] Good laboratory practice (GLP) is a set of principles to assure the quality and integrity of non-clinical laboratory studies to support research towards products regulated by government agencies. Non-clinical animal testing must be performed prior to approval of new drug products. Many jurisdictions assure GLP standards through regulation.

[25] According to Montreal Protocol Annex F 100-year Global Warming Potential.

[26] Jeswani, H., Corr, S., Azapagic, A., Reducing carbon footprints of metered dose inhalers, *Inhalation*, **11**(6), December 2017.

[27] Lewis, D., Breathe it in: The environmental concerns of inhalers, *European Pharmaceutical Manufacturer*, November 2018, https://www.epmmagazine.com/opinion/breathe-it-in/. Accessed December 2018.

GWP less than 1, that is commercially available and used in a number of non-medical applications. HFO-1234ze(E) is designated as a Class 2.2 non-flammable liquefied gas. Although classified as non-flammable under standard tests, HFO-1234ze(E) has a flammable range of 8.0-8.5 volume percent in air (at one atmosphere under certain conditions). Its adoption would require MDI manufacturing to address safety. This propellant is being investigated as to its suitability as an alternate propellant in MDIs, and, as with HFC-152a, will require toxicology and inhalational safety studies. A previous study has indicated low-level toxicological concerns associated with the HFOs in development, including HFO-1234ze(E)[28]. It is not yet clear whether there will be a role for unsaturated HFCs as safe propellants for MDIs.

No pharmaceutical industry consortium has yet formed that might accelerate the development of HFO drug combinations in a manner similar to that undertaken for HFCs.

2.3 Technical and economic assessment

2.3.1 Technical and economic considerations

- CFC MDIs were historically the inhaled delivery device of choice. They have now been phased out worldwide in response to the phase-out of CFCs under the Montreal Protocol.

- HFC MDIs are available to cover all key classes of drugs used in the treatment of asthma and COPD. Following the Kigali Amendment to the Montreal Protocol, HFCs, including -134a, -152a, and -227ea, are now listed as controlled substances under Annex F.

- Dry powder inhalers (DPIs) do not require a propellant, are a not-in-kind alternative to MDIs for some patient groups. DPIs fall into two categories; single-dose DPIs, which have been in use for more than 60 years, and multi-dose DPIs, which have been in use for more than 25 years. There are two main types of multi-dose DPI, reservoir and multi-unit dose devices. There are now DPI alternatives available to cover all key classes of drugs used in the treatment of asthma and COPD. Almost all new drugs are being developed in the DPI format, often exclusively.

- Nebulisers are used to inhale drug solutions and account for about 10 percent or less of the market on a dose basis.

- Propellant-free aqueous mist (soft mist) inhalers are small portable devices that produce aerosols of respirable diameter from aqueous formulations; one device from one pharmaceutical company (Respimat™) is now commercially available in a number of countries.

- MDIs using new propellants are in development. These propellants include isobutane, HFC-152a, and HFO-1234ze(E).

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[28] Lindley, A.A., and Noakes, T. J., Consideration of Hydrofluoroolefins (HFOs) as potential candidate medical propellants, Mexichem Fluor, April 2010. http://www.mexichemfluor.com/wp-content/uploads/2016/01/hfos-as-candidate-medical-propellants.pdf. Accessed December 2019.

Industry continues to innovate for MDIs, DPIs, soft mist inhalers, and new products are in the pipeline with enhanced benefits for patients that could improve adherence and health outcomes. The range of choices to treat asthma and COPD is expanding.

Currently, the major two categories of choices available to treat asthma and COPD are HFC MDIs and DPIs. A range of HFC MDIs and DPIs are commercially available worldwide for all key classes of drugs used in the treatment of asthma and COPD. HFC MDIs and DPIs have been subjected to extensive regulatory assessments for safety, efficacy and quality. Clinical trials have shown HFC MDIs to have a safety and efficacy profile comparable to that of CFC MDIs that they replaced, with more consistent dosing[29]. Clinical evidence also indicates that MDIs and DPIs are equally effective for the treatment of asthma and COPD for patients who use both devices correctly. New drugs are mainly being developed as DPIs. Salbutamol HFC MDIs account for the large majority of HFC use in inhalers and are significantly less expensive per dose than multi-dose DPIs. Nevertheless, a multi-dose dry powder inhaler Teva ProAir Respiclick containing salbutamol (albuterol) is now available in the United States.

The proportion of MDI versus DPI varies by country, even within a region. For example, the proportion of MDIs prescribed compared with multi-dose DPIs varies considerably across Europe, with 70 percent of MDIs prescribed in the UK, 30 percent in Scandinavia, and only 10 percent in Sweden[30]. This is more to do with market factors and clinician/patient practices and preferences than it is to do with commercial availability. However, as a global generalization, the MDI predominates for salbutamol, whereas for new combination products, DPI formulations generally predominate.

Short-acting bronchodilators (e.g. salbutamol) are generally cheaper when in MDIs than in multi-dose DPIs, although the price differential is narrowing in some markets, as the number of salbutamol DPI devices increases. For example, in the UK, where a 200-dose salbutamol MDI can cost the National Health Service (NHS) as little as £1-50, the equivalent DPI cost might double, but is still inexpensive at £3. This change would be affordable in a developed country. However, in emerging economies and health systems where patients pay for their own drugs, Hillman *et al*. correctly argue that salbutamol multi-dose DPIs will need to be cheaper if they are to be used more widely[30].

Single-dose DPIs are affordable and available for the short-acting bronchodilator salbutamol, as well as other inhaled therapies such as beclomethasone. Patients (in Article 5 Parties) buy the re-usable inhaler device once and generally re-use that device for about 12 to 24 months. Patients buy the medicines (capsules) for the inhaler as needed. Single-dose DPIs have the advantage that they permit low-income patients to afford a limited number of doses of their medication, where they may otherwise be unable to afford the expense of buying one month's therapy at a time (as necessary with MDIs and multi-dose DPIs). However, this purchasing behaviour also has the potential to undermine adherence to products that are required on a continuous basis (e.g. corticosteroids or combination therapies). In India and Bangladesh, doctors prefer single-dose DPIs for the majority of their economically challenged patients. In India, for example, single-dose DPIs account for more than 50 percent of inhaled therapy, and DPIs generally for about half of

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[29] Asthma patients to benefit from advancement in inhalers. *Business Recorder*, November 3, 2013, Pakistan.

[30] Hillman, T., Mortimer, F., Hopkinson, N. S., Inhaled drugs and global warming: time to shift to dry powder inhalers: Propellants in metered dose inhalers are powerful greenhouse gases, *British Medical Journal*. 2013, **346**, 3359.

the market value[31]. The use of single-dose DPIs for daily use medications may not necessarily be as cost effective over the long term as MDIs or multi-dose DPIs. In Russia, the cheaper, domestically produced salbutamol CFC MDI with 90 doses has previously been preferred to the imported HFC MDIs with 200 doses, despite the former being more expensive on a cost per dose basis.

Some studies have indicated that DPIs can be easier to use than MDIs because the patient's inhalation drives the drug delivery, and they do not require patient co-ordination.[32] However, DPIs have a minimum threshold inspiratory effort that is needed for proper use and drug efficacy, and may not be suitable for very young children, or frail elderly patients with very severe COPD. Instead these patients may use MDIs with valved holding chambers, spacers, or nebulisers, or aqueous sprays. If correct use remains a challenge with some of these options, nebulisers are the only realistic option. There is very little data on the therapeutic efficacy of different methods of delivery of inhaled therapies at the extreme ends of the spectrum for age or disease. For example, it was shown that between 12.5 and 30 percent of elderly COPD patients could not achieve an arbitrary pre-specified flow rate through a range of older high resistance DPIs, but there was no data on whether this made any difference to patient outcomes[33].

Older reservoir multi-dose DPIs can suffer from water ingress in high humidity environments that leads to clumping of the powder formulation. Some HFC MDIs are also affected by high humidity. In both cases the issue can be partially addressed by supplying the device in a foil pouch opened on first use. Newer multi-dose DPIs have improved moisture protection and are approved in countries with humid climates, such as experienced in many Article 5 Parties. Single-dose capsule DPIs can be more susceptible to humidity than some of the more recent multi-dose DPIs. However, an effective drug dose is likely to be delivered even with the effects of humidity, and pharmaceutical companies are working to improve blister pack technology and to ameliorate humidity problems.

In many circumstances, DPIs are technically and economically feasible alternatives that could substantially reduce the use of HFC MDIs. Nebulisers and emerging technologies may also be technically feasible alternatives for avoiding the use of some HFC MDIs. The main exception is salbutamol, where salbutamol multi-dose DPIs are generally more expensive than salbutamol HFC MDIs, which remain an essential and affordable therapy. It is not yet technically or economically feasible to avoid HFC MDIs completely in this sector because, currently:

- For salbutamol, there are economic impediments in switching from some HFC MDIs to multi-dose DPIs;
- Some patients (young children and frail elderly) cannot use DPI alternatives to HFC MDIs. The exact proportion of these groups depends on the definition of satisfactory use. It is probably less than 20 percent, although there is no real-world data.

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[31] Waite, D., *Comparison of OIP Experiences in Different Markets*, IPAC-RS Respiratory Conference, March 18-20, 2014.

[32] For a general bibliography see: Burnham, T., Inhaler use technique and related interventions, an annotated bibliography. *National Electronic Library for Medicines*, Medicines Management Overview, August 2012. https://use-inhalers.com/sites/default/files/publicationpdf/Reference_Studies_Tom_Burnham.pdf. Accessed February 2015.

[33] Janssens, W., VandenBrande, P., Hardeman, E., De Langhe, E., Philps, T., Troosters, T. , Decramer, M., Inspiratory flow rates at different levels of resistance in elderly COPD patients, *Eur. Respir. J.* 2008, **31**, 78–83.

A range of therapeutic options remains important because some devices, and/or drug products, are more effective for some patients. Some experts contend that ICS are more effective when delivered as ultrafine HFC MDI aerosols[34], although there is no guarantee that any reformulated MDIs with new propellants will be ultrafine. Some patients may also prefer one therapeutic option over another, which is significant because patient preference is an important factor for adherence to therapy.

2.3.2 Patient health considerations

It is important to note that MDIs, DPIs and other delivery systems all play an important role in the treatment of asthma and COPD, and no single delivery system is considered universally acceptable for all patients. Similarly, not all active ingredients are available equally as either an MDI or DPI. Healthcare professionals continue to consider that a range of therapeutic options is important. Any consideration of policy measures to minimise the environmental impact and carbon footprint of inhaled therapy should carefully assess patient health implications with the goals of ensuring patient health and maintaining a range of therapeutic options, as well as assessing economic implications. Each country has its own unique and complex makeup in terms of availability of medicines, overarching health care systems, and patient preferences.

Complex considerations are necessary when patients and healthcare professionals make an informed choice about a patient’s inhaled therapy, taking into account therapeutic options, patient history, patient preference, ability (e.g., dexterity, inspiratory flow, vision) and adherence, patient-borne costs, as well as environmental implications, with the overall goal of ensuring patient health. Patient choice may be enhanced with an increase in publicly available information about the environmental impact of different inhaler products. Healthcare professionals and their patients may benefit from this information in order to take environmental impact into account in their choice of inhaler.

2.3.3 HFC consumption for MDI manufacture

Based on HFC manufacturing industry estimates[35], approximately 800 million or more HFC MDIs (with average fill weight 13-14.5 g/MDI) are currently manufactured annually worldwide, using approximately 11,500 tonnes HFCs in 2018. HFC-134a makes up the major proportion of MDI manufacture (~10,600 tonnes in 2018), with HFC-227ea accounting for about 8 percent (~900 tonnes in 2018). This corresponds to direct emissions with a climate impact of approximately 18,000 ktCO$_2$-eq. For the year 2016, HFC propellant consumption for MDI manufacture corresponded to direct emissions that are estimated to be about 2 percent of global GWP-weighted total emissions of HFCs[36].

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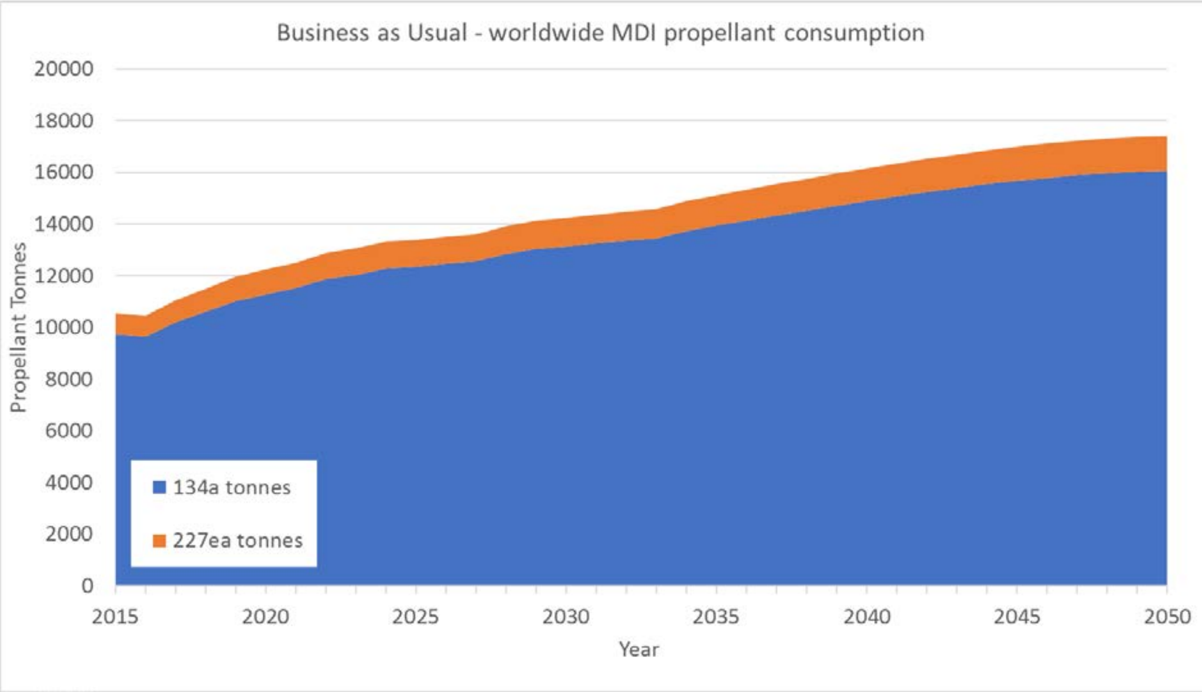
[34] van den Berge, M., ten Hacken, N. H. T., van der Wiel1, E., Postma, D. S., Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma, *Allergy*, 2013, **68**, 16–26.

[35] Noakes, T.J., Mexichem Fluor, United Kingdom, personal communications, 2018. HFC propellant consumption data, derived from HFC and cannister manufacturing industry sources, differs from that derived from inhaler market data. For the purposes of this report, the manufacturing industry data has been used to estimate HFC propellant consumption.

[36] As derived from atmospheric observations, total emissions of HFCs summed to 0.88 (± 0.07) GtCO$_2$-eq/year in 2016, taken from: World Meteorological Organization (WMO), *Executive Summary: Scientific Assessment of Ozone Depletion: 2018,* World Meteorological Organization, Global Ozone Research and Monitoring Project – Report No. 58, 67 pp., Geneva, Switzerland, 2018.

The use of HFC MDIs is projected to increase, especially with increasing use of MDIs in developing countries. Based on HFC manufacturing industry estimates, a projection of HFC propellant consumption is given under one business-as-usual scenario in Figure 2.1. This projection assumes: no new propellants are introduced; the market remains relatively flat in developed countries with some decline in later years; substantial market growth in developing countries; and the market share of MDIs remains similar to today relative to other dosage forms. Industry efforts are on-going to refine these estimates based on best available, evolving market information.

Figure 2.1 Projected global HFC propellant consumption (2015-2050) (tonnes)



2.3.4 *Carbon footprint of HFC MDIs, DPIs and other treatment methods*

This section presents available information on the carbon footprint of HFC MDIs, DPIs and other treatment methods.

In previous assessments[37], the Medical Technical Options Committee has presented industry estimates of carbon footprints for the manufacture and use of various respiratory devices and treatment methods based on a 200-dose equivalence (Table 2.1).

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[37] 2010 Report of the UNEP Medical Technical Options Committee, 2010 Assessment Report. 2014 Report of the UNEP Medical Technical Options Committee, 2014 Assessment Report.

Table 2.1 Estimates of carbon footprints of a selection of respiratory devices and treatment methods (*circa.* 2014)

Respiratory devices and treatment methods	Carbon footprint Per 200 actuations (Grams CO_2-eq)	Carbon footprint Per dose (Grams CO_2-eq)[38]
CFC MDI	150,000-200,000	1,500-2,000
HFC-134a MDI	20,000-30,000	200-300
HFC-227ea MDI	60,000-80,000	600-800
Dry Powder Inhaler	1,500-6,000	<20
Tablets	1,500-5,000	<20

These estimates indicate that by moving from CFC MDIs to HFC MDIs and DPIs, not only have emissions of ozone depleting substances been eliminated, but there have also been benefits for climate change. According to these estimates, the climate impact of HFC MDIs is about one-eighth the climate impact of CFC MDIs. DPIs have an even lower comparative climate impact, about one-hundredth of the impact of CFC MDIs and less than one-tenth the impact of HFC MDIs.

A more recent study considers different HFC MDI formulations and their associated carbon footprints. Information on the amount of HFC propellant in individual MDIs is not specified on the inhaler label. The amount of HFC-134a propellant varies according to the formulation, from 6g to 19g in a salbutamol MDI, and from 12.3g to 20g for inhaled corticosteroids. A life cycle analysis of a Proventil^{TM} inhaler containing 6.68g of HFC-134a propellant, estimated that the carbon footprint was around 10,000 gCO_2-eq per 200-actuation inhaler. Two LABA/ICS MDIs (Symbicort^{TM} and Flutiform^{TM}) use HFC-227ea, which has a greater GWP and is generally only used where necessary to meet technical and performance criteria. Flutiform^{TM} contains 11g of HFC-227ea and has an estimated carbon footprint of 36,500 gCO_2-eq per 200-actuation inhaler[39]. In summary, for a given dose, the climate impact of HFC inhalers can vary threefold.

Another recent lifecycle carbon footprint study has estimated that the carbon footprint of an HFC-152a MDI is projected to be about 90 percent less than an HFC-134a MDI (1,800 gCO2-eq/200-actuation inhaler)[40]. Aqueous mist inhalers also have much lower carbon footprints than current HFC MDIs, although there are no peer-reviewed data.

While acknowledging the complex considerations involved in making inhaled therapy choices, including patient health and broader public health implications, these examples indicate that it is possible to minimise the carbon footprint of inhaled therapy use through certain choices. These

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[38] One dose for an MDI is two actuations; for a DPI is one actuation; and for a tablet is one tablet.

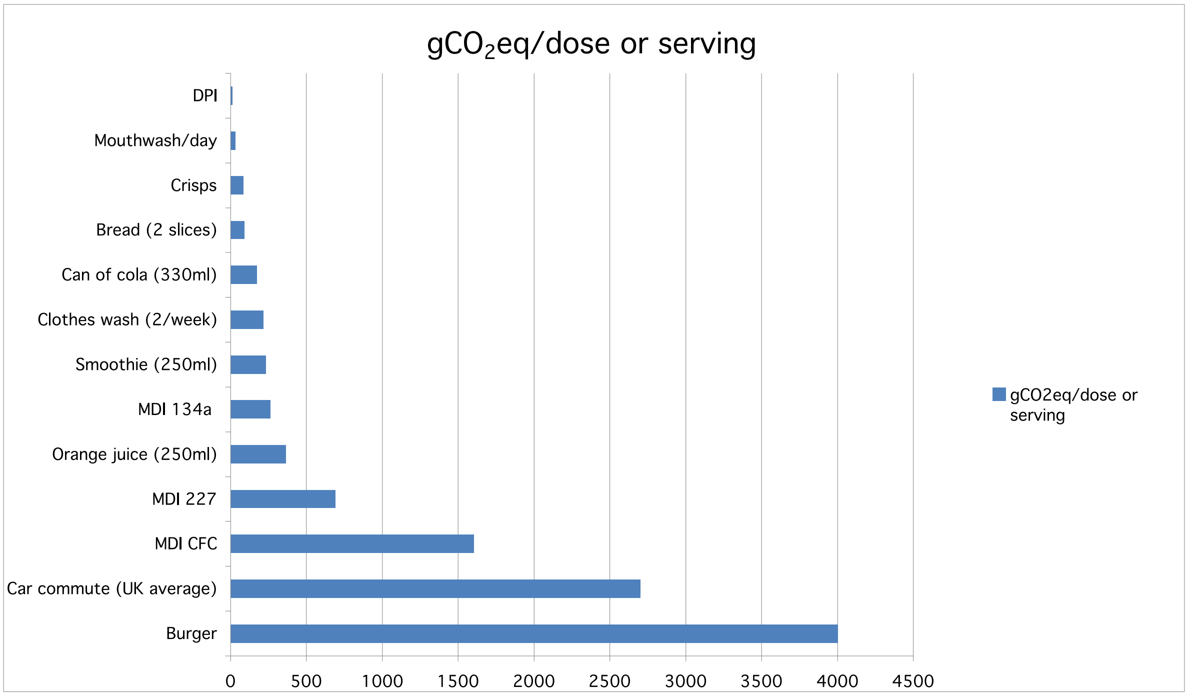
[39] Wilkinson, A., Braggins, R., Smith, J., Steinback, I., The Costs of switching to low global-warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England. *Submitted for publication.*

[40] Jeswani, H., Corr, S., Azapagic, A., Reducing carbon footprints of metered dose inhalers, *Inhalation*, **11**(6), December 2017.

choices include: minimising the use of MDIs containing the highest volumes of HFC-134a and those containing HFC-227ea; and giving preference to lower GWP propellants (if and when they become available, e.g. HFC-152a) and lower carbon footprint therapies (e.g. DPIs and aqueous mist inhalers). Carbon footprint is just one of many complex considerations for countries, healthcare professionals and patients when making choices about inhaled therapies that balance environmental implications with patient care and/or health system implications. With information, including about the relative environmental impact of inhalers, healthcare professionals and patients can make an informed choice about inhaled therapy to suit an individual's needs. Patient choice may be enhanced with an increase in publicly available information about the environmental impact of different inhaler products. Healthcare professionals and their patients may benefit from this information in order to take environmental impact into account in their choice of inhaler.

The estimated carbon dioxide equivalent of an average 2-puff dose of an HFC MDI (200 gCO_2-eq, Table 2.1) is comparable to the climate impact of everyday items, such as a 330ml can of Cola (170 gCO_2-eq), 250 ml of orange juice (360 gCO_2-eq), and a kilometre driven in a Seat Ibiza Ecomotive (99 gCO_2-eq). This can also be compared with the carbon impact of a one-way economy class flight from London to Frankfurt (180,000 gCO_2-eq per passenger), a popular burger (4,000 gCO_2-eq), or a loaf of commercially made bread (1,300 gCO_2-eq). Estimates of carbon dioxide equivalents associated with a dose of an asthma inhaler and everyday items are presented in Figure 2.2.[41]

Figure 2.2 Estimated relative carbon dioxide emissions of everyday items compared with asthma inhalers



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[41] The climate impact of everyday items was originally reported in the 2010 Report of the UNEP Medical Technical Options Committee, 2010 Assessment Report, from sources mentioned therein.

Taken cumulatively, the contribution of MDIs to a nation's carbon footprint can also be estimated. For example, the UK's National Health Service (NHS) contributes 3 percent of overall UK greenhouse gas emissions, and MDIs contribute an estimated 3.5 percent of the carbon footprint of the NHS[42].

2.3.5 Other environmental considerations

In the European Union, one pharmaceutical company uses up to 10 tonnes per year of perfluorooctyl bromide (PFOB) as a processing aid in the manufacture of porous particles providing a uniform suspension inside an MDI. The use of PFOB as a processing aid is critical to delivering the unique aerodynamic properties of the porous particles, which ensure the efficient delivery of the drug to the lungs. The PFOB is produced outside the European Union.[43] PFOB is not a controlled substance, but it is a brominated fluorocarbon similar to a halon. The pharmaceutical company reports that it has the best available technology to ensure there are negligible releases to the environment (in relation to environmental concerns about chemical impurities in PFOB).

2.4 Market Dynamics for Inhaled Therapies

Inhaler prices are declining as competition increases, with more multinationals and local companies coming into the market. In less mature markets, the market value is increasing due to rapidly increasing numbers of inhalers being used. In some mature markets (e.g. EU), the overall market value is declining due to competitive pricing.

2.4.1 Numbers of Inhalers

Based on HFC manufacturing industry estimates[44], approximately 800 million or more HFC MDIs (with average fill weight 13-14.5 g/MDI) are currently manufactured annually worldwide, using approximately 11,500 tonnes HFCs (-134a and -227ea) in 2018. Based on knowledge about DPI raw materials inputs, one industry estimate of the number of DPIs manufactured worldwide is 450 million annually.

Market data provided by IQVIA[45] of inhaler[46] units sold worldwide indicates 54 percent are MDIs and 46 percent are DPIs. This data is based on an analysis of prescriptions in markets

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[42] Creagh, M., Clark, C., Coffey, T. et al., UK Progress on reducing F-gas Emissions. House of Commons Environmental Audit Committee; 2018. https://publications.parliament.uk/pa/cm201719/cmselect/cmenvaud/469/469.pdf.

[43] European Chemicals Agency, *Report on the request to review a derogation request for the restriction of PFOA, its salts and PFOA-related substances (entry 68 of Annex XVII to REACH)*, 24 May 2018, https://echa.europa.eu/documents/10162/c9666f21-532b-49a0-ace3-c843b7b8e5b0. Accessed December 2018.

[44] Noakes, T.J., Mexichem Fluor, United Kingdom, personal communications, 2018. HFC propellant consumption data, derived from HFC and cannister manufacturing industry sources, differ from that derived from inhaler market data. For the purposes of this report, the manufacturing industry data has been used to estimate HFC propellant consumption.

[45] IQVIA, which is formerly IMS Health and Quintiles, gathers and analyses pharmaceutical market data. GSK is a subscriber to IQVIA and was granted permission to provide inhaler sales data to MCTOC for this assessment.

where this information is available. It provides another comparison of global MDIs and DPIs. In different markets, the proportion of MDIs to DPIs differs. For example, of inhalers worldwide: around 16 percent are sold in the US, of which 70 percent are MDIs; around 35 percent are sold in the EU, of which 50 percent are MDIs; and around 3 percent are sold in Japan, of which 20 percent are MDIs. These proportions vary for many reasons including prescribing practices, cost, availability, patient preference, and national government guidance.

2.4.2 Inhaler Market Value

Based on IQVIA[47] market data, the global inhalation device market size was worth approximately US$ 37.7 billion in 2017, with growth of around 2 percent from 2016, and with the US market alone valued at US$ 23.55 billion. In 2017, the developed country market value ($30.6 billion) remained around 15 times that of developing countries ($2.1 billion).

While the number of MDIs sold exceeds DPIs, because multi-dose DPIs contain more expensive controller medications, the DPI market value of US$17.39 billion exceeds the MDI market value of US$ 15.22 billion.

The value of MDIs sales continues to increase, driven mainly by increasing numbers of inhalers sold (from 2016 to 2017, at a rate of 4 and 18 percent in developed and developing countries respectively).

The value of DPI sales in developed countries was down slightly in 2017 (from US$ 16.37 billion to US$ 16.28 billion), mostly due to negative value growth in the EU region. This is likely owing to increasing competition and regulation driving down inhaler prices. From 2016 to 2017, DPIs had a positive growth of 7 percent in developing markets.

Salbutamol is by far the largest of the market by the number of inhalers sold. However, because it is relatively inexpensive in either single-dose DPI or MDI, salbutamol is only fourth in value terms with an 11 percent share of the market by value.

2.4.3 Price of MDI and DPI in Major Markets

Data are available for salbutamol MDI and tiotropium DPI showing that inhaler prices vary enormously around the world[48]. As a general rule, drug products sold in developing countries are cheaper than equivalent products in developed countries. For a salbutamol 200-dose MDI, prices range from $0.83 in India, to around $2 in most of Europe, and up to $48 in the US. For a tiotropium 30-dose DPI, prices range from $2.20 in Bangladesh, to $30-40 in Europe, and up to $330 in the US.

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[46] The analysis includes MDIs and DPIs but does not include nebulized solutions.

[47] IQVIA, which is formerly IMS Health and Quintiles, gathers and analyses pharmaceutical market data. Beximco Pharma is a subscriber to IQVIA and was granted permission to provide IQVIA market value data to MCTOC for this assessment.

[48] Clarivate Analytics gathers and analyses pharmaceutical market data. Beximco Pharma is a subscriber to Clarivate Analytics and was granted permission to provide inhaler price data to MCTOC for this assessment.

2.5 Inhaled therapy in different countries

Since the 2014 assessment, all Montreal Protocol parties have phased out the production of CFC MDIs, with a wide range of alternatives replacing their use. The patterns of prescribing for respiratory diseases vary widely between different countries. For example, in many developing countries, inexpensive oral medications or single-dose DPIs predominate. In developed countries, inhaled therapies predominate, with varying proportions of multi-dose DPIs and HFC MDIs. Global variations in drug pricing play a major role in determining the type and availability of medications that patients receive.

The following information describes some experiences of inhaled therapy from a selection of countries.

2.5.1 Bangladesh

In Bangladesh, more than 10 percent of the population (16 million) have asthma and/or COPD. The Bangladesh respiratory market is valued at $215 Million, with 5.33 percent annual growth.

Oral medications (especially montelukast), both solid and liquid dominate the market, with inhaled therapies at only 23 percent. Of inhaled therapies, DPIs account for 29 percent, MDIs 70 percent and nebuliser solutions 1 percent. However, over the last 4 years, the inhaler market has increased rapidly by 17 percent (MDIs by 13 percent, DPIs by 28 percent). Local industry is driving the increase in DPIs by launching many new drugs in DPIs only. Reformulation is easier for local companies, using single dose DPIs. Patients find the purchase of small numbers of single dose capsules affordable.

There are 9 pharmaceutical companies with inhaled therapies (7 local companies and two multinationals) with 11 molecules or combinations of molecules. In value terms, salmeterol/fluticasone combinations are the largest, but by unit consumption, salbutamol HFC MDI is the largest.

2.5.2 China

In China, there are about 100 million patients with COPD[49]. WHO has estimated that there are around 30 million patients with asthma. Around two thirds of respiratory drugs are delivered by the inhaled route. Multinational and local companies increasingly share the market with local companies having half the salbutamol MDI Market.

The China Market is unusual in several respects. The market value of the overall inhaler market has more than doubled between 2014 and 2018. The ICS market is remarkably almost entirely (98 percent) imported nebuliser solutions, with nebulised budesonide being the 4th largest pharmaceutical for all indications in China. In contrast, the LABA/ICS inhaler market is 98 percent DPI, in spite of the same drugs delivered by MDI being less than half the DPI price. The market is expected to evolve rapidly in coming years with increasing choice of inhalers, as new local brands become available.

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[49] Wang, C., Xu, J., et al., Prevalence and risk factors of Chronic Obstructive Pulmonary Disease in China: a national cross-sectional study. *[J]. Lancet*, 2018, **391**(10131), 1706-1717. DOI:10.1016/S0140-6736(18)30841-9.

2.5.3 Japan

Japan started the phase-out process of CFCs in MDIs in 1989. Fourteen pharmaceutical companies, which manufactured and/or imported MDIs for asthma and COPD, organized a special committee called “CFC Committee” as an affiliated group under the Federation of Pharmaceutical Manufacturers’ Associations of Japan (FPMAJ). In December 1998, the Japanese government submitted a transition strategy that was developed in cooperation with the CFC Committee. The strategy was unique in that it included a clear timeline of ‘by 2005’ for the complete phase-out, and it allowed for brand-by-brand substitution by each company. All companies finished production, import and delivery of CFC MDIs by the end of 2005. The key success factors for the transition were the technologies to manufacture CFC-free alternatives, the cooperation of the companies, the close cooperative relationship between the authorities and industry, and an appropriate transition strategy with a clear timeline

During the phase-out of CFC MDIs, the committee and member companies challenged simultaneously the reduction of HFCs used in MDIs. The committee and the FPMAJ proposed “Action Plan for Reduction of Emissions of HFCs Used in Medical Aerosols” in April 1998. The committee and member companies focused on the development and introduction of inhalers that do not contain HFCs, such as DPIs and other new types of inhalers, as the most effective way to reduce HFCs.

The Japan policy has driven towards less reliance on inhalers that use propellants. In 2006, 21 brands of CFC-free alternatives (HFC MDIs and DPIs) had been launched to replace the full range of CFC MDIs. By 2017, 73 brands of inhalers for asthma and COPD had been marketed in Japan, 24 HFC MDIs, 44 DPIs and 5 other inhalers. The ratios of each inhaler type were MDI 21 percent, DPI 72 percent, and other inhaled therapy 7 percent. Whilst the overall number of inhalers used in Japan has increased by 30 percent between 2006 and 2017, the amount of propellant used annually has reduced from a peak of 112 tonnes in 2006, to a range between 69 and 82 tonnes of HFCs over the period 2012 to 2017.

2.5.4 Pakistan

In Pakistan, the large majority of patients use oral (montelukast) treatments for asthma and COPD, which are increasing in prevalence. Treatments by inhalation account for only 1 percent of the market share ($45.7 million). Local companies are beginning to develop and market both DPIs and MDIs. From this low baseline, market growth in inhalers is around 15 percent per year, greatest for DPIs.

2.5.5 Russian Federation

In Russia, asthma is diagnosed in 6.2 percent of the population. Children suffer 2 times more often than adults. Death is extremely rare. The incidence of men and women is the same. Most often the disease is detected in children, as well as the elderly (after 50 years). Middle-aged people are more susceptible to the atopic disease, while the endogenous type is prone to children and older adults.

HFC-134a based MDIs are manufactured by four Russian pharmaceutical companies with salbutamol, beclomethasone, ipratropium bromide, and feneterol/ipratropium bromide combination. DPI production was started during 2018 by one Russian company, manufacturing about 450,000 per year with tiotropium bromide, budesonide/formoterol combination, and salmeterol/fluticasone combination.

2.5.6 Scandinavia: (Denmark, Finland, Norway, Sweden)

The Nordic countries have traditionally been using more DPIs compared to the rest of the European countries. There has been local production and development of DPI technologies, whereas MDIs are all imported. According to IQVIA data of all inhaled asthma and COPD therapies, the volume share of DPIs in 2017 was 67 percent and the share of MDIs was 33 percent. The respective proportions for controller medications were: for inhaled steroid and beta-agonist combination, DPI 77 percent, MDI 23 percent; for inhaled steroids, DPI 72 percent, MDI 28 percent; and for reliever medication, DPI 58 percent, MDI 42 percent. However, the total share of DPI has been slightly decreasing in recent years due to the introduction of newer MDI products. For the past 3 years, the share of DPI from total inhaler volume has been reported to be 71 percent in 2015, 69 percent in 2016, and 67 percent in 2017, respectively.

2.5.7 Uganda

In Africa, recent data from Uganda, suggests that asthma outcomes may be much worse than previously believed[50]. A one-year follow-up of 449 asthma patients in Uganda showed that 60 percent had at least one exacerbation, and 32 percent had three or more exacerbations. Mortality from asthma was 3.7 percent compared to 0.1 percent in a comparable Italian asthma cohort[51], and highest in patients with poor asthma control. Whilst 71 percent of patients were taking rescue salbutamol MDIs, only 33 percent of patients were taking preventive treatment with ICS. Increased access to asthma medication, and especially inhaled steroids, has been shown to improve asthma outcomes in a recent study in Brazil[52].

2.5.8 United Kingdom

The UK's National Health Service (NHS) contributes 3 percent of overall UK greenhouse gas emissions. MDIs contribute an estimated 3.5 percent of the carbon footprint of the NHS[53].

The UK has a proportionately large volume of MDI use (~70 percent compared to <50 percent in other European countries). A UK government review of the environmental impact of inhalers is ongoing. In May 2018, the UK's Environmental Audit Committee recommended that the NHS should set a target that by 2022 at least 50 percent of prescribed inhalers are low-GWP inhalers, but no specific action has been taken by the UK Government [54]. The Public Health England Sustainable Development Unit (SDU) is consulting stakeholders, including clinicians, specialists and pharmaceutical and product manufacturers, to evaluate the potential for increasing the proportion of low-GWP inhalers prescribed in the UK, taking account of the clinical and

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[50] Kirenga, B.J., et al., *Thorax*, 2018, **73**, 983-985.

[51] De Marco, et al., *Resp. Res.*, 2005, **6**, 95.

[52] Comaru, T., et al., *Respir. Med.*, 2016, **121**, 21-25.

[53] Creagh, M., Clark, C., Coffey, T., et al., UK Progress on reducing F-gas Emissions. House of Commons Environmental Audit Committee, 2018. https://publications.parliament.uk/pa/cm201719/cmselect/cmenvaud/469/469.pdf.

[54] The Environmental Audit Committee published its Fifth Report of Session 2017–19, *UK Progress on reducing F-gas Emissions* (HC 469) on 25 April 2018. The Government's response was received on 25 July 2018. https://publications.parliament.uk/pa/cm201719/cmselect/cmenvaud/1406/140602.htm.

economic implications and environmental benefits. The SDU is also working with the UK's National Institute for Health and Care Excellence (NICE) to provide information about the relative environmental impacts of inhalers to patients and healthcare professionals, enabling an informed choice. In 2017, the British Thoracic Society recommended that prescribers and patients "consider switching pMDIs to non-propellant devices whenever they are likely to be equally effective"[55].

A recent study estimated the total carbon footprint of MDIs prescribed in the community in England in 2017 to be 593 $ktCO_2$-eq. For every 10 percent of MDIs changed to low-GWP inhalers, about 55 $ktCO_2$-eq could be saved annually[56].

Most new drugs are becoming available in the UK as DPIs. A total of 43 different brands of inhalers of all types are listed in the British National Formulary, of which 26 are DPI and 17 MDI. Currently, 93 percent of prescriptions for long acting bronchodilator therapies (containing long acting anti-muscarinic or beta agonist or combinations) are in DPIs[57]. In contrast, 94 percent of short-acting beta-agonist (salbutamol for rescue) prescriptions are for MDIs. This can lead to a confusing mixture of inhalation techniques for patients. COPD patients, whose inhaler devices use the same inhalation technique, show better clinical outcomes than those prescribed devices requiring different techniques.[58].

A survey of inhaler users in the UK found that the most important factor when choosing a new inhaler was ease of use, but most respondents rated carbon footprint as being equally important as financial cost[59]. Changing an MDI preventer device to a DPI preventer could save 150 kg to 400 kg CO_2-eq each month, making it a "medium impact" personal action roughly equivalent to installing wall insulation, recycling, minimising food waste or hang-drying clothes[60].

Inhaler recycling has the potential to reduce the environmental impact of inhalers. One such scheme operates in the UK and captures HFC gases left in inhalers, before recycling them for use in other industries or destroying the gases in an environmentally friendly manner[61]. However,

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[55] British Thoracic Society, United Kingdom, The Environment and Lung Health Position Statement, 2017. https://www.brit-thoracic.org.uk/document-library/audit-and-quality-improvement/environment-and-lung-health/the-environment-and-lung-health.

[56] Wilkinson, A., Braggins, R., Smith, J., Steinback, I., The Costs of switching to low global-warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England. *Submitted for publication.*

[57] NHS Business Services Authority, United Kingdom. https://www.nhsbsa.nhs.uk/sites/default/files/2017-10/PCA Aug 17.xlsx. Cited in: Wilkinson, A., Braggins, R., Smith, J., Steinback, I., The Costs of switching to low global-warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England. *Submitted for publication.*

[58] Bosnic-Anticevich, S., Chrystyn, H., Costello, R.W., et al., The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes, *Int. J. Chron. Obstruct. Pulmon. Dis.*, 2017, **12**, 59–71.

[59] Liew, K.L., Wilkinson, A., How do we choose inhalers? Patient and physician perspectives on environmental, financial and ease-of-use factors, *Thorax*, 2017, **72**, A235 LP-A237.

[60] Wynes, S., Nicholas, K.A., The climate mitigation gap: education and government recommendations miss the most effective individual actions, *Environ. Res. Lett.*, 2017, **12**, 1–9.

[61] GSK, Complete the cycle – how we're recycling inhalers, 25th April 2018. https://www.gsk.com/en-gb/behind-the-

only a very small proportion of inhalers are currently recycled, so the overall impact of inhaler recycling on the release of its gases is currently minimal. The UK Government recognized that more should be done to encourage inhaler recycling and opened a dialogue with industry to investigate how recycling rates can be improved[62]. HFC MDI manufacturers are actively exploring ways to increase inhaler recycling rates.

2.5.9 United States

The US inhaler market is valued at around $24 billion. This is two thirds of the total world expenditure on inhaled therapies. There is a complete range of inhaled therapies with MDIs predominating overall, but DPIs constituting the majority for controller therapies (ICS and LABA/ICS).

The first salbutamol multi-dose DPI (ProAir Respiclick, Teva) has been launched. In November 2018, the FDA approved the application for an epinephrine suspension HFC-MDI for rescue use in asthma (Primatene MIST), which will be available OTC (over the counter without prescription) from early 2019. The same brand containing the same active ingredient in a CFC MDI had been withdrawn in 2011.

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science/how-we-do-business/complete-the-cycle-how-we-re-recycling-inhalers/. Accessed December 2018.

[62] The Environmental Audit Committee published its Fifth Report of Session 2017–19, *UK Progress on reducing F-gas Emissions* (HC 469) on 25 April 2018. The Government's response was received on 25 July 2018. https://publications.parliament.uk/pa/cm201719/cmselect/cmenvaud/1406/140602.htm.

3 Aerosols

3.1 Aerosol products

Aerosols are used in a wide range of different applications. The term aerosol product describes a product *pressurized* with a propellant that expels its contents from a canister through a nozzle. Aerosols incorporate propellants and solvents with the appropriate technical properties and characteristics in formulations designed to deliver a product for its intended purpose.

Propellants include compressed gases (nitrogen, nitrous oxide, carbon dioxide), or liquefied gases, which are liquid inside the pressurized container; these liquefied gas propellants include chlorofluorocarbons (CFCs) (no longer used), hydrochlorofluorocarbons (HCFCs e.g. HCFC-22) and hydrofluorocarbons (HFCs) (e.g. HFC-134a, HFC-152a), hydrofluoroolefins (HFO, e.g. HFO-1234ze(E)), hydrocarbons, and dimethyl ether (DME).

Some aerosol products also contain solvents, including HCFCs, HFCs, hydrofluoroethers, aliphatic and aromatic solvents, chlorinated solvents, esters, ethers, alcohols, ketones, and hydrochlorofluoroolefins (HCFO, e.g. HCFO-1233zd(E)). The use of CFC solvents has been phased out of aerosol use. HCFCs, including HCFC-141b, are still currently used and are being replaced by HFCs, HFEs and HCFOs, which are further discussed in the Solvents Chapter.

Aerosols can be divided into categories:

- Consumer aerosols, including personal care products like deodorants and hair sprays, cleaning products, air fresheners, furniture and textile care, household pesticides;
- Technical aerosols, including automotive and industrial, lubricant sprays, dusters, contact cleaners, safety horns, degreasers, mould release agents, paints;
- Miscellaneous aerosols, including food, veterinary and convenience products; and
- Medical aerosols**,** including metered dose inhalers (MDIs) that are the major medical application for aerosol products. Medical aerosols also include aerosols that deliver treatment for other medical purposes e.g., nasal and topical aerosol sprays. These non-MDI medical aerosols are used to deliver topical medication mostly onto the skin, but also to the mouth, and other body cavities.

This chapter on aerosols addresses, specifically, consumer, technical and non-MDI medical aerosols, referring to them generically as aerosols. MDIs are described elsewhere in this report and are treated separately from the analysis of aerosols that follows (unless otherwise specified).[63]

Technically and economically feasible alternatives to ozone-depleting propellants and solvents (CFCs and HCFCs) are available for aerosol products. Small uses of HCFCs remain in a few countries (China and the Russian Federation) for specific medical aerosol products. A significant proportion of aerosol propellants have migrated to hydrocarbons and DME, which dominate in the consumer aerosol market. Hydrocarbons and DME are highly flammable propellants. They

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[63] The captions embedded within figures in this section refer to "non-MDI Aerosols", which also refers specifically to consumer, technical and non-MDI medical aerosols.

are also used in technical aerosols where flammable propellants can be used safely. Hydrocarbons and oxygenated hydrocarbons (such as DME) are volatile organic compounds (VOCs) that contribute to photochemical smog generation. In some jurisdictions, strict VOC controls (e.g., in California) can have an impact on the choice of propellant, where hydrocarbons are avoided. The use of compressed gases as propellants has increased as a result of these regulations and the availability of better cans.

A smaller proportion of aerosols migrated to HFC propellants where:

- Emissions of VOCs, such as hydrocarbons and DME, are controlled;
- A non-flammable propellant is needed; and/or
- A propellant is necessary that is safe to inhale, such as HFC-134a[64].

HFC-134a is used more commonly as a propellant in technical and non-MDI medical aerosols where its non-flammable and inhalation safety properties have advantages. Extensive respiratory toxicological studies were conducted that proved its safety as a propellant in respiratory use (e.g. MDIs).

HFC-152a is used more commonly as a propellant in consumer aerosols. HFC-152a has moderate flammability, and is used alone, or in blends with hydrocarbons to meet VOC regulations. HFC-152a is also blended with HFC-134a to produce a propellant with lower GWP (than HFC-134a) and lower flammability (than HFC-152a).

HFO-1234ze(E) is starting to be used as a propellant in technical and consumer aerosols where non-flammable and low-GWP properties are needed. HFO-1234ze is also used in jurisdictions that have VOC emission controls.

Ozone-depleting substances (ODS) solvents (CFC-113, methyl chloroform, HCFC-141b) used in aerosols have migrated to hydrofluorocarbons (HFC-43-10mee, -365mfc, -245fa), hydrofluoroethers (HFEs), aliphatic and aromatic solvents, chlorinated solvents, oxygenated organic chemicals, and low-GWP chemicals, such as hydrofluoroolefins and hydrochlorofluoroolefins, including methoxytridecafluoroheptene (MPHE) and HCFO-1233zd(E).

3.2 HCFC use in medical aerosols

Available information indicates that HCFC use in China for medical aerosols for Traditional Chinese Medicines could be about 2,000-2,500 tonnes HFCF-22 or HCFC-22/HCFC-141b blend (HCFC-22: 1,500-2,000 tonnes and HCFC-141b: 500 tonnes). HCFC-22 is used as propellant, and HCFC-141b is used for its solvent properties. Flammability safety concerns with some economically feasible alternatives, such as DME or LPG, are currently a barrier to their use in this application. Other potential technical alternatives, such as HFC-134a, currently present an economic impediment in this particular application.

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[64] In China, HCFC-22 is also used for some non-MDI medical aerosols.

In the Russian Federation, topical medical aerosol applications also use HCFC-22 and -141b as propellant and solvent, respectively, in quantities of around 20 tonnes per year. The products are aerosol foams used to provide local anti-inflammatory and antiseptic action, and to stimulate healing.

Regarding the use of HCFC-141b in topical medical aerosols, it is worth noting that the National Institute for Occupational Safety and Health (NIOSH) have presented the immediately dangerous to life or health (IDLH) air concentration value for HCFC-141b to be 1,700 ppm (8,245 mg/m^3). Cardiac sensitization is the most sensitive indicator of toxicity and of a potentially lethal and irreversible health endpoint that serves as the basis for the IDLH value for HCFC-141b).[65] HCFC-141b is also classified as a grade 1 health hazard by the US Hazardous Materials Identification System (HMIS). HMIS is a voluntary hazard rating scheme developed by American Coatings Association (ACA) to help employers comply with workplace labelling requirements of the U.S. Occupational Safety and Health Administration's (OSHA) revised Hazard Communication Standard. The National Fire Protection Association (NFPA) also lists HCFC-141b as a grade 2 health hazard, as an irritant particularly to eyes.

Further information on these aerosol products is provided below.

3.3 Aerosol market developments

HFOs are becoming increasingly available as low-GWP alternatives for aerosol applications that would otherwise use HFCs. HFO-1234ze(E) is commercially available in the United States for technical and some consumer aerosol applications. One propellant supplier in France is advocating a mixture of 90 percent HFO-1234ze(E) and 10 percent HFC-134a for use as propellant in aerosols, such as dusters and tyre sealant/re-inflators, as a less flammable blend than pure HFO-1234ze(E). Duster products that were previously manufactured in the United States with HFC-134a propellant are now being manufactured with HFO-1234ze(E). HFCO-1233zd(E) and MPHE isomers can be used as solvents for technical aerosols[66].

There are also not-in-kind (NIK) technologies that compete with aerosol products to perform the same or similar functions, including trigger sprays, finger pumps, squeeze bottles, roll-on liquid products (e.g., for deodorants), and non-sprayed products (e.g., for polishes and lubricating oils). NIK alternatives are sometimes not as easy to use or achieve lower performance for some applications.

Some alternative propellants and solvents are suitable for certain product types depending on the properties of the alternative and/or the intended product purpose. Some alternatives will not be technically suitable for some formulations. Like CFCs before them, non-flammable and non-toxic HFCs are often used in aerosols when flammability or toxicity is a consideration. HFCs, including HFC-152a, are also used where emissions of VOCs are controlled. However, HFCs are

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[65] National Institute for Occupational Safety and Health (NIOSH), United States, Immediately dangerous to life or health (IDLH) value profile: 1,1-di- chloro-1-fluoroethane (HCFC-141b). By Dotson GS, Maier A, Parker A, Haber L. Cincinnati, OH: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication 2016-168. DHHS (NIOSH) Publication No. 2016-168 September 2016.

[66] ICF International, *Preliminary Assessment of Global HFC Consumption in Aerosols*, September 2016. Draft report prepared for U.S. EPA, made available through personal communications.

more expensive than hydrocarbons and are therefore mostly used when their properties are necessary for the aerosol product and the advantages outweigh the costs.

3.4 Availability and market penetration of alternatives

Recent assessments have been presented of the technical and economic feasibility of the alternatives to ODS-containing aerosols in the Technology and Economic Assessment Panel (TEAP) Update XXV/5 Task Force Report September 2015[67] and TEAP XXVII/4 Task Force report September 2016[68]. A summary of new and relevant information follows.

3.4.1 Aerosol market profile

Global aerosol demand is currently estimated at more than 17 billion units (cans) per year. Personal care aerosol products accounted for the largest application, with over 50 percent of global market demand in 2017. Medical (non-MDI) aerosols represent only around 1 percent and technical aerosols, 10 percent of global production. Europe is the largest regional aerosol producer and market, with estimated production of over 5 billion units, accounting for about 33 percent of global production. North America is the second largest regional market, accounting for about 22 percent, and China for about 13 percent. All three have declined as a proportion of the supplier base over the period 2006-2017, with Latin American countries growing from 6 to 16 percent of the global share over the same timeframe. Both Latin America and China more than doubled production over this period.

Whilst the European Union’s aerosol market is the largest overall at 32 percent (Grandview research), its HFC consumption for aerosols is much smaller than in the United States, reflecting market variations in aerosol propellant and solvent choices based on the different industry and regulatory environments for HFCs and VOCs. For example, the European Aerosol Federation (FEA) has agreed to a voluntary industry production and import ban of HFC-152a, facilitated by the absence of HFC-152a production plants in Europe.

Forecasts differ as to the overall global growth of the aerosol market, ranging from 3.9 percent (Variant) to over 5.5 percent ("Global Aerosol Propellants Market 2017-2021")[69]. Some of the factors behind this growth include:

- Increasing demand from cosmetics and personal care applications. In part, this is due to the trend towards gender-specific products.
- Rising popularity of aerosol products in the food industry. These rarely if ever contain HFCs.
- A growing demand for styling agents in the haircare industry

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[67] Report of the UNEP Technology and Economic Assessment Panel, Decision XXV/5 Task Force Update Report, September 2015, pp.106-111.

[68] Report of the UNEP Technology and Economic Assessment Panel, Decision XXVII/4 Task Force Update Report: Further Information on Alternatives to Ozone Depleting Substances, September 2016.

[69] https://www.researchandmarkets.com/research/dw2nrm/global_aerosol. Accessed December 2018.

- The increasing adoption of the online retail media as a distribution channel by the major manufacturers, leading to an ease in the purchase of finished goods, aided by high discounts and price reductions offered by the online retailers

- Technological developments including airless dispensers and steel monobloc cans

Asia Pacific is expected to be the fastest growing regional market with a CAGR of 6.5 percent (Grandview) owing to its economic development, a growing demand for personal care and household products, and a less stringent regulatory environment.[70] However, price fluctuations of crude oil and natural gas affect the aerosol propellants market to a great extent. If oil prices were to rise, they will adversely affect the consumption of aerosol products where low cost drives demand.

3.4.2 Propellant Availability

The traditional aerosol propellants are widely available worldwide. There are some differences in price depending on whether they are locally produced or imported. Their prices are also affected by the transportation costs from the supplier to the filling plant. In most cases compressed gases and LPG mixtures are relatively inexpensive, except in some Article 5 Parties that consequently do not have significant aerosol production. HFCs and DME are more expensive propellants as they are chemically synthesized, and their transportation costs may be significant when they are exported, particularly in Article 5 Parties where movement of pressurized vessels in and out of customs might be complicated. Novel HFOs are being produced in the US in Geismar, Louisiana, and announcements of construction of a plant in China have been made. HFOs are substantially more expensive than HFCs, they are finding use in high-end-use applications in markets that do not accept the HFCs that they replace. HFO-1234ze(E) is classified as a non-flammable gas, but it can be ignited under severe circumstances, hence replacement of HFC-134a propellant by HFO-1234ze(E) does not depend solely on cost, but also on the performance of the final product.

3.4.3 New technologies

There is ongoing work to improve the delivery of aerosols that work with air (compressed gas) and even to develop propellant-free alternatives for aerosol products. These patented technologies seek to provide continuous dispensing, deliver pure product (which could not be a benefit as this can result in coarser sprays, because it is the vaporization of the liquid propellant that creates the fine mist consumers want in some products), and work at any angle. It is likely that these technologies will capture some market segments depending on price and characteristics of the final product.

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[70] *Research Report on Global and China Aerosol Industry, 2013-2017*, Research and Markets, 2013, http://www.researchandmarkets.com/reports/2546162/research_report_on_global_and_china_aerosol, accessed August 2016. British Aerosol Manufacturer’s Association, http://www.bama.co.uk/history, accessed August 2016. *Aerosol Products Industry Steadfast, Survey Reveals North American Production Reaches All-Time High*, Consumer Specialty Products Association’s (CSPA), 2015, http://www.cspa.org/aerosol-pressurized-products-survey-2014-release/, accessed August 2016, European Aerosol Federation (FEA), http://www.aerosol.org/about-aerosols/history-of-aerosols, accessed August 2016.

3.4.4 Regulatory developments

Regulatory controls for HFCs used as aerosol propellants and solvents are increasingly limiting and/or prohibiting their use where other suitable alternatives are available. Recent regulatory developments affecting HFC use in aerosol products are summarised below.

3.4.4.1 United States

Multiple states in the U.S. led by California are quickly developing regulations that will closely mirror Kigali as well as the Paris Climate Accord. Like VOC regulations, adoption by major states can have the effect of a national regulation as major consumer product companies find it cost prohibitive to produce products for a state or even regional market.

3.4.4.2 European Union

The EU has enacted the F-gas regulation, promulgated in 2006 and 2014, that specifically prohibits the use of materials with a GWP of above 150 in technical aerosols, from 2018 onwards, except where the aerosol is needed to meet national safety standards or for medical applications. The European aerosol industry voluntarily began transitioning away from HFCs under a Code of Practice adopted in 2002. The EU aerosol producers have been converting products in the effected category to HFOs and hydrocarbon-based products. Technical aerosols containing HFCs are subject to a ban under Swiss legislation. The HFCs are now only used in aerosols where there are no other safe, practical, economic, or environmentally acceptable alternatives available.

3.4.4.3 Canada

In April 2018, the government of Canada launched an HFC phase-down plan to limit HFC consumption by 85 percent by 2030, in line with the Kigali Amendment to the Montreal Protocol. Much of the regulation focuses on imports. There are product-specific controls. Aerosols after 2019 should use propellants with a GWP lower than 150. There are exceptions such as certain cleaning products for electronics and, with the approval of the Minister of Environment, exceptions will be granted, if:

- The product is necessary for health and safety or is critical for the good functioning of society; and

- There are no technically and economically feasible alternatives.

The Amendments will not prevent the use and sale of products manufactured or imported before the date of prohibition.

3.4.4.4 Japan

Japan implemented voluntary measures to reduce the use of HFCs in aerosols as early as the year 2000. In 2013, Japan enacted a law updating their existing fluorocarbon regulation. The objective of the new legislation is to reduce HFC emissions through measures that cover the total life cycle of fluorocarbons from manufacture through disposal. In 2007 there was a limitation of HFC-134a use to applications without safe, practical, environmentally acceptable alternatives.

3.5 HFC use in aerosols

A preliminary assessment of global HFC consumption in aerosols made by ICF for U.S. EPA[71] characterised global and regional market consumption of aerosols containing HFCs. Global HFC demand[72] in aerosols was estimated to be around 45,000 tonnes (~15,000 tonnes HFCs -134a; ~30,000 tonnes HFC-152a) in 2015. This corresponds to a warming impact from direct emissions of about 25,000 $ktCO_2$-eq. HFC propellant consumption for aerosol manufacture corresponds to direct emissions that are estimated to be about 3 percent of global total GWP-weighted emissions of HFCs[73]. HFC demand in aerosols is dominated by the North American market, which consumes about 85 percent of the global total. The Asia and Asia-Pacific region is the next most significant, consuming around 10 percent of global total of HFCs in aerosols. Production is expected to expand in Article 5 parties.

Consumer aerosols are the largest category (78 percent), with technical aerosols (20 percent), and non-MDI medical aerosols (2 percent) making up the remainder. The majority of consumer aerosols use HFC-152a propellant (85 percent) and the remainder HFC-134a. For technical aerosols, the majority use HFC-134a propellant (80 percent) and the remainder HFC-152a. The majority of non-MDI medical aerosols use HFC-134a propellant (85 percent). Figure 3.1 presents a comparison of the relative HFC demand for each aerosol category by weight, and Figure 3.2 presents the comparison by the relative warming impact of direct HFC emissions.

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[71] ICF International, *Preliminary Assessment of Global HFC Consumption in Aerosols*, September 2016. Draft report prepared for U.S. EPA, made available through personal communications.

[72] HFC demand is equivalent to HFCs used for aerosol production, adjusted for imports and exports of HFC aerosol products, where that information was available. Specific data on imports and exports of HFC-containing consumer aerosol products for the United States was not readily available, so consumption for these products is assumed to be equivalent to production, based on data from the then Consumer Specialty Products Association (CSPA), now known as the Household & Commercial Products Association (HCPA), the United States' industry trade association for chemical products companies.

[73] As derived from atmospheric observations, total emissions of HFCs summed to 0.88 (± 0.07) $GtCO_2$-eq/year in 2016, as taken from: World Meteorological Organization (WMO), *Executive Summary: Scientific Assessment of Ozone Depletion: 2018*, World Meteorological Organization, Global Ozone Research and Monitoring Project – Report No. 58, 67 pp., Geneva, Switzerland, 2018.

Figure 3.1 Relative HFC demand in aerosols, by category and weight, 2015

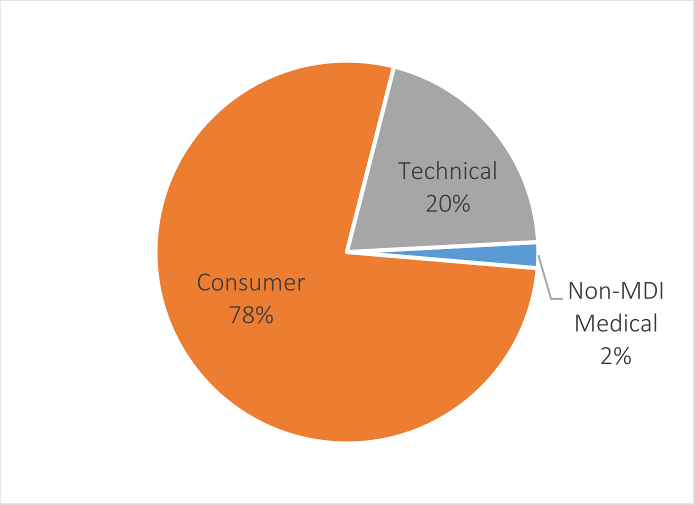
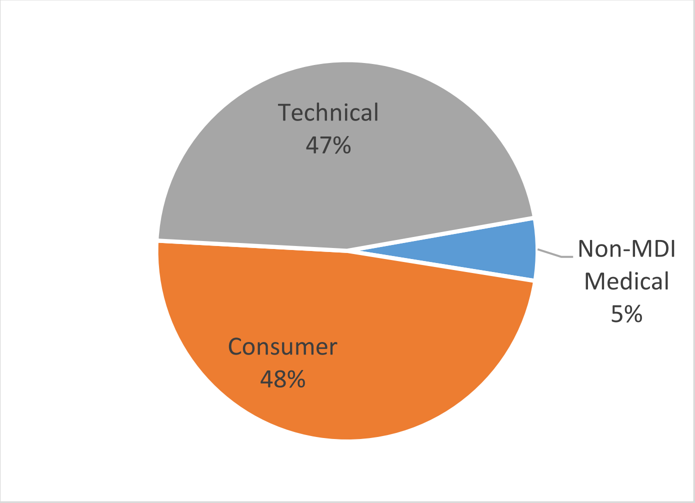


Figure 3.2 Relative warming impact from direct HFC emissions in aerosols, by category and GWP-weighted, 2015



In a recent TEAP report[74], a model was presented of projected HFC usage in aerosols from 2015 to 2050, based on certain key assumptions for a business-as-usual scenario. Due to differences between that model's assumptions and the current global regulatory environment, an updated business-as-usual scenario based on the previous model has not been included in this assessment. Based on a different set of business-as-usual assumptions, global HFC consumption in aerosols is now estimated to increase from a total of 45,000 tonnes in 2015 to 100,000 tonnes in 2050. In this scenario, over the period, HFC-134a usage in aerosols is estimated to decrease to 8,000 tonnes, while HFC-152a usage increases to more than 90,000 tonnes. For 2050, this would correspond to a warming impact from direct emissions of about 23,000 ktCO$_2$-eq, where the gains resulting

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[74] Report of the UNEP Technology and Economic Assessment Panel, Decision XXVII/4 Task Force Update Report: Further Information on Alternatives to Ozone Depleting Substances, September 2016.

from the reduction in HFC-134a usage are offset by the increase in HFC-152a usage. During the modelled period, the total cumulative HFC demand in aerosols is estimated to be around 2,600,000 tonnes (400,000 tonnes HFC-134a; 2,200,000 tonnes HFC-152a). This corresponds to cumulative direct emissions with a warming impact of approximately 840,000 ktCO$_2$-eq.

3.6 Minimising high-GWP aerosols

HFC use is limited, either owing to cost, safety or regulatory reasons, or to applications where VOC controls might limit hydrocarbon use, or where a propellant with low flammability and/or proven safety is needed. HFC consumption in this sector is ranked as the third largest after the refrigeration and air conditioning and foams sectors, where aerosols are a totally emissive use. There would be environment benefits in promoting low-GWP and climate-friendly alternatives and by avoiding high-GWP propellants and solvents. In many cases, HFC propellants and solvents can be substituted with low-GWP options, and NIK alternatives are commercially available where they are suited for the purpose.

The reformulation of aerosols to use alternative low-GWP propellants and solvents, or the development of NIK technologies as replacements, would incur costs to industry. It is technically feasible to replace HFC-134a used in consumer aerosols with alternatives. It also appears that it is technically feasible for technical aerosols to start to transition away from high-GWP HFCs based on the European Union’s 2018 prohibition, except perhaps where the aerosol is needed to meet national safety standards or for medical applications. However, it is possible that HFOs may be suitable as replacements for HFC-134a, although technical feasibility would need to be considered on a case-by-case basis. Despite the feasibility, there appears to be few products in development; most are for export outside of the European Union. The higher cost of HFOs might be an economic barrier to transition.

It is difficult to quantify the costs of conversion of high-GWP HFC-containing aerosol products to low-GWP and NIK alternatives. Costs may include reformulation, redesign, production re-engineering, safety, training and education, product testing, and consumer information, and will depend on the application, the market and its regulatory environment.

Parties may wish to consider the advantages of accounting for the use of HFCs in the aerosol sector. Given that aerosols are totally emissive, any action taken in this area would provide the faster returns and an understanding of the products and quantities involved. Detailed accounting by a country would help it determine the implications of any phase-down policies, including financial implications.

3.7 Aerosols in different countries

In the sections below, the current situation in the United States is discussed, given this market represents over 80 percent of HFC propellant use in aerosols today, with a small selection of other regions also discussed, including those that still use HCFCs.

3.7.1 United States

HFC use in aerosols in North America, which accounts for about 85 percent of usage globally, has shown a modest decline, as certain technical aerosols begin to convert slowly away from HFC-134a to HFO-1234ze(E).

HFC-152a, with its much lower GWP than HFC-134a, continues to be widely used as a propellant, often blended with hydrocarbons in personal care products. In addition to GWP, regulations to reduce volatile organic compounds or VOCs are the primary challenge for consumer product formulators in the U.S. HFC-152a remains a critical component in achieving ever lower VOC levels. HFO-1234ze(E) continues to gain traction, particularly in products that can command higher prices.

3.7.2 China

HCFC use in China for medical aerosols for Traditional Chinese Medicines could be about 2,000-2,500 tonnes (HCFC-22: 1,500-2,000 tonnes and HCFC-141b: 500 tonnes). Flammability safety concerns with some economically feasible alternatives, such as DME or LPG, are currently a barrier to their use in this application. Other potential technical alternatives, such as HFC-134a, currently present an economic impediment in this particular application. Around 500 tonnes HFC-134a is already used in other medical aerosols in China.

In 2016, China's aerosol production reached 2.2 billion cans. The main aerosol products in the China market are insecticide aerosols (17 percent), automotive and industrial (including construction) aerosols (30 percent), and paint aerosols (16 percent), using mainly LPG, DME or their mixtures. Compressed gases, HFC-134a and HFC-152a are used as aerosol propellants in personal care products, recreational (ribbons) and dust removing aerosols, which have a relatively smaller market share. Financial considerations are a key factor in the choice of propellant. Due to their higher cost, HFCs are currently less commonly used as propellants. However, with development of the economy in China, and improving living standards, environmental considerations are also now key factors in the choice of propellant.

Other than for MDIs, China banned the use of CFCs as aerosol propellants in 1997. Around the year 2000, China's state environmental protection administration established national standards for technical requirements for aerosols to protect the environment, with requirements for VOC content tightening the uses of LPG and DME as propellants. While personal care aerosol products currently hold a relatively smaller share on the domestic market (15 percent), their popularity is increasing. In 2013, the relative market share of personal care products was 9 percent of all aerosols whereas the market share had grown to 15 percent by 2016 and had doubled in absolute terms.

The industry is anticipating increasing use of HFCs in the short term. In the long term, compressed gases and HFOs are seen in China as the likely best candidates to replace HFCs, LPG and DME. There are their own challenges with these replacements. HFOs, such as HFO-1234ze(E) and HFO-1234yf, are currently expensive in China, although the use of HFO-1234ze(E) is emerging in some aerosols, including for novelty aerosols, duster products, and pet training aerosols. There can be technical challenges in formulating aerosol products to use compressed gases. Despite these challenges, "safe and green" propellants are seen as the future trend.[75]

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[75] You, Y. and Shao, Q., (eds.), *The Chinese Aerosol Industry, Products and Market,* Aerosol Europe Pub., Germany, 2018. Print.

3.4.2 Russian Federation

HCFCs are used by one company, located in Siberia, that produces oil of sea-buckthorn (hipopheae oleum) from local plantations and uses it in the manufacture of pharmaceutical medical preparations, including aerosols. The company consumes about 20 tonnes annually of HCFC-22 (as a propellant) and HCFC-141b (as a solvent) in the production of two very popular foam aerosol products: Olasol and Hyposol. The indications for use of Olasol are for wounds of any origin, rehabilitation period after skin transplantation, dermatitis, trophic ulcer, burns (including solar and thermal), skin infections, discomfort, itching etc.

Indications for use of the drug Hyposol H are for colpitis (nonspecific, trichomoniasis), vulvitis, erosion or condition after cervical diathermocoagulation, condition after removal of the uterus body; proctitis (erosive and radial), proctosigmoiditis, anal fissures, ulcerative colitis (distal and limited forms), Crohn's disease, rectal and perineal wounds, intraoperative diagnostics and prevention of intestinal anastomosis insufficiency in operations on the large intestine, inflammatory processes in the disconnected rectum in preparation for recovery operations, erosive and ulcerative lesions of the mucous membrane of the oral cavity and periodontal (acute, chronic), burns (II-III degree), in wounds (after radical excision of purulent focus).

3.4.3 United Kingdom

The United Kingdom is the largest producer of aerosol products within Europe. In the event of the United Kingdom leaving the European Union, it is understood that the UK Government still intends to follow the European F-gas regulations. In 2016, it is estimated that HFC-containing aerosols accounted for 5 percent of F-gas emissions in the UK, with HFC MDIs accounting for a further 6 percent. Refrigeration and air conditioning comprise the vast majority of HFC emissions, at nearly 80 percent. If F-gas regulations are fully implemented, and there is little change in MDI HFC consumption in the foreseeable future, then by 2032 aerosols (other than HFC MDIs) would account for only 1 percent of the anticipated annual F-gas emissions.

4 Sterilants

4.1 Background

The provision of good quality health services requires effective disinfection or sterilization of health care products to prevent transmission of infection. Sterilization, in particular, requires strict application of the principles of quality management to ensure validation of the selected process and implementation of effective routine control; reliable equipment; and knowledge of materials compatibility. Sterilization of medical devices can be performed in facilities ranging from industrial settings with large outputs of similar items (for example by manufacturers of sterile medical devices such as single-use syringes or specialist contractors offering a sterilization service to medical device manufacturers) and dissimilar items (such as procedure packs and kits), to smaller facilities including hospitals with much smaller outputs but great diversity of items. Process requirements for these two settings are similar but the types of sterilization processes used, and the challenges presented to assuring sterility, differ.

There is a range of commercially available sterilization methods including: heat (moist heat or dry heat), ionizing radiation (gamma ray, electron beam, x-ray), alkylating processes (such as ethylene oxide (EO), formaldehyde) and oxidative processes (including hydrogen peroxide gas, gas plasma systems, liquid or gaseous peracetic acid, and ozone). Further sterilization methods based on these and other chemical agents are under investigation for commercialization.

Sterilization using EO under controlled conditions is used to treat heat and moisture sensitive medical devices, which are packaged in breathable materials that maintain sterility once the product is removed from the sterilization chamber. EO can penetrate many types of packaging materials and internal areas of medical devices, inactivate micro-organisms and be removed from the product through the package. Following exposure, adequate aeration is essential after processing to achieve acceptable levels of residues. EO is toxic, mutagenic, carcinogenic, flammable and explosive, and stringent regulations are applied to protect the environment and ensure worker safety. Great efforts have been made to replace EO, particularly in hospitals where the potential for personnel exposure is of great concern. The fact that EO is still used as a sterilant, and its use grows in the industrial sector, is evidence that for numerous applications the benefits of its use outweigh these disadvantages.

EO can be used as a sterilant either alone or diluted with other gases to make non-flammable mixtures. A mixture of 12 percent by weight EO and 88 percent dichlorodifluoromethane (CFC-12) (12/88) was once widely used for this purpose. On an industrial scale, non-flammable mixtures can be created *in situ* within the sterilizer chamber using nitrogen. Non-flammable EO mixtures can be supplied for industrial or hospital use with carbon dioxide (CO_2) as a diluent. Hydrochlorofluorocarbons (HCFCs) were introduced as drop-in replacement for EO/CFC-12 mixtures but have been phased out in Europe and the United States; HCFC/EO may continue to be used in Article 5 Parties, but this also will be phased out over time. Hydrofluorocarbons (HFCs) were investigated as alternative replacement diluents but were not widely adopted for technical reasons and the environmental impact of the use of HFCs.

Some hospitals and other healthcare facilities continue to rely on EO sterilization and new sterilizers are used more efficiently than the previous EO/CFC units. Efficiency has increased in developed economies by centralising the provision of sterilization facilities, enabling use of a smaller number of sterilizers under controlled conditions and reducing sterilant consumption. Furthermore, improvements in validation practices have enabled the use of processes at lower EO concentrations, reducing sterilant usage, and decreasing levels of residues in products. It is common to use abatement equipment in conjunction with an EO sterilizer in order to reduce emissions to acceptable levels.

4.2 CFC and HCFC use for sterilization worldwide

The use of EO/CFC blends for sterilization has been successfully phased out in non-Article 5 Parties, and in most, if not all, Article 5 Parties, and only then from any remaining stockpile. Although it is difficult to be certain, global total use of CFCs for this application is believed to be zero.

EO/HCFC mixtures (10 percent by weight EO in a mix of HCFC-124 and HCFC-22) were virtual drop-in replacements for the 12/88 mixture using CFC and were introduced as transitional products for sterilization in those countries that employed 12/88 extensively. Estimated global use of HCFCs in sterilization is now considered less than 50 metric tonnes, which amounts to less than 2 ODP tonnes worldwide. EO/HCFC use has been significantly reduced by using less gas per sterilizer load, 100 percent ethylene oxide, and by hospital conversion to other technologies.

European Union regulations banned the use of HCFCs as carrier gas for sterilization in closed systems from 1 January 1998. In the United States, HCFC-22 production, import and export were restricted on 1 January 2010 and the HCFC-124 blend was phased out on 31 December 2014[76]. HCFC-22 cannot be produced or imported for uses other than servicing existing appliances as of 1 January 2010. Whilst there was an exception for the continued use of HCFC-22 as a sterilant when the HCFC was produced prior to 1 January 2010, this exception only applied until 31 December 2014. Excluding financial limitations, there is no reason for not converting sterilization equipment in hospitals. Medical device manufacturers that previously used EO/HCFC have converted to alternatives, with the major providers in the United States now using 100 percent EO-based processes.

The complete phase-out of HCFCs in sterilization uses is readily achievable in Article 5 Parties to meet the Montreal Protocol schedule. In addition, the useful lifetime of existing EO/HCFC sterilizers is about 20 years when well maintained. Therefore, by 2030 at the latest, any remaining sterilizers should be ready for replacement with available alternative technologies that do not use ozone-depleting substances. Hospital procurement should take the HCFC phase-out, and the coming redundancy of EO/HCFC sterilization equipment, into consideration in making future investment decisions.

HFC mixtures (10.4 percent by weight EO in a mix of HFC-125 and HFC-227) used in existing sterilization equipment with modified process controls were initially tested in the United States. Technical problems were identified that would require re-engineering, and potentially new equipment, in addition to validation of the new process. The technical problems include: higher vapour pressure mixes requiring higher pressure feed lines and ancillary equipment; tendency of the mix to separate; and, for users that recover fluorocarbons, more complicated, less efficient operation unless the entire recovery system re-engineered and rebuilt. New HFC blends have not been broadly adopted or used worldwide, although some sterilization service providers in Asia

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[76] U.S. EPA, United States, Protection of Stratospheric Ozone: Adjustments to the Allowance System for Controlling HCFC Production, Import, and Export; Final Rule, Federal Register, Volume 74, No. 239, December 15, 2009 (74 FR 66445-66446).

continue to explore the potential application. In the European Union, there are restrictions on certain uses of HFCs, for example as refrigerants. The use of HFCs in sterilizing equipment is not explicitly excluded. One company in Poland supplies EO/HFC-134a (5.6 percent by weight EO and 94.4 percent HFC-134a) for use in hospital sterilizers[77]. EO/HFC blends have also been investigated to replace EO/methyl bromide blends to fumigate, *inter alia*, archives and antiquities[78].

4.3 Available options for replacing ozone-depleting substances

Methods for sterilization of medical devices developed differently in each country due to the respective regulations on fire protection and occupational safety; requirements on process validation; liability considerations; availability of sterilization equipment and materials; and, medical practices. Over time, these differences have become less due to international standardization and harmonization.

An effective infection control strategy requires the availability of sterile medical devices. Validation of sterilization processes is important to ensure product safety and functionality including the attainment of sterility, lack of toxicity, and avoidance of material compatibility problems. No single sterilant or sterilization process is compatible with the range of potential products, be they designed for single-use or designed to be reprocessed in healthcare facilities and used multiple times. The nature and complexity of items and loads to be sterilized will vary according to the user requirements. Some items are more robust than others with regard to pressure, temperature, moisture and radiation. Therefore, a number of different processes are available for use and each will offer specific advantages depending on the need.

Opportunities and technologies that can be considered to avoid processes using ozone-depleting EO/HCFC blends include: use of heat-sterilizable devices, use of single-use devices, use of 100 percent EO sterilization processes, and a range of other methods that will sterilize most of the heat sensitive medical devices used in healthcare or industrial settings. Alternative low temperature processes for disinfection and particularly sterilization that have been commercialised include hydrogen peroxide gas (used with or without the generation of plasma during the process), humidified ozone gas, nitrogen dioxide gas, liquid phase peracetic acid formulation and low temperature steam-formaldehyde processes. Other low temperature methods have been reported but have yet to be widely deployed.

A summary of alternatives to reduce or phase out the use of ozone-depleting substances (ODS) follows. A number of processes and systems have been described or are under development, but the examples described herein do not represent an exhaustive list of such developments. This

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[77] http://www.sterylgaz.com.pl/en/main.php?k0=PRODUCTS&k1=GS-1z. Accessed April 2018.

[78] Methyl bromide or mixtures of methyl bromide and EO are used for de-infestation of historical artefacts, archives and antiquities. Methyl bromide is also an ODS and its use is controlled under the Montreal Protocol. Blends of HFCs and EO have been validated to replace methyl bromide and EO fumigation blends. There is also a range of other alternatives that can be suitable for these fumigation uses depending on the infestation, including: nitrogen (insects); carbon dioxide (insects); sulfuryldifluoride (insects); heat (fungi); irradiation (fungi). There may be rare occasions where no alternative to methyl bromide is appropriate.

summary updates information included in the 2014 *Assessment Report of the Medical Technical Options Committee*[79].

4.3.1 Heat

Dry heat – This process is non-toxic, economical and relatively safe. Devices must be able to tolerate exposure to a temperature greater than 160ºC in order to use the process.

Moist heat (e.g. steam) – This process is non-toxic and relatively safe. Pressurized steam is a particularly effective and well-used sterilization method. Available sterilizing equipment ranges from small self-contained bench-top sterilizers to large installations requiring supporting utilities. Devices must be able to tolerate a temperature greater than 115ºC, very high moisture levels and changes in pressure in order to use the process.

4.3.2 Radiation

Ionising radiation – Ionising radiations (gamma rays, accelerated electrons, x-rays) are widely used for sterilization, but only in large, industrial facilities; governments operate these facilities in some Article 5 Parties. Operation of ionising radiation facilities is not generally appropriate for hospitals or centralised sterilization facilities supplying hospitals due to complexity, costs and safety implications. Not all materials are compatible with radiation. *Gamma radiation* and *electron beam* are well established. Facilities using gamma radiation need to dispose of spent isotopes used as radiation sources. Systems using low energy electron beams have been introduced for in-line treatment of certain materials such as those being introduced into the aseptic processing of pharmaceuticals, thereby reducing the need for treatment with gaseous sterilants. A small number of facilities using *x-ray* sterilization equipment are operated commercially.

Ultraviolet (UV) radiation and intense pulsed light – UV radiation has been widely employed for disinfection of water systems and air. The lack of penetration and shadowing effect limit the application to exposed surface treatment. Specialised industrial applications for sterilization of particular medical devices have been developed and small-scale units for specific applications have been commercialised. Intense pulsed light, including a significant element in the UV range of the spectrum, has also been investigated for specific industrial sterilization applications.

4.3.3 Alkylating agents

100 percent EO – Despite being a flammable and hazardous gas, 100 percent EO can be effectively used when proper safety requirements are met (such as installation requirements, ventilation, personal protection equipment, etc.). Equipment ranges from large industrial sterilizers to small sterilizers used in healthcare facilities. On an industrial scale, the use of deep vacuum cycles and/or nitrogen may also be used or added to the sterilizer chamber during the sterilization process to render the process non-flammable. 100 percent EO processes typically operate at sub-atmospheric pressures to ensure adequate penetration of EO. The increased safety measures employed when using 100 percent EO, and updated technologies to limit worker exposure and environmental issues, have been major factors in the increased use and resurgence of pure EO in the industrial marketplace.

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[79] 2014 Report of the UNEP Medical Technical Options Committee, 2014 Assessment Report.

Blends of EO and CO_2 – Carbon dioxide (CO_2) is used to produce flammable and non-flammable mixtures with EO. Those containing more than 8.5 percent by weight EO are flammable. In the past, EO/CO_2 mixes were generally not used to replace other non-flammable mixes, but more recently, due to the declining use of other EO blends, there is a renewed interest in considering CO_2 blends. Sterilant container pressures are about ten times higher than for 12/88 EO/CFC mixtures, and chamber pressures are about three times higher. Additionally, processes include phases operating both below atmospheric pressure (to ensure penetration of EO) and pressure in excess of 3 atmospheres (to achieve the required EO concentration[80]). Use of EO/CO_2 blends has other disadvantages, such as composition changes during the use of a single tank or cylinder, potential for increased EO polymerization, and compatibility and corrosion problems caused by the acidity of CO_2.

Aldehydes – Formaldehyde, in combination with steam at sub-atmospheric pressure, is used mainly in northern Europe, China and parts of South America for materials that are able to withstand temperatures of up to 80-85ºC and high levels of moisture, although uses at 60-65ºC have also been reported. Sterilization processes include humidification, formaldehyde exposure and aeration. Formaldehyde is toxic and a suspected carcinogen, and this technology has not been widely accepted in many countries due to these concerns. Other aldehydes, such as glutaraldehyde and ortho-phthalaldehyde (OPA), are widely used for high level disinfection purposes, but the use of these is also decreasing due to concerns with operator safety and bacterial resistance.

Oxidising agents

Hydrogen peroxide vapour – Sterilization processes based on hydrogen peroxide vapour are commercially available. These are vacuum-based processes that use hydrogen peroxide for sterilization. Some of these systems use plasma generation during the process for the removal of residual gas/liquid from the load. Low energy plasma may also be used for heating or vaporization purposes, depending on the specific sterilizer design. A wide variety of sterilization processes are in commercial use with many sterilizers sold worldwide, mostly to healthcare facilities, and these systems continue to be used extensively. They offer shorter cycle times in comparison to traditional EO systems, depending on the sterilization cycle design.

Liquid peracetic acid – Available equipment uses cassettes in which items to be sterilized (e.g. endoscopes) are placed. The cassette is designed to provide a chamber for exposure to a peracetic acid containing solution (with dedicated flow to internal components) for sterilization, followed by rinsing with sterile (or extensively treated) water, followed by draining. Sterilized items are not, to date, packaged for storage. It is recommended that they be used immediately after removal from the cassette in order to ensure safety at point of use. Gaseous peracetic acid systems have also been described.

Low temperature plasmas – a variety of methods of surface treatment with plasmas generated from different gases/combinations of gases have been investigated for their antimicrobial effectiveness. Examples of systems under investigation that use plasma directly for sterilization are nitrogen and nitrogen/oxygen gas plasma. Systems using low temperature plasma are under development for in-line treatment of certain materials being introduced into the aseptic processing of pharmaceuticals. None have yet reached commercial application.

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[80] These are also necessary for blends of EO/HCFCs, and blends of EO/HFCs.

Ozone – One process operating at less than 30°C has become recently available for use in hospitals, but, to date, has had limited commercial success. Ozone is generated within the sterilizer from an oxygen source. The humidified process must be carefully controlled to ensure effectiveness, and it can also have the potential to affect surface materials.

Peracetic acid/gas plasma – A process was commercialised but was unfortunately associated with patient injuries when ophthalmic surgical instruments sterilized with this system were used. The process had not received US FDA approval for this specific application and a global recall was mandated. No further processes or equipment have been deployed.

Chlorine dioxide – A system for sterilizing medical devices using humidified chlorine dioxide was initially developed and patented but was not successful commercially. Chlorine dioxide is generated *in situ*, for example from sodium chlorite and chlorine gas in a nitrogen carrier. Gaseous chlorine dioxide is drawn into an evacuated chamber to achieve the required concentration at the appropriate temperature and relative humidity.

Nitrogen dioxide gas – A USA-based sterilisation equipment supplier has developed a nitrogen dioxide (NO_2) gas sterilisation process. NO_2 sterilisation is performed on products in primary packaging, prior to final packaging in boxes. Product is aerated as part of the exposure cycle, which is typically between 60 and 90 minutes in duration. Some medical device polymers are incompatible with the NO_2 sterilisation process including polyurethanes, nylon and polyacetal. Cellulosic materials such as paper and cardboard are also incompatible.

Combination processes – Combinations of oxidising agents such as hydrogen peroxide and ozone or nitric oxide and nitrogen dioxide in combination have been investigated and developed but have had limited commercial success to date.

Supercritical carbon dioxide – Carbon dioxide in a supercritical state[81] has been reported as having activity against vegetative micro-organisms. However, it has little activity against bacterial spores without further chemical additives in the process, thus limiting its application as a sterilizing agent. No processes or equipment have reached commercial application at this time.

4.4 Conclusions

Sterilization is an important process in the provision of good quality healthcare services. It is also a process that requires strict application of the principles of quality management, reliability and long-term materials compatibility. Therefore, any alternative to the use of ozone-depleting substances needs to be well proven and tested to avoid putting the health of patients unnecessarily at risk. It is legal requirement in pharmaceutical and medical devices industries that any change in manufacturing processes, including sterilization, must be validated using appropriate guidelines before implementation.

CFC-12 use in the sterilization sector has been phased out in non-Article 5 Parties, and in most, if not all, Article 5 Parties, and only then from any remaining stockpile. EO/HCFC blends have small ozone depletion potentials (ODP) (0.03) and have been used as virtual drop-in replacements for EO/CFC blends. There are a number of viable ODS-free alternatives, based on high or low

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[81] Carbon dioxide in a supercritical state is where the liquid and vapour phases become indistinguishable and is formed at temperatures around 32˚C and pressures above 74 atmospheres.

temperature technologies. Many of these alternative technologies provided significant advances, such as better safety profiles and turn-around times, and reduced cost per cycle. The complete phase-out of HCFCs in sterilization uses to meet the Montreal Protocol schedule is readily achievable.

5 Feedstocks

5.1 Use of ozone-depleting substances for chemical feedstock

Ozone-depleting substances (ODS) feedstocks are chemical building blocks that allow the cost-effective commercial synthesis of other chemicals. The use of ODS as feedstocks, including carbon tetrachloride (CTC), 1,1,1-trichloroethane (TCA) (also referred to as methyl chloroform), chlorofluorocarbons (CFCs), hydrochlorofluorocarbons (HCFCs), allows incorporation of chlorine and fluorine atoms into molecule structures. The resulting products, such as refrigerants, blowing agents, solvents, polymers, pharmaceuticals and agricultural chemicals, find important uses that benefit society.

Feedstocks are carefully selected for specific uses to provide the most technologically and economically viable routes available to the final products. Such choices of manufacturing routes involve large initial capital investments over US$100 million, not including the required and supporting infrastructure. Properly designed chemical manufacturing facilities can operate for as long as 50 years, when properly maintained and upgraded.

As raw materials, ODS feedstocks are converted to other products, except for *de minimus* residues and emissions of unconverted raw material. Emissions from the use of ODS feedstock consist of residual levels in the ultimate products, and fugitive leaks in the production, storage and/or transport processes. Significant investments and effort are spent to handle ODS feedstocks in a responsible, environmentally sensitive manner and, in most countries, are regulated through national pollution control measures.

The Montreal Protocol specifies those ODS that are controlled substances, including those that are also used for chemical feedstock, according to Article 1, clause 4, which states: " *"Controlled substance" means a substance in Annex A, Annex B, Annex C or Annex E to this Protocol, whether existing alone or in a mixture. It includes the isomers of any such substance, except as specified in the relevant Annex, but excludes any controlled substance or mixture which is in a manufactured product other than a container used for the transportation or storage of that substance.*"

The definition of production under the Montreal Protocol excludes the amount of controlled substances used as feedstock, according to Article 1, clause 5: "*Production means the amount of controlled substances produced, minus the amount destroyed by technologies to be approved by the Parties and minus the amount entirely used as feedstock in the manufacture of other chemicals. The amount recycled and reused is not to be considered as Production.*"

The guidance and requirements for feedstock were further elaborated in Decision VII/30:

"*…the amount of controlled substances produced and exported for the purpose of being entirely used as feedstock in the manufacture of other chemicals in importing countries should not be the subject of the calculation of "production" or "consumption" in exporting countries. Importers shall, prior to export, provide exporters with a commitment that the controlled substances imported shall be used for this purpose. In addition, importing countries shall report to the Secretariat on the volumes of controlled substances imported for these purposes*"; and,

"*… the amount of controlled substances entirely used as feedstock in the manufacture of other chemicals should not be the subject of calculation of "consumption" in importing countries.*"

5.2 How the ODS feedstocks are used

ODS feedstocks are fed directly into a manufacturing process as a raw material stream or as an intermediate in the synthesis of another product. Emissive losses can occur during production, storage, transport, if it is necessary, and transfers between production facilities. Intermediates are normally stored and used at the same site thereby reducing fugitive leaks. Economic considerations mean that considerable efforts are made to minimize such losses.

Table 5.1 shows common feedstock applications, although the list is not exhaustive. Parties report amounts of ODS used as feedstock to the Ozone Secretariat, but they do not report how they are used. Processes are proprietary and there is no official source to define the manufacturing routes followed and their efficacy. The table provides some examples and is the product of the collective experience and knowledge of Medical and Chemical Technical Options Committee (MCTOC) members. Products included are both intermediates as well as final products, including fluoropolymers.

Table 5.1 Common feedstock applications of ozone-depleting substances (this list is not exhaustive)

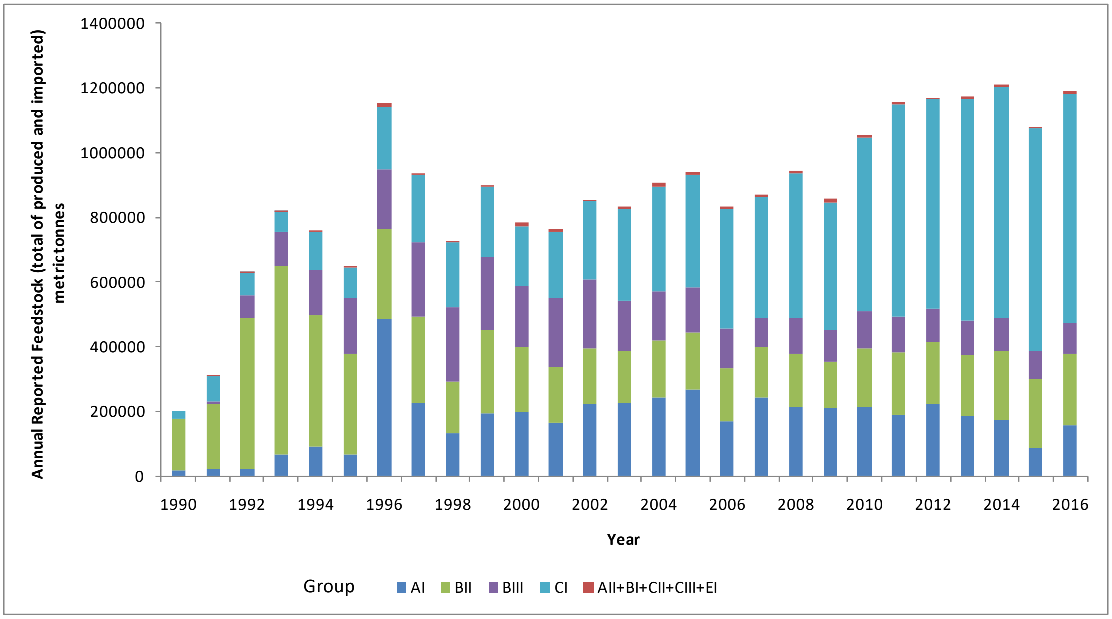
Feedstock ODS	**Product**	**Further conversion**	**Comments**
CFC-113	Chlorotrifluoroethylene	Chlorotrifluoroethylene based polymers	Polymers include poly-chlorotrifluoroethylene (PCTFE), and poly-fluoroethylenevinyl ether (PFEVE).
CFC-113, CFC-113a	Trifluoroacetic acid and pesticides	HFO-1336mzz	Production processes in China and India. CFC-113a is as an intermediate in this process.
CFC-113, CFC-113a	HFC-134a and HFC-125		High-volume use. The sequence for production of this refrigerant may begin with CFC-113, which is converted to CFC-113a and then to CFC-114a.
CFC-114, -114a	HFC-134a		The sequence for production of this refrigerant gas may begin with CFC-113, which is converted to CFC-113a and then to CFC-114a.
CTC	CFC-11 and CFC-12		Production and consumption of these CFCs have fallen to zero based on recent data.
CTC	Perchloroethylene		High volume use.
CTC	Chlorocarbons	Feedstocks for production of HFCs, such as HFC-245fa, HFC-365mfc, HFC-236fa	
CTC	Chlorocarbons	Feedstock for production of HFOs and HCFOs, such as HFO-1234yf, HCFO-1233zd	HFOs are low-GWP fluorocarbons used in refrigeration, air conditioning and insulation.
CTC	Intermediates (DVAC)	Pyrethroid pesticides.	CCl_3 groups in molecules of intermediates become $=CCl_2$ groups in pyrethroids.
1,1,1-trichloroethane	HCFC-141b, -142b, and HFC-143a		Note that an alternative feedstock is 1,1-dichloroethylene (vinylidene chloride), which is not an ODS.
HCFC-21	HCFC-225		Product used as solvent.
HCFC-22	Tetrafluoroethylene	Polymerized to homopolymer (PTFE) and also co-polymers	Very high-volume use. Work has been done for decades to find an alternative commercial route, without success.
HCFC-123	HFC-125		
HCFC-123, HCFC-133a and Halon-1301	Production of pharmaceuticals, TFA and agrochemicals		
HCFC-124	HFC-125		
HCFC-141b	HFC-143a		
HCFC-142b	Vinylidene fluoride	Polymerized to poly-vinylidene fluoride or co-polymers.	Products are fluorinated elastomers and a fluororesin.
HCFC-225		HFO-1234yf	

5.3 Recent and Historical Trends in ODS feedstock uses

Data have been provided to the MCTOC by the Ozone Secretariat on production, import and export of ODS used as feedstock for the year 2016. These also include quantities used as process agents because parties are required to report such consumption in a manner consistent to that for feedstock. For 2016, a total of 17 parties reported use of ODS as feedstock, while 12 of these parties were also producers of ODS for these uses. In 2015, 17 parties also reported use of ODS as feedstock.

In 2016, total ODS production for feedstock uses was 1,189,536 tonnes (2015: 1,084,101 tonnes), representing a total of 438,712 ODP tonnes (2015: 375,488 ODP tonnes). Use of ODS as feedstock grew significantly between 1990 and 2011, although not at a uniform rate (see Figure 5.1). Since 2011, use has been roughly constant, fluctuating around a mean total of 1,116,000 (±44,000) tonnes per year.

Figure 5.1 Annual use of ODS for feedstock, categorised by Montreal Protocol Group[82]



The largest feedstock uses currently are HCFC-22 (45 percent of the total mass quantity), CTC (19 percent), and HCFC-142b (11 percent). The quantity of HCFCs, in total, used as feedstock has been growing since the record began in 1990, mainly as a consequence in the growth of fluoropolymers. HCFC-22 is used to produce tetrafluoroethylene (TFE), which can be both homo- and co-polymerized to make stable, chemically resistant fluoropolymers with many applications. Polyvinylidene fluoride is made from HCFC-142b. The growth in fluoropolymers can be expected to continue for the near future, offset to a small extent by reduced demand for

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[82] Annex AI CFCs -11, -12, -113, -114, -115; Annex BII carbon tetrachloride; Annex BIII 1,1,1 trichloroethane; Annex CI HCFCs. Annex AII Halons -1211, -1301, -2402; Annex BI CFCs -13, -111, -112, -211, -212, -213, -214, -215, -216, -217; Annex CII HBFCs; Annex CIII bromochloromethane; and Annex EI methyl bromide.

HFCs with higher GWP, such as HFC-143a. Similarly, the increasing demand for HFCs with lower GWPs is thought to be responsible for the long-term reduction in use of 1,1,1-trichloroethane. CTC use is growing slowly; from a minimum in 2009, use is now growing at an average of 6,700 tonnes per year due to growing demand for low-GWP hydrofluoroolefins (HFOs) and perchloroethylene.

CFCs, mainly CFC-113, have shown a long-term decline in use. The reasons for this are complex – a reduction in the fluoropolymers produced from CFC-113 is possible, but unlikely in view of the increased demand for other fluoropolymers. However, changes in the production technology for HFCs can impact use of CFC-113, as can changes in the reporting of in-house production and inventories.

Table 5.2 Amount of ODS used as feedstock in 2016

Substance	ODP	Tonnes	ODP Tonnes[83]
HCFC-22	0.055	539,473	29,671
Carbon tetrachloride	1.1	221,554	243,709
HCFC-142b	0.065	129,692	8,431
CFC-113	0.8	104,122	83,297
1,1,1-trichloroethane (methyl chloroform)	0.1	93,036	9,304
CFC-114	1	51,755	51,755
HCFC-124	0.022	24,017	528
HCFC-141b	0.11	13,010	1,431
HCFC-123	0.02	4,822	96
Methyl bromide	0.6	4,248	2,549
Bromochloromethane	0.12	1,965	236
HCFC-133a	0.06	943	57
HALON-1301	10	753	7,535
HBFC-22B1	0.74	124	91
CFC-12	1	20	20
HBFC-31B1 (CH_2FBr)	0.73	3	2
Total		1,189,536	438,712

5.4 Estimated emissions of ODS

Emissions are not reported by parties, and the estimation of ODS emissions is also inexact. The sophistication of the operating facility can heavily influence emission levels. Highly automated, tight and well-instrumented facilities with proper, closely observed, procedures can have ODS emission levels as low as 0.05 percent of the ODS amount used as feedstock. At the other extreme, batch processes of limited scale with less tight facilities, with less concern for operational excellence, could have emission levels up to 5 percent of the ODS amount used as

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[83] While ODP tonnes are included, it should be noted that ODP is relevant to emissions. From the total amount of ODS used as feedstock, only an insignificant quantity will be released as emissions.

feedstock. For example, estimates of emissions from feedstock use of CTC throughout the world varied according to the scale of the processes and were 0.3 percent for perchloroethylene and HFC production, rising to 4.8 percent of the quantity used to make the pesticide intermediate DVAC[84]. The largest volumes of feedstock use are likely to be at the least emissive end of the scale because large capacity plants have the most investment and are better able to control emission levels. The higher emissions levels are based on industry input and anecdotal experience, with no citable references.

Data compiled by the European Environment Agency (EEA) from reports by companies under the European ODS Regulation show that 164,992 metric tonnes of ODS were produced for feedstock use within the EU in 2016[85]. Total emissions of feedstocks were quoted as 82 metric tonnes, an emission factor of 0.06 percent (compared to a revised estimate of 0.05 percent in 2015). The emissions are less than half of the quantities reported in the European Pollutant Release and Transfer Register[86] from chemicals manufacture, which totalled 180 metric tonnes in 2015 (20 carbon tetrachloride, 0 methyl chloroform, 39 CFCs and 121 HCFCs) but these include *all* emissions from *all* chemical manufacturers. Nevertheless, the relatively low rate of emissions achieved illustrates the effectiveness of local regulation and oversight, and industrial diligence, in the management and control of ODS emissions in feedstock uses.

For the purpose of compiling national greenhouse gas inventories, the Intergovernmental Panel on Climate Change (IPCC) recommends a default emissions factor for HFCs from their manufacture of 0.5 percent.[87] There is no similar international technical consensus for estimating ODS emissions associated with ODS feedstock uses, however, the chemicals, operational processes, and emissions abatement technologies involved are very similar and can be considered technically analogous to those for HFC production.

The IPCC guidelines recommend default emissions factors for greenhouse gases, which are considered to be maximal values. Actual emissions from feedstock uses may be lower at well managed facilities. Where available, actual emissions data is reported by developed countries in their submissions to the United Nations Framework Convention on Climate Change (UNFCCC), although this is not required of developing countries, nor is this required for any substances in Annexes A to E of the Montreal Protocol. Improved emissions factors could be achieved with improved UNFCCC guidelines or other accepted practices, based on the analysis of a broader collection of actual emissions data.

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[84] Sherry, D., McCulloch, A., Liang, Q., Reimann, S., and Newman, P. A., Current Sources of Carbon Tetrachloride (CCl_4) in our Atmosphere, *Environ. Res. Lett.*, 2018, **13**(2), 024004. https://doi.org/10.1088/1748-9326/aa9c87.

[85] Ozone-depleting substances 2016, Aggregated data reported by companies on the import, export, production, destruction, and feedstock and process agent use of ozone-depleting substances in the European Union, European Environment Agency Report No 12/2017, Luxembourg: Publications Office of the European Union, 2017, doi:10.2800/179166.

[86] European Pollutant Release and Transfer Register (E-PRTR), available at http://prtr.ec.europa.eu/, accessed February 2018.

[87] This can be found in the 2006 IPCC Guidelines for National Greenhouse Gases Inventories, Volume 3, Chapter 3.10, http://www.ipcc-nggip.iges.or.jp/public/2006gl/pdf/3_Volume3/V3_3_Ch3_Chemical_Industry.pdf, accessed March 2016. The Guidelines state, "*For Tier 1, in the absence of abatement measures, a default emission factor of 0.5 percent of production, not counting losses in transport and transfer of materials, is suggested for HFCs and PFCs, based on data supplied to AFEAS (2004).*"

Nevertheless, in order to generate some indicative estimations of ODS emissions, the IPCC emission factor of 0.5 percent for HFC production has been applied as a surrogate emission factor uniformly across all Groups. For guidance purposes only, estimated emissions associated with ODS feedstock and process agent uses in 2016 can be calculated as 5,948 tonnes, or 2,194 ODP tonnes.

5.5 How to minimize ODS feedstock emissions

Both regulators and producers can act to assure that emissions from feedstock uses of ODS are kept at minimal levels. In the European Union, the United States, China, and several other countries, all new operations are required to be licensed for operation. These licences usually define specific maximum emission limits, as well as the methodology to quantify them.

Producers can follow specifically defined responsible use practices, which, *inter alia*, define equipment to control processes, closed-loop loading and recovery, and thermal destruction of vapour emissions. When strictly followed, these responsible use practices can limit ODS emissions to about 0.1 percent of the ODS amount used as feedstock in continuous processes. Less responsible operation, and batch processes, can lead to emissions as high as 5 percent of feedstock quantities. Close cooperation between producers and regulators can continue to make these operations safe and environmentally sustainable.[88]

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[88] More information on requirements to minimise emissions from feedstock use can be found for example in European Chemicals Agency (ECHA) guidance on intermediates and the use of “Rigorous containment of the substance by technical means, supported by procedural and control technologies in place, used to minimise emissions and resulting exposure during the whole life cycle of the intermediate” see for example “How to assess whether a substance is used as an intermediate under strictly controlled conditions and how to report the information for the intermediate registration in IUCLID Practical Guide 16” at https://echa.europa.eu/view-article/-/journal_content/title/new-practical-guide-on-intermediates-launched, accessed March 2018.

6 Process Agents

6.1 What are process agents

Process agents have been characterised as controlled substances that, because of their unique chemical and/or physical properties, facilitate an intended chemical reaction and/or inhibit an unintended (undesired) chemical reaction.[89] Process agent uses can be differentiated from feedstock uses, where controlled substances undergo transformation in processes in which they are converted from their original compositions except for insignificant trace emissions as allowed by decision IV/12.

Parties have made a range of decisions relating to the use of controlled substances as process agents. Decisions were taken to clarify certain chemical process uses that were being confused with feedstock uses; some parties had interpreted the use of controlled substances in certain applications, where they were used as process agents, as feedstock applications, while other parties had interpreted similar applications as use and thereby subject to phase-out. The Technology and Economic Assessment Panel (TEAP) had also been unable to recommend production and consumption of controlled substances for these uses because they could not meet the essential use criteria established under decision IV/25.

Decision VI/10 sought to clarify the situation by instructing parties to treat chemical process agents in a manner similar to feedstock for a limited duration, and also requesting TEAP to identify uses of ozone-depleting substances (ODS) as chemical process agents, to estimate emissions, and to elaborate available alternatives.

Following further technical elaboration, decision X/14 clearly delineated that:

- the term “process agents” should be understood to mean the use of controlled substances for applications listed in Table A in that decision, and

- to treat process agents in a manner similar to feedstock, and not to include them in the calculation of production and consumption provided that emissions from these processes were reduced to insignificant levels, as defined by Table B in that decision.

Subsequent decisions updated Tables A and B with new information.

To qualify as a process agent use, TEAP’s Task Force on Process Agents used a working definition where the ODS in a specified process must meet at least two of the following technical criteria:

1. Chemical inertness during the process;
2. Physical properties, such as boiling point, vapour pressure, or specific solvency;
3. Action as a chain-transfer reagent in free radical reactions;
4. Control of product physical properties, such as molecular weight or viscosity;

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[89] Definition from the 1997 Report of the TEAP Task Force on Process Agents , as reproduced in the Report of the TEAP Task Force on Process Agents, October 2004, pg. 27.

5. Ability to increase yield;
6. Non-flammable/non-explosive; or
7. Minimisation of by-product formation.

Most of the process agent uses are long-standing processes, where the ODS are used as solvents to create unique yields, selectivity and/or resistance to harsh chemical environments, with the result that production is achieved with high efficiency. Legacy processes built around these properties make it difficult or impossible to convert to alternatives in a cost effective and timely manner, and only a few examples are known. In this regard, the process agent uses have much in common with feedstock uses, which are covered separately in this report.

6.2 Applications defined as process agent uses

The process agent uses first defined in Table A of decision X/14 included 25 applications of ODS, including carbon tetrachloride, trichlorotrifluoroethane (CFC-113), trichlorofluoromethane (CFC-11), and dichlorodifluoromethane (CFC-12), with total maximum emissions limits of about 200 tonnes for 4,500 tonnes of make-up or consumption. In subsequent decisions, Table A grew to more than 40 applications, adding halon 1011 (bromochloromethane, BCM) to the group of controlled substances used in these applications. Table B emissions reached a maximum of 511 tonnes in decision XXIII/7 in 2011. From 2010 onwards, Article 5 parties were included in the measures for process agent uses. By 2017, when Table A was last updated, the number of process agent applications had reduced to 11 across 4 parties (China, the European Union, Israel and the United States).

Almost all of the removals of process agents from Table A have resulted from plant closures, rather than substitution of other substances for the ODS process agent. Since 2014, three process agent applications have stopped:

- The production of chlorinated polypropene;
- The production of chlorinated ethylene vinyl acetate (CEVA);
- The production of methyl isocyanate derivatives.

Also, specific parties have indicated that the use of ODS as process agents has stopped in their country:

- Elimination of NCl_3 in chlor-alkali production in Colombia;
- Chlorine recovery by tail gas absorption in chlor-alkali production in Mexico and the European Union;
- Production of chloro-sulfonated polyolefin (CSM) in United States of America;
- Preparation of perfluoropolyether diols with high functionality in the European Union.

The list of process agent uses in Table A of decision XXIX/7 and the status of process agent uses, as reported by parties for 2016, are shown in Table 6.1 below.

Table 6.1 List of process agent uses of controlled substances in Table A, and status in parties reporting for 2016 [90]

No.	Process agent applications Decision XXIX/7 Table A	Substance	Permitted Parties Decision XXIX/7 Table A	Parties no longer requiring ODS for process agent application, as reported for 2016
1	Elimination of NCl_3 in chlor-alkali production	CTC	European Union, Israel, United States of America	
2	Chlorine recovery by tail gas absorption in chlor- alkali production	CTC	European Union, United States of America	European Union
3	Production of chlorinated rubber	CTC	European Union	
4	Production of chlorosulfonated polyolefin (CSM)	CTC	China	
5	Production of aramid polymer (PPTA)	CTC	European Union	
6	Production of synthetic fibre sheet	CFC-11	United States of America	
7	Photochemical synthesis of perfluoropolyetherpolyperoxide precursors of Z-perfluoropolyethers and difunctional derivatives	CFC-12	European Union	
8	Preparation of perfluoropolyether diols with high functionality	CFC-113	European Union	European Union
9	Production of cyclodime	CTC	European Union	
10	Bromination of a styrenic polymer	BCM	United States of America	
11	Production of high modulus polyethylene fibre	CFC-113	United States of America	

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[90] Table A was last updated in 2017 with Decision XXIX/7: Use of controlled substances as process agents. The table shows Dec. XXIX/7 Table A alongside the reported information received from Parties for the year 2016.

In considering the need to continue process agent use, Medical and Chemical Technical Options Committee (MCTOC) members are mindful that the lifetime of a chemical production plant could be as long as 50 years. If the product is important enough to warrant continued production, and the plant is maintained in good condition and not in need of renewal, then the large investment required to put into operation a new process that does not use ODS is unlikely to be justified.

While each of the process agent applications is unique, there exists a suite of measures that can be applied to minimize make-up/consumption and emissions and each one needs to be considered by an operator. These measures include limiting make-up/consumption to the essential minimum, ensuring tight systems (no leaking valves and joints); evacuation and purging with recovery, prior to opening equipment; closed-loop transfer systems; proximity of production and use of the ODS; monitoring sensors at potential leak locations to provide alerts for prompt repair; use of absorbents such as activated charcoal on vents; and destruction of vent gases.

6.3 Make-up and emissions

Table B defines the maximum quantities of make-up and emissions associated with process agents defined in Table A. The quantity of make-up is the quantity of controlled substance, per year, needed to continue the manufacture of products in a process agent use, owing to transformation, destruction and inadvertent losses (i.e. emissions and residual amounts in final product. Parties are requested to submit information to the Ozone Secretariat on quantities of make-up/consumption and emissions from applications for which process agent exemptions exist.

The maximum quantities of make-up and emissions in Table B of decision XXII/7, and the status of reported quantities as reported by parties for 2016, are shown in Table 6.2 below.

Table 6.3 presents an overview of the quantities of make-up or consumption reported by parties for 2009 to 2016. Table 6.4 presents an overview of the emissions reported by parties for 2009 to 2016.

Table 6.2 Maximum make-up and emissions for process agent uses in Table B, and as reported by parties for 2016 (in metric tonnes[91] per year)[92]

Party	**Make-up or consumption** **Table B Decision XXIII/7**	**Maximum emissions** **Table B Decision XXIII/7**	**Reported make-up or consumption for 2016**	**Reported emissions for 2016**
China	1,103	313	177.42	105.05
European Union	1,083	17	365.28	3.808
Israel	3.5	0	0	0.0143
United States of America	2,300	181	Not reported	[31.2 ODP tonnes]
Total	4,489.5	511	*[542.70]**	*[108.8723]**

*Nominal totals are given for 2016, which exclude data not reported or data reported in ODP-weighted metric tonnes.

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[91] Except for the United States, which is given in ODP-weighted metric tonnes.

[92] Table B was last updated in 2011 with Decision XXIII/7: Use of controlled substances as process agents. The table shows Dec. XXIII/7 Tables B alongside the reported information received from Parties for the year 2016.

Table 6.3 Data reported by parties on make-up or consumption associated with process agent uses for 2009-2016

Party	**Reported make-up or consumption (metric tonnes)**							
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Brazil	0	-	-	-	-	-	-	-
China	313	179.3	179.92	179.24	88.92	178.44	179.84	177.42
Colombia	-	0.64	-	-	-	-	-	-
European Union	669	1116.231	954.42	547.178	622.101	508.741	283.313	365.28
Israel	2.4	3.3	2.1	3.6	2.4	2.4	1.8	0
Mexico	-	40.9954	-	-	-	-	-	-
United States of America	NR	NR	NR	NR	NR	NR	NR	NR
Nominal Total	984.4*	1340.4664*	1136.44*	730.018*	713.421*	689.581*	464.953*	542.70*

* Nominal totals exclude data not reported by parties, as indicated by NR. The United States reports emissions data and does not report make-up/consumption data.

Table 6.4 Data reported by parties on emissions associated with process agent uses for 2009-2016

Party	**Reported emissions in metric tonnes *[ODP tonnes given in square brackets]***							
	2009	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**
Brazil	0	-	-	-	-	-	-	-
China	-	179.3	179.2	179.24	52.64	105.63	106.46	105.05 *[115.56]*
Colombia	-	-	-	-	-	-	-	-
European Union	1.6	1.287	116.428	27.192	15.808	7.338	6.414	3.81 *[4.15]*
Israel	0	-	-		0.000038	0.1794	0.0617	0.0143 *[0.016]*
Mexico	-	40.9954	-	-	-	-	-	-
United States of America	*[47.1]*	*[59.79]*	*[44.35]*	*[34.63]*	*[34.5]*	*[34.1]*	*[33.2]*	*[31.2]*
Total	1.6*	221.5824*	295.628*	206.432*	68.448038*	113.1474*	112.9357*	108.86* *[150.92]*

*Nominal totals in metric tonnes exclude data reported in ODP-weighted metric tonnes by the United States. This table updates a similar table presented in the 2017 TEAP Progress Report, which incorrectly attributed ODP-weighted emissions quantities reported by the United States in metric tonnes. This table also presents the 2016 data for parties other than the United States in metric tonnes and ODP-weighted tonnes for comparison purposes.

6.4 Progress in reducing controlled substances in process agents uses

The number of applications using ODS as process agents decreases slowly, while the emissions and make-up quantities from process agents are stabilizing. For some of the remaining applications, no alternatives are available to date.

6.4.1 Reduction in make-up quantity of controlled substances

The information reported in Table 6.3 demonstrates that the total reported make-up or consumption quantities of ozone depleting substances used for the reported processes has decreased from its peak in 2010. This excludes information on make-up or consumption in the United States, which is not reported for these years. For the parties reporting (China, the EU and Israel), there is a significant reduction in the quantities of make-up/consumption of controlled substances compared with the maximum quantity of make-up/consumption contained in decision XXIII/7. These reductions could be the result of a reduction in the number of processes using ozone-depleting substances as process agents or implementation of improvements in the processes.

6.4.2 Progress made in reducing emissions from process-agent uses

The information reported in Table 6.4 demonstrates that the quantities of ozone depleting substances emitted from the reported processes have stabilised over the past years and have decreased significantly from the maximum quantity of emissions contained in decision XXIII/7 Table B. These reductions could be the result of a reduction in the number of processes using ozone-depleting substances as process agents or/and implementation of improvements in the processes to further reduce emissions.

6.4.3 Implementation and development of emissions-reduction techniques

In the past period many emission reduction techniques are operational and new techniques are being developed and implemented. For example, Israel has noted that it uses compression and purification systems obtained from Krebs Swiss and has continuous chlorine analysers that activate the safety interlockers system when the chlorine concentration in the air is 0.5 ppmv.

The United States has also provided a list of containment technologies that are used to minimise emissions of controlled substances. These are as follows: continuous air monitoring of stacks; fugitive emission monitoring and repair; vent emission recycling back into process; bio-treatment and carbon bed filtration; stack gas sent to vent incineration; nitrogen used to clear the transfer lines; used material sent to THROX incineration unit; solvent recovery system; carbon absorption system; wastewater treatment system; emergency discharge system routed through a blow-down collection tank; air sweep to a carbon absorption system from suspected leak areas; redundant process controls to minimize mis-operation; full system drainage and vapour purge prior to maintenance; refrigerated vent condensers to minimize BCM emissions; multi-disciplined conservation team overseeing leak detection technology and process optimization; mechanical seal pumps replaced by seal-less pumps for CTC transfer lines; compressor suction automation valves and heat exchangers to improve recovery control; recycling and recovery operations to maximize material re-use; internal mechanisms for rapid-response to threshold shifts in daily emission values.

6.4.4 Alternative processes and products not using ozone-depleting substances

Alternative processes are investigated and implemented where possible. For example, the European Union provided information on its process agent applications and the availability of alternatives. It reported that a company has introduced a process to remove the ammonium impurity using NaClO, putting an end to the use of CTC for the elimination of nitrogen trichloride in the production of chlorine and caustic soda at one production unit in France. It has also noted that the use of CTC in the recovery of chlorine in tail gas from the production of chlorine has been eliminated through the introduction of gas burners, through which the tail gas circulates. Work is also underway to eliminate the use of CFC-12 in the photochemical synthesis of perfluoropolyetherpolyperoxide precursors of Z-perfluoropolyethers and di-functional derivatives within the European Union, and HFE-7100 has replaced the use of CFC-113 in the preparation of perfluoropolyether diols with high functionality.

7 Solvents

7.1 Solvent uses of controlled substances

The main applications of solvents are metal cleaning where metal working oil, grease, pitch wax, etc., are cleaned, electronics cleaning where flux is mainly cleaned, and precision cleaning where particulate or dust is mainly cleaned.

Among controlled substances, trichlorotrifluoroethane (CFC-113) and 1,1,1-trichloroethane (TCA) use as solvents has been phased out in both of Article-5 and non-Article 5 parties, with the exception being the use of CFC-113 as a cleaning solvent in aerospace applications until stockpiles are depleted. The use of 1,1-dichloro-1-fluoroethane (HCFC-141b) and dichloropentafluoropropane (HCFC-225) for solvent cleaning has been largely phased out in non-Article 5 parties, with the exception of aerospace and military applications. In Article 5 parties, hydrochlorofluorocarbon (HCFC) use for solvent cleaning has declined and will continue to reduce further as more critical uses of HCFCs, such as in refrigeration, are given priority and as available quantities decline under the HCFC phase-out schedule of the Montreal Protocol.

It is estimated that aerospace and military applications currently require small quantities of HCFCs globally, possibly less than about 50 tonnes annually. Aerospace or military applications might require small quantities of HCFCs, potentially to service existing equipment (e.g. HCFC-122, -122a, -141b, -225), after 2020 in non-Article 5 parties. For example, HCFC-225 replaced CFC-113 in precision cleaning and cleanliness verification of sensitive equipment, such as oxygen systems, in aerospace applications. A hydrochlorofluoroolefin (HCFO-1233zd(E)) has undergone successful laboratory testing for this application, but for at least one important user there is currently no on-going production of large systems that would allow the proving of the efficacy of this solvent in the actual conditions of use. If HCFO-1233zd(E) or other alternatives, such as hydrofluoroethers (HFEs), fail to demonstrate adequate performance, the application would need to continue to use HCFC-225 (or the original CFC-113). Such HCFC solvent uses are unlikely to exceed several hundred metric tonnes (i.e., several ODP tonnes) annually for the period 2020-2030. It is not clear whether quantities would be available or suitable from stockpiled or recycled sources. Although stockpiled sources can be infeasible due to the formation of chemical impurities unsuitable for these precision cleaning uses.

There is a reported solvent use of HCFC-225 for syringe/needle coating in Japan. HCFC-141b is used for this purpose in Article 5 parties. This solvent application coats silicone oil on the surface of the needle/syringe to reduce pain at injection. The solvent properties required are non-flammability, good solvency with the silicone oil, and quick evaporation after coating. Alternative non-ozone-depleting substances (ODS) solvents are under investigation in Japan, and already used in Europe and the United States (e.g. HFEs). Topical creams are also available as pain relief for injections.

In Japan, several manufacturing processes use HCFCs as solvents in processes that might be considered similar to process agent uses. They are used either as reaction solvents, or as solvents for extractive distillation due to the unique affinities to certain chemicals. Known applications include processes using HCFC-141b and HCFC-225 as solvents. Alternative processes and/or solvents are under development. There is a small possibility that such HCFC use may remain after the 2020 phase-out if alternatives cannot be found by then.

It is difficult to obtain accurate figures of the total manufacture, imports and use of ODS solvents, particularly in Article 5 parties. Small- and medium-sized enterprises (SMEs) collectively make up a major portion of the solvent market. Alternatives are generally readily available in Article 5 parties, except the unsaturated chemicals (e.g., HFOs). Economic factors are a major factor for Article 5 parties in the selection of alternatives. SMEs that do not have enough investment tend to use chlorinated solvents as they are cheaply available and existing facilities can be used with minimum modifications.

7.2 Alternatives to HCFCs

Many alternative solvents and technologies developed for CFC alternatives since 1980s are also the candidates for HCFC alternatives. These include not-in-kind technologies such as aqueous cleaning, semi-aqueous cleanings, hydrocarbon and alcoholic solvents, and in-kind solvents such as chlorinated solvents and fluorinated solvents, including hydrofluorocarbons (HFCs) and low-GWP HCFO-1233zd(E) and HFEs, with various levels of acceptance. Alternatives to HCFCs are being used for automotive, aerospace, precision component and optical cleaning where high levels of cleanliness are required.[93]

The choices for alternative technologies to ODS solvents are summarised as:

- Aqueous/hydrocarbon-surfactant cleaning;
- Organic solvent cleaning (with solvents less toxic than non-ozone-depleting halogenated solvents);
- Non-ozone-depleting halogenated unsaturated solvents (trichloroethylene (TCE), perchloroethylene (PCE), *trans*-1,2-dichloroethylene (TDCE, a hydrochloroolefin (HCO)), hydrofluoroolefins (HFOs), HCFOs, chlorofluoroolefins (CFOs));
- Organic solvent cleaning (with solvents more toxic than non-ozone-depleting halogenated solvents);
- Fluorinated solvents (HFCs, HFEs).

HCFCs have been used in several different industries, for example in aerospace, micro-mechanical part manufacturing, plating, aerosol cleaners, circuit flushing, electronics defluxing/cleaning, oxygen service cleaning and the medical industry in deposition. Each of these industries has its own set of specific cleaning requirements and associated test procedures to ensure the cleaned parts are acceptable for use. The consequences of incomplete cleaning can be anything from poor performance in the next step, which can be seen in applications like plating, decreased product lifetime or performance in electronics cleaning, and even large potential safety concerns, such as when parts are cleaned for use in oxygen services.

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[93] Several reports that describe the use of ODS and their alternatives in solvent applications have been published in the past. These include the IPCC TEAP Special Report, the Decision XXI/9 TEAP Task Force Report, the Decision XXIII/9 TEAP Task Force Report, the Decision XXIV/7 TEAP Task Force Report, the Decision XXV/5 TEAP Task Force Reports, and the STOC and CTOC Assessment Reports.

As manufacturers transition away from HCFC-based solvents, such as HCFC-141b and HCFC-225ca/cb, it is important that they match their cleaning requirements with the new solvent or cleaning system. Typically, when manufacturers look to transition from a HCFC cleaning system they evaluate alternative solvents, aqueous cleaners, no clean solutions or complete system changes. Each of these alternatives will be evaluated to assess how they meet the specific cleaning requirements, as well as cost requirements.

7.2.1 Newly developed halogenated solvents

This section focuses on newly developed halogenated solvents that can be used as substitutes for HCFCs. Table 7.1 lists some of the important solvent properties that a manufacturer considers when evaluating a new solvent in their process.

Table 7.1 HCFC solvents and halogenated alternatives

Solvent	Solvent Class	GWP	Boiling Point (ºC)	Flash Point (ºC)	KB value	Surface Tension (dynes/cm)
HCFC-141b	HCFC	782	32	none	56	19
HCFC-225ca/cb		127/525	54	none	31	16
HFC-43-10mee	HFC	1650	55	none	13	14
HFC-365mfc		804	40.2	-24	14	15
HFE-449s1 [7100]	HFE	421	61	none	10	14
HFE-569sf2 [7200]		57	76	none	10	14
HFE-64-13s1 [7300]		310	98	none	7	15
HFE-347pc-f2		580	56	none	13	16
HCFO-1233zd(E)	HCFO	1	19	none	25	13
TDCE	HCO	1	48	-6	117	28

Several blends of HFCs, HFEs, and HFOs are also available as HCFC alternatives. These blends take advantage of key properties of the solvent alternatives, for example, blending a non-flammable solvent with one that has high solvency while also reducing the cost. For example, chlorinated solvents with stronger solvency, such as TDCE, are added to improve the solvency of HFCs and HFEs. Examples of these blends are shown in Table 7.2.

Table 7.2 Examples of fluorinated solvent mixtures in use

Solvent Mixtures	Solvent Class	GWP	Boiling Point (ºC)	Flash Point (ºC)	KB value	Surface Tension (dynes/cm)
HFC-43-10mee with 38 wt% *trans*-1,2-dichloroethylene	HFC	1023	39	none	23	15
HFC-365mfc with 30 wt% *trans*-1,2-dichloroethylene		563	36	none	25	18
HFE-449s1 with 50 wt% *trans*-1,2-dichloroethylene	HFE	210	41	none	27	17
HFE-569sf2 and HFE-449s1 with 70 wt% *trans*-1,2-dichloroethylene		54	43	none	52	19
HFE-64-13s1 with 85 wt% *trans*-1,2-dichloroethylene		47	48	none	83	20
HFE-347pcf2 with 50 wt% *trans*-1,2-dichloroethylene		445	38	none	32	18

Unsaturated fluorochemicals, HFOs, with zero ODP and ultra-low GWP are being commercialized for the replacement of high-GWP HFC and low- or moderate- GWP HFE solvents. The major trend in the development of new solvents is the introduction of substances with unsaturated molecules, and thus short atmospheric lifetimes, near zero-ODP and low-GWP, such as HCFOs, CFOs and hydrobromofluoroolefins (HBFOs). HCFOs, CFOs and HBFOs are unique in their balanced solvency due to the presence of chlorine (or bromine) and fluorine atom in the molecule. Those with appropriate boiling points, low toxicity and sufficient stability may replace HCFCs totally in the future. A recent development is the production of HCFO-1233zd (CF_3-CH=CH-Cl, *trans* isomer). This substance has boiling point 19ºC and useful solvency property.

The main groups of new substances are unsaturated HFCs (HFOs, such as HFO-1234yf and HFO-1234ze) and unsaturated HCFCs (HCFOs). Such substances are expected to replace HCFCs in a number of uses and also to compete with HFEs in the solvent sector.

7.3 *n*-Propyl bromide

n-Propyl bromide (1-bromopropane, $CH_3CH_2CH_2Br$, *n*-PB, CAS No. 106 94 5) is being used as a solvent in a range of applications. Its boiling point, 71ºC, is comparable to that of CFC-113 (48ºC), hexane (69ºC), methyl chloroform (TCA, 74ºC) and trichloroethylene (87ºC), making it attractive as a solvent with similar physical properties. Its solvent properties are typical of those of lower molecular weight hydrocarbons and organohalogen compounds. *n*-Propyl bromide is used as an electrical cleaning agent, degreaser or carrier solvent, as an intermediate in chemical manufacture, in spray adhesives, dry cleaning, insulation, and as a refrigerant flushing agent. n-Propyl bromide has also appeared in consumer aerosol cans as electronics cleaning and degreasing products, as adhesive products, as textile spot removers, and as paintable mould release agents.

Due to the presence of bromine in the molecule, however, concerns have been expressed based both on its potential for ozone depletion and its toxicity. The atmospheric lifetime, and impact on ozone depletion, of *n*-propyl bromide have been evaluated in several studies, with derivations dependent on emissions location. In 2011, using a current-generation chemistry-transport model of the troposphere and stratosphere, Wuebbles *et al*. derived an atmospheric chemical lifetime of 19.6 days, and ODP of 0.011, for the global emissions case, and 24.7 days, and an ODP of 0.0049 at northern hemisphere mid-latitudes[94]. *n*-Propyl bromide is not a controlled substance under the Montreal Protocol.

Regarding its toxicity, the National Toxicology Program report (NTP TR 564, August 2011) and the American Conference of Governmental Industrial Hygienists (ACGIH®) (February 2012) established a threshold limit value (TLV®) for n-propyl bromide of 0.1 ppm. In 2013, a peer-reviewed Draft Report on Carcinogens prepared by the U.S. National Toxicology Program concluded that n-propyl bromide is reasonably anticipated to be a human carcinogen[95]. In 2014,

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[94] Wuebbles, D. J., Patten, K. O., Wang, D., Youn, D., Martinez-Avile, M., and Francisco, J. S., Three-dimensional model evaluation of the Ozone Depletion Potentials for n-propyl bromide, trichloroethylene and perchloroethylene, Atmos. Chem. Phys., 2011, **11**, 2371–2380.

[95] National Toxicology Program, U.S. Department of Health and Human Services, Draft Report on Carcinogens Monograph for 1-Bromopropane, January 18, 2013, available at

ACGIH published a time weighted average exposure limit (TWA) of 0.1ppm for n-propyl bromide. The Japan Society for Occupational Health set a TLV of 0.5ppm for n-propyl bromide in 2013.

The European Chemical Agency (ECHA) has classified *n*-propyl bromide as a Substance of Very High Concern (SVHC) and it is included in the list of substances included in Annex XIV of REACH ("Authorisation List"). The substance is subject to authorisation, meaning it cannot be placed on the market or used after 4th July 2020 (the sunset date), unless an authorisation is submitted for specific use(s) by 4th January 2019 (the application date) and an authorisation is granted, or an authorisation application has been submitted before the application date but the Commission decision on the application for authorisation has not yet been taken, or the specific use is exempted from authorisation. There are no exempted (categories of) uses for *n*-propyl bromide[96].

According to the harmonised classification and labelling (CLP00) approved by the European Union, *n*-propyl bromide "*...may damage fertility and may damage the unborn child, is a highly flammable liquid and vapour, causes serious eye irritation, may cause damage to organs through prolonged or repeated exposure, causes skin irritation, may cause respiratory irritation and may cause drowsiness or dizziness*". In addition, the classification identifies that *n*-propyl bromide "*...is suspected of causing cancer and is harmful to aquatic life with long lasting effects*".[97]

The Toxic Substances Control Act (TSCA) requires the U.S. EPA to establish a risk evaluation process. In performing risk evaluations for existing chemicals, U.S. EPA is directed to "*determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator under the conditions of use*." In December 2016, *n*-propyl bromide was identified as one of ten chemicals designated by U.S. EPA for chemical risk evaluation, based on high hazard concerns due to its toxicity profile and high exposure concerns due to its use in consumer products.

TSCA requires that U.S. EPA publish the scope of the risk evaluation to be conducted, as part of the public consultation process. The scope of risk document for *n*-propyl bromide was published in June 2017.[98] It included information about conditions of use, hazards, exposures, and potentially exposed or susceptible subpopulations, that U.S. EPA expects to consider in the risk evaluation. The document presents the scope of the risk evaluation to be conducted for *n*-propyl bromide by U.S. EPA, and the occupational scenarios in which workers and occupational non-

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https://ntp.niehs.nih.gov/ntp/about_ntp/monopeerrvw/2013/march/draftroc1bpmonograph_508.pdf, accessed April 2017.

[96] European Chemicals Agency (ECHA) authorisation list entry for n-propyl bromide https://echa.europa.eu/authorisation-list/-/dislist/details/0b0236e1804d5364, accessed March 2018.

[97] European Chemicals Agency (ECHA), *Brief Profile of n-propyl bromide*, available at https://echa.europa.eu/brief-profile/-/briefprofile/100.003.133, accessed March 2018.

[98] United States Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention, EPA Document # EPA- 740-R1-7009, *Scope of the Risk Evaluation for 1-Bromopropane*, CASRN: 106-94-5, June 2017, available at https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-1-bromopropane-1-bp, accessed April 2018.

users may be exposed during a variety of conditions of use. TSCA requires that these chemical risk evaluations be completed within three years of initiation (from December 19, 2016 for *n*-propyl bromide), allowing for a single 6-month extension.

The scope of risk evaluation states that in the United States *n*-propyl bromide is primarily used as a solvent cleaner in vapour and immersion degreasing operations to clean optics, electronics and metals. It has also been used as an alternative solvent carrier for other ozone- depleting substances and chlorinated solvents, e.g. in industries using spray adhesives such as foam cushion manufacturing. Past uses include as a solvent for fats, waxes or resins and as an intermediate in the synthesis of pharmaceuticals, insecticides, quaternary ammonium compounds, flavours and fragrances. *n*-Propyl bromide was also recently listed on the Toxics Release Inventory (TRI), with data on environmental releases of *n*-propyl bromide to air, landfills or water likely to become available in the near future.

In China, *n*-propyl bromide is identified as one of nearly 3,000 hazardous chemicals controlled under the Regulation on the Safety Management of Hazardous Chemicals. Based on this regulation, stakeholders handling *n*-propyl bromide must prevent and reduce hazardous chemical accidents and guarantee the use of *n*-propyl bromide will not impact the life and safety of the general public and the environment during its production, storage, use, dealing and transport.

The relatively low workplace exposure standards indicate that use of *n*-propyl bromide in solvent applications is likely to be problematic, and its use will likely be limited to applications where worker exposure is controlled and will require significant emission control. Nevertheless, *n*-propyl bromide continues to appear as a marketed solvent at trade exhibitions with demand in a number of markets (e.g. China, Japan and the United States).

Manufacture is occurring in a small number of countries, including China, Israel and the United States. Chemical manufacturers do not publicise their *n*-propyl bromide production data for commercial reasons. Parties to the Montreal Protocol are not required under Article 7 to report the production and consumption n-propyl bromide because it is not a controlled substance. China has previously estimated production capacity of about 10,000 tonnes per year, consumes (about 3-4,000 tonnes per year), and exports (about 5,000 tonnes) to other markets. The United States manufactured and imported about 8,500 tonnes in 2012, and nearly 12,000 tonnes in 2015 and 2016.[98,99.] Japan imported about 5,000 tonnes in 2015. The European Union imports about 2,000 tonnes, with maximum production of 3,600 tonnes. Information is not available for Israel.

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[99] U.S. EPA, Office of Chemical Safety and Pollution Prevention, *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1-Bromopropane*, CASRN: 106-94-5, February 2017, Support document for Docket EPA-HQ-OPPT-2016-0741, available at https://www.epa.gov/sites/production/files/2017-02/documents/1-bromopropane.pdf, accessed April 2017.

8 Other chemicals issues

This chapter presents information about carbon tetrachloride (CTC), dichloromethane (DCM), dichloroethane (DCE), and CFC-11 (trichlorofluoromethane, CCl_3F) and their emissions, in response to scientific atmospheric observations and their analysis, and concerns about their potential for ozone-depletion.

8.1 Carbon tetrachloride

The Chemicals Technical Options Committee (CTOC) reported for a number of years on the discrepancy between emissions of CTC to the atmosphere calculated as ‘bottom up’ estimates based on production and consumption and typical emission rates, and ‘top down’ estimates based on atmospheric concentrations of CTC and estimates of its atmospheric lifetime.

Subsequent to the 2014 CTOC Report[100], the discrepancies between emissions of CTC calculated from atmospheric observations and those estimated from industrial activity were re-examined by a group of experts under the auspices of Stratosphere-troposphere Processes And their Role in Climate (SPARC), a core project of the World Climate Research Programme. The SPARC report[101] concluded that some of the discrepancy could be explained by previously unaccounted emission sources unrelated to (UNEP) reported production, including contaminated soils and industrial waste. Additional explanations included unreported emissions from chloromethanes production. Revised estimates of partial CTC lifetimes (stratosphere, ocean, or soil) result from changes in the understanding of mechanisms for removal of CTC from the environment. These result in an increase of the total lifetime from 26 years, quoted in the 2014 Science Assessment[102], to 33 (28-41) years. Consequently, CTC is lost at a slower rate from the atmosphere; with this new total lifetime, the global top-down emissions calculation decreases to 40 (25-55) ktonnes per year.

The new industrial bottom-up emissions estimate (including unreported emissions from chloromethanes plants, feedstock fugitive emissions, legacy emissions and unreported inadvertent emissions, for example from use of chlorine as disinfectant) could be up to 25 ktonnes per year[103]. While this is still less than the aggregated top-down values, the estimates from SPARC reconcile the CTC budget discrepancy, when considered at the edges of the ranges of their uncertainties. Figure 8.1 shows the apportionment of the anthropogenic emissions estimates[104].

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[100] 2014 Report of the UNEP Chemicals Technical Options Committee, 2014 Assessment Report.

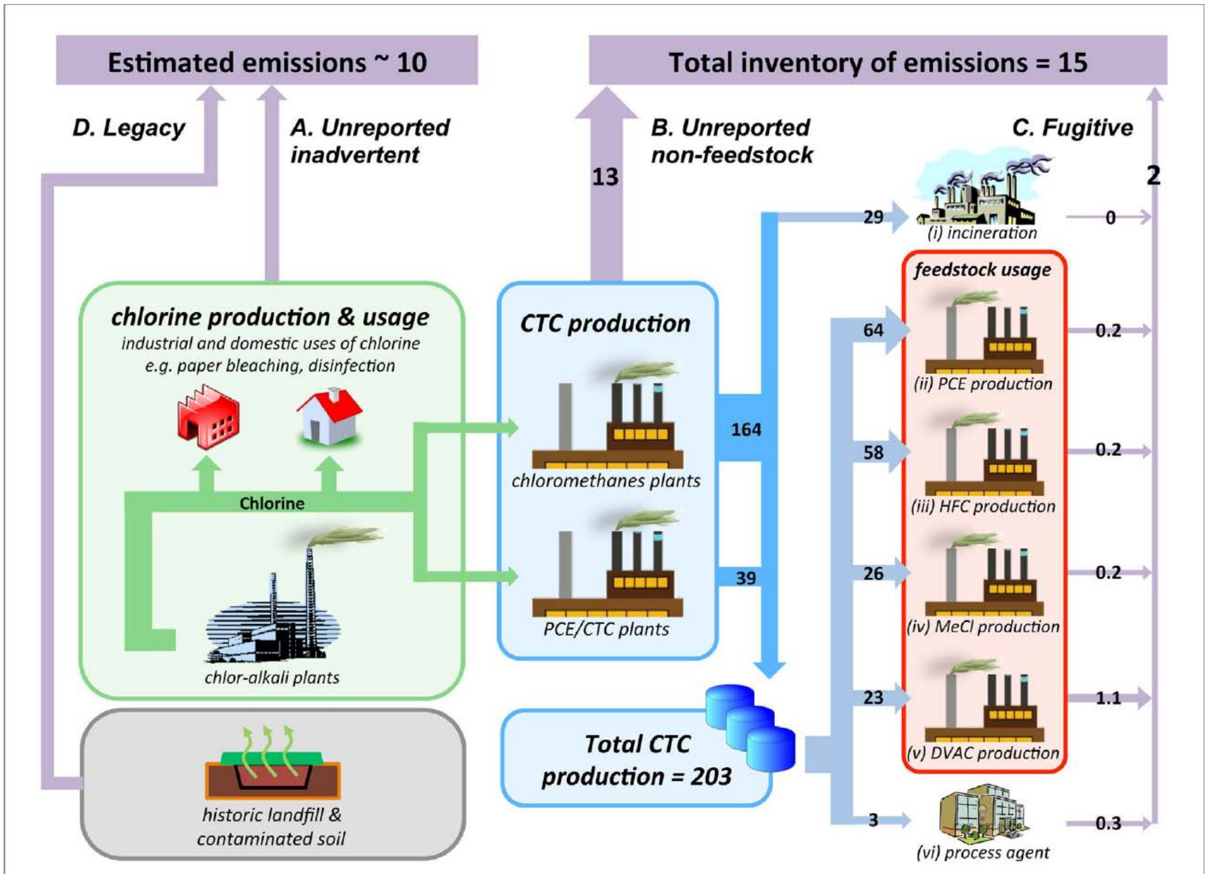
[101] Liang, Q., Newman, P.A., Reimann, S. (eds.), SPARC Report on the Mystery of Carbon Tetrachloride, 2016, SPARC Report No. 7, WCRP-13/2016.

[102] Carpenter, L. J., and S. Reimann (Lead Authors), J. B. Burkholder, C. Clerbaux, B. D. Hall, R. Hossaini, J. C. Laube, and S. A. Yvon-Lewis, Ozone-depleting substances (ODSs) and other gases of interest to the Montreal Protocol, Chapter 1, Scientific Assessment of Ozone Depletion: 2014, Global Ozone Research and Monitoring Project – Report No. 55, World Meteorological Organization, Geneva, Switzerland, 2014.

[103] Sherry, D., McCulloch, A., Liang, Q., Reimann, S., and Newman P.A., Current sources of carbon tetrachloride (CCl_4) in our atmosphere, *Environ. Res. Lett.*, 2018, **13**, 024004. https://doi.org/10.1088/1748-9326/aa9c87.

[104] The numbers given are estimates, in ktonnes, for 2014. Feedstock uses of CTC are in red (PCE is perchloroethylene, HFC is hydrofluorocarbon, MeCl is methyl chloride, and DVAC is divinyl acid chloride). Emissions are shown as purple lines from: A. unreported inadvertent chlorine gas usages; B. unreported non-feedstock from CM and PCE

Figure 8.1 **Schematic of CTC routes and emissions from: production and use of chlorine gas (green arrows); industrial CTC co-production from chloromethanes plants (blue box and arrows); and CTC use (bluish grey arrows).**



The discrepancy has been further reduced by recent estimates of uncontrolled emissions from China calculated using atmospheric measurements at Gosan Island, Korea[105]. From 2011 to 2015, the annual average emission was 24 ktonnes per year. This is 11 ktonnes per year greater than the previous estimate of this source and, coupled with the estimates of other source strengths, gives a new source-based estimate of 36 ktonnes per year, consistent with SPARC's 40 ktonnes per year top-down estimate.

The SPARC Report, and subsequent interpretation of the analyses of South East Asian atmospheric observations, have almost closed the gap between top-down and bottom-up estimates of CTC emissions. However, much of the apportionment of sources is uncertain and subjective. Indeed, most of the emissions appear to arise from unregulated sources.

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plants; C. fugitive emissions from contained usages; and D. legacy emissions from landfills and contaminated soils.

[105] Park, S., Li, S., Muehle, J., O'Doherty, S., Weiss, R.F., Fang, X., Reimann, S., and Prinn, R.G., Toward resolving the mysterious budget discrepancy of ozone-depleting CCl_4: An analysis of top-down emissions from China, *Atmos. Chem. Phys.*, 2018, **18**, 11729–11738.

Parties may wish to consider examining potential unregulated sources of CTC emissions with a view to increasing the understanding of those emissions and accuracy of emissions estimates.

8.2 Dichloromethane

Dichloromethane (DCM) has a high solvent power for oils and greases and for some polymeric materials. These properties, coupled with its volatility (boiling point 40.1ºC), have led to its widespread use as an industrial solvent, in applications such chemicals and pharmaceuticals production, and to a lesser extent as a food extraction solvent, and for metal cleaning and paint removal. It is also a component of special adhesives and has been used in PU foam blowing, in aerosols, paint strippers and as a laboratory agent[106]. Many of these uses can result in much of the DCM employed being emitted into the environment (so-called emissive uses). More recently, smaller quantities of DCM have been used as chemical feedstock to produce HFC-32 (CH_2F_2, difluoromethane) but, except for small losses (fugitive emissions), use as feedstock does not result in significant emission of DCM.

Production (and hence availability) of DCM is closely linked to the demand for HCFC-22 (chlorodifluoromethane, $CHClF_2$) through production of chloroform, which is the raw material for HCFC-22 (itself a raw material for fluoropolymers, mainly PTFE (polytetrafluoroethylene)) production. DCM and chloroform are produced together in plants with limited scope for varying their relative quantities and, as a consequence, the rapid growth in HCFC-22 production, particularly in China, has led to DCM becoming readily (and relatively cheaply) available. Production of HCFC-22 is set to remain steady or even decline in the future, due both to controls under the Montreal Protocol and to maturity in the fluoropolymer market. This will have an impact on future production and availability of DCM, which is consistent with the fact that its atmospheric concentration and emissions have not changed since 2013.

DCM is defined in the Scientific Assessments of Ozone as a *very short-lived substance* (VSLS). Its atmospheric lifetime is 0.4 years and atmospheric concentrations depend on the geographical location, altitude and season of emissions. Its concentration shows very strong seasonal cycles; furthermore, the concentration at the point of injection of air into the stratosphere is about half that at the earth's surface. Due to this variability of the effect of an emission, VSLS cannot be given a conventional ozone depletion potential.

The average atmospheric concentration of DCM started to grow in the 1930s, reaching a peak in 1990, and then declined until 2003. Subsequently, growth in atmospheric concentration, likely fuelled mainly by growth in Chinese choromethanes production, then continued until 2013; since then, there has been no significant growth. This pattern is similar to the changes in HCFC-22 production.

The present level of DCM emissions, inferred from atmospheric measurements, is about 1.3 million tonnes per year. This is consistent with historical capacity in the developed world of about 700 ktonnes per year and the reported growth of emissions from China[107]. These emissions

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[106] Leder, A.E., Blyth, W., and Ishikawa-Yamaki, M., Chlorinated Methanes, Section 635.2000/2002, *Chemical Economics Handbook*, SRI International, Menlo Park, CA, U.S.A., and subsequent updates.

[107] See Figure 8.3 and Feng, Y., Bie, P., Wang, Z., Wang L., and Zhang, J., Bottom-up anthropogenic dichloromethane emission estimates from China for the period 2005–2016 and predictions of future emissions, *Atmos. Environ*., 2018, **186**, 241–247.

contribute less than 1 percent to the current total stratospheric chlorine loading, which is small and within the uncertainty of the total chlorine loading estimate. Given the reductions in HCFC-22 production, resulting from the Montreal Protocol phase-down of HCFCs, and other trends in DCM usage, global DCM production is unlikely to increase significantly.

8.2.1 Atmospheric sources of DCM

There is strong evidence for natural production of DCM by phytoplankton in the sub-surface layer of seawater at depths of 20 to 150 metres, both from direct measurement[108] and from observations of concentrations higher than expected over the sea surface[109]. Calculations based on the direct measurements indicate a flux into the atmosphere from seawater of about 25 ktonnes per year. There is an additional source from biomass burning, that may have a large natural component, which has been estimated at 60 ktonnes per year[110].

Analyses of air trapped in frozen snow (firn air) from Antarctica are consistent with these estimates, suggesting that the seawater source amounts to 28 ktonnes per year and biomass burning contributes 40 ktonnes per year. These amounts are small in comparison to anthropogenic emissions[111]. Nevertheless, this indicates that DCM is a natural substance and that small amounts have been present in the environment on a geological timescale. Anthropogenic emissions have added considerably to the natural flux. Analysis of the firn air from Antarctica shows that the atmospheric concentration was relatively constant at 1.5 pmol/mol in the early part of the 20th century, a consequence of the natural sources mentioned above, and grew rapidly from 1950 to reach a southern hemisphere maximum of 9.4 pmol/mol in 1990. This pattern is consistent with the changes in production and emissions estimated from industrial data in the last part of the 20th century[112,113].

Because of its relatively low solubility in water (2 percent) and high volatility at ambient temperatures (vapour pressure at 20°C ca 45 kPa), any DCM released into the environment will tend to migrate into the air where it is removed by natural oxidation. Environmental impacts concern the accumulation of DCM in the atmosphere, which is a balance between its rate of

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[108] Ooki, A. and Yokouchi, Y., Dichloromethane in the Indian Ocean: Evidence for in-situ production in seawater, *Marine Chemistry*, 2011, **124**(1-4), 119–124.

[109] Koppmann, R., Johnen, F.J., Plassdulmer, C., Rudolph, J., Distribution of methylchloride, dichloromethane, trichloroethene and tetrachloroethene over the North and South-Atlantic, *J. Geophys. Res.*, 1993, **98**(D11), 20,517–20,526.

[110] Lobert, J. M., Keene, W.C., Logan, J.A., and Yevich, R., Global chlorine emissions from biomass burning: Reactive chlorine emissions inventory, *J. Geophys. Res.*, 1999, **104**, 8373–8389.

[111] Trudinger, C. M., Etheridge, D. M., Sturrock, G. A., Fraser, P. J., Krummel, P. B., McCulloch, A., Atmospheric histories of halocarbons from analysis of Antarctic firn air: Methyl bromide, methyl chloride, chloroform, and dichloromethane, *J.Geophys. Res.*, 2004, **109**(D22), D22310. doi.org/10.1029/2004JD004932.

[112] McCulloch, A. and Midgley, P.M., The production and global distribution of emissions of trichloroethene, tetrachloroethene and dichloromethane over the period 1988-1992, *Atmos. Environ.*, 1996, **30**(4), 601-608.

[113] McCulloch, A., Aucott, M.L., Graedel, T.E., Kleiman, G., Midgley, P.M., and Yi-Fan, Li, Industrial emissions of trichloroethene, tetrachloroethene, and dichloromethane: Reactive Chlorine Emissions Inventory, *J. Geophys. Res.*, 1999, **104**(D7), 8417-8428.

release and the rate at which it is removed, and the effect of this atmospheric burden on local pollution or global climate change and ozone depletion.

Many of the uses of DCM, particularly in solvent applications, can result in the emission of the material into the atmosphere, unless steps are taken to capture and destroy releases. The principal exception is its use as a chemical feedstock, for example for difluoromethane (HFC-32) production; as the DCM feedstock is chemically transformed in this process, releases are confined to fugitive emissions, which amount to less than 0.1 percent of use.

8.2.2 Uses of dichloromethane

DCM is a highly effective solvent that has been used extensively since the middle of the 20th century. These uses have changed through the years; an earlier major requirement in the manufacture of photographic film has now shrunk to virtually nothing while other industrial solvent uses have grown. Unless it is recovered and destroyed, DCM used in solvent applications will be emitted into the environment and transport into the atmosphere. the use in developed countries was reflected in a peak in atmospheric concentration in about 1990. Since then, use and emissions in the developed world have been falling, for example at between 4 percent per year in Europe and 5 percent per year in the United States in the early 21st century[106].

Use as a chemical feedstock effectively destroys the substance; it is converted into the desired product and the only emissions are of feedstock that has not been effectively contained. These so-called fugitive emissions amount to a maximum of 0.5 percent of the total feedstock usage. This is the default value recommended by the Intergovernmental Panel on Climate Change for fugitive emissions of similar chemicals that are greenhouse gases[114]. The actual rate of emissions is often far smaller; for example, the European emission rate for ozone depleting substances used as feedstock amounts to 0.06 percent (2016) having shrunk from 0.1 percent (2012)[115]. DCM is the feedstock in the main route to difluoromethane (HFC-32) production, which has expanded rapidly this century, particularly in China where 6,197 tonnes was produced in 2005 and 18,387 tonnes in 2009[116]. While there are no reliable global data on the production of HFC-32, an estimate based on measured emissions suggests that about 60,000 tonnes were produced in 2015[117]. HFC-32 is mainly used in the refrigerant blends that are replacing HCFC-22; nevertheless, it is a greenhouse gas that is controlled under both the Kyoto and the amended Montreal Protocols and so its production and use will be capped by controls resulting from those treaties. At the current volume of production and current fugitive emissions rates, the quantity of DCM released into the

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[114] Intergovernmental Panel on Climate Change, Revised 1996 Guidelines for National Greenhouse Gas Inventories, Reference Manual, vol 3, IPCC/IGES, Kanagawa, Japan, 1996 and subsequent revisions.

[115] Ozone-depleting substances 2016: Aggregated data reported by companies on the import, export, production, destruction, and feedstock and process agent use of ozone-depleting substances in the European Union, EEA Report No 12/2017, Luxembourg: Publications Office of the European Union, ISBN 978-92-9213-895-0, doi:10.2800/179166.

[116] Zhang, J., and Wang, C., China's hydrofluorocarbon challenge, *Nature Climate Change*, 2014, **4**, 943, DOI: 10.1038/NCLIMATE2377, and supplementary material.

[117] Simmonds, P.G., Rigby, M., McCulloch, A., O'Doherty, S., Young, D., Muehle, J., Krummel, P.B., Steele, L.P., Fraser, P. J., Manning, A. J., Weiss, R.F., Salameh, P. K., Harth, C. M., Wang, R. H. J., and Prinn, R.G., Changing trends and emissions of hydrochlorofluorocarbons (HCFCs) and their hydrofluorocarbon (HFCs) replacements, *Atmos. Chem. Phys.*, 2017, **17**, 4641-4655, atmos-chem-phys.net/17/4641/2017/, https://doi.org/10.5194/acp-17-4641-2017, and supplementary material.

atmosphere from this source is less than 100 tonnes per year. Given the limit on HFC-32 production, which is likely to be much less than 100 times the current production level, fugitive emissions of DCM are not likely to exceed 10,000 tonnes per year.

8.2.3 Production of DCM

Most of the global production of DCM is from chloromethanes plants that also make methyl chloride, chloroform and carbon tetrachloride. Some of the processes involve direct chlorination of methane, but for the majority methanol is first reacted with hydrogen chloride to give methyl chloride, which is then chlorinated directly at high temperature. This route makes more effective use of chlorine (because hydrogen chloride generated during the direct chlorination may be recycled to the first stage) and enables easier control of the mix of products from the second stage. This control is effected mainly by varying the ratio of chlorine to methyl chloride, with some additional flexibility from recycling under-chlorinated product (unreacted methyl chloride and DCM). Nevertheless, the product is always a mixture, generally DCM and chloroform, with a relatively small amount of carbon tetrachloride[106].

Process economics are determined by the range of this product mixture (the scope for change of which is limited by process configuration) and the contemporary demand for, and hence value of, the individual products. It is apparent that, in a modern chloromethanes plant (as in China), the ratio of DCM to chloroform can be changed from 60 percent DCM: 40 percent chloroform to 40 percent DCM: 60 percent chloroform[118]. At present, the demand for carbon tetrachloride is relatively low. Its production and consumption (excluding feedstock use) were phased out under the Montreal Protocol in all countries in 2010. The only significant legitimate outlet for any carbon tetrachloride produced in a chloromethanes plant is as a chemical feedstock. It is used to make tetrachloroethene (perchloroethylene (PER)), some HFCs and insecticide intermediates, but about 25 percent of production is either incinerated or emitted into the environment. To minimise production of carbon tetrachloride, a "shallower" chlorination is required and, as a consequence, the product mix will contain substantial amounts of DCM, even if chloroform is the more desirable product. By far the largest use for chloroform (more than 95 percent) is as a chemical feedstock for production of HCFC-22[106].

8.2.4 Influence of HCFC-22 demand

HCFC-22 is used in two ways: the commercial product, used in the refrigeration and air-conditioning (RAC) industry; and as a chemical feedstock, as the raw material for the manufacture of PTFE and other fluoropolymers, effectively being destroyed in the process.

The estimated global production of HCFC-22 for both uses is shown in Figure 8.2. It is apparent that HCFC-22 production in the developed countries (those that are not operating under Article 5 of the Montreal Protocol) remained almost constant until 2008, in the range of 300 to 400 ktonnes per year. From then on, production in these countries has fallen but is still in the region of 200 ktonnes per year. From 1996 onwards, production in India and China has grown rapidly and, in

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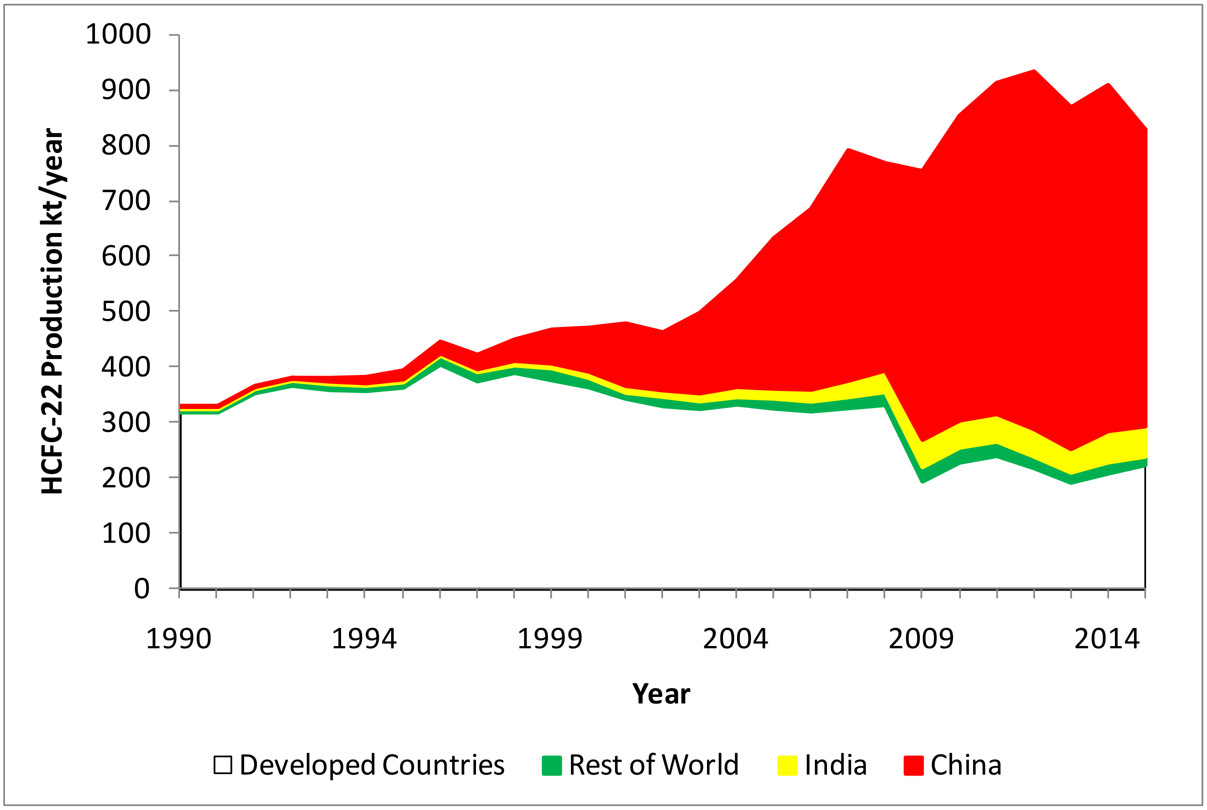
[118] Oram, D. E., Ashfold, M. J., Laube, J. C., Gooch, L. J., Humphrey, S., Sturges, W. T., Leedham-Elvidge, E., Forster, G. L., Harris, N. R. P., Mead, M. I., Samah, A. A., Phang, S. M., Ou-Yang, C.-F., Lin, N.-H., Wang, J.-L., Baker, A. K., Brenninkmeijer, C. A. M., and Sherry, D., A growing threat to the ozone layer from short-lived anthropogenic chlorocarbons, *Atmos. Chem. Phys.*, 2017, **17**, 11929-11941, https://doi.org/10.5194/acp-17-11929-2017.

2015, 65 percent of the global total was produced in China[119]. Production in other Article 5 parties (Argentina, North and South Korea, Mexico and Venezuela) is relatively small.

Figure 8.2 Global production of HCFC-22 (ktonnes per year), showing contributions from developed countries (not under Article 5 of the Montreal Protocol), India, China and the rest of the world[119]



The increase in production resulted from demand both for RAC and for feedstock use in the manufacture of fluoropolymers. The RAC use is potentially emissive so that related HCFC-22 production and consumption have been controlled under the Montreal Protocol, with restriction of production from 2003 onwards in non-Article 5 parties and from 2015 in Article 5 parties.

Since it is effectively a destruction technology, and a process with minimal emissions, the production and consumption of HCFC-22 for use as a chemical feedstock for fluoropolymers is not controlled under the Montreal Protocol. Feedstock use was a major component in the rapid growth of Chinese HCFC-22 production before 2010 and subsequently has remained roughly constant[120].

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[119] Simmonds, P.G., Rigby, M., McCulloch, A., Vollmer, M. K., Manning, A.J., Henne, S., O'Doherty, S., Krummel, P. B., Fraser, P. J., Mühle, J., Young, D., Weiss, R. F., Salameh, P. K., Harth, C.M., Steele, L. P., Trudinger, C., Wang, R.H.J., Ivy, D., and Prinn, R.G. et al., Recent increases in the growth rate and emissions of HFC-23 (CHF_3) and the link to HCFC-22 ($CHClF_2$) production, *Atmos. Chem. Phys.*, 2018, **18**, 4153-4169, https://doi.org/10.5194/acp-18-4153-2018.

[120] Li, Z., Bie, P., Wang, Z., Zhang, Z., Jiang, H., Xu, W., Zhang, J., Hu, J., Estimated HCFC-22 emissions for 1990-

The sharp decline in production in developed countries is consistent with the closure of plants in the United States and Europe, which is reflected in by-product emission reports[121,122]. Demand for feedstock could have been met by imports from China.

In the developed world growth in HCFC-22 was slow, so that the infrastructure of plants to provide chloroform feedstock grew up over several decades. This allowed time for uses for co-produced DCM to be developed and for the chloromethanes plants to be tuned to meet the quantities of each product that the market required. As a result, despite local and short-term imbalances that gave rise to temporary fluctuations in the relative values of the products, the DCM/chloroform/HCFC-22/fluoropolymer system was in balance both technically and commercially.

On the other hand, growth in China, was very rapid up to 2010. At one point in the early 2000s, demand for HCFC-22 in fluoropolymer production was growing at 33 percent per year[123], although it has remained roughly constant since 2010[120]. This led to a similarly rapid growth for chloroform feedstock and a large number of chloromethanes plants was constructed. By 2010, production in China of all chloromethanes was 3 million tonnes per year, of which 90,000 tonnes was carbon tetrachloride[124]. At this time, the chloroform required for HCFC-22 production would have been about 800,000 tonnes per year. It is not known how much additional chloroform was produced in China and either used in other processes or exported, nor is there information about the production of methyl chloride. However, the growth in DCM capacity, shown in Figure 8.3, is consistent with the estimated chloroform production and with emissions estimates[107].

2050 in China and the increasing contribution to global emissions, *Atmos. Environ.*, 2016, **132**, 77-84, and supplementary material.

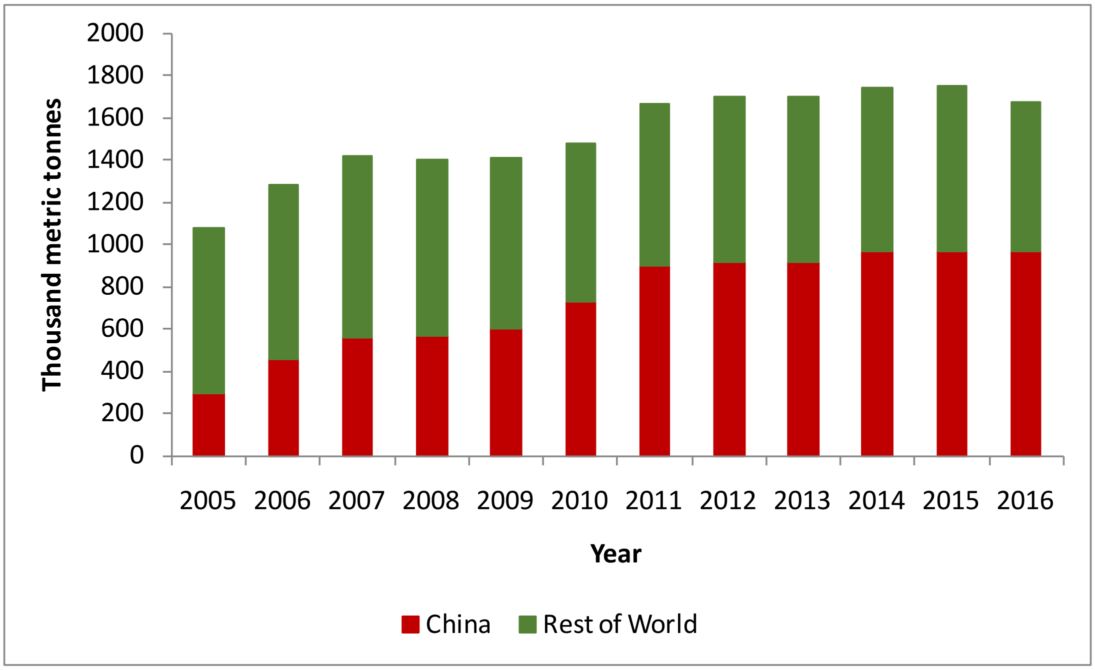
[121] U.S. EPA Facility Level Greenhouse Gas Emissions Data, available at https://ghgdata.epa.gov/ghgp/main.do#.

[122] European Pollutant Release and Transfer Register (E-PRTR), available at http://prtr.ec.europa.eu.

[123] Market Report: Fluorochemical develops rapidly in China, *China Chemical Reporter*, **13**, Sep 6, 2002.

[124] Zhang, L., Yang, W., Zhang, L., Li, X., Highly chlorinated unintentionally produced persistent organic pollutants generated during the methanol-based production of chlorinated methanes: A case study in China, *Chemosphere*, 2015, **133**, 1-5.

Figure 8.3 Global DCM capacity[125]



Furthermore, the pattern of growth in the atmospheric concentration (and hence in emissions) of DCM matches the growth in HCFC-22 production up to 2010 and then the subsequent plateau. At its lowest point in 2003, the global average atmospheric concentration of DCM would require emissions of 630,000 tonnes per year; between 2010 and 2015 the atmospheric concentration of DCM would have been sustained by emissions of 1.3 million tonnes per year. The extra 700,000 tonnes per year is consistent with the change in Chinese chloromethanes capacity over the same time period.

The fact that the pattern of change in the atmospheric concentration of DCM is very similar to the pattern of change in HCFC-22 production is unlikely to be a coincidence, given the close relationship between HCFC-22 and chloromethanes production. Unlike the situation with developed countries, where growth occurred slowly enough for the production and economic systems to remain roughly balanced, the rapid Chinese growth in HCFC-22 resulted in a similarly rapid growth in the requirement for chloroform that, because of the relative inflexibility of chloromethanes production, has driven up the availability of DCM. Inevitably, the surplus of DCM has driven down its price. The consequence of this is wider usage (in applications that might not have been attractive at higher prices) and also less incentive to conserve material.

Furthermore, international trade in DCM is, again, consistent with the decline of North American and European importance as producers and exporters and the rise of China (as a producer and exporter) and India (as a consumer and importer) [126].

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[125] European Chlorinated Solvents Association and Halogenated Solvents Industry Alliance, personal communication, 2018.

8.2.5 Future Scenarios for DCM

A simple extrapolation of an historic trend does not lead to a rational scenario for future emissions, in view of the relative complexity of the DCM market, with interactions between:

- supply (as a co-product of the more commercially desirable chloroform);
- use in emissive solvent applications;
- use as an industrial feedstock and solvent which does not lead to emission; and
- the changing trade between countries.

It is to be expected that, in the next few years (perhaps up to 2030), total demand for HCFC-22 will either remain constant or slowly decline, depending on the extent to which the increasing requirements for fluoropolymer manufacture match the reductions in production for dispersive uses required by the Montreal Protocol. Thus, the global requirement for chloroform is unlikely to change significantly. As the productive capacity for chloroform already exists, one side effect of a limited demand for chloroform is that the availability of DCM becomes fixed in a range controlled by the limits of operation of the chloromethanes plants. A fixed availability of DCM will not only limit the quantity available to be emitted but will tend to promote better husbandry and emission control as DCM supply becomes limited and its value increases.

In the period up to 2030, for the reasons discussed above, DCM emissions are unlikely to change much; the decline in emissions from non-Article 5 parties is likely to be offset by relatively slow emissions growth in China, for which a growth rate of 6 percent per year is projected. The long-term demand for HCFC-22 as a feedstock is critically dependent on the growth in demand for fluoropolymers, especially PTFE. If demand for fluoropolymers were to grow, then the requirement for feedstock HCFC-22 could reach the point where it matches current capacity for chloroform (and DCM) production. As a commodity material, the expected growth rate in fluoropolymers would be close to the growth in global gross domestic product (GDP) and any significant increase in demand is likely to occur considerably later than 2030, assuming that technology remains the same as now. However, if technology advances, the projected demand for fluoropolymers may never materialize.

Although there is a natural source of DCM (about 70,000 tonnes per year from seawater and biomass burning), most of the material emitted to the atmosphere is man-made. These emissions have remained relatively constant since 2013. However, a recent paper by Hossaini *et al.* [127], and subsequent press reports, have contained scenarios with high growth rates in DCM emissions that would give rise to significant stratospheric ozone depletion. These scenarios are extrapolations of short-term sub-sets of historic measurements. Since 1995, the concentrations of DCM in the atmosphere have been measured at a number of sites, worldwide, and have been inferred from air trapped in Antarctic snow since 1920; however, the scenarios used in Hossaini *et al.*[127] are based

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[126] Simoes, A., Dichloromethane in The Observatory of Economic Complexity, Masters Thesis in Media Arts and Sciences at the MIT Media Lab, 2017, available at http://atlas.media.mit.edu/en/profile/hs92/290312/.

[127] Hossaini, R., Chipperfield, M.P., Montzka, S.A., Leeson, A.A., Dhomse, S.S., and Pyle, J. A., The increasing threat to stratospheric ozone from dichloromethane, *Nature Communications*, 2017, **8**, 15962, DOI: 10.1038/ncomms15962.

on much shorter time scales. One scenario uses the average rate of growth of DCM in the lower atmosphere over the period 2006 to 2015 and, even though the uncertainty of this will double every 6 years, the scenario extrapolates this growth for 35 years. The other more widely reported scenario uses growth in the three years from 2011 to 2013, which is then extrapolated for 37 years. Such extrapolations would appear to have no commercial or technical rationale, based on the technical assessment provided above. As such, there is little reason to expect long-term high growth rates for DCM emissions.

In summary, based on an assessment of the current commercial and economic situation for chloromethanes, the concentration of DCM in the atmosphere is not expected to change significantly in the foreseeable future. High growth rates in emissions are very unlikely to materialise given the current lack of commercial drivers for such growth. Continued monitoring and reporting of atmospheric data of DCM will provide information on any changes in emissions. The short atmospheric lifetime of DCM also means that any reduction in emissions would have a very rapid impact in reducing atmospheric levels.

8.3 Dichloroethane

Dichloroethane (1,2-dichloroethane or ethylene dichloride (EDC)) is the principal raw material for the production of vinyl chloride, which is the monomer for polyvinylchloride (PVC). About 40 million tonnes per year of vinyl chloride is currently consumed, requiring about 65 million tonnes per year of EDC. EDC is also used as a chemical feedstock for ethylene diamines, although the highly emissive use as a scavenger in leaded petrol ceased when lead based anti-knock compounds stopped being used. Applying the same factor as that for DCM (0.1 percent), fugitive emissions from these feedstock uses would be in the region of 65,000 tonnes per year, globally. However, this is likely to be an over-estimate; according to E-PRTR, European emissions during 2015 were 860 tonnes, from capacity for PVC production in excess of 6 million tonnes per year[128], thus giving a notional emission factor of less than 0.01 percent.

Like DCM, EDC is a very short-lived substance, with a global average atmospheric lifetime of 65 days (range 41-555 days) [129]. Using the global average atmospheric lifetime, possible emission of 65,000 tonnes per year results in a calculated atmospheric burden of 11,000 tonnes, yielding an average global atmospheric concentration of less than 1 ppt (part per trillion). Reported observed concentrations in the remote atmosphere near 9 ppt are substantially higher[129]. The discrepancy could be due to a number of uncertainties, including the estimation of EDC emissions based on an emission factor. In addition, there are greater uncertainties associated with using a globally averaged lifetime to estimate atmospheric concentrations of a short-lived species because the average lifetime depends strongly on the geographic and seasonal distribution of emissions[130]. Further investigation of these uncertainties is required to resolve this apparent discrepancy.

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[128] ICIS Chemical Profile Europe: PVC available at www.icis.com/resources/.

[129] World Meteorological Organization (WMO), Scientific Assessment of Ozone Depletion: 2018, World Meteorological Organization, Global Ozone research and Monitoring Project—Report No. 58, Geneva, Switzerland, 2018.

[130] David W. Fahey, NOAA Earth System Research Laboratory, Chemical Sciences Division, personal communications, January 2019.

Predicted growth rates for PVC production and EDC consumption are about 6 percent per year[128] so that, by 2030 the background atmospheric concentration of EDC could double.

8.4 CFC-11 (trichlorofluoromethane)

Decision XXX/3 requests the Technology and Economic Assessment Panel (TEAP) to provide parties with information on potential sources of emissions of CFC-11 (trichlorofluoromethane, CCl_3F) and related controlled substances from potential production and uses, as well as from banks, that may have resulted in emissions of CFC-11 in unexpected quantities. A preliminary report will be provided to the Open-ended Working Group at its 41st meeting and a final report to the 31st Meeting of the Parties. TEAP will respond separately to decision XXX/3.

This chapter presents a summary by Medical and Chemical Technical Options Committee (MCTOC) of some preliminary background information about the recent growth of emissions of CFC-11.

8.4.1 Recent growth of emissions

In a recent paper by Montzka and colleagues[131], measurements carried out in Hawaii, USA, showed that, up until 2012, the atmospheric concentration of CFC-11 had declined at a rate consistent with the low emissions expected from a declining bank in equipment and zero production[132]. However, since then, observations show that the rate of decline in concentration has slowed. Using atmospheric models, the authors infer that an additional 13,000 ± 5,000 tonnes per year of CFC-11 has been released into the atmosphere from 2014 to 2016, with the increase (from zero to this level) occurring over the course of a year (see Figure 8.4). Using back trajectories of winds, the authors indicate that evidence strongly suggests increased CFC-11 emissions from eastern Asia after 2012.

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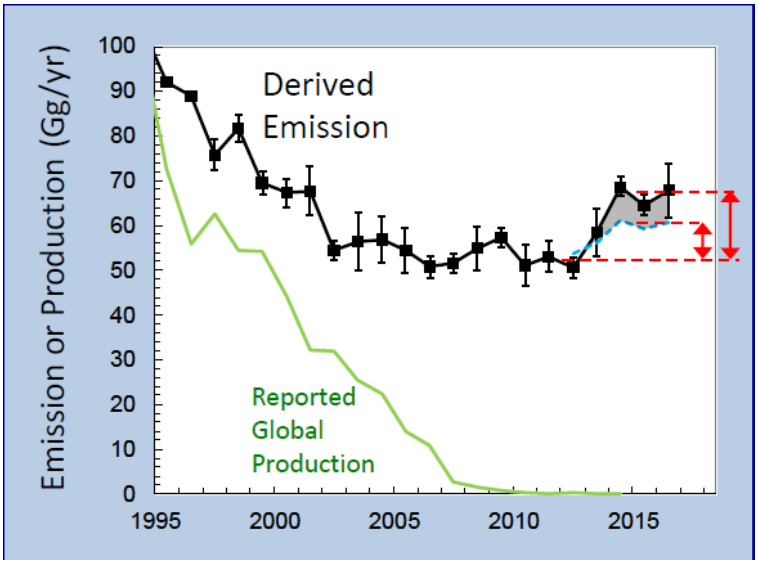
[131] Montzka et al., An unexpected and persistent increase in global emissions of ozone-depleting CFC-11, *Nature*, 2018, **557**, 413-417, https://doi.org/10.1038/s41586-018-0106-2.

[132] Harris, N. R. P. et al., in Scientific Assessment of Ozone Depletion: 2014. Global Ozone Research and Monitoring Project—Report No. 55, Chapter 5, 5.1–5.58 (World Meteorological Organization, Geneva, 2014).

Figure 8.4 Growth in emissions of CFC-11 [from Montzka *et al*, 2018][131]



Calculated by 3-D modelling of transport and loss processes in the atmosphere, an increase of 13,000 (±5000) tonnes per year would be required to fit the observations. Using a different modelling process, the absolute minimum increase is 6,000 tonnes per year. The total excess emission over the four-year period to 2016 was about 40,000 tonnes.

8.4.2 Historical CFC-11 usage

Historically, CFC-11 was used primarily as a foam blowing agent (for flexible and polyurethane insulating foams) and as a refrigerant for air conditioners (centrifugal chillers, used in large commercial buildings), and in a range of other smaller or less common uses, including asthma inhalers (as a solvent in the manufacturing process), tobacco expansion, and as a solvent/carrier for fire extinguishing agents. Alternative products or technologies have replaced the use of CFC-11 in these uses. Nevertheless, a significant “bank” of CFC-11 remains in products and systems, particularly in foam insulation where the emission rate into the atmosphere from an installed foam is very low.

8.4.3 Potential sources of emissions in production of CFC-11

The historic commercial CFC-11 production installations consisted most simply of a heated reaction vessel charged with a pentavalent antimony catalyst dissolved in partly fluorinated organic intermediates. This reactor was surmounted by a conventional distillation column and condenser, which returned a liquid reflux stream containing any vaporised catalyst or undesired organic intermediates. The system was pressurised and totally enclosed.

Anhydrous hydrogen fluoride (HF) and carbon tetrachloride are fed into the reactor, and simultaneously (through proper control of the condenser temperature) hydrogen chloride (HCl) and the desired organic products (CCl_3F, CFC-11; and CCl_2F_2, CFC-12) are removed as vapour from the top of the reflux condenser. Satisfactory operating conditions cover wide ranges; pressures from 100 kPa to 35 MPa, reactor temperatures from 45 to 200°C, catalyst concentrations from 10 to 90 wt. percent, and product take off temperatures from -30 to +100°C. Because of the simplicity of the chemistry and the interdependence of the operating variables, there is no single optimum set of conditions for any one process, but rather a series of essentially equivalent combinations that yield both CFC-11 and CFC-12 products.[133]

The relative proportions of CFC-12 and CFC-11 can be controlled by varying the operating conditions, with 100 percent CFC-12 achieved relatively easily and 100 percent CFC-11 more difficult to achieve but not impossible. Until around 1990, before Montreal Protocol controls were introduced, most processes were operated to achieve around 50:50 CFC-12 and CFC-11, with a comfortable operating range of 30:70 either way.

The reaction mixture can normally be contained in vessels made of simple materials, like mild steel. However, somewhat unpredictably, when process conditions are changed, the reaction mixture can become very, very corrosive, eating through fairly thick metals in a matter of hours. This makes operators wary about changing conditions drastically.

Nevertheless, it is possible to produce almost 100 percent CFC-11 in a detuned CFC-11/-12 plant. Modifications could be made to the system pressure so that the reactor temperature could be reduced, then the antimony catalyst loading increased so that it has a lower fluoride concentration, which is less aggressive. The effect on throughput, and how close one could get to 100 percent CFC-11 production, would depend on the individual plant. There would be limited scope to recycle CFC-12 to extinction, implying use/disposal of any remaining CFC-12.

Under the Montreal Protocol, production of CFC-11 in developed countries was phased out in 1996; production of CFC-11 in developing countries was phased out in 2010. Exceptions were made for small amounts of CFC-11 production for essential uses (i.e. asthma inhalers) and production for feedstock uses[134]. Any production of CFC-11 for non-feedstock and feedstock uses is required to be reported to UNEP under Article 7. Production of CFC-11 to supply essential uses was less than 400 tonnes each year after 2010 and ceased altogether after 2014. No feedstock uses of CFC-11 have been reported from parties.

8.4.3.1 Emissions associated with CFC-11 production

Highly automated, tight and well-instrumented facilities with proper, closely observed, procedures can have ozone-depleting substances (ODS) emission levels as low as 0.05 percent of the ODS amount used as feedstock. At the other extreme, batch processes of limited scale with less tight facilities, with less concern for operational excellence, could have emission levels up to 5 percent of the ODS amount used as feedstock. For unregulated illegal production with inadequate controls emission levels could be even higher.

Emissions are not reported under the Montreal Protocol and MCTOC has estimated emissions resulting from the production of ODS. For indicative estimations of ODS emissions, an emission factor of 0.5 percent has been applied uniformly for the production of all controlled ODS.

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[133] Hamilton Jr., J.M., The Organic Fluorochemicals Industry in Advances in Fluorine Chemistry, Volume 3, (M Stacey, J.C. Tatlow and A.G. Sharpe eds.), Butterworths, London, 1963, 281pp.

[134] Feedstock uses refer to the use of ODS as chemical building blocks for the commercial synthesis of other chemicals.

Losses of 13,000 tonnes per year of CFC-11 are not economical from a chemical production process. At the upper end of possible emission levels (5 percent losses) for an economically run process, this would equate to production of 260,000 tonnes CFC-11 per year. By comparison, CFC-11 production in the 1980s peaked between about 350,000-400,000 tonnes per year.

8.4.3.2 CFC-11 produced as a by-product of a manufacturing process

Montzka suggested that inadvertent CFC-11 production is possible from the fluorination of chlorinated methanes (for example, to produce HCFC-22). CFC-11 produced as a by-product in other chemical manufacturing pathways is unlikely for technical reasons. Under normal operating conditions, CFC-11 production as a by-product of HCFC-22 production is negligible (around 0.1 percent). It is technically possible that minor CFC-11 emissions (much smaller than observed) could arise from processes to produce the hydrofluoroolefins (HFOs). Any CFC-11 produced in this manner is more likely to be captured and recycled or destroyed. This by-production would count as CFC-11 "production" and is required to be reported under the Montreal Protocol unless it is insignificant[135].

The observed rapid rate of increase of CFC-11 emissions to a relatively constant value is not consistent with CFC-11 emissions as a by-product from a process to manufacture a new chemical, where the increase might be expected to occur more slowly as production of the new chemical increased. In addition, the cost of producing this CFC-11, only to release it into the atmosphere, is not consistent with an economically operated process.

8.4.3.3 Emission from a stockpile of previously reported CFC-11 production

Any stockpile accumulated from ODS production is not reported under the Montreal Protocol. Consumption of CFC-11 stockpile after the production phase-out is not prohibited under the Montreal Protocol. However, there is not likely to be enough CFC-11 in the stockpile inventory to account for the total amount of unaccounted CFC-11 emissions. The observed rapid rate of increase in emissions to a relatively constant value is also not consistent with continuous leakage from a stockpile, nor with a catastrophic emissions release. Stockpiles have a commercial value as they can continue to be used and are unlikely to be intentionally released.

8.4.3.4 CFC-12

The fate of any CFC-12 produced as a by-product of CFC-11 production is not yet clear. Indeed, it is not yet clear whether the observed unexplained increase in CFC-11 emissions is associated with CFC-11 production to supply emissive CFC-11 uses, or whether CFC-11 is being produced as a by-product of CFC-12 production for the purpose of supplying CFC-12 uses.

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[135] Decision IV/12 "that insignificant quantities of controlled substances originating from inadvertent or coincidental production during a manufacturing process, from unreacted feedstock, or from their use as process agents which are present in chemical substances as trace impurities, or that are emitted during product manufacture or handling, shall be considered not to be covered by the definition of a controlled substance contained in paragraph 4 of Article 1 of the Montreal Protocol;"

9 Laboratory and Analytical Uses

9.1 Background

Laboratory and analytical uses (LAUs) of controlled substances have included: 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.

Decision IV/25 establishes criteria and procedures that permit the production and consumption of controlled substances beyond their production phase-out, in relation to the control measures under Article 2. A controlled substance qualifies as essential only if:

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

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

Production and consumption are permitted only if:

i) all economically feasible steps have been taken to minimize the essential use and any associated emission of the controlled substance; and

ii) the controlled substance is not available in sufficient quantity and quality from existing stocks of banked or recycled controlled substances, also bearing in mind the developing countries' need for controlled substances;

At the 6th Meeting, parties authorised an essential use exemption for laboratory and analytical uses for the first time in decision VI/9, according to conditions set out in Annex II of the report for that meeting (see Appendix 1). Annex II authorises essential use production for laboratory and analytical purposes only if the controlled substances are manufactured to high purity and supplied in re-closable containers and in small quantities[136]; this became known as the global essential use exemption. Other than these quality specifications, Annex II also required that parties shall annually report for 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. The Annex also required that parties shall also submit copies of published instructions, standards, specifications, and regulations requiring the use of the controlled substance.

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[136] The purity standards and other requirements placed on laboratory and analytical uses are given in Annex II of the report of the Sixth Meeting of the Parties, and include the following: (i) purity requirements; (ii) criteria that controlled substances for laboratory and analytical uses shall be supplied only in re-closable containers or high pressure cylinders smaller than three litres or in 10 millilitres or smaller glass ampoules; and (iii) advice concerning preparation of mixtures containing the controlled substances, labelling, recovery and reuse, and annual reporting of activities.

"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, parties adopted at their 7th Meeting (decision VII/11), a non-exhaustive illustrative list of categories and examples of laboratory uses, as specified in Annex IV of the meeting report. This decision also excluded specific uses from the global exemption that were not exclusive to laboratory and analytical uses and/or where alternatives were available (see Appendix 1).

Various decisions have subsequently extended the global laboratory and analytical use exemption under these specified conditions, excluded additional specific uses from the global exemption, and/or requested the Technology and Economic Assessment Panel (TEAP) to report on developments in alternatives to the use of controlled substances. Decision XXI/6 extended the applicability of the global essential use exemption to countries operating under Article 5 for controlled substances subject to relevant Article 2 control measures. Decision XXX/8 includes Annex C, group I, substances in the global laboratory and analytical use exemption under the same conditions as specified in Annex II of the 6th Meeting (decision VI/9).

Where alternatives are available for laboratory and analytical uses of controlled substances, decisions have been made to exclude those uses from the exemption because they were no longer considered essential. Decisions VII/11, XI/15, XVIII/15 and XIX/18 have eliminated the following laboratory and analytical uses from the global exemption for laboratory and analytical uses:

a) Refrigeration and air conditioning equipment used in laboratories, including refrigerated laboratory equipment such as ultra-centrifuges;

b) Cleaning, reworking, repair, or rebuilding of electronic components or assemblies;

c) Preservation of publications and archives;

d) Sterilization of materials in a laboratory;

e) Testing of oil, grease and total petroleum hydrocarbons in water;

f) Testing of tar in road-paving materials;

g) Forensic finger-printing;

h) All laboratory and analytical uses of methyl bromide except:

    i) As a reference or standard:

        - To calibrate equipment which uses methyl bromide;
        - To monitor methyl bromide emission levels;
        - To determine methyl bromide residue levels in goods, plants and commodities;

    ii) In laboratory toxicological studies;
    iii) To compare the efficacy of methyl bromide and its alternatives inside a laboratory;
    iv) As a laboratory agent which is destroyed in a chemical reaction in the manner of feedstock;

i) Testing of organic matter in coal.

Decision XVIII/15 authorizes the production and consumption of methyl bromide subject to the conditions applied to the global essential use exemption for laboratory and analytical uses contained in Annex II to the report of the 6th Meeting of the parties, and adopts a category of laboratory and analytical uses of methyl bromide allowable under the global exemption:

a) As a reference or standard:
    i) To calibrate equipment which uses methyl bromide;
    ii) To monitor methyl bromide emission levels;
    iii) To determine methyl bromide residue levels in goods, plants and commodities;
b) In laboratory toxicological studies;
c) To compare the efficacy of methyl bromide and its alternatives inside a laboratory;
d) As a laboratory agent which is destroyed in a chemical reaction in the manner of feedstock.

Decision IX/17 added that data for consumption and production should be reported annually under a global essential use exemption framework to the Secretariat so that the success of reduction strategies may be monitored. Decision X/19 further clarified 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, as set out in decision IV/25.

The former Chemicals Technical Options Committee (CTOC) reported in detail in 2008[137], 2009[138], 2010[139] and 2011[140] on the availability of alternatives for laboratory and analytical uses of ozone-depleting substances (ODS) in response to decisions by parties. TEAP recommended a range of additional laboratory and analytical uses for their removal from the global essential use exemption. A recent Medical and Chemical Technical Options Committee (MCTOC) report[141], and its findings reproduced in this assessment, built on the previous work and considered

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[137] May 2008 Report of the UNEP TEAP, Volume 1, Progress Report, 2008, pg. 54.

[138] May 2009 Report of the UNEP TEAP, Volume 1, Progress Report, 2009, pg. 51.

[139] May 2010 Report of the UNEP TEAP, Volume 2, Progress Report, 2010, pg. 53.

[140] May 2011 Report of the UNEP TEAP, Volume 1, Progress Report, 2011, pg. 51.

[141] Report of the UNEP TEAP, September 2018, Volume 4: Response to Decision XXVI/5(2) on Laboratory and Analytical Uses.

available alternatives to laboratory and analytical uses of ODS, and potential barriers to their adoption, in Article 5 and non-Article 5 parties.

International and/or national standards for laboratory and analytical uses are often adopted across a number of countries. A country without its own national standards-setting organisation can adopt international standards or national standards published by another country. As such, there is some technical uniformity in the suite of standards for laboratory and analytical methods, which are adopted across Article 5 and non-Article 5 parties. The scientific community also adopts laboratory methods based on the body of international publications, scientific theory and knowledge. As such, there is also reasonable technical uniformity in the suite of laboratory methods adopted across Article 5 and non-Article 5 parties. However, technical and economic barriers to the adoption of alternatives can differ depending on individual circumstances (e.g. availability of specialized scientific equipment or laboratory and analytical reagents). A main barrier to change is often the adoption of new standards and the associated resource-intensive process.

The review of standard analytical procedures is challenging for the following reasons:

- There is a considerable body of documented international and national standard analytical methods, and the adopted standards can vary from country to country and cover a wide range of different applications;

- It is difficult to identify and access a complete range of relevant published standards set by organisations, such as the International Organization for Standardization (ISO), ASTM International (ASTM), the European Committee for Standardization (CEN).

With the limited resources available to it, and in the absence of recent input from parties, TEAP has been limited in its capacity to undertake a comprehensive review of the circumstances of individual countries. Nevertheless, a review of standards for analytical procedures has been undertaken, within the limitations, and recommendations have been made based on currently available information and building on the previous reviews by CTOC.

The global essential use exemption applies to controlled substances in Annex A, B, C Groups II and III, and Annex E, as relevant to the Article 2 control measures for Article 5 and non-Article 5 parties. This report limits its focus primarily on controlled substances already included in the global essential use exemption for laboratory and analytical uses. Annex C Group I (hydrochlorofluorocarbons, HCFCs) are not yet included under the global essential use exemption; control measures for 100 percent reduction do not take effect in non-Article 5 parties until 2020. This report provides some information on the known laboratory and analytical uses of Annex C Group I. Annex F controlled substances are not included in this report.

MCTOC has conducted online and literature research, reviewed other publicly available information, and consulted with experts. Standards organisations, such as the International Organization for Standardization (ISO), ASTM International (ASTM), the European Committee for Standardization (CEN), the Standardization Administration of the People’s Republic of China (SAC) and U.S. EPA, were referenced. Article 7 data, on controlled substances used for laboratory and analytical purposes, was provided by the Ozone Secretariat to MCTOC.

9.2 Production and consumption data reported for laboratory and analytical uses

9.2.1 Reported data

Parties have reported the production and consumption of controlled substances used for laboratory and analytical purposes to the Ozone Secretariat from 1996 onwards. The Ozone Secretariat provided data to the MCTOC on production and consumption from 1996 to 2016. 40 Parties have reported their consumption data to Ozone Secretariat, covering more than 46 different ODS, with their consumption data varying greatly from tonnes to grams. Only ten parties operating under non-Article 5, and one party operating under Article 5, have reported production data.

Table 9.1 List of parties that reported production/consumption data for LAUs to the Ozone Secretariat during the period 1996-2016

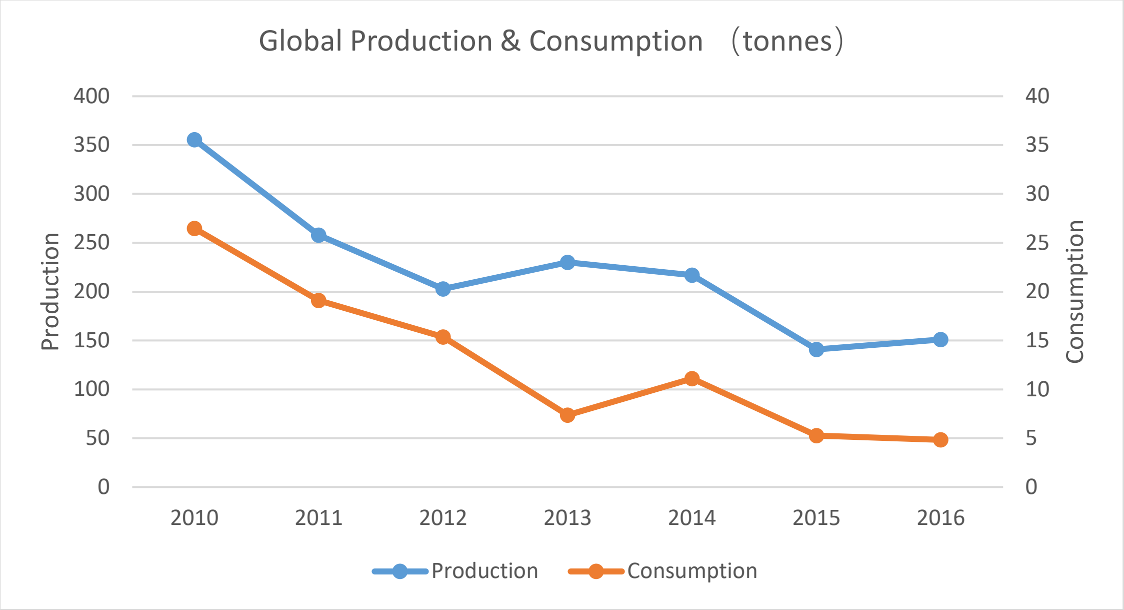
	Non-Article 5	Article 5
1	Australia	Argentina
2	Belarus	Bahrain
3	Canada	Bhutan
4	Croatia	Bolivia
5	Czech Republic	Bosnia and Herzegovina
6	EU	Brazil
7	Israel	Chile
8	Italy	China
9	Japan	Colombia
10	Korea	Cuba
11	Liechtenstein	Ecuador
12	Netherlands	El Salvador
13	New Zealand	Guyana
15	Norway	Haiti
16	Poland	Indonesia
17	Romania	Mauritius
18	Russian	Mexico
19	San Marino	Nepal
20	Serbia	Oman
21	Singapore	South Africa
22	Slovakia	Sri Lanka
23	Slovenia	
24	Switzerland	
25	The former Yugoslav Republic of Macedonia	
26	Turkey	
27	Turkmenistan	
28	USA	

9.2.2 Global production and consumption data for LAUs

Figure 9.1 shows the total global production and consumption reported in recent years. A general decreasing trend in both production and consumption can be seen, indicating effectiveness of the global efforts to control the ODS in laboratory and analytical uses. In 2016, the global production of all reported controlled substances for LAUs was 151 metric tonnes, carbon tetrachloride (CTC) being the main ODS produced. In 2016, the global consumption of ODS for LAUs is 4.828 tonnes, with CTC and CFC-113 (1,1,2-trichloro-1,2,2-trifluoroethane, $C_2Cl_3F_3$) being the main ODS.

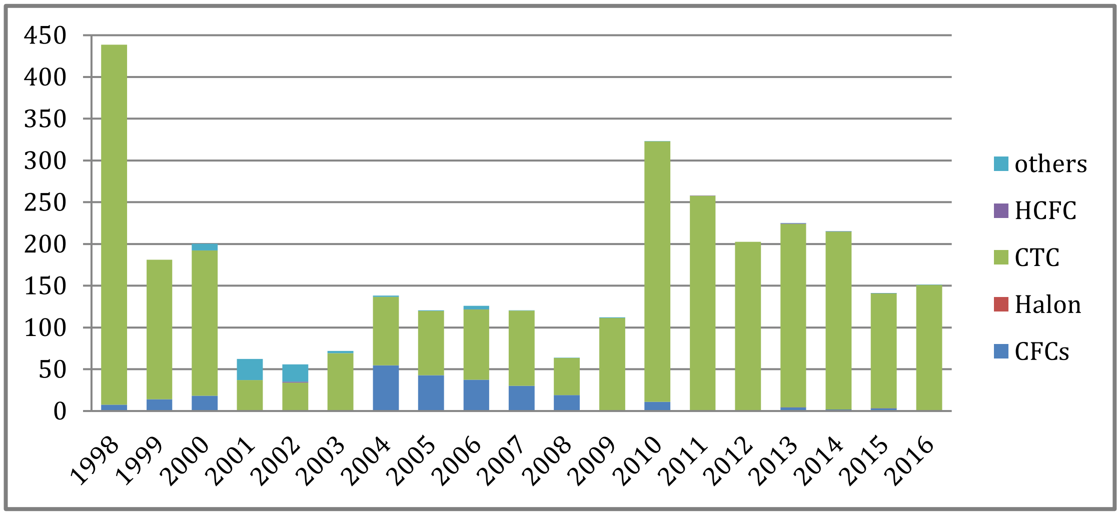
It also can be found that the total global consumption data amounts to much less than the production data. From consultations about the data, MCTOC understands that the production data may be more accurate due to the production quota and data collecting systems in some parties. Therefore, the following discussion on LAUs will be focused primarily on the production data.

Figure 9.1 Reported global production and consumption for LAUs, 2010-2016



The global production since 1998 has been categorized by ODS type in Figure 9.2. There are 25 ODS that have been reported as production for laboratory and analytical use. CTC is the dominant ODS of total global production for LAUs, followed by CFC-113 and 1,1,1-trichloroethane (TCA) in tonnes of annual production. In 2016, the total reported production of CTC was 150.9 tonnes, which represents 99.96 percent of the total global production of ODS for LAUs. The production of other ODS is relatively very small, in the kilograms.

Figure 9.2 Reported global production for LAUs by ODS type (tonnes), 1998-2016



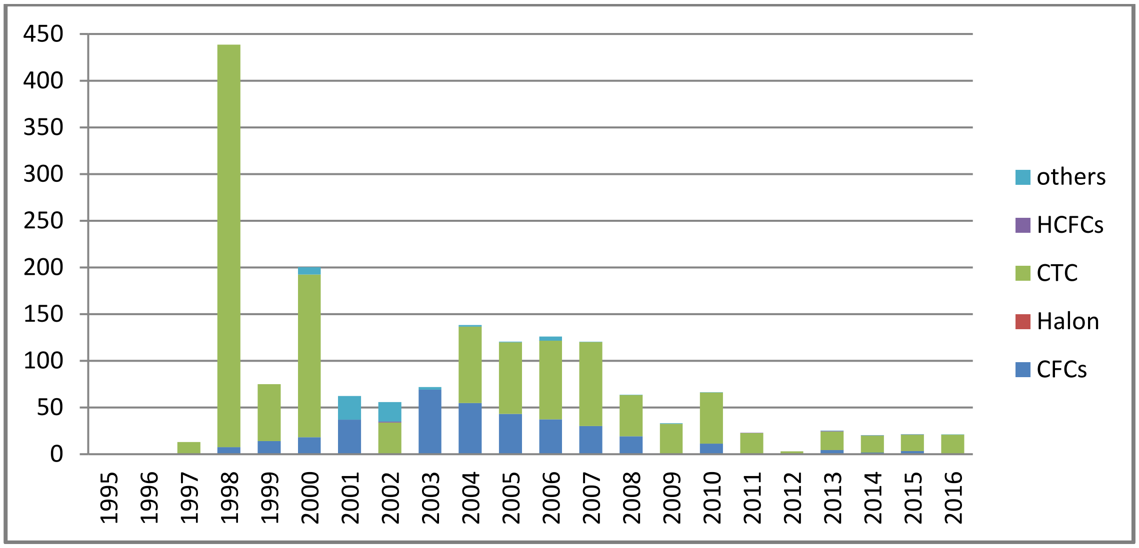
*Others includes Annex B, Group III 1,1,1-trichloroethane (TCA) and Annex E, Group I methyl bromide (CH_3Br)

Figure 9.2 shows that the global production of ODS of LAUs dropped from 438.6 tonnes in 1998 to 150.965 tonnes in 2016, a decrease of about 70 percent. Figure 9.2 also shows that CTC is produced during all the years, while other ODS are produced occasionally, indicating storage of these ODS.

9.2.3 Production of ODS in non-Article 5 and Article 5 parties for LAUs

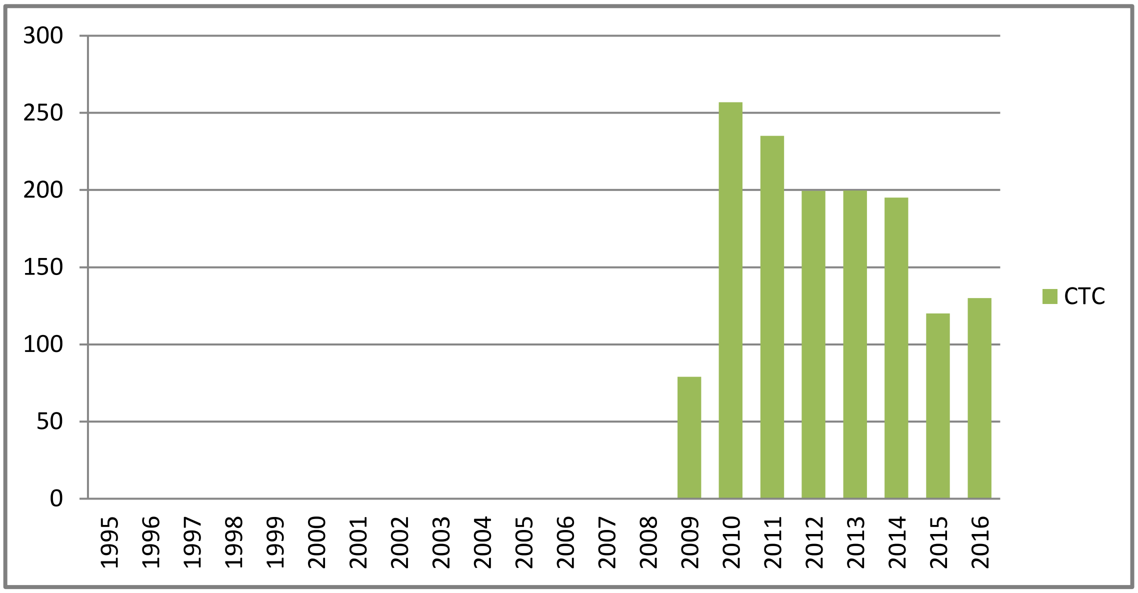
The reported production of ODS for LAUs in non-Article 5 parties is presented in figure 9.3. Production in all non-Article 5 parties has dropped from 438.6 tonnes in 1998 to 20.9 tonnes in 2016. CTC is the predominant ODS being produced for LAUs in recent years, followed by CFC-113, which is produced in some years.

Figure 9.3 Total production for LAUs reported by non-Article 5 parties, 1995-2016 (tonnes)



Article 5 parties began reporting production data for LAUs in 2009, as shown in Figure 9.4. CTC is the only ODS reported by Article 5 parties. A gradual overall decrease in reported production can be seen during the period, from a peak of 257 tonnes in 2010 to 130 tonnes in 2016.

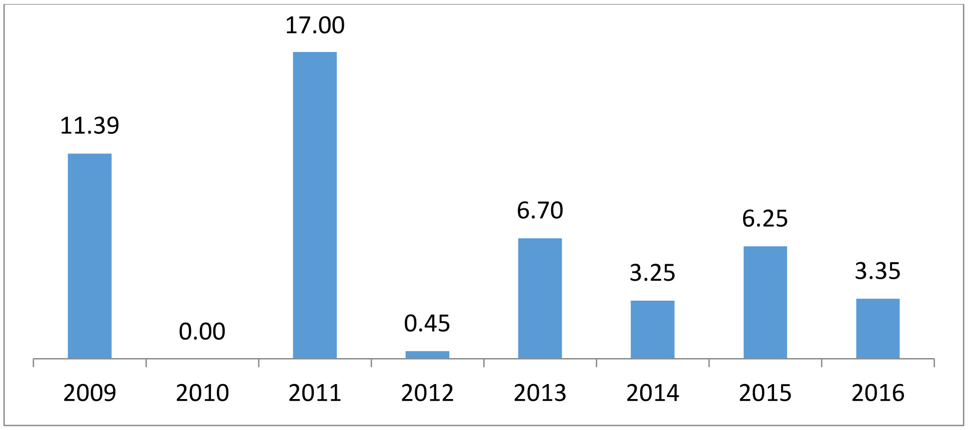
Figure 9.4 Total production for LAUs reported by Article 5 parties, 1995-2016 (tonnes)



9.2.4 Consumption of methyl bromide for LAUs

The reported global consumption of methyl bromide for LAUs has decreased greatly in the last decade. In 2006, the total reported consumption of methyl bromide reported by the parties was 604 kg, while the amount of consumption in 2009 was 11.39 kg, as shown in Figure 9.5, with a further drop in consumption to 3.35 kg in 2016. This reported quantity is relatively very minor compared with the total reported ODS consumption in laboratory and analytical uses.

Figure 9.5 Reported global consumption of methyl bromide for LAUs, 2009-2016 (kg)



When compared with the reported quantity of methyl bromide consumed in quarantine and pre-shipment (QPS) (8,370 tonnes[142]), in critical uses (554 tonnes[143]), and produced for feedstock uses (4,200 tonnes) in 2016, the reported quantity of methyl bromide consumed for laboratory and analytical uses is very minor (3.35 kg).

9.2.5 Consumption of HCFCs for LAUs

From data reported by parties on laboratory and analytical uses of HCFCs in 2016, the annual consumption of HCFCs in Article 5 and non-Article 5 parties was reported to be 20 kg (HCFC-21, -22, -123, -141b, -233, -242, -252, HBFC-21B2, -22B1).

9.3 Laboratory and analytical uses and their alternatives

9.3.1 Background

Following reviews by the CTOC in 2008[144], 2009[145], 2010[146] and 2011[147], alternatives to the use of controlled substances were identified for a range of laboratory and analytical uses. As a result, TEAP recommended a list of laboratory and analytical uses for possible removal from the global essential use exemption. These were not adopted through a decision of parties.

An overview review of these and other laboratory and analytical uses has been undertaken by MCTOC[148], with recommendations made based on currently available information and building on the previous reviews by CTOC. This section provides details of this review.

9.3.2 Laboratory solvent and reagent uses

Many laboratory uses of controlled substances have been phased out through the use of alternative chemicals and/or procedures. Laboratory uses of ODS, e.g. as a common solvent or cleaning agent, have largely been phased out in developed countries and are disappearing from laboratories in developing countries, by using alternatives with similar chemical properties (e.g. polarity and solvent properties).

CTC is a useful laboratory chemical for one or more of the following reasons: reasonably good solvency; does not attack common materials including many elastomers used in reaction vessels;

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[142] May 2018 Report of the UNEP TEAP, Volume 3, Progress Report, 2018, pg. 18.

[143] May 2018 Report of the UNEP TEAP, Volume 3, Progress Report, 2018, pg.17.

[144] May 2008 Report of the UNEP TEAP, Volume 1, Progress Report, 2008, pg. 54.

[145] May 2009 Report of the UNEP TEAP, Volume 1, Progress Report, 2009, pg. 51.

[146] May 2010 Report of the UNEP TEAP, Volume 2, Progress Report, 2010, pg. 53.

[147] May 2011 Report of the UNEP TEAP, Volume 1, Progress Report, 2011, pg. 51.

[148] Report of the UNEP TEAP, September 2018, Volume 4: Response to Decision XXVI/5(2) on Laboratory and Analytical Uses.

non-flammable, and not easily degraded under conditions of use; easily removed by evaporation or distillation without excessive energy consumption; readily available at affordable prices.

For these reasons, CTC has been widely used as a solvent in synthetic organic chemistry for reactions in which two or more components are dissolved in the solvent to react under heating to form new substances. The products of these reactions are recovered by cooling, followed by appropriate ‘work up’ that often involves evaporation (and potential recovery) of the CTC. Many of the industrial uses of CTC stem from patented procedures that were developed in laboratories. Where such laboratory work is destined to become an industrial process, consideration needs to be given to finding an alternative solvent at the outset.

TEAP has reported in its progress reports the details of CTC uses in laboratory and analysis procedures and has identified alternative procedures for which CTC can be replaced. As part of investigations made by the CTOC in 2008[144], 2009[145], 2010[146] and 2011[147], TEAP recommended a list of procedures that could be removed from the global exemption for laboratory and analytical uses of CTC. MCTOC has reviewed the use of CTC as a solvent in reactions involving *N*-bromosuccinimide[149].

It has been difficult to find alternatives to some laboratory uses of ODS where portions of the ODS molecules are incorporated into the products of the chemical reactions, e.g. methyl bromide used as a methylating agent. Since the ODS can be destroyed, through conversion to non-ODS products, and/or the laboratory procedures are conducted on a much smaller scale (e.g. than those in industry), the emissions from such uses are likely to be miniscule. MCTOC has made recommendations regarding methyl bromide used as a methylating agent[150].

9.3.2.1 CTC used as a solvent in reactions involving N-bromosuccinimide

There has been one laboratory solvent use of CTC that has proven difficult to replace with suitable alternatives: bromination reactions using *N*-bromosuccinimide (NBS).

TEAP reported in the past decade that CTC was the only solvent suitable for use in certain reactions of organic chemicals, notably bromination reactions involving NBS. In its progress report in 2015, TEAP identified that α,α,α-trifluorotoluene could be a suitable alternatives for CTC in NBS reactions.

MCTOC has made a comprehensive literature search and found that many studies have been done in recent years on alternative procedures for NBS related bromination reactions. Detailed information is provided in Appendix 2: Alternatives for Use of Carbon Tetrachloride (CTC) as a Solvent for Bromination Reactions involving NBS.

Table 9.2 summarises the reaction procedures and the relative alternatives to CTC (see also Appendix 2). It is found that for different reaction procedures there are different options available for alternatives to the use of CTC, under similar reaction conditions and with comparable reaction results.

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[149] Report of the UNEP TEAP, September 2018, Volume 4: Response to Decision XXVI/5(2) on Laboratory and Analytical Uses.

[150] Report of the UNEP TEAP, September 2018, Volume 4: Response to Decision XXVI/5(2) on Laboratory and Analytical Uses.

These findings have allowed TEAP and its MCTOC to recommend that CTC used as a reaction solvent (including in reactions involving NBS) can be excluded from the global essential use exemption for laboratory and analytical uses.

Table 9.2 Alternatives, or alternative procedures, for CTC in reactions involving NBS

Reaction Procedure	Alternatives to CTC
Wohl–Ziegler bromination	Chlorinated solvents (chloroform, 1,2-dichloroethane, dichloromethane) Non-chlorinated solvents ((trifluoromethyl)benzene, acetonitrile, ionic-liquid etc.)
Electrophilic substitution reaction	DMF, THF, acetic acid-chloroform
Electrophilic addition reaction	DME, THF, or t-butanol, dichloromethane
Oxidation reaction	Cyclodextrin-water, aqueous THF-H_2SO_4

DMF: *N,N*-Dimethylformamide; THF: Tetrahydrofuran, H_2SO_4: sulfuric acid.

9.3.2.2 Methyl bromide used as a methylating agent

One of main laboratory uses of methyl bromide is as a methylating agent in chemical reactions to deliver a methyl group to a chemical substrate. Literature research shows that there are many alternatives to using methyl bromide as a methylating agent (see Appendix 3). These alternatives are nearly always used in preference to methyl bromide. Methyl bromide is a toxic gas, which limits greatly its practicality in this application. Cost and availability are not barriers to uptake of the alternatives, although long-term users of methyl bromide in these applications may need to experiment so as to adapt their practice to the alternative methylating agents.

These findings have allowed TEAP and its MCTOC to recommend that methyl bromide used as a methylating agent in laboratories can be excluded from the global essential use exemption for laboratory and analytical uses.

9.3.3 Standards related to laboratory and analytical use of ODS and their alternatives

Standards play an important role in leading and facilitating the replacement of ODS in laboratory and analytical uses. Standard methods are adopted and followed because they allow comparisons over time and between different laboratories. The use of a standard method is often required by a customer as a form of quality assurance for a product, or by a regulatory authority. Considerations, such as the ease and reliability of the assay, workplace health and safety, or the availability of substances under inter-governmental agreements, such as the Montreal Protocol, can cause new standards to be written. Standards development or revision has to undergo a rigorous procedure, which usually takes time and is accompanied by a cost, and often lags behind the identification of the need for change. In addition, users can be slow to adopt new standards for a number of reasons, including cost, familiarity with techniques, availability of equipment, and validation of the new method including comparability of results measured using previous and new methods.

In its previous progress reports, the former CTOC provided some information on the development of standards that do not use ODS, especially in relation to standards that previously used CTC. It shows that international bodies, such as ASTM International and ISO, have been continuing to work on the development of new standard methods to replace ODS in laboratory and analytical uses. The European Commission published a laboratory ODS Registry Manual in January 2017, to guide laboratories and suppliers of ODS for laboratory and analytical uses in the registration process allowing continued use of ODS. The manual also provides a list of standard methods for which alternatives exist for ODS in LAUs[151].

MCTOC reviewed[152] the current status of standards; the major standards related bodies, such as ISO, ASTM International, the European Committee for Standardisation (CEN), the Standardization Administration of the People's Republic of China (SAC) and U.S. EPA, were considered in this review. Since it is difficult to acquire the full paper of all of the standards, instead abstracts of the standards containing key words were relied upon for information on alternatives or alternative procedures that do not use ODS. Some bodies seemed to have eliminated the use of some ODS for their standards; for example, a search for CTC on the CEN database discovered no results. A list of standards identified that do not use ODS is provided in Appendix 4 (updated since September 2018). A summary sample of a few standards for which alternatives are available follows.

For the test on the **determination of hydrocarbons** (oil, grease etc.) in water or soil, CTC is the common solvent used in this standard procedure, CFC-113, which is also an ODS, was previously selected as an alternative for CTC, in some cases due to the toxicity concern of CTC. A wide range of alternatives are now available for both CTC and CFC-113, including hydrocarbons, such as hexane, and chlorinated solvents, such as methylene chloride.

For the test on the **determination of iodine index or bromine index**, in which CTC and 1,1,1-trichloroethane were used as solvent, a mixture of glacial acetic acid with other solvents, such as cyclohexane, methanol and chloroform, could be adopted.

For the test on the **determination of moisture and water** in animal and vegetable fats and oils, or petroleum products and bituminous materials, alternatives such as xylene, methanol, aromatic solvents, and paraffinic solvents could be selected for different analytical procedures.

For the test on the **determination of phenol in water**, chloroform is recognized as alternative for CTC by organisations, such as ISO, ASTM and U.S. EPA. However, ISO still allows the use of ODS for the standard, "Water quality — Determination of phenol index — 4-Aminoantipyrine spectrometric methods after distillation" (see Appendix 5).

ASTM also developed a new procedure that uses methyl isobutyl ketone as a solvent for the replacement of CTC in the **determination of lead in gasoline**, which will be helpful in the development of new analytical methods for the determination of the content of other metals in water or soil. There are many standards to determine the content of metals in water or soil, and more time will be needed before the use of ODS can be eliminated for this category.

However, even though the international standard bodies and non-Article 5 parties have made great progress on standards development or revision to replace ODS in analytical use, there are standards that still allow the use of ODS (see Appendix 5). For some standards, the alternative or

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[151] EC Manual for the ODS Licensing System, the European Commission, 2017, available at https://ec.europa.eu/clima/policies/ozone/ods_en, accessed September 2018.

[152] Report of the UNEP TEAP, September 2018, Volume 4: Response to Decision XXVI/5(2) on Laboratory and Analytical Uses.

alternative procedures may exist, but the ODS method still remains as an active standard for these standard bodies, implying some barrier in adopting the alternatives or alternative procedures in standards development or revision.

Difficulties and/or complexities in adopting the alternatives may be creating greater barriers for Article 5 parties. China, for example, investigated CTC in laboratory and analytical uses in China[153] and listed more than 30 standards using CTC that require revision. Recent information indicates that little progress has been made for most of these standards, except for some standards for the determination oil and grease in water, some of which are still under development.

As previously outlined in 2011 TEAP Progress Report, the reasons that non-ODS methods are not adopted in Article 5 parties are adherence to standard methods that use ODS, and the cost of implementing new methods including training. In the first instance, where purely national standards are involved, skilled practitioners within those countries have the capability to adopt the alternative procedures. Only in the few cases, where an international standard exists and there is no non-ODS alternative, should it be necessary to persist with the use of ODS. In the second instance, the cost of transition should be sustainable, although the cost of alternative substances or procedures may be higher than those of the ODS methods they replace. It takes time and skilled resources to implement new methods; however, in many cases, non-ODS alternatives are available and may have been adopted already by international standards bodies or in non-Article 5 parties.

Parties may wish to consider establishing cooperation with standards organisations, to facilitate and accelerate the development or revision of standards for the replacement of ODS in analytical uses.

9.3.4 Methyl bromide used as a reference or standard, or in laboratory studies

Decision XVIII/15 authorizes the production and consumption of methyl bromide for laboratory and analytical uses subject to the conditions applied to the global exemption, and adopts a category of laboratory and analytical uses of methyl bromide that is allowable:

(a) As a reference or standard:

  (i) To calibrate equipment which uses methyl bromide;

  (ii) To monitor methyl bromide emission levels;

  (iii) To determine methyl bromide residue levels in goods, plants and commodities;

(b) In laboratory toxicological studies;

(c) To compare the efficacy of methyl bromide and its alternatives inside a laboratory;

(d) As a laboratory agent which is destroyed in a chemical reaction in the manner of feedstock;

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[153] http://odslab.chinareagent.com.cn/, accessed September 2018 (in Chinese).

TEAP believes that the current usage of methyl bromide as a reference or standard, in laboratory toxicological studies, and for comparison of methyl bromide and its alternatives inside a laboratory, is likely to be minor, possibly in the kilograms range globally. The likelihood of significant amounts (or any amounts) used this way has diminished as there are very few trials done on methyl bromide, with fewer on insect mortality studies and laboratory emission studies with barrier films. There is a possibility that these amounts, especially for insect mortality studies, could increase slightly if QPS uses were controlled further under the Montreal Protocol although the global quantities would remain very small. Nevertheless, methyl bromide used as a reference or standard, or in laboratory studies, will likely continue for as long as methyl bromide is used in applications (e.g. QPS or horticultural uses).

9.3.5 Laboratory and analytical uses of HCFCs

Non-Article 5 parties are likely to require HCFCs for laboratory and analytical uses, for example to be used as analytical standards for the measurement of atmospheric levels of HCFCs, and for the research into and development of new substances. The following laboratory and analytical uses for HCFCs have been reported and may continue to require HCFCs post-2020 due to slow progress in moving to alternatives.

- Reference chemical (in analytical methods and for enforcement) e.g. HCFC-21, HCFC-22, HCFC-31, HCFC-122, HCFC-123, HCFC-124, HCFC-133a, HCFC-141b, HCFC-142b, HCFC-151a, HCFC-233;
- Feedstock (reagent in laboratory chemical synthesis) e.g. HCFC-22, HCFC-242, HCFC-252;
- Solvent (inert solvent in laboratory chemical synthesis) e.g. HCFC-31;
- Reference chemical (in toxicological studies) e.g. HCFC-21;
- ODS as a component in samples to be tested.

Laboratory and analytical use of HCFCs as a reference chemical will continue for as long as HCFCs are used in applications.

9.4 Laboratory and analytical uses that can be performed without using controlled substances

Following investigations made by the CTOC in 2008[154], 2009[155], 2010[156] and 2011[157], TEAP identified a number of laboratory and analytical procedures, for which alternatives to the use of ODS were available, and it recommended their removal from the global essential use exemption. In the preambular text of Decision XXI/6 in 2009, parties noted these identified procedures (see Appendix 1, Decision XXI/6).

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[154] May 2008 Report of the UNEP TEAP, Volume 1, Progress Report, 2008, pg. 54.

[155] May 2009 Report of the UNEP TEAP, Volume 1, Progress Report, 2009, pg. 51.

[156] May 2010 Report of the UNEP TEAP, Volume 2, Progress Report, 2010, pg. 53.

[157] May 2011 Report of the UNEP TEAP, Volume 1, Progress Report, 2011, pg. 51.

Case studies presented in the 2009 TEAP Progress Report showed that most laboratory and analytical uses of ODS in non-Article 5 Parties had ceased. Alternatives were identified by CTOC for almost all uses[158], and the list of methods for which alternatives were available included in the preambular text of decision XXI/6.

In that decision, among other things, parties were concerned to understand the potential impact on Article 5 parties of making changes to the global exemption to exclude additional laboratory and analytical uses. At the time, in 2009, Article 5 parties were soon to be subject to the 2010 control measures under Article 2, and then the global exemption for laboratory and analytical uses and its related exclusions would apply.

The adoption of alternatives to ODS laboratory and analytical uses is still underway in Article 5 parties, with barriers such as adherence to standards using ODS, cost and time. In addition, in some cases, ISO and ASTM International still list standards requiring the use of ODS.

The procedures listed in Table 9.3 are laboratory and analytical uses that can be performed without using controlled substances, in addition to those already removed for the global exemption. Parties may wish to consider removing these additional procedures from the global exemption for laboratory and analytical uses of ODS, at a date to be determined by parties. This list is shorter than the previous list that was recommended by TEAP (as reflected in the preambular text of Decision XXI/6) to allow more time for the revision of old standards or the development of new standards and for the adoption of those standards in Article 5 parties.

Table 9.3 Recommendation for laboratory and analytical procedures to be removed

ODS Type	Procedures
Methyl bromide	Laboratory uses as a methylating agent
Carbon tetrachloride (CTC)	Reaction solvents
CTC	A solvent for IR, Raman and NMR spectroscopy
CTC	Grease removal and washing of NMR tubes
CTC	Iodine partition and equilibrium experiments
CTC	Determination of hydrocarbons in water, air, soil or sediment
CTC	Determination of moisture and water
1,1,1-trichloroethane (TCA)	Determination of bromine index
CTC	Determination of iodine index

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[158] See Appendix 6, Report of the UNEP TEAP, September 2018, Volume 4: *Response to Decision XXVI/5(2) on Laboratory and Analytical Uses.*

In addition, parties may wish to consider recalling that any decision taken to exclude a use from the global exemption would not prevent a party from nominating a specific use for an exemption under the essential uses' procedure, as set out in decision IV/25.

Parties may wish to consider establishing cooperation with standards organisations, to facilitate and accelerate the development or revision of standards for the replacement of ODS in analytical uses.

Parties may also wish to consider providing:

- more comprehensive data (e.g. on consumption);
- sharing information on alternatives and on the revision of standards that use ODS;
- possible support for the development and/or revision of standards, and/or training, where needed.

Many standards still require the use of small quantities of ODS. There may come a point when the continued exclusion of specific laboratory and analytical uses on a case by case basis from the global exemption creates potential confusion for practitioners and regulators. Monitoring of, and adherence to, specific authorised uses of ODS in laboratory and analytical applications may become increasingly challenging as the exclusion list expands.

At the 30th Meeting of the Parties, a number of parties noted the relatively insignificant quantities of ozone-depleting substances produced to supply laboratory and analytical uses, and the MCTOC's suggestion that excluding specific uses on a case by case basis could be confusing for practitioners and regulators. In light of those considerations, parties discussed a proposal to take a fresh look at how to continue to reduce the use of ODS in laboratory and analytical procedures without sacrificing clarity or introducing excessively complicated measures for such as small quantity of ODS. Parties agreed to consider a draft decision on laboratory and analytical uses at the 41st meeting of the Open-ended Working Group.

10 Destruction Technologies

10.1 Introduction

Under the Montreal Protocol, the definition and data reporting requirements for production of controlled substances require parties to determine the quantity of ozone-depleting substances (ODS) destroyed in destruction facilities, in order to meet their reporting and compliance obligations.

Article 1, paragraph 5, of the Montreal Protocol states,

> *"Production" means the amount of controlled substances produced, minus the amount destroyed by technologies to be approved by the Parties and minus the amount entirely used as feedstock in the manufacture of other chemicals. The amount recycled and reused is not to be considered as "production".*

In accordance with Article 7 of the Montreal Protocol, Parties are required to report data on the production of controlled ODS. These definitions require parties to determine the quantity of ODS destroyed in destruction facilities, in order to meet their reporting and compliance obligations.

The Montreal Protocol also allows remanufacture of ODS to replace a portion of ODS destroyed under specific conditions (within the same year as destruction, within the same group of substances, etc.). In practice, parties have not typically remanufactured ODS to offset quantities otherwise destroyed.

In addition to these obligations, ODS destruction has been implemented to meet regulatory requirements and voluntary objectives to help protect stratospheric ozone and climate.

In 2016, the Kigali Amendment to the Montreal Protocol included hydrofluorocarbons (HFCs) as controlled substances and, in relation to their destruction, states in Article 2J, paragraphs 6 and 7, that[159]:

> *6. Each Party manufacturing Annex C, Group I, or Annex F substances shall ensure that for the twelve-month period commencing on 1 January 2020, and in each twelve-month period thereafter, its emissions of Annex F, Group II, substances generated in each production facility that manufactures Annex C, Group I, or Annex F substances are destroyed to the extent practicable using technology approved by the Parties in the same twelve-month period.*
>
> *7. Each Party shall ensure that any destruction of Annex F, Group II, substances generated by facilities that produce Annex C, Group I, or Annex F substances shall occur only by technologies approved by the Parties.*

The First Meeting of the parties decided in Decision I/12F with regard to destruction:

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[159] Annex C, Group I, relates to HCFCs, Annex F to HFCs, and Annex F, Group II to HFC-23, as listed in the Montreal Protocol.

> *(a) to agree to the following clarification of the definition of Article 1, paragraph 5 of the Protocol: "a destruction process is one which, when applied to controlled substances, results in the permanent transformation, or decomposition of all or a significant portion of such substances";*

Parties have taken a number of related subsequent decisions to approve destruction technologies for the purposes of Montreal Protocol requirements. Over time, a list of destruction technologies approved by parties has been updated and included in progressive decisions. The most recent list of destruction processes were approved in decision XXX/6, "*for the purposes of paragraph 5 of Article 1 of the Montreal Protocol, and, with respect to Annex F, group II, substances, also for the purposes of paragraphs 6 and 7 of Article 2J, as additions to the technologies listed in annex VI to the report of the Fourth Meeting of the Parties and modified by decisions V/26, VII/35 and XIV/6, as reflected in annex II to the report of the Thirtieth Meeting of the Parties*".

Decision XXX/6 confirmed a range of approved destruction technologies for their applicability to HFCs and approved thermal decay for the destruction of methyl bromide. In so doing, parties noted that destruction and removal efficiency is the criterion considered in approving destruction technologies under the Montreal Protocol, and suggested that parties consider the advice on emissions of pollutants other than controlled substances in the development and implementation of their domestic regulations. Parties also noted that the Code of Good Housekeeping Procedures[160] provides useful guidance for local management for appropriate handling, transportation, monitoring and measurement in destruction facilities, where similar or stricter procedures do not exist domestically, but that these procedures do not provide a framework that can be used for comprehensive verification.

The recent reports of the Technology and Economic Assessment Panel (TEAP) Task Force on Decision XXIX/4[161], on destruction technologies for controlled substances, outline the range of known destruction technologies available to destroy controlled substances. No new technical information on these destruction processes is included in this assessment. Instead, this assessment focuses on related technical and economic considerations for the destruction of controlled substances.

Non-Article 5 parties generally have well established requirements to minimise emissions of ODS, including through the destruction of ODS. Recently, the Multi-lateral Fund of the Montreal Protocol (MLF) supported pilot destruction projects in Article 5 parties with an objective of overcoming some of the barriers to ODS destruction in those countries. Some of these projects had the intention of linking to other difficult to destroy hazardous wastes, such as polychlorinated biphenyls (PCBs). As a broad strategy to be advocated, combining the two waste streams remains a technically sound measure for destroying ODS, if funding, regulatory and institutional barriers can be overcome. A recent study on the management and destruction of existing ozone depleting

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[160] The Code of Good Housekeeping Procedures are set out in Annex III to the report of the 15th Meeting of the Parties in accordance with paragraph 6 of decision XV/9.

[161] 2018 TEAP April Report, Volume 2, Decision XXIX/4 TEAP Task Force Report on Destruction Technologies for Controlled Substances; 2018 TEAP Report, Supplement to the April 2018 Decision XXIX/4 TEAP Task Force Report on Destruction Technologies for Controlled Substances; September 2018 TEAP Report, Volume 1, Decision XXIX/4 TEAP Task Force Report on Destruction Technologies for Controlled Substances (Addendum to the May 2018 Supplemental Report – Revision).

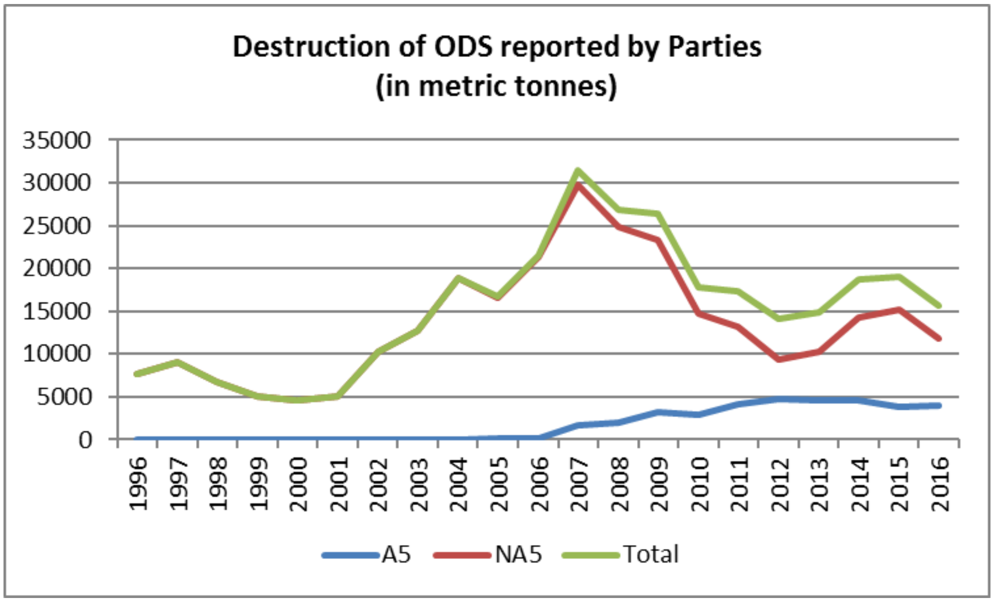
substances banks[162] provides a thorough analysis of the issues and challenges for the destruction of ODS, particularly in Article 5 parties.

Some non-Article 5 parties mandate the destruction of waste HFCs. Where a phase-down limits HFC availability, it is expected that, similar to hydrochlorofluorocarbons (HCFCs), and particularly if the HFCs still have value and can be reclaimed economically, they will be re-used rather than being destroyed. The requirement to destroy refrigerant can be minimised by effective refrigerant management, reclaim of HFC refrigerants and by well-established recycling and re-use activities for the servicing and maintenance of refrigeration and air-conditioning systems. In addition, the Clean Development Mechanism (CDM) and, more recently, country initiatives have resulted in most HCFC-22 plants having access to on-site or off-site HFC-23 destruction capability.

10.2 ODS destruction quantities and trends

The Ozone Secretariat has provided data on reported destruction of ODS. The data is summarised in Figure 10.1, which shows the quantities (in metric tonnes) destroyed each year since 1996. Cumulatively, over 300,000 tonnes of ODS have been destroyed. The ODS destroyed includes some quantities of mixtures of unknown composition. Mixtures may consist of a number of ODS substances, and may also contain HFCs, particularly where the substances have been recovered from refrigeration and air-conditioning equipment and bulked up for ease of transportation to destruction facilities.

Figure 10.1 Destruction of ozone depleting substances since 1996



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[162] *Management and destruction of existing ozone depleting substances banks*, GIZ Proklima, 2015.

The reported data includes a significant proportion of carbon tetrachloride (CTC). CTC continues to be produced for feedstock use. The reported CTC destroyed is likely to be for unintentional by-production, for CTC quantities that are taken out of the process cycle and are at least temporarily stored before being destroyed or sent for destruction in a facility outside the production site. Figure 10.2 shows the CTC, and ODS excluding CTC, destroyed each year. This illustrates the destruction trend for ODS used mainly as refrigerant and foam blowing agent. Cumulatively, excluding CTC, over 90,000 tonnes of other ODS have been destroyed since 1996. In 2016, Japan accounted for about 40 percent of the destruction of ODS excluding CTC.

Figure 10.2 CTC and ODS excluding CTC destroyed each year

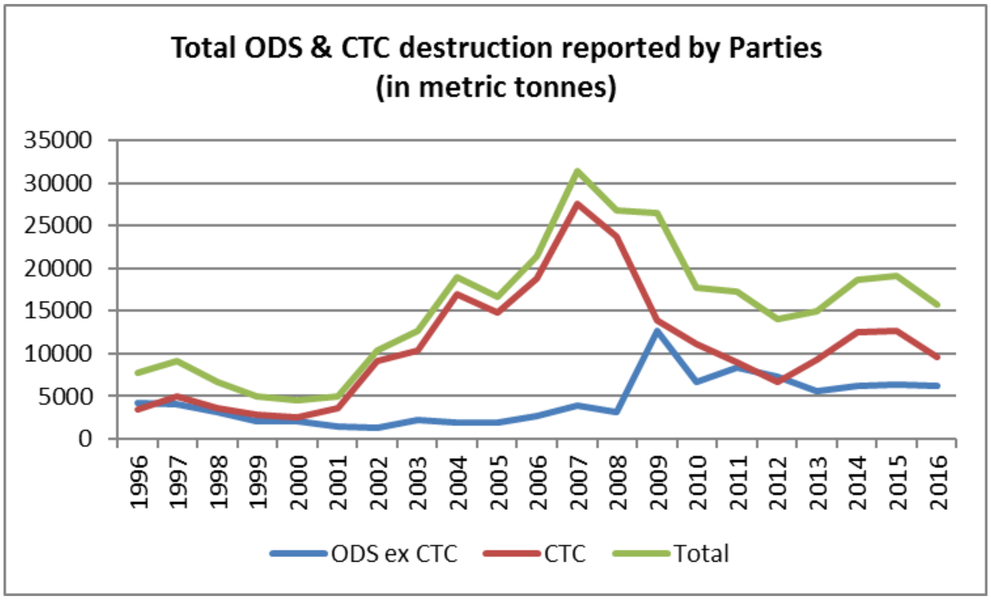
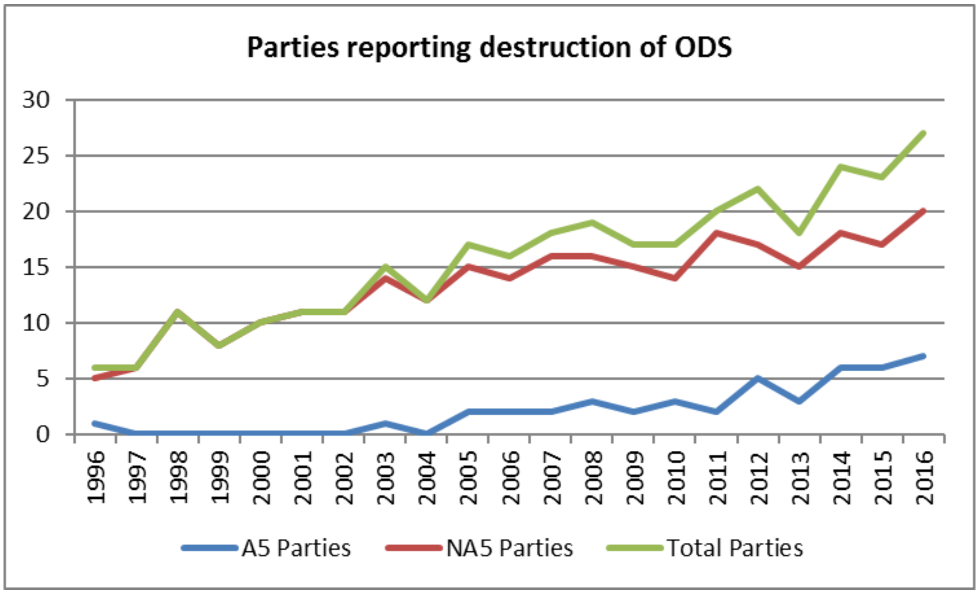


Figure 10.3 presents the number of parties reporting destruction, which has increased to 27 parties in 2016, including 7 Article 5 parties. Only relatively small quantities of recovered ODS are imported or exported for destruction. According to information provided by parties in accordance with Articles 7 and 9 (Annex IXa), in 2016, excluding halons, Article 5 parties did not report the export of any recovered ODS. Some recovered ODS is exported for destruction in non-Article 5 parties. For example, Canada exports recovered ODS for destruction.

Figure 10.3 Parties reporting destruction



10.3 ODS banks and destruction

A 2015 report on ODS banks[163] estimated that the annual amount of ODS, excluding CTC, that reaches the waste stream, and is therefore potentially available for ODS management and destruction, was projected to peak globally in 2016 at 200,000 tonnes. From this quantity available for destruction, and the quantities of destroyed ODS reported to the Ozone Secretariat, it is possible to estimate the annual destruction rate that is achieved. Based on this previous estimate of 200,000 tonnes potentially available for destruction, and ODS destruction reported to the Ozone Secretariat of 6,145 tonnes (excluding CTC), a global destruction rate of about 3 percent was apparently achieved in 2016. For developed countries, the TEAP Task Force on Decision XX/7 report-phase 2, 2009[164], estimated that under one scenario about 75,000 tonnes of ODS could potentially be available for ODS management and destruction in 2016, resulting in a destruction rate of about 8 percent based on the ODS destruction reported to the Ozone Secretariat. However, destruction quantities of ODS are not always known accurately, or may not be reported to the Ozone Secretariat, such as from foam and appliance destruction, meaning that the destruction rates based on annually reported data are likely to be under-estimated for developed countries.

The 2015 report and the TEAP Task Force on Decision XX/7 Report both provided analyses of the sources of ODS that could be available for potential waste management and destruction.

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[163] *Management and destruction of existing ozone depleting substances banks*, GIZ Proklima, 2015, page 23.

[164] UNEP Report of the TEAP Task Force on Decision XX/7, Phase 2, *Environmentally sound management of banks of ozone-depleting substances*, October 2009.

10.4 Destruction projects in Article 5 parties

Excluding CTC, the reported quantities of ODS destroyed in Article 5 parties are relatively small. Cumulatively, destruction of over 300 tonnes of ODS, excluding CTC, has been reported for Article 5 parties since 1996, with the number of Article 5 parties reporting ODS destruction increasing from 3 in 2010, to 7 in 2016. Availability of, and access to, destruction facilities, transboundary movement of waste, recovery equipment, transportation infrastructure, and cost are some of the significant barriers to destruction in Article 5 parties.

A comprehensive study on ODS disposal[165] (ICF, 2008) has defined five categories of barriers that hinder the effective collection and destruction of ODS in developing and developed countries and gives recommendations for developing countries on how to address them. These are informational, financial, technological, logistical and legal barriers. According to the 2015 report on ODS banks[166], the most important factors, which decide the success of ODS life cycle management in developing countries, are the creation of financial incentives for returning ODS or ODS-containing equipment, and regulatory controls for the management of ODS waste, including destruction if substances cannot be reused.

In 2015, the Executive Committee of the MLF (ExCom) reviewed a total of 15 approved ODS destruction demonstration projects approved in 2009, involving 12 countries, two regions, and one global project[167]. The results of this review indicated that there were only two main approaches to destruction selected by countries, namely domestic destruction through local facilities and export of the ODS waste abroad for destruction in another country. Local facilities/technologies were selected on the basis of what already existed, and what could be used with some modifications. Thermal destruction technologies were utilised, including (thermal oxidation destruction technologies) commercial rotary kilns and cement kilns, and, in one case, plasma arc. The selection of in-country options, where available, was motivated by cost factors, national constraints prohibiting export, and national development objectives related to future sustainability in waste management infrastructure.

All countries exporting their ODS waste are signatories to the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal. This allows for exports only after the transit and receiving countries give their approval. Those countries choosing to export their waste do so primarily because there was no local infrastructure for ODS waste destruction, noting that, in the absence of economies of scale, this option is subject to high incremental transaction costs associated with Basel Convention requirements.

Logistical planning is a substantial part of the preparatory work for successful disposal of ODS waste and the need to raise awareness among waste management operators on the importance of having detailed procedures for the management and disposal of ODS waste.

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[165] ICF, *Study on the Collection and Treatment of Unwanted Ozone-Depleting Substances in Article 5 and Non-Article 5 Countries*. Prepared for the Multilateral Fund, 2008.

[166] *Management and destruction of existing ozone depleting substances banks*, GIZ Proklima, 2015, chapter 4

[167] *Desk study on the evaluation of the pilot demonstration projects on ODS disposal and destruction*, UNEP/OzL.Pro/ExCom/75/10, 24 October 2015.

The review reported that further investigation would be needed to collect additional data on the results of such projects, which currently are mostly at an incipient stage of implementation. Field work is needed to collect detailed practical data on management and financing modalities for ODS disposal in a variety of countries, including very low-volume-consuming (LVC) countries. It was also noted that one objective of the MLF program was to explore synergies with disposal and destruction of other hazardous waste, specifically POPs covered under the Stockholm Convention, and this objective was achieved for one project only.

The MLF demonstration work is now generally completed. Appendix 6 provides a summary of the national demonstration projects, based on the ExCom 2015 desk top survey report and published completion reports available in the ExCom meeting documents[167]. The following summarises some results and conclusions drawn from this work, as interpreted by the Medical and Chemical Technical Options Committee (MCTOC).

1. At present, for Article 5 parties, the practical, commercially available options for destruction of ODS are limited to three generic technologies: high temperature incineration (HTI) in commercial waste hazardous waste facilities (primarily rotary kilns) qualified for destruction of halogenated chemicals being co-disposed with a larger base commercial hazardous waste stream; co-disposal cement kilns; and commercial plasma arc units. The MLF projects being undertaken have selected one or more of these options. Four projects selected domestic HTI facilities, six selected export to HTI facilities in the European Union, three selected domestic cement kilns, and one selected commercial plasma arc.

2. HTI rotary kilns appear to be reasonably cost effective, particularly in the one case where it was associated with POPs destruction initiatives. Cement kilns are likely to destroy ODS at somewhat higher cost than HTI, although data is limited. The one project using commercial-scale plasma arc appears to be at somewhat higher cost.

3. Experience in a number of demonstration projects indicates that only relatively small amounts of end-of-life ODS were practically available, suggesting that an effective capability to capture end-of-life waste ODS, and the associated finance to support this, are important in developing sustainable and effective long-term ODS destruction programs.

In terms of the environmental performance of the destruction technologies evaluated in the MLF demonstration program, these were specific to the facility and the location. National standards/regulations impose emission limits for destruction facilities. However, destruction technologies were generally qualified for ODS destruction consistent with or similar to performance criteria used by TEAP in assessing destruction technologies for the Montreal Protocol, which were sometimes more stringent than national standards. The Code of Good Housekeeping Procedures[168] can provide useful guidance for local management for appropriate handling, transportation, monitoring and measurement in destruction facilities, where similar or stricter procedures do not exist domestically, but these procedures do not provide a framework that can be used for comprehensive verification.

Best available standards and practices employs air pollution control (APC) technology to commercial thermal destruction technologies, and this should also be the benchmark for

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[168] The *Code of Good Housekeeping Procedures* are set out in Annex III to the report of the 15th Meeting of the Parties in accordance with paragraph 6 of decision XV/9.

destruction technologies in Article 5 parties. However, even with investment in APC systems, smaller units, which are more typically available in some Article 5 parties, may have higher emissions. Experience shows that to remain within pollutant emissions limits (polychlorinated dibenzo-p-dioxins (PCDD) and dibenzo-furans (PCDF), hydrogen chloride (HCl), hydrogen fluoride (HF), and particulates) requires the restriction of chlorine and fluorine input content, with resulting limitations on destruction capacity[169]. It has also been noted that for some facilities, fluorine rather than chlorine content in the feed was a governing limitation. This may require further investigation in the future if large quantities of HFCs become available for destruction. Suitable cement kilns are often facilities operating with good APC systems that limit inherent particulate and other emission issues and are supported by the technical capabilities of a substantive operator.

The recently created Moana Taka Partnership is established to address waste management in the Pacific islands and to enable recyclable waste to be transported to ports in the region for sustainable treatment and recycling. The China Navigation Company (CNCo) and the Secretariat of the Pacific Regional Environment (SPREP) signed a memorandum of understanding creating the partnership. CNCo vessels will carry containers of recyclable waste, including ODS from Pacific island ports, free of charge, to be sustainably treated and recycled off the islands and in other suitable ports in the Asia Pacific region.[170]

According to the submission by the United States[171] in response to decision XXIX/4, the voluntary carbon market has been used as a funding source for ODS destruction. The three most widely traded voluntary offset programs in the United States with ODS destruction protocols are the Verified Carbon Standard (VCS), the Climate Action Reserve (CAR), and the American Carbon Registry (ACR). The sale of carbon credits on the compliance and voluntary markets is one potential method for funding ODS destruction projects. In 2015, approximately 300,000 tonnes CO_2-eq (equivalent to about 30 tonnes for dichlorodifluoromethane, CFC-12) from ODS destruction projects were transacted globally in the voluntary market. There are additional costs associated with the preparation, validation, and verification of ODS destruction projects. There are challenges throughout the process, particularly for developing countries, where up-front capital is rarely available, and even more difficult to access due to the drop in offset prices. There are expanding air-conditioning and refrigeration markets in many developing regions of the world, including regions and countries with high ambient temperatures. In these expanding heating, ventilation, air-conditioning and refrigeration (HVACR) markets, there is an increasing focus on green strategies, such as better energy efficiency, insulation and smart/green building standards, as well as increasing awareness among consumers of the benefits of using sustainable systems. Servicing, maintenance and refrigerant logistics are fundamental parts of this HVACR market and could form the basis for end-of-life management that supports destruction.

Relevant technical information and data on ODS and HFC issues in the context of destruction and recovery/recycling needs to be identified, collected and disseminated to support these strategies.

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[169] Report of 81st ExCom Meeting, June 2018, *Status Reports and Reports on Projects with Specific Reporting Requirements*, page 431, Pilot demonstration project on ODS waste management and disposal in Colombia, UNDP, April 2008, http://www.multilateralfund.org/81/English/1/8110.pdf.

[170] IISD SDG Knowledge Hub, 27th March 2018.

[171] ICF, *ODS Destruction in the United States and Abroad*, prepared for the U.S. Environmental Protection Agency, February 2018.

Even in a relatively large HVACR market, a main barrier to destroying end-of-life ODS/HFCs is recovery/collection and having the capability in place to generate minimum quantities at a predictable rate for viable destruction. If destruction is to be part of an overall end-of-life strategy, selecting suitable approved technologies and achieving the required investments will be mainly dependent on this recovery and collection capability, and a reliable analysis of the material available for destruction. A major determinant of viable destruction infrastructure is achievable economies of scale that might then also utilise already available destruction capacity. In some regions, destruction capacity may already be utilised for waste heavy hydrocarbon destruction. Centralised regional destruction capacity presents challenges due to the issues associated with cross-border shipment and the Basel Convention. The Basel Convention requires considerable effort, due to the paperwork involved for each step of the transport, including interim transit ports. This results in a relatively high cost for small volume shipments; with larger quantities of hazardous waste and regular established shipment routes, shipments are much more cost effective.

10.5 HFC destruction in practice

Many non-Article 5 parties already undertake and report on destruction of waste HFCs. Typically, waste HFCs are destroyed using the same processes that are used for ODS destruction, and the processes must meet local emissions and performance regulatory requirements.

The European Union (EU) Regulation 517/2014 on fluorinated greenhouse gases (F-Gas Regulation) requires recovery of HFCs from a wide range of refrigeration, air-conditioning and other equipment, for recycle, reclaim or destruction. Destruction or recovery for re-use of HFC-23 produced as a by-product of chemical manufacture is also required. In 2016, the EU reported that approximately 600 tonnes of HFCs were destroyed, of which about half was HFC-23[172].

In Japan, HFCs must be recovered from home appliances, cars, and commercial equipment when the equipment containing these gases is discarded. Recovered gas must be recycled or destroyed, instead of being released into the air. There are more than 40 home-appliance recycling plants, more than 20 HFC recycling facilities and more than 60 HFC destruction facilities in commercial operation using various technologies. In 2015, about 2,000 tonnes of HFCs was destroyed. The “Act on Rational Use and Proper Management of Fluorocarbons” requires comprehensive measures throughout the life cycle of fluorocarbons to minimise emissions.

In Canada, participants in an industry scheme, Refrigerant Management Canada established in 2000, pay a levy on the HCFC (and more recently on the HFC) refrigerants imported into Canada for the HVACR industry. This levy funds the cylinder handling, testing, storage transportation and destruction of waste ODS and HFC refrigerants, to help ensure that refrigerants that cannot be reused or recycled are sent for destruction. Canada destroyed 127 tonnes of HFCs in 2016, and 93 tonnes in 2017[173].

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[172] European Environment Agency, EEA Report No 20/2017, *Fluorinated greenhouse gases in 2017: Data reported by companies on the production, import, export and destruction of fluorinated greenhouse gases in the European Union, 2007-2016*, https://www.eea.europa.eu/publications/fluorinated-greenhouse-gases-2017.

[173] Canada provided HFC destruction data for the TEAP Task Force on Decision XXIX/4 Report on Destruction Technologies for Controlled Substances.

In Australia, Refrigerant Reclaim Australia (RRA) works nationally with industry to share the responsibility for, and costs of, recovering, reclaiming and destroying surplus and unwanted refrigerants. In 2003, RRA expanded the recovery program to include HFCs. Also, in 2003, it became mandatory for the refrigeration and air conditioning industry to recover, return and safely dispose of HFCs and PFCs, in the same manner as CFCs and HCFCs by passing the Ozone Protection and Synthetic Greenhouse Gas Management Act. The 2016/2017 RRA annual report[174] provides information on destruction of HFCs, reporting about 250 tonnes destroyed.

In the United States, the Clean Air Act (CAA) prohibits knowingly venting or releasing ozone-depleting and substitute refrigerants in the course of maintaining, servicing, repairing, or disposing of appliances or industrial process refrigeration.

For the purposes of the Montreal Protocol, at their 30th Meeting, parties approved destruction of Annex F, group I, substances using the following technologies: cement kilns; gaseous/fume oxidation; liquid injection incineration; porous thermal reactor; reactor cracking; rotary kiln incineration; argon plasma arc; nitrogen plasma arc; portable plasma arc; chemical reaction with H_2 and CO_2; gas phase catalytic dehalogenation; superheated steam reactor; and for diluted sources of Annex F, group I, substances, municipal solid waste incineration, and rotary kiln incineration. Approved destruction technologies for HFC-23 (Annex F, group II) are outlined below.

10.5.1 HFC-23 Destruction

Trifluoromethane (HFC-23) is generated as a by-product during the production of HCFC-22. Destruction of HFC-23 is different to other HFCs, which are typically destroyed after use and recovery. The Kigali Amendment requires, from 2020, parties manufacturing Annex C, Group I, or Annex F substances to ensure that emissions of HFC-23 from production facilities *"are destroyed to the extent practicable using technology approved by the Parties in the same twelve-month period"*.

At their 30th Meeting, in order for parties to meet their obligations under the Kigali Amendment, parties approved destruction of HFC-23 (Annex F, group II) using the following technologies: gaseous/fume oxidation; liquid injection incineration; reactor cracking; rotary kiln incineration; argon plasma arc; nitrogen plasma arc; chemical reaction with H_2 and CO_2; superheated steam reactor.

The following information summarises the current status for the destruction of HFC-23 in relevant countries.

Destruction[175] of HFC-23 generated as by-product is voluntary in Japan, and emission data on fluorocarbons, including HFC-23, has been reported annually under Industrial Voluntary Action plans.

In the United States, under the mandatory reporting of greenhouse gas (GHG) rule, owners or operators of facilities producing HCFC-22 or destroying HFC-23 are required to report on emissions of HFC-23 from HCFC-22 production and HFC-23 destruction processes located either at the HCFC-22 production facilities or (for destruction of more than 2.14 tonnes of HFC-23

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[174] https://refrigerantreclaim.com.au/about/publications/. Accessed December 2018.

[175] The information summarised here on HFC-23 destruction is from UNEP/OzL.Pro/ExCom/79/48 and /78/9.

annually) elsewhere. While monitoring of HFC-23 emissions is mandatory, destruction is voluntary.

According to the European Union Regulation 517/2014 on fluorinated greenhouse gases, producers of fluorinated compounds shall take all necessary precautions to limit emissions of fluorinated GHGs (including those produced as by-products) to the greatest extent possible during production, transport, and storage.

In the Russian Federation, one company owns two facilities that produce HCFC-22 to be used for feedstock in fluoropolymer production. The company has two plants for destruction of fluorine-containing wastes, including HFC-23 by-product, and meets the requirements of Paris Agreement regulations on emissions of greenhouse gases including HFCs, which were enacted in 2015[176]. Federal legislation on the national regulation of greenhouse gases emissions is being prepared in the Russian Federation.

In China, with the support of the Government, the construction of 13 new destruction facilities, for 15 HCFC-22 production lines[177] not covered by CDM, was started in 2014. Once these new destruction facilities are completed, 30 out of 32 production lines[178] will be equipped with a destruction facility. As reported by the independent verification on HCFC production commissioned by the World Bank, the 15 CDM lines were operating their respective HFC-23 destruction facilities in 2015.

In India, the Government issued orders directing manufacturers of HCFC-22 not to emit or vent HFC-23 in the atmosphere on 13 October 2016[179]. Five HCFC-22 production facilities have implemented a CDM project.

In Mexico, HFC-23 by-product from HCFC-22 production is either emitted, separated for a specific use (rare), or destroyed and are currently not specifically regulated. In the Republic of Korea, HFC-23 by-product was destroyed by an incineration facility supported by CDM until the 1 May 2013. The HCFC-22 production facilities in the Democratic People's Republic of Korea and the Bolivarian Republic of Venezuela (one each) have neither implemented a CDM project nor built a destruction facility (as reported by the MLF). It is therefore anticipated that HFC-23 is vented at those two facilities. In Argentina, HFC-23 is currently being vented, although previously it was destroyed under the CDM.

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[176] Methodological instructive regulations and guidelines for quantifying greenhouse gas emissions by organizations engaged in business and other activities in the Russian Federation (approved by order of the Ministry of Natural Resources and Environment of the Russian Federation of June 30, 2015 No. 300).

[177] Two destruction facilities each covered two production lines.

[178] Including the newly established feedstock plant, Yinguang. One of the two lines without destruction facility recovers all HFC-23 and sells it as feedstock for pesticide production; another plant vented all HFC-23 generated as a by-product.

[179] *Government bans some manufacturers from emitting greenhouse gas: HFC-23 gas is a by-product of the process of manufacture of HCFC-22 gases*, The Indian Express, December 5, 2016, http://indianexpress.com/article/india/government-bans-some-manufacturers-from-emitting-greenhouse-gas-4411938. Accessed January 2019.

Appendix 1: Selected decisions for laboratory and analytical uses

This collation of relevant decisions, or parts thereof, is not exhaustive.

Decision VI/9: Essential-use nominations for controlled substances other than halons for 1996 and beyond

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 authorized as specified in Annex II to the report of the Sixth Meeting of the Parties;

Annex II of the report of the 6th Meeting of the Parties in relation to Decision VI/9

Conditions applied to exemption for laboratory and analytical uses

1. Laboratory purposes are identified at this time to include equipment calibration; use as extraction solvents, diluents, or carriers for chemical analysis; biochemical research; inert solvents for chemical reactions, as a carrier or laboratory chemical and other critical analytical and laboratory purposes. Production for laboratory and analytical purposes is authorized provided that these laboratory and analytical chemicals shall contain only controlled substances manufactured to the following purities:

	%
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 w/Boiling P>20º C	99.5
Other w/Boiling P<20º C	99.0

2. 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.

3. These high purity substances and mixtures containing controlled substances shall be supplied only in re-closable containers or high-pressure cylinders smaller than three litres or in 10 millilitre or smaller glass ampoules, marked clearly as substances that deplete the ozone layer, restricted to laboratory use and analytical purposes and specifying that used or surplus substances should be collected and recycled, if practical. The material should be destroyed if recycling is not practical.

4. Parties shall annually report for 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, standards, specifications, and regulations requiring the use of the controlled substance.

Decision VII/11: Laboratory and analytical uses

5. To adopt an illustrative list of laboratory uses as specified in Annex IV of the report of the Seventh Meeting of the Parties to facilitate reporting as required by decision VI/9 of the Sixth Meeting of the Parties;

6. To exclude the following uses from the global essential-use exemption, as they are not exclusive to laboratory and analytical uses and/or alternatives are available:

   - Refrigeration and air-conditioning equipment used in laboratories, including refrigerated laboratory equipment such as ultra-centrifuges;

   - Cleaning, reworking, repair, or rebuilding of electronic components or assemblies;

   - Preservation of publications and archives; and

   - Sterilization of materials in a laboratory;

Annex IV of the Report of the Seventh Meeting of the Parties

Categories and examples of laboratory uses

(This list is not exhaustive)

1. Research and development (e.g. pharmaceutical, pesticide, CFC and HCFC substitutes)

   1.1 Reaction solvent or reaction feedstock (e.g. Diels-Alder and Friedel-Craft Reactions, RuO_3 oxidation, allelic side bromination, etc.)

2. Analytical uses and regulated applications (including quality control)

   2.1 Reference

      - Chemical (ODS monitoring, volatile organic compound (VOC) Detection, Equipment Calibration)

      - Toxicant

      - Product (adhesive bond strength, breathing filter test)

   2.2 Extraction

      - Pesticide and heavy metal detection (e.g. in food)

      - Oil mist analysis

      - Colour and food additive detection

      - Oil detection in water and soil

2.3 Diluent

  - Zinc, copper, cadmium detection in plants and food
  - Micro-chemical methods to determine molecular weight or oxygen
  - Measuring drug purity and residual determination
  - Sterilization of lab equipment

2.4 Carrier (Inert)

  - Forensic methods (e.g. fingerprinting)
  - Titration (cholesterol in eggs, drug chemical characteristics, "Iodine value", e.g. in oils and chemical products)
  - Analytical equipment (Spectroscopy (Infra-red, Ultra-violet, Nuclear Magnetic Resonance, fluorescence), chromatography (High-pressure liquid chromatography, gas chromatography, thin-layer chromatography)

2.5 Tracer

  - Sanitary engineering

2.6 Miscellaneous (including testing)

  - Ingredient in material for testing (e.g. asphalt, metal fatigue and fracturing)
  - Separation media (separation of extraneous materials such as filth and insect excreta from stored food products)

3. Miscellaneous (including biochemical)

3.1 Laboratory method development

3.2 Sample preparation using solvent

3.3 Heat transfer medium

Decision XI/15: Global exemption for laboratory and analytical uses

The *Eleventh Meeting of the Parties* decided in Dec. XI/15 to eliminate the following uses from the global exemption for laboratory and analytical uses for controlled substances, approved in decision X/19, from the year 2002:

(a) Testing of oil, grease and total petroleum hydrocarbons in water;

(b) Testing of tar in road-paving materials; and

(c) Forensic finger-printing.

Decision XVI/16: Laboratory and analytical uses

The *Sixteenth Meeting of the Parties* decided in Dec. XVI/16:

Recalling decision IX/17 on essential-use exemptions for laboratory and analytical uses of ozone-depleting substances,

Noting the report of the Implementation Committee requesting guidance from the Parties on the use of bromochloromethane for laboratory and analytical uses,

Considering that decision XV/8 requests the Technology and Economic Assessment Panel to report annually on the development and availability of laboratory and analytical procedures that can be performed without using controlled substances in Annexes A, B and C, groups II and III, of the Protocol,

1. To include in the global laboratory and analytical use exemption under the conditions set out in annex II of the report of the Sixth Meeting of the Parties substances in Annex C, groups II and III, of the Protocol,

2. To apply the conditions set out in paragraphs 3, 4 and 5 of decision X/19 to paragraph 1 of the present decision.

Decision XVIII/15: Laboratory and analytical critical uses of methyl bromide

The *Eighteenth Meeting of the Parties* decided in Dec. XVIII/15:

Noting with appreciation the work undertaken by the Chemicals Technical Options Committee and the Methyl Bromide Technical Options Committee in considering, in accordance with decision XVII/10, the relevance to laboratory and analytical critical uses of methyl bromide of the categories of uses listed in annex IV to the report of the Seventh Meeting of the Parties,

Acknowledging that in decision VII/11, adopted in 1995, Parties were encouraged to identify and review the use of ozone-depleting substances in order to adopt where possible ozone-depleting substance-free technologies,

Noting that the aforementioned committees have reported that alternatives to methyl bromide are available for many laboratory and analytical critical uses, including methylating agent uses,

Noting that the aforementioned committees were not in favour of classifying field trials using methyl bromide as laboratory and analytical critical uses because of the impracticality and cost of using a large number of small containers of 99 percent pure methyl bromide and that Parties wishing to carry out such field trials could submit critical-use nominations for that purpose,

Recognizing that some laboratory and analytical critical uses listed in the committees’ report are applicable to both quarantine and pre-shipment and to feedstock uses, which are not controlled under the Montreal Protocol,

1. To authorize, for Parties not operating under paragraph 1 of Article 5, the production and consumption of the controlled substance in Annex E of the Protocol necessary to satisfy laboratory and analytical critical uses and subject to the conditions established in paragraph 2 of the present decision;

2. Subject to the conditions applied to the exemption for laboratory and analytical uses contained in annex II to the report of the Sixth Meeting of the Parties, to adopt a category of laboratory and analytical critical use to allow methyl bromide to be used:

   (a) As a reference or standard:

      (i) To calibrate equipment which uses methyl bromide;

      (ii) To monitor methyl bromide emission levels;

      (iii) To determine methyl bromide residue levels in goods, plants and commodities;

   (b) In laboratory toxicological studies;

   (c) To compare the efficacy of methyl bromide and its alternatives inside a laboratory;

   (d) As a laboratory agent which is destroyed in a chemical reaction in the manner of feedstock;

3. That any decision taken pursuant to the present decision does not preclude a Party from nominating a specific use under the critical use procedure described in decision IX/6.

Decision XXI/6: Global laboratory use exemption

The *Twenty-First Meeting of the Parties* decided in Dec. XXI/6:

Noting the reports of the Technology and Economic Assessment Panel (TEAP) provided under Decision XVII/10 and under Decision XIX/18 on laboratory and analytical uses of ozone depleting substances (ODS).

Noting that TEAP has identified in its report a number of procedures for which alternatives to the use of ODS are available, as summarised below:

a) Analyses in which the ODS is used as a solvent for spectroscopic measurements:

   i) of hydrocarbons (oil and grease) in water or soil

   ii) of simethicone (polydimethylsiloxane)

   iii) when recording infrared and nuclear magnetic resonance (NMR) spectra, including hydroxyl index

b) Analyses in which the ODS is used as a solvent for electrochemical methods of analysis of:

   i) cyanocobalamin

   ii) bromine index

c) Analyses involving selective solubility in the ODS of:

    - i) cascarosides
    - ii) thyroid extracts
    - iii) polymers

- d) Analyses in which the ODS is used to preconcentrate the analyte, for:
    - i) liquid chromatography (HPLC) of drugs and pesticides
    - ii) gas chromatography of organic chemicals such as steroids
    - iii) adsorption chromatography of organic chemicals
- e) Titration of iodine with thiosulfate (iodometric analyses) for determination of:
    - i) iodine
    - ii) copper
    - iii) arsenic
    - iv) sulphur
- f) Iodine and bromine index measurements (titrations)
- g) Miscellaneous analyses, namely
    - i) stiffness of leather[180]
    - ii) jellification point
    - iii) specific weight of cement
    - iv) gas mask cartridge breakthrough
- h) Use of ODS as a solvent in organic chemical reactions
    - i) O- and N-difluoromethylation
- i) General use as laboratory solvent, namely
    - i) washing of NMR tubes
    - ii) removal of greases from glassware

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[180] TEAP/CTOC noted in the 2010 Report of the UNEP TEAP, Progress Report, 2010, pg. 56, that information provided about the use of CTC in determining stiffness of leather had been in error, and therefore the procedure mentioned (ASTM D2821) was not relevant or of concern to the global exemption.

Recalling Decisions VII/11, XI/15, XVIII/15 and XIX/18 that already eliminated the following uses from the global exemption for laboratory and analytical uses:

(a) Refrigeration and air conditioning equipment used in laboratories, including refrigerated laboratory equipment such as ultra-centrifuges;

(b) Cleaning, reworking, repair, or rebuilding of electronic components or assemblies;

(c) Preservation of publications and archives;

(d) Sterilization of materials in a laboratory;

(e) Testing of oil, grease and total petroleum hydrocarbons in water;

(f) Testing of tar in road-paving materials;

(g) Forensic finger-printing;

(h) All laboratory and analytical uses of methyl bromide except:

  (i) As a reference or standard:

  - To calibrate equipment which uses methyl bromide;
  - To monitor methyl bromide emission levels;
  - To determine methyl bromide residue levels in goods, plants and commodities;

  (ii) In laboratory toxicological studies;

  (iii) To compare the efficacy of methyl bromide and its alternatives inside a laboratory;

  (iv) As a laboratory agent which is destroyed in a chemical reaction in the manner of feedstock;

(i) Testing of organic matter in coal

Recalling the conditions applied to the exemption for laboratory and analytical uses contained in Annex II of the report of the Sixth Meeting of the Parties.

1. to extend the applicability of the global laboratory and analytical use exemption also to countries operating under Article 5(1) from 1 January 2010 until 31 December 2010 for all ODS except those in Annex B Group III, Annex C Group I and Annex E.

2. to extend the global laboratory and analytical use exemption beyond 31 December 2010 until 31 December 2014:

   (a) for Parties operating under Article 5(1) for all ODS except those in Annex B Group III, Annex C Group I and Annex E, and

(b) for Parties not operating under Article 5(1) for all ODS except those in Annex C Group

3. to request all Parties to urge their national standards-setting organisations to identify and review those standards which mandate the use of ODS in laboratory and analytical procedures with a view to adopting, where possible, ODS-free laboratory and analytical products and processes;

4. to request the Ozone Secretariat to enter into discussion with the International Organization for Standardization (ISO), ASTM International (ASTM), the European Committee for Standardization (CEN) as well as with other relevant multinational standardisation organisations encouraging them to identify methods based on ODS and to expedite the inclusion of non-ODS alternative methods, techniques and substances in their standard methods;

5. to request the TEAP and its Chemicals Technical Options Committee to complete the report as requested under Decision XIX/18 and to provide for the 30th Open-ended Working Group meeting

   (a) a list of laboratory and analytical uses of ODS, including those uses where no alternatives exist.

   (b) to identify the international and national standards that require the use of ODS and to indicate the corresponding alternative standard methods not mandating the use of ODS.

   (c) to consider the technical and economical availability of those alternatives in Article-5 and non- Article-5 parties as well as to ensure that the alternative methods show similar or better statistical properties (for example accuracy or detection limits).

6. to request TEAP while continuing its work as described in paragraph 5, to evaluate the availability of alternatives for those uses already banned under the global exemption in Parties operating under Article 5(1), considering technical and economical aspects. By the 30th meeting of the Open-ended Working Group TEAP should present its findings and recommendations whether exemptions would be required for parties operating under paragraph 1 of Article 5 for any of the uses already banned.

7. to allow Parties operating under paragraph 1 of Article 5 until 31 December 2010 to deviate from the existing laboratory and analytical use bans in individual cases, where a Party considers that this is justified, and to ask Parties to revisit this issue at the 22nd Meeting of the Parties.

8. to request the Ozone Secretariat to update the list of laboratory and analytical uses that the Parties have agreed should no longer be eligible under the global exemption, as required by Decision X/19 and to write to Parties reporting laboratory and analytical uses of ozone depleting substances encouraging them to transition to non-ozone depleting alternatives, where allowed by their national standards.

9. to request Parties to continue to investigate domestically the possibility of replacing ODS in those laboratory and analytical uses listed in the report by the TEAP and to make this information available to the Ozone Secretariat by 30 April 2010.

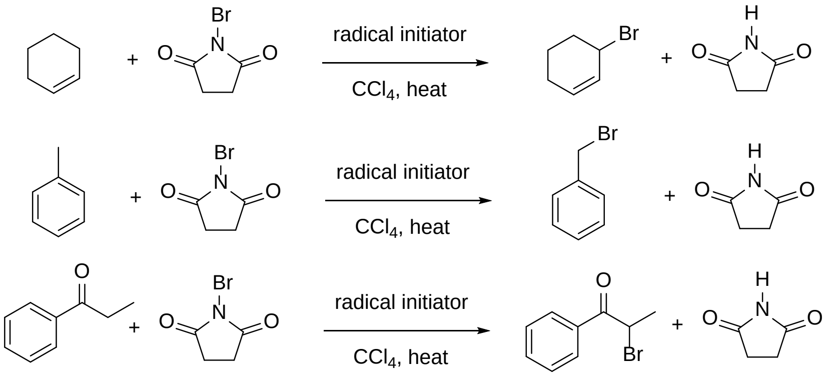
10. to encourage UNEP to invite representatives of the Chemicals Technical Options Committee to regional network meetings to raise awareness of ODS alternatives for laboratory and analytical uses where problems have been specifically identified by members of that network. Where considered necessary other representatives from competent authorities of Parties could be invited to participate in the meeting.

Appendix 2: Alternatives for use of carbon tetrachloride (CTC) as a solvent for bromination reactions involving *N*-bromosuccinimide (NBS)

N-Bromosuccinimide (NBS) is a relatively safe and user-friendly brominating agent that is used as a source for bromine, both in radical reactions and various electrophilic reactions. NBS is also an oxidizing agent. For example, bromination of substrates such as alcohols and amines with NBS, followed by elimination of HBr in the presence of a base, leads to the products of net oxidation, in which no bromine has been incorporated. In these reactions, CTC has long been used as a solvent, owing to its good solvency, non-flammability and chemically stability, and readily availability at affordable prices. However, it is both toxic and carcinogenic and, because it exhibits ozone-layer damaging properties, efforts have been made in the past few years to develop greener bromination procedures, mainly focusing on the substitution of hazardous CCl_4 by more benign solvents. Below is a brief review of the studies on alternatives for CTC as a solvent in these processes.

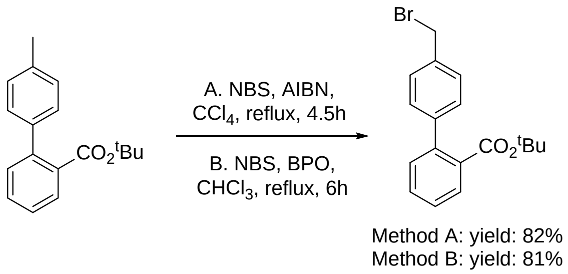
1. Radical substitution reactions (Wohl–Ziegler bromination)

The classical Wohl–Ziegler bromination is a radical reaction that involves the allylic, benzylic or α-carbonylic bromination of hydrocarbons using NBS in refluxing CCl_4 in the presence of a radical initiator such as UV, benzoyl peroxide (BPO) or 2,2-azobis(isobutyronitrile) (AIBN) and nowadays is still often the method of choice for this type of substitutions. The traditional choice of solvent has been CCl_4 which combines optimum properties of solubility, reaction temperature, and ease of product isolation.

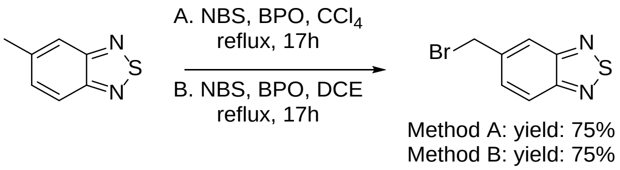


Several bromination protocols using chlorinated solvents (chloroform, 1,2-dichloroethane, dichloromethane, etc.) or non-chlorinated solvents (benzene, petroleum ether, heptane, CS_2, trifluoromethylbenzene, acetonitrile, methyl formate, methyl acetate, ethyl acetate and pivalate, methanol (MeOH), ethanol (EtOH), water, ionic liquids, even solvent-free, etc.) have been developed[1].

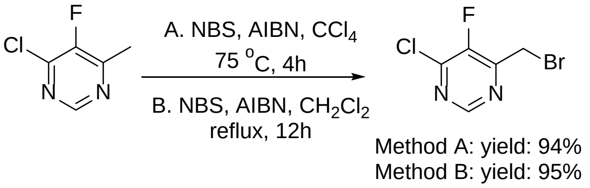
Generally, chlorinated solvents such as chloroform, 1,2-dichloroethane, dichloromethane are the most common alternatives for this type of radical substitution. Sometimes, chloroform gives similar or better results particularly in large-scale runs, since succinimide is soluble in hot chloroform, thus yielding a homogeneous solution. Tert-butyl 4'-(bromomethyl)-biphenyl-2-carboxylate could be obtained in the same yield both in CCl_4 and chloroform[2].



CCl_4 also could be replaced by 1, 2-dichloroethane for the bromination of 5-methyl-2, 1, 3-benzothiadiazole[3].



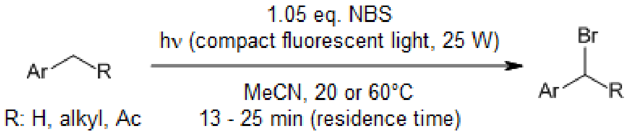
Dichloromethane is less toxic than CCl_4. However, the bromination with NBS needs longer reaction time due to its low boiling point[4].



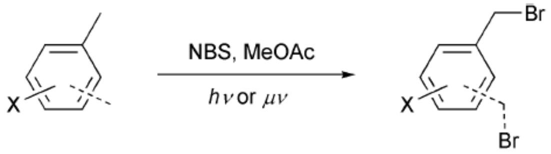
A variety of benzylic brominations were performed by using *N*-bromosuccinimide in (trifluoromethyl)benzene with photochemical activation. This system provides clean, rapid, and high-yielding reactions with replacement of conventional solvents, such as CCl_4, by less-toxic (trifluoromethyl)benzene[5].

$$\mathrm{Ar{-}CH_3}\ \xrightarrow[\text{(trifluoromethyl)benzene}]{\substack{\text{NBS, AIBN/BPO}\\ h\nu\ \text{(200 W tungsten lamp)}}}\ \mathrm{Ar{-}CH_2Br}$$

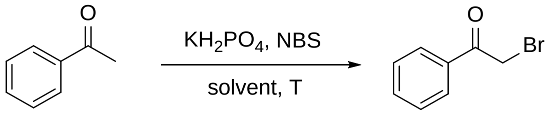
The radical reactions were activated with a readily available household compact fluorescent lamp (CFL) using a simple flow reactor design based on transparent fluorinated ethylene polymer tubing. All of the reactions were carried out using acetonitrile as the solvent, thus avoiding hazardous chlorinated solvents such as CCl_4[6].



Instead of the commonly used CCl_4 or other chlorinated solvents, methyl acetate (MeOAc) was used as an environmentally more benign solvent for these bromination reactions. Benzylic bromides became accessible in short reaction times via direct a-bromination of the corresponding arenes in MeOAc under microwave conditions[7].

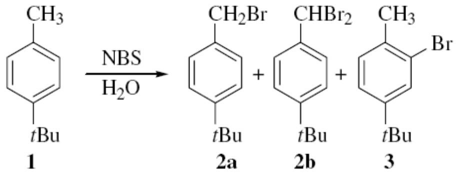


Ketones are regioselectively mono-brominated using NBS in EtOH in presence of 10% KH_2PO_4 as catalyst, with good to excellent isolated yields of the desired products within a short period of time (10-20 min). This approach increased the selectivity of monobromination vs. dibromination[8].



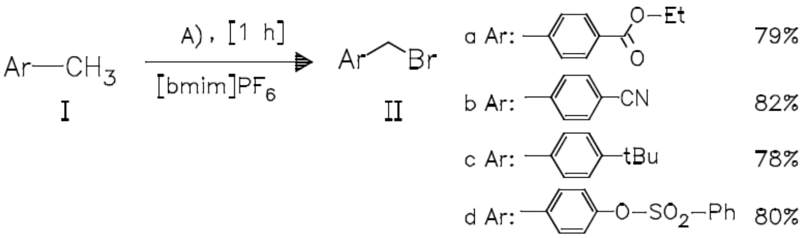
Entry	Solvent	Temp (°C)	Time	Yield[b] (%)
1	Et_2O	25-30	2 h	24
		Reflux	30 min	32
2	THF	25-30	4 h	18
		Reflux	20 min	35
3	MeOH	25-30	5 h	61
		Reflux	25 min	82
4	EtOH	25-30	7 h	52
		Reflux	10 min	96

This report showed that water is a very good medium for a ‘greener’ protocol for the Wohl–Ziegler bromination and moreover the initiator and heat are substituted by visible light activation of the radical chain reaction. A further advantage of this reaction system is the simple isolation protocol, as the only reaction residue is succinimide which is soluble in water[9].



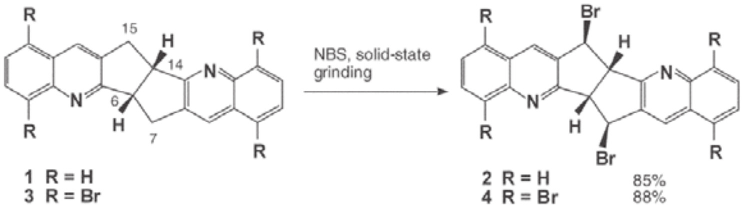
40 W bulb, 27 °C, 22 h 86% 6%

Environmentally-friendly Wohl–Ziegler bromination of benzylic methyl groups was successfully carried out in ionic-liquid systems[10].



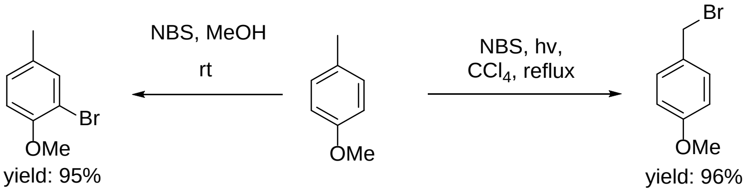
A): 1.2 equiv. NBS, 0.1 equiv. AIBN (cat.), 60–65°C

Bromination also can takes place in the solid state in the absence of toxic and ozone-depleting CCl_4 solvent. Most importantly, the regio- and stereo-selectivity encountered in the solution phase reactions is retained when solvent is omitted[11].



2. Electrophilic substitution reactions

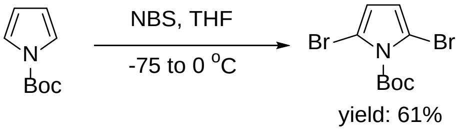
NBS is an available and popular reagent employed mostly in free radical substitutions but also for the electrophilic substitution of aromatic rings. Under some conditions, aromatic compounds can be brominated using NBS as electrophile. It is shown that the electrophilic substitution of benzene ring is favoured in more polar solvents. Otherwise, the free radical reaction in the *α*-site was favourable[12].



Phenols, anilines, and other electron-rich aromatic compounds can be mono-brominated using NBS in DMF with higher yields and higher levels of para selectivity than with Br_2[13].

$$\text{Ar—H} \xrightarrow[\text{rt, 24 h}]{\text{NBS, DMF}} \text{Ar—Br}$$

N-Substituted pyrroles are brominated with NBS in THF to afford 2-bromopyrroles (1 equivalent) or 2,5-dibromopyrroles (2 equivalents) with high selectivity, whereas bromination with Br_2 affords the thermodynamically more stable 3-bromopyrroles[14].

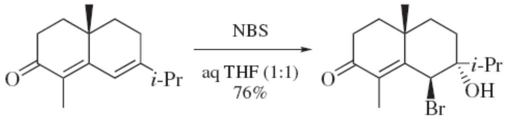


Thiophenes are also selectively brominated in the 2-position using NBS in acetic acid–chloroform[15].

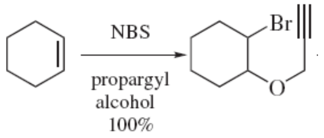
$$\mathrm{Ar{-}H} \xrightarrow[\text{70\% HClO}_4\text{, rt}]{\text{NBS, CHCl}_3} \mathrm{Ar{-}Br}$$

3. Electrophilic addition reactions

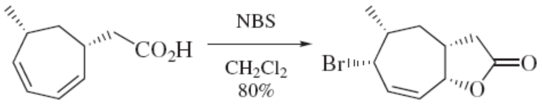
NBS also can be used for electrophilic additions to C=C such as bromohydration, bromolactonization, and other additions. The conditions for the bromohydration of alkenes involve the portion-wise addition of NBS to a solution of the alkene in 50–75% aqueous DME, THF, or t-butanol at 0°C. High selectivity for Markovnikov addition and anti stereochemistry results from attack of the bromonium ion intermediate by water. In the bromohydration of polyalkenic compounds, high selectivity is regularly achieved for attack of the most electron-rich double bond[16].



Bromoetherification of alkenes can be achieved using NBS in the desired alcohol as the solvent. Using propargyl alcohol the reaction has been extended to an annulation method for the synthesis of α-methylene-γ-butyrolactones[17].

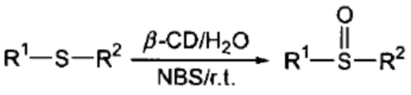


NBS is also an effective reagent for bromolactonization of unsaturated acids and acid derivatives with the same high stereo and Markovnikov selectivity. Dienes, such as the cycloheptadiene derivative shown, may react exclusively via syn-1,4-addition[18].



4. Oxidation reactions

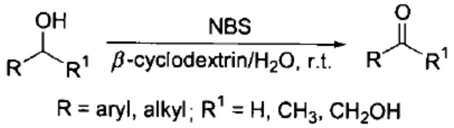
The selective oxidation of sulfides to sulfoxides could be performed with NBS catalyzed by cyclodextrin in water. Moreover, the reaction proceeds under neutral and mild conditions and can be carried out easily at room temperature with recycling of cyclodextrin[19].

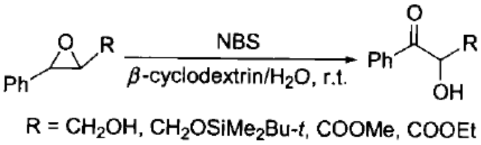


$$R^1{-}S{-}R^2 \xrightarrow[\text{NBS/r.t.}]{\beta\text{-CD/H}_2\text{O}} R^1{-}\overset{\overset{\displaystyle O}{\|}}{S}{-}R^2$$

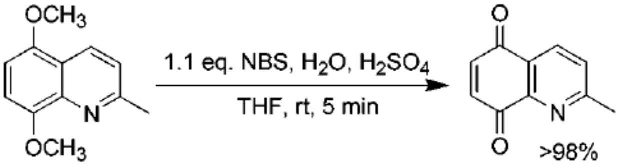
R^1 = aryl, naphthyl; R^2 = alkyl

The biomimetic oxidation of various alcohols and epoxides with NBS catalyzed by cyclodextrin in water has also been developed[20].

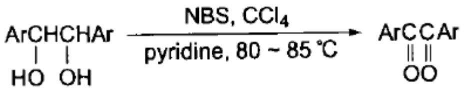


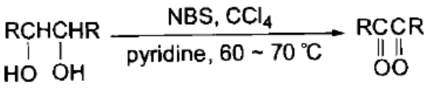


Fused 1,4-dimethoxybenzenes could be oxidized to benzoquinones by oxidation. The oxidative demethylation of 5,8-dimethoxy-2-methylquinoline using 1.1 equivalents of NBS in aqueous THF and a catalytic amount of H_2SO_4 at 20°C for 5 min gave 2-methylquinoline-5,8-dione in 98% yield without bromination[21].



The synthesis of benzils and aliphatic 1,2-diketones of cyclic and open chain compounds from corresponding hydrobenzoins and 1,2-diols by refluxing with NBS in CCl_4 in presence or absence of pyridine was also reported[22].





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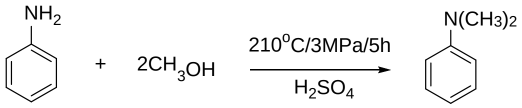
Appendix 3: Methylating agent alternatives to methyl bromide

Methyl bromide can be used in a laboratory as a methylating agent in chemical reactions to deliver a methyl group to a chemical substrate. This application is believed to be very minor. There are many alternatives to using methyl bromide as a methylating agent. A summary of alternative methylating agents is presented below. These alternatives are nearly always used in preference to methyl bromide.

1. Methylating agent used under acidic conditions (methanol, dimethyl ether, dimethylaniline)

Methanol, dimethyl ether and dimethylaniline are very weak methylating agents. In the case of acidic conditions (Brønsted or Lewis acid), they methylate active amines and carboxylic acids as nucleophiles. Many of these reactions require the use of special catalyst or an autoclave.[2]



2. Methylating agent used under basic conditions

2.1 Methyl halide

2.1.1 Methyl Iodide (MeI)

Methyl iodide is an excellent substrate for SN_2 substitution reactions. It is sterically open for attack by nucleophiles, and iodide is a good leaving group. It is used for alkylating carbon, oxygen, sulfur, nitrogen, and phosphorus nucleophiles.[3] The iodide leaving group in MeI may cause side reactions, as it is a powerful nucleophile. Being highly reactive, MeI is more toxic and carcinogenic than other methyl halides.

2.1.2 Methyl Chloride (MeCl)

Chloromethane is employed as a methylating agent attacking C-, O-, N-, P-, S-, Se-, and Te-based nucleophiles; organometallic derivatives provide source of $Me^{\delta-}$in reactions with >C=O, M–X, halogen, etc., and also as a base towards C–H; radical substitution of Me by C•, halogen, etc. The reactivity of methylation is lower than methyl iodide and methyl bromide.[4]

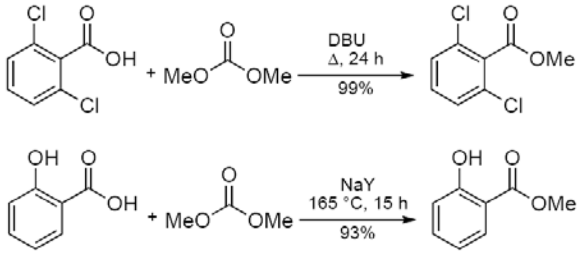
2.2 Methyl ester

2.2.1 Dimethyl sulfate (DMS)

Dimethyl sulfate is best known as a powerful reagent for the methylation of phenols, amines, and thiols. Typically, one methyl group is transferred more quickly than the second. Methyl transfer is typically assumed to occur via an SN_2 reaction.[5] Compared to other methylating agents, dimethyl sulfate is preferred by the industry because of its low cost and high reactivity.

2.2.2 Dimethyl carbonate (DMC)

Dimethyl carbonate methylates anilines, phenols and carboxylic acids. It has been shown to be a safe and environmentally friendly replacement for DMS and methyl halides. But it is a relatively weak methylating agent compared to those traditional reagents.[6] In the presence of K_2CO_3 or DBU it is more reactive. The reagent also methylates phenols but can be chemoselective for acids in the presence of NaY Faujasite.



2.2.3 *Methyl trifluoromethansulfonate (MTFS)*

Methyl trifluoromethansulfonate is a powerful methylating reagent (about four orders of magnitude more reactive than methyl iodide and Me_2SO_4). It alkylates faster and with wider range of substrates than traditional methylating agents. One ranking of alkylating agents is $(CH_3)_3O^+ >$ MTFS ≈ MFS $> (CH_3)_2SO_4 > CH_3I$. It will alkylate many functional groups that are only weakly basic such as aldehydes, amides, and nitriles. It does not methylate benzene or the bulky 2,6-di-tert-butylpyridine.[7]

2.2.4 *Methyl fluorosulfonate (MFS)*

Methyl fluorosulfonate is closely related to methyl trifluoromethansulfonate.[7]

2.2.5 *Methyl methanesulfonate (MMS)*

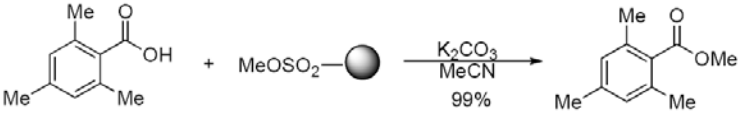
Methyl methanesulfonate is an exogenous alkylating agent and a carcinogen in biological research. It is also a suspected reproductive toxicant and may also be a skin/sense organ toxicant. It is used in cancer treatment.[8]

2.2.6 *Trimethyl phosphate (TMP)*

Trimethyl phosphate is a mild methylating agent for the preparation of methyl esters of hindered carboxylic acids and serves as an alternative to toxic dimethyl sulfate. It can also affect the *O*-methylation of unprotected amino acids, dimethylation of anilines and related heterocyclic compounds (purine, pyrimidine, imidazole et al.).[9]

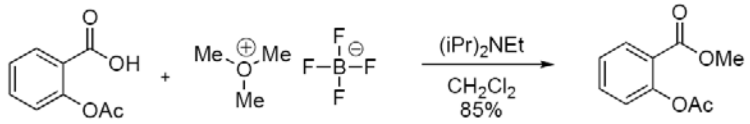
2.2.7 *Polymer-bound methyl sulfonate*

Instead of the sulfonate esters, modern alternative is to use polymer-bound methyl sulfonate, which is easily handled, allows simple work-up and is recyclable.[10]



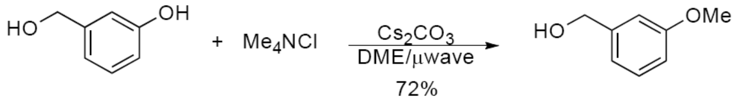
2.3 Oxonium salts ($Me_3O•BF_4$)

In aqueous conditions, it is possible to use Meerwein methylation, using the corresponding oxonium salts ($Me_3O•BF_4$) with $NaHCO_3$. However, these salts are rapidly hydrolyzed in water. A better procedure with these reagents is to use dichloromethane as solvent and a bulky amine as base. Under these conditions, even sterically hindered or sensitive acids can be alkylated.[11]



2.4 Tetramethylammonium salts

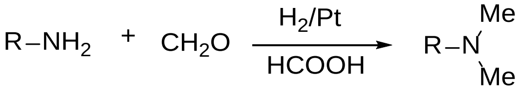
Tetramethylammonium salts are other replacement alkylating agents which are non-volatile and non-carcinogenic. However, due to their lower reactivity, high temperatures (such as the injection port during a gas chromatographic analysis) are required. For the alkylation of phenols, microwave conditions have been used with success. The reaction is chemoselective for the phenolic hydroxyl group over the alcohol.[12]



3. Methylating agent used under neutral conditions

3.1 Formaldehyde aqueous solution

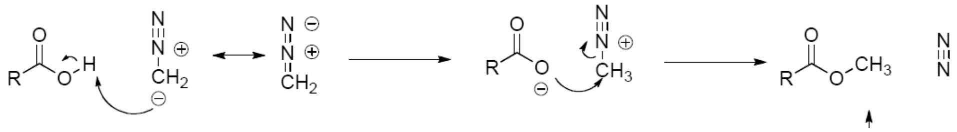
Formaldehyde aqueous solution can be used in methylation of primary or secondary amine (Eschweiler–Clarke reaction). Formic acid or H_2/Ptis is also needed as the source of hydride. This reaction will not produce quaternary ammonium salts, but instead will stop at the tertiary amine stage.[13]



$$R{-}NH_2 + CH_2O \xrightarrow[HCOOH]{H_2/Pt} R{-}N(Me)_2$$

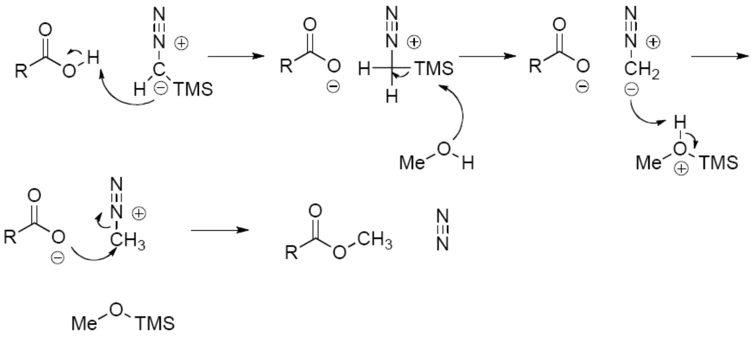
3.2 Diazomethane

The methylation of carboxylic acids and other acidic functional groups is often carried out in neutral conditions using diazomethane (CH_2N_2).[14] However, due to its toxicity and the explosive nature of diazomethane (as well as the danger in the preparation and the carcinogenicity of the commercially available precursors), several alternative reagents recently have been developed.

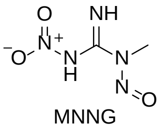


3.3 Trimethylsilyldiazomethane (TMSCHN$_2$)

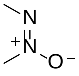
Trimethylsilyldiazomethane (TMSD) has been touted as a stable and safe alternative to diazomethane, but its use is constrained by its high cost and lower efficiency.[15]

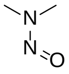


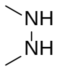
3.4 Methylnitronitrosoguanidine (MNNG), N-methyl-N-nitrosourea (MNU), Azoxymethane (AOM), **N**-*Nitrosodimethylamine (NDMA), 1,2-dimethylhydrazine (DMH)*


MNNG


MNG


AOM

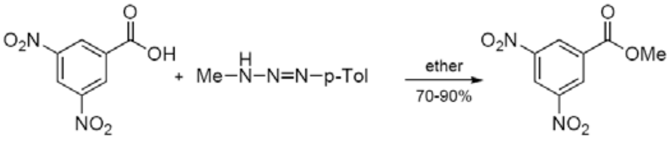

NDMA


DMH

MNNG, NMU, AOM, NDMA, and DMH are reliable carcinogen, mutagen, and teratogen in biological research. They all exhibit the toxicity by transferring methyl group to nucleobases in nucleic acids, which can lead to AT:GC transition mutations. The corresponding mechanisms of methylation are similar to diazomethane.[8]

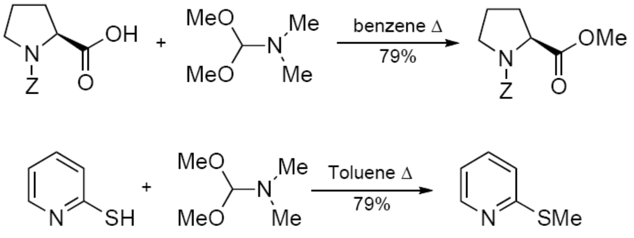
3.5 Aromatic triazenes

The aromatic triazenes, especially of *p*-toluidine, can be used as alkylating agents of carboxylic acids and vinylogous acids. However, these reagents are also carcinogenic and have the risk of being explosive.[16]



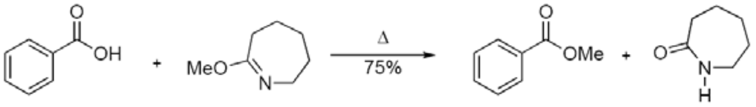
3.6 Dimethyl acetals of **N,N**-*dimethylformamide (DMF)*

Dimethyl acetals of *N,N*-dimethylformamide (DMF) is often useful alkylating agents under neutral conditions. It is most commonly used to form the corresponding esters. Heterocycles with SH, NH and OH can also be methylated with DMF dimethyl acetal.[17]



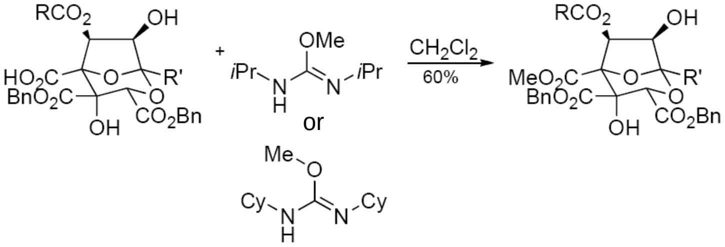
3.7 **O**-*Methylcaprolactam*

Related to the DMF acetals are the corresponding lactim ethers of cyclic amides. For example, *O*-methylcaprolactam has been shown to alkylate carboxylic acids at high temperatures.[18]



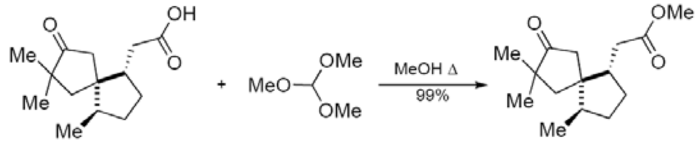
3.8 **O**-*Methyl isourea*

A variety of esters can be prepared, even in the presence of various functional groups, with *O*-methyl isourea.[19]*O*-Methyl isourea is easily formed from methanol and dicyclohexylcarbodiimide (DCC) or diisopropylcarbodiimide (DIC).



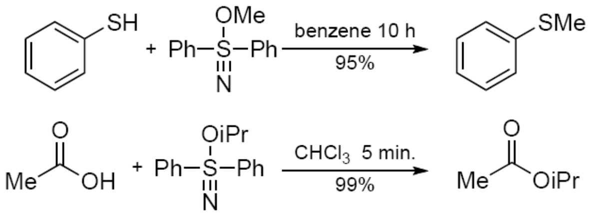
3.9 Trimethyl Orthoformate

Trimethyl orthoformate can be used for the methylation of acids, including amino acids. The reaction is mild enough to chemoselectively form the ester in the presence of other functional groups. The reaction can also be run efficiently in room temperature ionic liquids as solvents.[20]



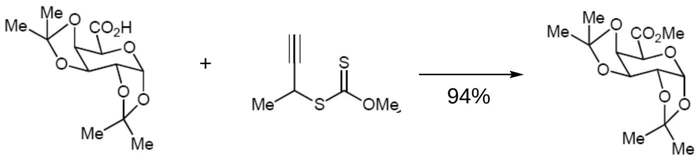
3.10 Alkoxy-λ6-sulfanenitriles (thiazynes)

The surprising chemistry of alkoxy-λ6-sulfanenitriles (thiazynes) has been investigated and these compounds have been found to alkylate carboxylic acids, thiols, phenols and sulfonic acids in essentially quantitative yields at room temperature.[21]



3.11 S-Propargyl xanthates

S-propargyl xanthates have been used for the esterification of acids. This method shows high reactivity (even for the synthesis of neopentyl esters, which are notoriously difficult to form) and complete inversion of stereochemistry for secondary alcohols.[22]



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Appendix 4: Non-exhaustive list of standards that do not use ODS

Determination of hydrocarbons (oil, grease, etc.) in water

Standard number	Standard Title	Alternative
ASTM D7066-04(2017)	Standard Test Method for dimer/trimer of chlorotrifluoroethylene (S-316) Recoverable Oil and Grease and Nonpolar Material by Infrared Determination	Dimer/trimer of chlorotrifluoroethylene (S-316)
ASTM D7575-11(2017)	Standard Test Method for Solvent-Free Membrane Recoverable Oil and Grease by Infrared Determination	Membrane
ISO 17993:2002	Water quality-Determination of 15 polycyclic aromatic hydrocarbons (PAH) in water by HPLC with fluorescence detection after liquid-liquid extraction	Hexane, PAHs
ISO 9377-1:2000	Water quality - Determination of hydrocarbon oil index - Part 1: Method using solvent extraction and gravimetry	Petroleum ether
ISO 9377-2:2000	Water quality - Determination of hydrocarbon oil index - Part 2: Method using solvent extraction and gas chromatography	n-Hexane
ISO 15680:2003	Water Quality - Gas-chromatographic Determination Of A Number Of Monocyclic Aromatic Hydrocarbons, Naphthalene And Several Chlorinated Compounds Using Purge-and-trap And Thermal Desorption	Purge-and-trap
ISO 20595:2018	Water quality — Determination of selected highly volatile organic compounds in water — Method using gas chromatography and mass spectrometry by static headspace technique (HS-GC-MS)	HS-GC-MS
ISO 10301:1997	Water quality — Determination of highly volatile halogenated hydrocarbons — Gas-chromatographic methods	Pentane, hexane, petroleum ether, heptane or xylene
US EPA Method 502.2 Revision 2.1	Volatile Organic Compounds in Water by Purge and Trap Capillary Column Gas Chromatography with Photoionization and Electrolytic Conductivity Detectors in	Purge-and-trap

Standard number	Standard Title	Alternative
	Series	
US EPA Method 524.2 Revision4.1	Measurement of Purgeable Organic Compounds in Water by Capillary Column Gas Chromatography/Mass Spectrometry	GC-MS
US EPA Method 3560	Supercritical Fluid Extraction of Total Recoverable Petroleum Hydrocarbons (TRPHs)	Supercritical CO_2
US EPA Method 1664 Revision A	Extraction of Oil and Grease from Water Samples Using Solid-Phase Extraction (SPE) Cartridge Configuration	Hexane
US EPA 3810	Headspace gas chromatography	Methyl alcohol
US EPA 3820	Hexadecane extraction and screening of purgeable organics	Hexadecane
US EPA 5021B	Volatile organic compound in various sample matrices using equilibrium headspace analysis	Headspace analysis
US EPA 8021B	Aromatic and halogenated volatiles by gas chromatography using photo-ionisation and/or electrolytic conductivity detectors	GC
HJ 637-2018 (replaces HJ 637-2012)	Water quality − Determination of petroleum, animal fats and vegetable oils − Infrared spectrophotometry	Perchloroethylene (PCE)
HJ 970-2018	Water quality − Determination of petroleum − Ultraviolet spectrophotometric method	Hexane
HJ 893-2017	Water quality–Determination of volatile petroleum hydrocarbons (C6-C9)–Purge and trap / gas chromatography	Purge and trap
HJ 894-2017	Water quality—Determination of extractable petroleum hydrocarbons (C10-C40)—Gas chromatography	Dichloromethane

Determination of hydrocarbons (oil, grease, etc.) in air, soil or sediment

Standard number	**Standard Title**	**Alternative**
ISO 16703：2004	Determination of hydrocarbon content (C10 to C40) by gas chromatography after extraction with heptane	Heptane
ISO15009：2016	Gas-chromatographic determination of the content of volatile aromatic hydrocarbons, naphthalene and volatile halogenated hydrocarbons after methanol extraction and purge-and-trap	Methanol
ISO 10694:1995	Soil quality -- Determination of organic and total carbon after dry combustion (elementary analysis)	Elementary analysis
ISO 18287:2006	Soil quality — Determination of polycyclic aromatic hydrocarbons (PAH) — Gas chromatographic method with mass spectrometric detection (GC-MS)	Acetone/petroleum ether
ASTM D5765-16	Solvent extraction of total petroleum hydrocarbons from soil and sediments using closed vessel microwave heating	Acetone/hexane
US EPA 9071B	n-Hexane extractable material (HEM) for sludge, sediment, and solid samples	n-Hexane
US EPA Method 8261A	Volatile organic compounds by vacuum distillation in combination with gas chromatography/mass spectrometry (VD/GC/MS)	VD/GC/MS
US EPA 3550B	Ultrasonic extraction	Acetone/methylene chloride or acetone/hexane
EN 14039:2004	Characterization of waste - Determination of hydrocarbon content in the range of C10 to C40 by gas chromatography	Heptane
EN 14345:2004	Characterization of waste. Determination of hydrocarbon content by gravimetry	Acetone/petroleum

Determination of Iodine value or Bromine value[181]

Standard number	**Standard Title**	**Alternative**
ISO 3961:2013	Animal and vegetable fats and oils -- Determination of iodine value	Cyclohexane/glacial acetic acid
ASTM D5768-02(2018)	Standard Test Method for Determination of Iodine Value of Tall Oil Fatty Acids	iso-Octane/cyclohexane
ASTM D1492-13	Bromine index of aromatic hydrocarbons by coulometric titration	Glacial acetic acid/ methanol
ASTM D5554 -15	Standard Test Method for Determination of the Iodine Value of Fats and Oils Standard Test Method for Determination of the Iodine Value of Fats and Oils	Glacial acetic acid/cyclohexane
ASTM D5776-14a	Standard Test Method for Bromine Index of Aromatic Hydrocarbons by Electrometric Titration	1-Methyl-2-pyrrolidinone
ASTM D4252 -89(2017)	Standard Test Methods for Chemical Analysis of Alcohol Ethoxylates and Alkylphenol Ethoxylates	Chloroform

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[181] Value is also referred to as index.

Determination of moisture and water

Standard number	Standard Title	Alternative
ISO 662:2016	Animal and vegetable fats and oils -- Determination of moisture and volatile matter content	Heating method
ISO 934:1980	Animal and vegetable fats and oils. Determination of water content- Entrainment method	Xylene
ISO 8534:2017	Animal and vegetable fats and oils. Determination of water content. Karl Fischer method (pyridine free)	Methanol
ISO 3733:1999	Petroleum products and bituminous materials- Determination of water- Distillation method	Aromatic solvent, petroleum distillate solvent, paraffinic solvents
ISO 6296:2000	Petroleum products. Determination of water. Potentiometric Karl Fischer titration method	Sodium dioctylsulfosuccinate
ISO 12937:2000	Petroleum products. Determination of water. （Coulometric Karl Fischer titration method）	Sodium dioctylsulfosuccinate

Determination of phenol in water

Standard number	Standard Title	Alternative
ASTM D1783 - 01(2012)e1	Standard test methods for phenolic compounds in water	Chloroform
ISO 6439:1990	Water quality — Determination of phenol index — 4-Aminoantipyrine spectrometric methods after distillation	Chloroform
US EPA Method 4 20.1	Phenolics (Spectrophotometric, Manual 4-AAPWith Distillation)	Chloroform

Determination of metal content

Standard number	**Standard Title**	**Alternative**
ASTM D3237-06e1	Standard Test Method for Lead in Gasoline by Atomic Absorption Spectroscopy	Methyl isobutyl ketone

Appendix 5: Non-exhaustive list of standards that still use ODS

	Standard No.	**Standard Title**
1	ASTM D3467-04(2014)	Standard Test Method for Carbon Tetrachloride Activity of Activated Carbon
2	ASTM D5566-95(2011)	Standard Test Method for Determination of Inorganic Salt Content of Sulfated and Sulfonated Oils
3	ASTM F754 - 08(2015)	Standard Specification for Implantable Polytetrafluoroethylene (PTFE) Sheet, Tube, and Rod Shapes Fabricated from Granular Molding Powders
4	ASTM D3124 - 98(2011)	Standard Test Method for Vinylidene Unsaturation in Polyethylene by Infrared Spectrophotometry
5	ASTM D3703 – 18	Standard Test Method for Hydroperoxide Number of Aviation Turbine Fuels, Gasoline and Diesel Fuels
6	ASTM E1683 - 02(2014)e1	Standard Practice for Testing the Performance of Scanning Raman Spectrometers
7	ASTM D2008 - 12	Standard Test Method for Ultraviolet Absorbance and Absorptivity of Petroleum Products
8	ASTM E169 - 16	Standard Practices for General Techniques of Ultraviolet-Visible Quantitative Analysis
9	ASTM E2036 - 15	Standard Test Method for Nitrogen Trichloride in Liquid Chlorine by High Performance Liquid Chromatography (HPLC)
10	ASTM D1505 - 18	Standard Test Method for Density of Plastics by the Density-Gradient Technique
11	ASTM F218 - 13	Standard Test Method for Measuring Optical Retardation and Analyzing Stress in Glass
12	ASTM E50 - 17	Standard Practices for Apparatus, Reagents, and Safety Considerations for Chemical Analysis of Metals, Ores, and Related Materials
13	ASTM C670 – 15	Standard Practice for Preparing Precision and Bias Statements for Test Methods for Construction Materials
14	ASTM E2106 - 00(2011)	Standard Practice for General Techniques of Liquid Chromatography-Infrared (LC/IR) and Size Exclusion Chromatography-Infrared (SEC/IR) Analyses

15	ASTM C799 - 12	Standard Test Methods for Chemical, Mass Spectrometric, Spectrochemical, Nuclear, and Radiochemical Analysis of Nuclear-Grade Uranyl Nitrate Solutions
16	ASTM D3869 - 15	Standard Test Methods for Iodide and Bromide Ions in Brackish Water, Seawater, and Brines
17	ASTM D5160 - 95(2014)	Standard Guide for Gas-Phase Adsorption Testing of Activated Carbon
18	ASTM E1252 - 98(2013)e1	Standard Practice for General Techniques for Obtaining Infrared Spectra for Qualitative Analysis
19	ASTM D4448 - 01(2013)	Standard Guide for Sampling Ground-Water Monitoring Wells
20	ASTM E1982 - 98(2013)	Standard Practice for Open-Path Fourier Transform Infrared (OP/FT-IR) Monitoring of Gases and Vapors in Air
21	ASTM D460 - 91(2014)	Standard Test Methods for Sampling and Chemical Analysis of Soaps and Soap Products
22	ASTM D629 - 15	Standard Test Methods for Quantitative Analysis of Textiles
23	ASTM C761 - 18	Standard Test Methods for Chemical, Mass Spectrometric, Spectrochemical, Nuclear, and Radiochemical Analysis of Uranium Hexafluoride
24	ASTM C169 – 16	Standard Test Methods for Chemical Analysis of Soda-Lime and Borosilicate Glass
25	ASTM D297 - 15	Standard Test Methods for Rubber Products—Chemical Analysis
26	ISO 6439:1990	Water quality — Determination of phenol index — 4-Aminoantipyrine spectrometric methods after distillation
27	ISO 7523:1985	Nickel — Determination of silver, arsenic, bismuth, cadmium, lead, antimony, selenium, tin, tellurium and thallium contents — Electrothermal atomic absorption spectrometric method
28	ISO 7106:1985	Liquefied anhydrous ammonia for industrial use — Determination of oil content — Gravimetric and infra-red spectrometric methods

29	ISO 5796:2000	Rubber compounding ingredients — Natural calcium carbonate — Test methods
30	ISO 1183-1:2012	Plastics — Methods for determining the density of non-cellular plastics — Part 1: Immersion method, liquid pyknometer method and titration method
31	ISO 1183-2:2004	Plastics — Methods for determining the density of non-cellular plastics — Part 2: Density gradient column method
32	ASTM D3326 - 07(2017)	Standard Practice for Preparation of Samples for Identification of Waterborne Oils
33	ASTM D1783 - 01(2012)e1	Standard Test Methods for Phenolic Compounds in Water
34	ASTM D1574 - 04(2013)	Standard Test Method for Extractable Matter in Wool and Other Animal Fibers
35	ASTM D3698-04(2015)	Standard Practice for Solvent Vapor Degreasing Operations
36	ASTM F1147-05(2017)e1	Standard Test Method for Tension Testing of Calcium Phosphate and Metallic Coatings
37	ASTM B322-99(2014)	Standard Guide for Cleaning Metals Prior to Electroplating
38	ISO 15001:2010	Anaesthetic and respiratory equipment — Compatibility with oxygen

Appendix 6 Summary of national end-of life demonstration projects

Country	Approval	IA	Destruction Option	Implementation Status/Remarks	Reference
Algeria	2014	UNIDO/France	Cement kiln	Cancelled	Report of 79th EXCOM Meeting July 2017, http://www.multilateralfund.org/79/English/1/7951.pdf
Brazil	2012/ 2014	UNDP	National HW facilities – HTI rotary kiln, Plasma arc Initial parallel development of two de-manufacturing plants	Project restructured to focus on competitive selection of HW disposal facility Implementation restarted based on national commercial HTI rotary kiln	No information
China	2012	UNIDO/ Japan	Existing HTI rotary kiln facilities	Completed Destroyed 194.9 t (11.9 t CFC-12, 11 t CFC-11, 172 t CFC-11 in foam) 8.0-12.5 USD/kg ODP	Report of 81st ExCom Meeting, June 2018, *Status Reports and Reports on Projects with Specific Reporting Requirements*, page 399, http://www.multilateralfund.org/81/English/1/8110.pdf
Colombia	2012	UNDP	National HW HTI facility for CFCs/HCFC EAF steel furnace/cement kilns for foams Integrated with existing refrigeration servicing system and HW service providers. EPR funding and energy efficiency incentives being phased in to sustain	Completed Test burns completed to qualify domestic HTI rotary kiln – Destroyed 6.6 t CFC-11, 2.1 t CFC-12, 6.0 t CFC-11 foam, 5.6 t HCFC foam. Estimated Commercial Cost – US$5-6 US$/kg ODP for refrigerant Trials on refrigerator components containing foam in EAF in completed in 2017 Integrated with	Report of 81st ExCom Meeting, June 2018, *Status Reports and Reports on Projects with Specific Reporting Requirements*, page 431 http://www.multilateralfund.org/81/English/1/8110.pdf

Country	Approval	IA	Destruction Option	Implementation Status/Remarks	Reference
			system	expanding ERP financed RAC equipment collection - 4 cities Planned Processing of 300,000 refrigerator units involving destruction of destruction of 100 t of CFCs	
Cuba	2010	UNDP	CFC-12 in cement kilns	Reported completed Destruction quantities and performance testing results not yet reported	No information
Georgia	2013	UNDP	Export to EU HTI facilities	Completed – 2.13 t CFC-12 destroyed in an EU rotary kiln Export combined with GEF POPs project	Report of 79th ExCom Meeting, July 2017, *Status Reports and Reports on Projects with Specific Reporting Requirements*, page 12, http://www.multilateralfund.org/79/English/1/7914.pdf
Ghana	2011	UNDP	Initial intent to purchase ISADA unit (dropped), Export to EU HTI facility	Completed 1.2 t CFC-12, 5.2 t MB destroyed	Report of 79th ExCom Meeting, July 2017, *Status Reports and Reports on Projects with Specific Reporting Requirements*, page 29, http://www.multilateralfund.org/79/English/1/7914.pdf
Lebanon	2014	UNIDO	Export to EU HTI facility	Potential opportunity to combine with POPs project	No information
Mexico	2011	UNIDO/France	Domestic plasma arc facility and cement kiln	Completed 113 t CFC-12 destroyed (74 t argon plasma arc, 39 t cement kiln) Plasma arc- 9.2 US$.kg, Cement Kiln 8 US$/kg	Demonstration Project for Unwanted ODS in Mexico, UNIDO, Sept. 2017, (presented at the 80th ExCom Meeting, Nov. 2017) http://www.multilateralfund.org/80/Document%20Library1/1/8012p2.pdf

Country	**Approval**	**IA**	**Destruction Option**	**Implementation Status/Remarks**	**Reference**
Nepal	2009	UNEP	Export to HTI rotary kiln facility	Completed 10 t CFC-12 destroyed	Report of 79th ExCom Meeting, July 2017, *Status Reports and Reports on Projects with Specific Reporting Requirements*, page 46, http://www.multilateralfund.org/79/English/1/7914.pdf
Nigeria	2012	UNIDO	Utilized local small rotary kiln	Completed. 1.5 kg CFC-12 collected and being destroyed as local industrial incinerator.	Report of 81st ExCom Meeting, June 2018, *Status Reports and Reports on Projects with Specific Reporting Requirements*, page 504. http://www.multilateralfund.org/81/English/1/8110.pdf
Turkey	2012	UNIDO	Initial intent to export to commercial plasma arc facility (potentially qualify national HTI unit in future)	Completed. Encountered limited EOL ODS availability and export barriers (originally 103 t CFC-12 targeted). Exported 9.2 to EU in association with E. Europe regional project. US$10.37 US$/kg ODP	Report of 81st ExCom Meeting, June 2018, *Status Reports and Reports on Projects with Specific Reporting Requirements*, page 513 http://www.multilateralfund.org/81/English/1/8110.pdf
E. Europe	2013	UNIDO/UNEP	Export to HTI facility	Completed 33t ODS (Bosnia and Herzegovina – 0.5 t, Croatia- 28 t, Montenegro – 0.5 t), destroyed in rotary kilns in Germany and Poland 8.0 US$/kg	Demonstration of a Regional Strategy for ODS Waste Management and Disposal in the ECA Region, UNIDO/UNEP, Sept. 2017, (presented at the 80th ExCom Meeting, Nov. 2017), http://www.multilateralfund.org/80/pages/English.aspx

Annex 1: MCTOC membership information

The disclosure of interest (DOI) for each member can be found on the Ozone Secretariat website at: http://ozone.unep.org/en/assessment-panels/technology-and-economic-assessment-panel.

TEAP's Terms of Reference (TOR) (2.3) as approved by the Parties in Decision XXIV/8 specify that *"… the Meeting of the Parties shall appoint the members of TEAP for a period of no more than four years…and may re-appoint Members of the Panel upon nomination by the relevant party for additional periods of up to four years each*". Each term of appointment for TEAP members ends as of 31st December in the final year of appointment.

TEAP's TOR (2.5) specifies that "*TOC members are appointed by the TOC co-chairs, in consultation with TEAP, for a period of no more than four years…[and] may be re-appointed following the procedure for nominations for additional periods of up to four years each.*" Each term of appointment for TOC members starts from the date of appointment by TOC co-chairs and ends as of 31st December in the final year of appointment, for periods of up to four years.

Medical and Chemical Technical Options Committee (MCTOC)

Co-chairs	**Affiliation**	**Country**	**Appointed through**
Kei-ichi Ohnishi	Asahi Glass	Japan	2019
Helen Tope	Energy International Australia	Australia	2021
Jianjun Zhang	Zhejiang Chemical Industry Research Institute	China	2019
Members	**Affiliation**	**Country**	**Appointed through**
Emmanuel Addo-Yobo	Kwame Nkrumah University of Science and Technology	Ghana	2018*
Fatima Al-Shatti	Consultant to the International Ozone Committee of the Kuwait Environmental Protection Authority	Kuwait	2018*
Paul Atkins	Oriel Therapeutics Inc. (A Novartis Company)	USA	2018*
Bill Auriemma	Diversified CPC International	USA	2021
Olga Blinova	Russian Scientific Center "Applied Chemistry"	Russia	2018*
Steve Burns	AstraZeneca	UK	2021
Nick Campbell	Arkema	France	2018*
Jorge Caneva	Favaloro Foundation	Argentina	2018*
Nee Sun (Robert) Choong Kwet Yive	University of Mauritius	Mauritius	2018*
Rick Cooke	Man-West Environmental Group Ltd.	Canada	2021
Davide Dalle Fusine	Chiesi Farmaceutici (seconded at Chiesi China)	Italy	2018*
Maureen George	Columbia University School of Nursing	USA	2021
Kathleen Hoffmann	Sterigenics International Inc.	USA	2020
Eamonn Hoxey	E V Hoxey Ltd	UK	2018*
Jianxin Hu	College of Environmental Sciences & Engineering, Peking University	China	2018*
Ryan Hulse	Honeywell	USA	2020
Biao Jiang	Shanghai Institute of Organic chemistry, Chinese Academy of Sciences	China	2018*
Javaid Khan	The Aga Khan University	Pakistan	2018*
Andrew Lindley	Independent consultant to Mexichem (UK) Ltd. and to the European Fluorocarbon Technical Committee	UK	2020
Gerald McDonnell	DePuy Synthes, Johnson & Johnson	USA	2018*
Robert Meyer	Independent Consultant to Greenleaf Health	USA	2018*
John G. Owens	3M	USA	2020
Jose Pons Pons	Spray Quimica	Venezuela	2019
Hans Porre	Teijin Aramid	Netherlands	2018*
John Pritchard	Private Consultant	UK	2018*
Rabbur Reza	Beximco Pharmaceuticals	Bangladesh	2018*
Paula Rytilä	Orion Corporation Orion Pharma	Finland	2019
Surinder Singh Sambi	Indian Institute of Chemical Engineers (Northern Region)	India	2018*
Rajiev Sharma	GSK	UK	2021
Roland Stechert	Boehringer Ingelheim	Germany	2018*
Jørgen Vestbo	University of Manchester	Denmark	2021
Kristine Whorlow	Non-Executive Director	Australia	2018*
Ashley Woodcock	University Hospital of South Manchester	UK	2019
Yizhong You	Journal of Aerosol Communication	China	2018*
Consulting Experts	**Affiliation**	**Country**	**One-year renewable terms**
Archie McCulloch	Independent Consultant to European Fluorocarbon Technical Committee (EFCTC)	UK	
Hideo Mori	Tokushima Regional Energy	Japan	
Tim Noakes	Mexichem (UK) Ltd.	UK	
Lifei Zhang	National Research Center for Environmental Analysis and Measurement	China	

* Indicates members whose terms expire at the end of the current year