

AMERICAN LINK ASSOCIATION

PHOTOCOPY
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**Fight Lung Disease
With Christmas Seals®**

November 18, 1993

Brian Burke
Senior Policy Analyst
Domestic Policy Council
Old Executive Office Building
Room 210
Washington, D.C. 20036

Dear Brian,

As promised, I would like to update you on the status of regulations affecting the availability of chlorofluorocarbons (CFCs) for use in metered dose inhalers (MDIs). As a result of the request for nomination of essential uses made by the American Lung Association and the International Pharmaceutical Aerosol Consortium, the U.S. government submitted a nomination for essential uses for CFCs to the United Nations Environment Programme. (see attached)

While we remain confident that the nomination will receive favorable action, many hurdles remain. Key concerns include the structure of the exemption including the use of caps to limit an exemption and the timeframe for a decision on the exemption.

The ALA would appreciate the opportunity to brief Council members and staff regarding these concerns. Please advise me if this would be appropriate.

Sincerely,

Fran Du Melle
Deputy Managing Director

attachment

Fran Du Melle
Deputy Managing Director

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John R. Garrison
Managing Director

Founded in 1904, the American Lung Association includes affiliated associations throughout the U.S., and a medical section, the American Thoracic Society.



United States Department of State

*Bureau of Oceans and International
Environmental and Scientific Affairs*

Washington, D.C. 20520

September 27, 1993

Mr. K. M. Sarma
Co-ordinator, Ozone Secretariat
United Nations Environment Programme
P.O. Box 30552
Nairobi, KENYA

Dear Mr. Sarma:

The United States submits the enclosed nominations for essential uses for chlorofluorocarbons (CFCs), methyl chloroform (MCF), and carbon tetrachloride (CTC) under Decision IV/25 of the Copenhagen Meeting of the Montreal Protocol. These nominations are intended for consideration by the Parties at their meeting in 1994.

The nominations submitted in this letter represent only a very small percentage of historic use of ozone-depleting chemicals in the United States and involve applications that may qualify under the criteria established under Decision IV/25 for essential uses. We request that the Technology and Economic Assessment Panel review these nominations.

We are pleased that the vast majority of U.S. consumers of ozone-depleting substances (ODSs) are successfully responding to the accelerated phaseout requirements and are not seeking exemptions for additional production at this time. We are particularly encouraged by the efforts of major users of ODSs such as the telecommunications, electronics, air conditioning, aerospace, and the rigid polyurethane industries. Many companies in these areas and others have voluntarily implemented aggressive phaseout programs that make it possible to phase out use of ozone-depleting chemicals in many sectors ahead of the schedules imposed under Protocol and U.S. government regulation.

The essential use nominations submitted in this letter are for uses of ODSs in the following areas: metered dose inhalers, vapocoolants and topical anesthetics, nonflammable pesticides, nonflammable adhesives, critical bonding for the Space Shuttle rocket motors, nonflammable lubricants for plastics and elastomers, and laboratory and research practices. Our application includes production of medical products that are manufactured in the United States but are used by patients worldwide. Specific quantities required for these applications,

except for laboratory uses, and supporting information for each are attached to this letter. One of the companies has yet to provide us with complete information on volumes needed. These figures should soon be available, and we will forward them to the Secretariat for distribution and review.

The nomination for laboratory and research uses is not submitted for a specific company. Although we did receive company-specific exemption requests, we are instead nominating laboratory and research applications of high-grade ODSs for a general exemption as an essential use. We request that this nomination be considered for the United States and all other countries as a global exemption. We have prepared this nomination for laboratory and research uses as presented in the attachment to this letter in consultation with the UNEP Solvents, Coatings, and Adhesives Technical Options Committee. Overall, the proposal has been well received, but it will be necessary to work out details such as recordkeeping, use tracking, reporting, and suitable filtration, distillation, and gas chromatography parameters to ensure that recovered material meets "as received" specifications. We ask that the Technology and Economic Assessment Panel review our global laboratory and research exemption and include their advice in the recommendation to the Parties on our nominations.

Controlled substances are generally used in very small quantities in laboratories and research for:

- . equipment calibration as a reference material (such as for gas chromatography or high performance liquid chromatography, mass spectrometry, or infrared, ultraviolet or fluorescent spectroscopy);
- . extraction solvents, diluents, carriers, or reaction solvents or feedstock for specific chemical analysis (such as testing for CTC in contaminated groundwater);
- . inducing chemical-specific health effects for biochemical research (such as inducing hepatotoxicity); and,
- . other critical purposes in research and development where substitutes with comparable chemical properties and effects are not readily available or where standards set by national and international agencies require use of the controlled substances.

Granting this nomination on a global basis as outlined in our proposal would allow developed country Parties to produce or import controlled substances for important laboratory uses under national control if distributed in laboratory grade, in small quantities, under guidelines that minimize use, and with full reporting. An important part of the strategy is to have the

Technology & Economic Assessment Panel annually review uses and recommend additional restrictions, if necessary, based on changing circumstances of technical and economic feasibility.

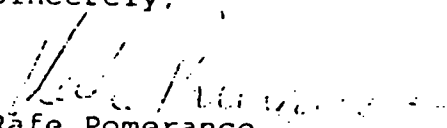
The reason to allow sale of controlled substances for laboratory and research purposes only as fine chemicals in small, labeled containers is to discourage unnecessary use as a consequence of high price (US\$100/kg) and inconvenience for high volume use. The reporting could be the responsibility of manufacturers and distributors of the products via the Parties.

We will continue to work with companies requesting essential use exemptions in each of these applications to determine whether their needs can be met by other alternatives or by existing stocks of the controlled substances. If alternatives or additional supplies do become available, we intend to withdraw these nominations prior to the Sixth Meeting of the Parties. However, unlike with halons, there may not be a bank of sufficient recycled materials for companies with important uses to rely on. Furthermore, some controlled substances (e.g., MCF for rocket motor assembly, CFCs for medical products) may not be usable after prolonged storage as a consequence of stabilizer breakdown in MCF or contamination of CFCs. As a result, there is a strong possibility that these companies' needs for continued production of CFCs, MCF, and CTC will persist beyond the phaseout date.

Even though the applications presented in the enclosed nominations request production for multiple future years, the U.S. reserves the right to and may need to submit nominations in future years for additional applications should we determine that supplies are not available for specific uses. In the United States, servicing of existing refrigeration and air conditioning systems remains a concern. Although we have an aggressive program that prohibits venting and mandates recycling and recovery at disposal, an exemption may yet be necessary if stocks of available or reclaimed CFCs prove inadequate to service equipment or if retrofit technologies prove infeasible.

We appreciate your consideration of these nominations and look forward to working with you to answer any questions that you may have during the review process.

Sincerely,


Rafe Pomerance
Deputy Assistant Secretary for
Environment and Development

Attachments:

- . Draft text: Proposal for Global Essential Laboratory and Research Uses of ODSs
- . U.S. Essential Use Nominations
- . Supporting documentation on individual nominations

DRAFT TEXT
PROPOSAL FOR GLOBAL ESSENTIAL LABORATORY
AND RESEARCH USES OF ODSs

(Exemption to be reviewed by the Parties and granted annually
with reporting)

Parties are authorized to manufacture and/or import controlled substances as necessary for laboratory and research purposes, identified at this time to include equipment calibration, use as extraction solvents, dilutents, or carriers for chemical analysis, biochemical research, and other critical laboratory and testing purposes provided that:

These chemicals are distributed only as spectroscopic grade ("fine") chemicals with purity greater than 99.7-99.9%, supplied only in re-closable one liter or smaller stainless steel or glass containers with qualified leak-tight gaskets, marked clearly as substances that deplete the ozone layer, and specifying the address where surplus chemicals should be returned for recycling or disposal;

Parties report annually the quantities and uses of all such chemicals; and

Parties endeavor to minimize use and emissions by all feasible control technologies.

The Parties direct the Technology and Economic Assessment Panel to review uses reported by the Parties and to list alternatives and substitutes to those uses no longer requiring controlled substances and to recommend technically and economically feasible methods to minimize emissions.

U.S. ESSENTIAL USE NOMINATIONS
September 23, 1993

Summary of Chemicals Requested, by Application
(in kgs)

APPLICATION	1996	1997	1998	1999	2000	2001
Metered dose inhalers						
CFC-11	749,800	658,300	521,500	477,500		
CFC-12	2,363,200	2,177,000	1,918,500	1,894,700		
CFC-114	343,700	343,100	338,300	300,700		
Vapocoolants and topical anesthetics						
CFC-11	37,700	38,400	39,000			
CFC-12	5,600	5,600	5,600			
CFC-114	10,400	10,700	11,100			
Pesticides for high-voltage telephone and electric utility maintenance						
MCF ¹	58,800	58,800	58,800			
Contact bond adhesives for commercial shops not able to use flammable or toxic adhesives safely						
MCF	454,600	454,600				
Flight critical bonding for Space Shuttle rocket motor						
MCF	56,800	56,800	56,800	56,800	56,800	56,800
Nonflammable lubricants for plastics and elastomers						
MCF ²	- ²	- ²	- ²	- ²		
Laboratory and research uses						
All CFCs, MCF, CTC and HBFCs ³	- ³	- ³	- ³	- ³		

¹ Two companies submitted applications, but only one company specified the quantity of MCF requested.

² The company submitting an application for this exemption did not specify a volume. We will forward this information to the Secretariat when we receive it from the company.

³ Requested to be estimated by the Technology and Assessment Panel, as needed.

Summary of Uses Requested, by Company

Medical Devices

SUBMITTER	USE	PERIOD/VOLUME
Cetylite Industries, Inc.	CFC-11 and CFC-114 in Cetacaine anesthetic spray	1996: 6,200 kg CFC-11 3,400 kg CFC-114 1997: 6,900 kg CFC-11 3,700 kg CFC-114 1998: 7,500 kg CFC-11 4,100 kg CFC-114
Gebauer Co.	CFC-11, CFC-12 in Fluorimethane (vapocoolant) CFC-114 in Fluro-ethyl (topical anesthetic) CFC-114 in Gebauer 114 (topical anesthetic)	1996: 31,500 kg CFC-11 5,600 kg CFC-12 7,000 kg CFC-114 1997: 31,500 kg CFC-11 5,600 kg CFC-12 7,000 kg CFC-114 1998: 31,500 kg CFC-11 5,600 kg CFC-12 7,000 kg CFC-114 1999: 31,500 kg CFC-11 5,600 kg CFC-12 7,000 kg CFC-114
International Pharmaceutical and Aerosol Consortium /American Lung Assn (representing Abbott Laboratories, Armstrong Pharmaceuticals, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., Glaxo, Inc., 3M, Rhone- Poulenc Rorer Pharmaceuticals, Inc., and Shering Corp.)	CFC-11, CFC-12, CFC- 114 in MDIs	1996: 749,800 kg CFC-11 2,353,200 kg CFC-12 314,100 kg CFC-114 1997: 658,300 kg CFC-11 2,166,500 kg CFC-12 311,400 kg CFC-114 1998: 529,500 kg CFC-11 1,907,400 kg CFC-12 304,800 kg CFC-114 1999: 477,500 kg CFC-11 1,894,700 kg CFC-12 300,700 kg CFC-114

SUBMITTER	USE	PERIOD/VOLUME
Sterling Winthrop	CFC-12 and CFC-114 in 4 MDIs	1996: 10,000 kg CFC-12 29,600 kg CFC-114 1997: 10,500 kg CFC-12 31,700 kg CFC-114 1998: 11,100 kg CFC-12 33,500 kg CFC-114

Laboratory and Research Uses

Nomination for global exemption for laboratory and research uses: Please see attached proposal.

Misc Uses

SUBMITTER	USE	PERIOD/VOLUME
Chase Products	MCF in wasp killer for high-voltage telephone and electric utility maintenance	1996: 58,800 kg MCF 1997: 58,800 kg MCF 1998: 58,800 kg MCF
Columbia Cement	MCF in contact bond adhesives for commercial shops not able to use flammable or toxic adhesives safely	1996: 454,600 kg MCF 1997: 454,600 kg MCF
NASA/Thiokol	MCF in flight critical bonding for Space Shuttle rocket motors	1996: 56,800 kg MCF 1997: 56,800 kg MCF 1998: 56,800 kg MCF 1999: 56,800 kg MCF 2000: 56,800 kg MCF 2001: 56,800 kg MCF
Sherwin Williams	MCF in lubricants for plastics and elastomers where the lubricant must be nonflammable for safe use MCF in wasp killers for high-voltage telephone and electric utility maintenance	1994-1998: [volumes yet to be provided]*

- * EPA is working with this company to determine the amount of MCF needed for these two end uses.

Fran Du Melle
Deputy Managing Director

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John R. Garrison
Managing Director



September 22, 1993

Brian Burke
Senior Policy Analyst
Domestic Policy Council
Old Executive Office Building
Room 210
Washington, D.C. 20500

Dear Brian,

As per our conversation, enclosed are recent studies on particulate matter. The most recent results, the subject of the Times article, will be published in the New England Journal of Medicine this fall. I will be sure to get you a copy. Also enclosed is ALA's notice of intent to sue the EPA regarding the National Ambient Air Quality Standard for Particulate Matter. We anticipate filing the actual suit within the next two weeks.

Please feel free to call if you would like additional information or would like a briefing from the authors.

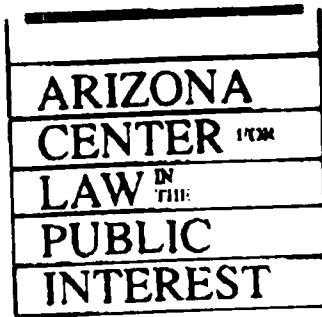
Sincerely,

Fran Du Melle
Deputy Managing Director

enclosures

**When You Can't
Breathe,
Nothing Else
Matters™**

Founded in 1904, the
American Lung Association
includes affiliated
associations throughout
the U.S., and a medical section,
the American Thoracic
Society.



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July 16, 1993

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Carol Browner, Administrator
U.S. Environmental Protection Agency
401 M Street, SW [A-100]
Washington, D.C. 20460

Re: Criteria and National Ambient Air Quality Standards for
Particulate Matter

Dear Ms. Browner:

We are writing to give notice that the Administrator of EPA (the Administrator) has failed to perform certain nondiscretionary duties that are mandated pursuant to sections 108 and 109 of the Clean Air Act (the Act), 42 U.S.C. §§ 7408 and 7409, with respect to review and revision of air quality criteria and standards for particulate matter (PM).

Section 108(a)(2) of the Act requires that for listed air pollutants the Administrator shall issue air quality criteria that reflect the latest scientific knowledge concerning all identifiable effects on public health or welfare to be expected from the presence of a pollutant in the ambient air. Since 1971, PM has been a listed air pollutant subject to the requirements of section 108(a)(2). The Act further requires the Administrator to promulgate primary and secondary national ambient air quality standards (NAAQS) for each air pollutant for which air quality criteria have been issued. 42 U.S.C. § 7409(a)(1).

Section 109(d)(1) of the Act, added in 1977, requires the Administrator to periodically review and revise the criteria and NAAQS as follows:

Not later than December 31, 1980, and at five-year intervals

Carol Browner
July 16, 1993
Page 2

thereafter, the Administrator shall complete a thorough review of the criteria published under section 108 and the national ambient air quality standards promulgated under this section and shall make such revisions in such criteria and standards and promulgate such new standards as may be appropriate in accordance with section 108 and subsection (b) of this section.

The above-referenced provisions of the Act impose nondiscretionary duties on the Administrator to review the air quality criteria and NAAQS for PM, to make a formal decision as to whether any revisions or additions to the criteria and NAAQS are appropriate, and to promulgate a final decision, including final regulations embodying any such revisions, at five year intervals commencing on December 31, 1980. Review and appropriate revision of the PM criteria and NAAQS therefore should have occurred by December 31, 1980, again by December 31, 1985, and once again by December 31, 1990.

The Administrator has failed to perform the nondiscretionary duties set forth in the preceding paragraph. Drawing from a 1969 air quality Criteria Document for PM, the Administrator first promulgated primary and secondary standards for PM in April 1971. 36 Fed. Reg. 8186 (1971). The next review of the air quality criteria for PM was not completed by the Administrator until December 1982, and no subsequent review has been conducted. The Administrator has completed only one review of the NAAQS for PM since 1971 - a review that was completed in 1987 with a revision of the PM standards. 52 Fed. Reg. 24634 (1987). Thus, the Administrator has completed only one review of the criteria, and one review of the NAAQS during a period in which he/she was mandated to complete three separate reviews of each. Even if past failures by the Administrator to timely complete these reviews could somehow be excused (and we do not believe they can be), the Administrator is presently in violation of the most recent deadline for completing review of the PM criteria and standards - December 31, 1990.

There is an urgent need for an immediate review of the PM standard. Since EPA's last revision of the standards, numerous scientific studies have documented that the current standards are woefully inadequate to protect human health. Simply put, these studies show that PM pollution is killing people, even at levels within current standards. According to an EPA researcher, the studies suggest tens of thousands of people are dying each year as a result of air pollution that is within current standards. This deplorable situation demands swift and decisive action by EPA.

Accordingly, we call upon the Administrator to immediately perform her nondiscretionary duties to complete a thorough review

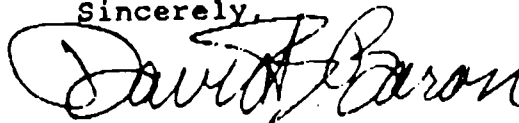
Carol Browner
July 16, 1993
Page 3

of the criteria and NAAQS (both primary and secondary) for PM and make such revisions in such criteria and standards as are appropriate. If the Administrator fails to so act, we will consider appropriate legal action.

This letter is submitted on behalf of: Arizona Center for Law in the Public Interest, 3208 East Ft. Lowell, #106, Tucson, AZ 85716 (602-327-9547); American Lung Association, 1740 Broadway, New York, NY 10019-4374 (212-315-8700); Arizona Lung Association, 102 West McDowell Road, Phoenix, AZ 85003 (602-258-7505); Brian McCarthy, 1030 North Euclid, Tucson, AZ 85719 (602-623-2250); Dana Larsen, 3014 North 27th Street, Phoenix, AZ 85016 (602-468-9771); Raena Honan, 516 East Portland, Phoenix, AZ 85004 (602-253-8633).

I am acting as counsel to the above-named parties and ask that all communications on this matter be directed to me at the address and phone number shown in the letterhead.

Sincerely,

A handwritten signature in dark ink, appearing to read "David S. Baron". The signature is fluid and cursive, with the first name "David" being more prominent and the last name "Baron" following in a similar style.

David S. Baron
Assistant Director

DSB:ylc

Particulate Air Pollution and Health

New Evidence on an Old Problem

Combustion of fossil fuels releases a complex mixture of pollutants into the air that includes particles and the gaseous sulfur oxides and nitrogen oxides; secondary pollutants that are generated by chemical reactions include photochemical oxidants, which are indexed by ozone concentration, and acidic aerosols. The health effects of inhaling combustion-related air pollutants have been extensively investigated using the complementary disciplines of toxicology and epidemiology. The resulting evidence on adverse health effects, now voluminous, has been used throughout the world in setting emissions and concentration standards designed to protect public health. In the United States, the Clean Air Act regulates particles, sulfur oxides, and nitrogen oxides as "criteria pollutants" for which National Ambient Air Quality Standards (NAAQS) are established and periodically revised following a review of evidence assembled in a "criteria document."

The most recent revision of the NAAQS for particulate matter is the present PM_{10} standard. This standard sets maximum concentrations of $150 \mu\text{g}/\text{m}^3$ for 24 hours and of $50 \mu\text{g}/\text{m}^3$ as the annual average for particles equal to or less than $10 \mu\text{m}$ in aerodynamic diameter. The new standard replaced the previous particulate matter standard that regulated the concentration of total suspended particles (TSP). This revision of the standard in 1987 reflected the recognition that a size-fractionated index of particulate matter exposure was more biologically appropriate than TSP, which includes particles of all sizes. The evidence available for the revision included the results of many epidemiologic and toxicologic investigations that focused on the health effects of combustion-related pollutants.

Since the promulgation of the PM_{10} standard, new epidemiologic findings suggest that the present NAAQS for particulate matter may not be protecting against adverse health effects with the "adequate margin of safety" mandated by the Clean Air Act. Some of these new findings include positive associations between mortality rates and levels of particulate matter in a number of U.S. cities (1-5) and between respiratory morbidity and PM_{10} pollution in the Utah Valley, the site of a steel mill (2, 6, 7). In this issue of the Review, Pope and Kanner (8) add to this literature with the findings of another study from Utah on the effect of PM_{10} pollution on lung function in Salt Lake City area participants in the Lung Health Study.

The new mortality findings are remarkable for the demonstration of an apparent adverse effect of particulate matter pollution in concentration ranges under currently allowable levels. The findings of the studies are consistent in indicating small, but statistically significant effects of measures of particulate matter pollution on all-cause mortality. Data from Philadelphia (3) and from Athens, Greece (9), suggest that the increments of pollution-associated mortality may be greatest for respiratory causes.

These new studies used pollution concentrations from centrally sited monitors to estimate population exposures. For particulate matter, personal exposures directly measured by portable pumps have been only weakly associated with outdoor concentrations in some studies (10, 11). The impact of elevations of outdoor concentrations on personal exposures varies with time-activity patterns and the penetration of the particles into indoor environments. For example, assuming 40% penetration of outdoor particles into indoor air (10), the mean absolute change in PM_{10} concentration of $30 \mu\text{g}/\text{m}^3$ reported by Pope and Kanner (8) would increase indoor concentration by only $12 \mu\text{g}/\text{m}^3$. For comparison, smoking in residences increases the concentration of respirable suspended particles from about $30 \mu\text{g}/\text{m}^3$ to 60 to $70 \mu\text{g}/\text{m}^3$ or higher (12). For most persons, time spent outdoors is limited and the contribution of the $30 \mu\text{g}/\text{m}^3$ increment to total personal exposure would be small. Thus, for most individuals, variation in outdoor levels of particulate matter is not tightly linked to variation in personal exposure. Use of outdoor concentrations as a surrogate for personal exposures would tend to misclassify personal exposures; exposure-response relationships would be attenuated as a result, implying that the effects of particulate pollution could be greater than estimated from the epidemiologic studies.

Persons with chronic lung conditions have long been considered susceptible to adverse effects of air pollution. At times of higher air pollution levels, persons with severe chronic obstructive pulmonary disease or asthma might be placed at increased risk of dying if inhaled pollutants directly affected lung function or compromised host defenses against infectious organisms. If, in fact, particulate air pollution can increase mortality of persons with lung disease, then clinically significant effects of inhaling pollutants on such individuals would be anticipated.

In their report involving Salt Lake City participants in the Lung Health Study with mild to moderate airflow limitation, Pope and Kanner (8) provide evidence relevant to this hypothesis. The subjects' lung function was measured on two occasions with spirometry; the variation in lung function between the two visits was significantly associated with the difference in PM_{10} concentration on the 2 days. The effect was small and change in PM_{10} concentration accounted for only a few percent of the variation in lung function.

This finding, although seemingly consistent with the hypothesized causal pathway by which inhaled particulate matter could lead to death, needs to be considered in the context of relevant data from toxicologic studies. Prolonged exposures of animals to acidic particles have produced persistent decreases in mucociliary clearance (13), suggesting that chronic acid exposure could be used as a model of chronic airways disease (14). Since effects of more acute exposures in animals include airway hyperreactivity, changes in tracheobronchial mucus transport rates, and alterations in alveolar macrophage function (15), it is not surprising that controlled exposures of exercising asthmatics to acidic particles at concentrations as low as $75 \mu\text{g}/\text{m}^3$ have produced mild bronchoconstriction (16, 17). In contrast, however, subjects with

Correspondence and requests for reprints should be addressed to Jonathan M. Samet, M.D., Department of Medicine, University of New Mexico, Albuquerque, NM 87131.

chronic obstructive lung disease with an average FEV₁ of approximately 50% predicted, the group reasonably assumed at highest risk from the epidemiologic data, had no reduction of lung function with similar acute exposures (17). Acute changes in respiratory mechanics, in comparison with such markers of response as pulmonary inflammation, alterations in permeability, or biochemical changes may be relatively insensitive in detecting subtle particle-induced injury. Yet the evidence is meager linking relevant ambient concentrations of particles with an acute inflammatory response; in a recent study, inhalation of sulfuric acid aerosols at 1,000 µg/m³ for 3 hours by healthy volunteers without lung disease followed by lavage 18 hours later did not cause an influx of inflammatory cells into the alveolar space nor evidence for alterations in antimicrobial defenses (18). Perhaps a clue to toxicity lies in the *in vitro* cytotoxicity studies of urban particles; in this laboratory system, the presence of metal ions dramatically enhances the induction of respiratory inflammation induced by sulfates (19).

These toxicologic considerations suggest that the associations of adverse health effects with current levels of particulate matter should not yet be accepted as causal. However, while urging caution in the interpretation of these findings, we cannot strongly support specific alternative explanations. Statistically significant association of mortality with level of particulate pollution has been replicated in diverse communities. The analyses have controlled for some potentially confounding factors such as temperature and humidity. However, confounding by winter-time epidemics of respiratory infection (20) could explain increased mortality of persons with chronic lung conditions on days having higher pollution levels. Effects of temperature and season not adequately controlled by regression models could also contribute to the apparent effect of particulate air pollution (21, 22).

The new evidence from Pope and Kanner and the mortality findings provide a strong rationale for further investigations of the health effects of particulate matter. The toxicologic evidence on the health effects of particles may be strengthened by following the leads suggested by the new epidemiologic findings. Further exposure studies of the most susceptible subjects may confirm whether exposures to particles are in fact responsible for the increased mortality of subjects, by showing effects on function of a clinically significant magnitude. Our understanding of the toxicity of urban particles should be increased by investigations directed at the combined effects of metal ions and particles. Human experimental studies which replicate exposures to ambient atmospheres would provide additional complementary data. We also suggest that personal exposures of potentially susceptible persons to particles should be monitored to describe better the doses of pollutants delivered to the lungs during times of increased pollution.

Inevitably, the findings of the recent epidemiologic studies will lead to questioning of the protection of cardiopulmonary health provided by the current NAAQS for particulate matter. However, until the findings of new toxicologic studies on particulate matter become available, the framework for interpreting the epidemiologic findings will be inadequate.

MARK J. UTELL
Pulmonary/Critical Care and
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University of Rochester Medical Center
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JONATHAN M. SAMET
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University of New Mexico Medical Center
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References

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Particulate Air Pollution and Hospital Emergency Room Visits for Asthma in Seattle

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Recent studies have associated short-term exposure to respirable particulate matter (PM_{10}) exposure with peak flow decrements, increased symptoms of respiratory irritation, increased use of asthma medications, and increased hospitalization for asthma. Increased mortality from chronic respiratory disease has also been reported. To help confirm whether PM_{10} exposure is a risk factor for the exacerbation of asthma, we compiled daily records of asthma emergency room visits from eight hospitals in the Seattle area. In Poisson regressions controlling for weather, season, time trends, age, hospital, and day of the week, the daily counts of emergency room visits for persons under age 65 were significantly associated with PM_{10} exposure on the previous day. The mean of the previous 4 days' PM_{10} was a better predictor ($p < 0.005$). The relative risk for a $30 \mu\text{g}/\text{m}^3$ increase in PM_{10} was 1.12 (95% confidence interval 1.20 to 1.04). Daily PM_{10} concentrations never exceeded 70% of the current ambient air quality standards during the period. The consistency of investigations of the health effects of PM_{10} suggest that increased attention should be given to the control of particulate matter air pollution.

Asthma morbidity has been growing rapidly in certain subpopulations and different areas of the world in the past few years. The causes of this increase have eluded many researchers who have tried to discover factors influencing this complex disease. In addition to the increasing morbidity, there has been an accompanying increase in mortality due to asthma (1). As a lower respiratory illness, it is natural to hypothesize that there is a relationship between asthma and air pollution (2). There is some evidence that air pollution episodes aggravate respiratory disease, especially asthma (3, 4).

Relatively low concentrations of inhalable particulate matter (PM_{10}) have been associated with increased risk of acute bronchitis in children (5). The rate of bronchitis in children was approximately twice as high in communities with airborne particle concentrations at the U.S. Environmental Protection Agency annual average air quality standard ($50 \mu\text{g}/\text{m}^3$ of particles with an aerodynamic diameter of $10 \mu\text{m}$ or less, abbreviated PM_{10}) as in communities having near background concentrations of particles (5). Subjects with a history of wheeze appeared to be particularly sensitive to the impact of airborne particles. A recent study by Pope and coworkers reported that short-term PM_{10} exposure was associated with approximately 3 to 6% decreases in peak expiratory flow in mildly asthmatic school children (6). PM_{10} also was associated with increased reports of symptoms in a diary and increased use of medication (6). For example, a 24-h PM_{10} concentration of $150 \mu\text{g}/\text{m}^3$ (which is the current 24-h ambient air quality

standard) was estimated to be associated with a 26% increase in upper respiratory symptoms, a 50% increase in lower respiratory symptoms, and a 217% increase in the use of regular asthma medication compared to the number of cases at $50 \mu\text{g}/\text{m}^3$. PM_{10} has also been associated with lower respiratory symptoms in a diary study of schoolchildren in six communities (7).

Bates and Sizto (8) reported sulfate particulate matter and ozone were associated with hospital admissions for asthma in Ontario. A more recent study in Vancouver (9), where sulfate concentrations were considerably lower and less acid, found a significant association between asthma emergency visits in the summer and the previous day's sulfate concentration in both the 0- to 14-yr and 15- to 60-yr age group. The magnitude of the correlation was essentially identical in these age groups. A similar association was not seen in persons over age 60. A strong peak in asthma emergency visits in September was also seen in the lower ages but not in persons over age 60. This peak did not appear to be related to air pollution. Pope recently reported an association between inhalable particles and hospital admissions for asthma in Utah Valley, Utah (10) and Salt Lake City (11). The Utah Valley study was notable because there was little pollution in the valley except particles, and the particles were not acid (6). The effect also was more pronounced in the younger age groups.

Airborne particles also have been associated with increased daily mortality, particularly from respiratory illness, again at concentrations commonly observed in U.S. communities today (12-15).

To further delineate the association between PM_{10} exposure and asthmatic response, we examined the association between hospital emergency room visits for asthma and PM_{10} concentrations in eight hospitals in the Seattle metropolitan area. Exposure periods of a week or less were identified as the most relevant in the majority of the preceding studies.

METHODS

Emergency room visits for asthma and gastroenteritis symptoms from eight

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hospitals in the Seattle metropolitan area (University, Ballard, Children's, Harborview, Northwest, Overlake, Providence, and Swedish) were abstracted by a graduate student during the period September 1, 1989 through September 30, 1990 (16) (see figure 1). We were unable to obtain data from the three additional hospitals in this area (also shown in figure 1). Asthma was defined as a diagnosis of ICD9 Codes 493, 493.01, 493.10, 493.90, and 493.91, and the gastroenteritis control was defined as ICD9 Code 558.90. During the study period there were 2,955 visits for asthma and 3,810 visits for gastroenteritis symptoms at the eight hospitals. Steps for quality assurance of recorded data involved constant review of log pages during data entry. After each page of the log was scanned and cases entered, the page was rescanned to check for possible missed diagnoses and errors in entered numbers. Errors were also detected through a system of counting entries in the data base and comparing these to multiples of the numbers of entries per page on the data printouts; several omissions were detected in this fashion. Data files created from hospital data printouts were checked in a similar manner. The information gained from computer files was checked at one hospital by pulling a sample of 100 medical records that were referenced by medical record number in the file. The medical record was compared to the computer report. The only discrepancies found were the reporting of two gastroenteritis cases. There was a complete match between the asthma cases in the data base report and those in the corresponding medical record file.

Air quality data were obtained from the Washington State Department of Ecology and the Puget Sound Air Pollution Control Agency. Sulfur dioxide (SO₂) values were available only from an industrial site. Daily light-

scattering (b_{sp}) and PM₁₀ values were available from a residential site in a wood-burning neighborhood (figure 1). Ozone values were obtained from a site approximately 20 km east of Seattle. The ozone was monitored for only 5 months (May through September).

Past studies have shown a high correlation between airborne particle concentrations measured across the airshed in the Seattle metropolitan area (17). For example, the weekly mean PM_{2.5} concentrations at our monitoring site, at a site at Puyallup, approximately 45 km south of downtown Seattle, and at Marysville, approximately 60 km north of Seattle, are shown in figure 2. In addition, every sixth day PM₁₀ data were available from the Harbor Island and South Park monitoring stations near central Seattle (see figure 1). For those days the correlation between these PM₁₀ values and the measurements at our monitoring site were 0.72 and 0.78, respectively.

Recently, unpublished work in nine homes in Seattle, Washington without stoves and without smokers found a median indoor/outdoor ratio less than 1.0 for over 3,000 h of continuous nephelometer data, with elevated indoor levels in wood-burning neighborhoods (J. Anusewski, M.S.E. thesis, University of Washington, 1992).

Statistical Analysis

The fraction of the population suffering from serious asthma attacks on a given day is quite small. The counts of independent rare events randomly occurring in time generally follow the Poisson distribution. Poisson regression analysis assumes that conditional on the explanatory variables, the counts of events follow Poisson distribution, and this was used in our main analysis. In contrast, ordinary least-squares regression assumes that, conditional on the explanatory factors, the outcome is normally distributed. This is clearly not true in our data, in which the mean count per day in each hospital ranged from 0.3 to 2.4, with even lower counts if the data were broken down by subject age.

Serial correlation in imperfectly controlled for or omitted explanatory factors, such as weather or epidemics, may result in serial correlation in the counts of asthma emergency visits, even after conditioning on the explanatory variables. Uncontrolled differences in the underlying risk of different subpopulations can lead to a greater variability in the data than in a classic Poisson process. Ignoring either of these factors can lead to understating the standard errors of the regression coefficients and consequently to biased hypothesis tests. To address these issues we used

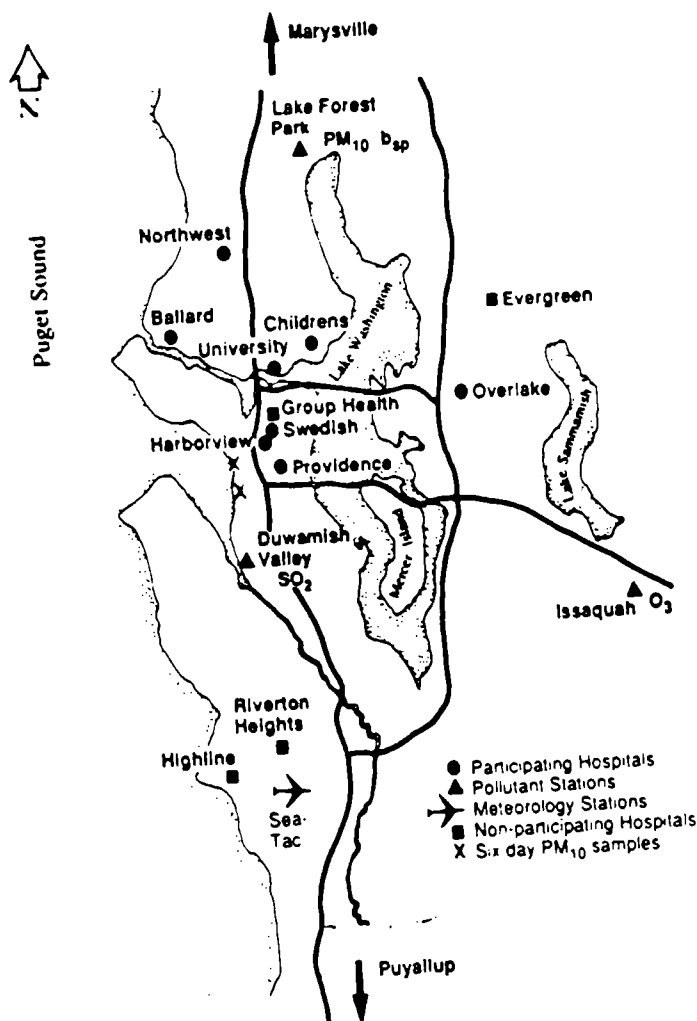


Figure 1. Map of the study area showing the location of hospitals and atmospheric monitoring stations.

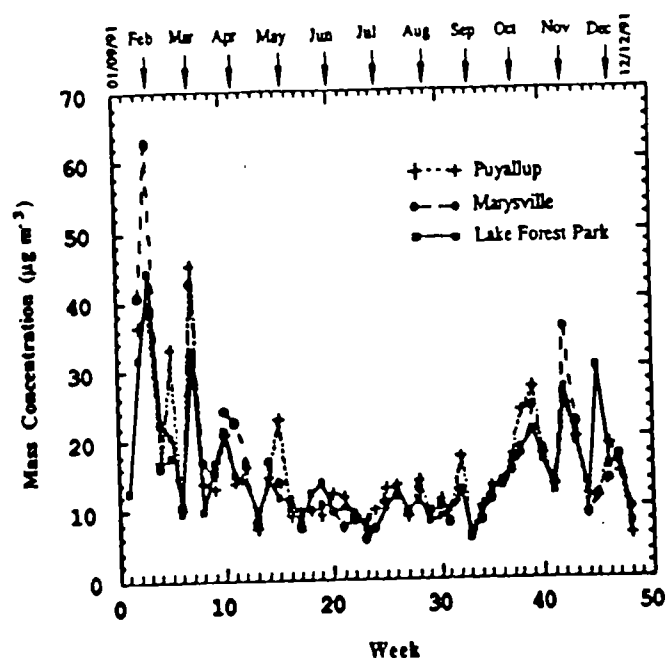


Figure 2. Weekly mass concentrations of PM_{2.5} for three sampling sites during 1991. These sites are plotted on the map in figure 1. Crosses = Puyallup; circles = Marysville; squares = Lake Forest Park.

the general estimating equations of Liang and Zeger (18). As in the classic Poisson model, they assume

$$\log E(Y_{ijk}) = X_{ijk}\beta$$

where $E(Y_{ijk})$ denotes the expected number of emergency room visits for asthma in Hospital i for age Strata j on Day k , X_{ijk} is the matrix of covariates on Day k for age Strata j and Hospital i , and β is the vector of estimated regression coefficients. The covariance was assumed to have the autoregressive structure often found in long time series. The Liang and Zeger approach incorporates the covariance structure into the estimation of the regression coefficients as well as their variances, giving more efficient estimates of the parameters. The extra-Poisson variability was

estimated using the technique of McCullagh and Nelder (19) and also incorporated into estimating the standard errors of the regression coefficients. This approach has been used successfully in the past to model daily counts of mortality (12, 13), counts of respiratory symptoms in preschool children (20), and counts of pediatric visits for croup (21). Separate counts were kept for each hospital because of the potential heterogeneity in the populations served by each hospital. Counts were also stratified into four age groups (<5, 5 to 20, 21 to 65, and >65).

Asthma attacks may be triggered directly by weather conditions (such as cold, dry air), or weather may be associated with infectious disease that subsequently triggers attacks (22). In either case, the dependence on weather is likely to be highly non-linear. To control for this, temperature was divided into 6 ranges, and indicator variables were used for each range. Previous studies (6, 11) found that the minimum daily temperature was a better predictor of asthma symptoms and hospital admissions than the mean or maximum daily temperature. We followed this strategy. The ranges of minimum temperature chosen were $T \leq -3^\circ\text{C}$, $-3^\circ\text{C} < T \leq 2^\circ\text{C}$, $2^\circ\text{C} < T \leq 7^\circ\text{C}$, $7^\circ\text{C} < T \leq 12^\circ\text{C}$, $12^\circ\text{C} < T \leq 16^\circ\text{C}$, and $T > 16^\circ\text{C}$. As a sensitivity test, ranges of average daily temperature were used instead. Previous studies of respiratory symptoms also suggested the previous day's temperature was most predictive (7). We used categories of the previous day's temperature in this analysis. Again, we tested the sensitivity of air pollution associations to changes in this approach.

Seasonal variation in other risk factors, such as pollen, may not be adequately captured by the temperature variables. Therefore, indicator variables for season were also included. Day of the week indicator variables also were used to capture such effects as the possibly greater use of hospital emergency rooms on the weekend, when fewer physicians' offices are open (9). In addition, there has been a time trend in reported asthma morbidity and mortality in the United States in recent years (23). We therefore included a term for a continuous time trend in our regression model.

Neither the lag with which particles influence asthma symptoms nor the appropriate averaging time have been established. The results of Pope and coworkers suggest that several previous days may contribute to asthma symptoms (6). In contrast, Bates and colleagues (9) report a 24-h lag. Hence we considered several previous days' pollution concentrations, as well as the average of several days, in our analysis.

A control diagnosis of emergency room visits for gastroenteritis was used. The same regression model was fit to both asthma and gastroenteritis visits.

RESULTS

The distribution of asthma visits, gastroenteritis visits, temperature, humidity, PM_{10} , and SO_2 in Seattle during the study period is shown in table 1. PM_{10} concentrations were quite low, with a maximum 24-h concentration of $103 \mu\text{g}/\text{m}^3$ and a mean of $29.6 \mu\text{g}/\text{m}^3$. Total asthma emergency visits for all ages by month, with the September peak evident, is plotted in figure 3. A peak in March is also apparent. PM_{10} concentrations were near their annual mean in September and highest in February, when asthma visits were very low. The September peak was absent in the population over 65, for whom 25 emergency visits were seen during the two September periods, compared to an expected value of 22 cases based on the average number of cases per month in this age group.

TABLE 1
DISTRIBUTION OF VARIABLES USED IN ANALYSIS

Variable	Mean	Minimum	Maximum	SD
Asthma*	7.1	0	18	3.2
Control*	.9	-1	21	3.5
PM_{10} , $\mu\text{g}/\text{m}^3$	29.6	6	103	18
SO_2 , ppb	6.5	0	29	5
Minimum temperature $^\circ\text{C}$	7.9	-7	19	4.7
Humidity, %	74	33	100	13.8

* Sum for all hospitals on each day, age less than 65 yr.

TABLE 2
ASTHMA EMERGENCY VISITS BY QUARTILE OF PM_{10} *

PM_{10} Concentration ($\mu\text{g}/\text{m}^3$)	Range ($\mu\text{g}/\text{m}^3$)	Asthma Emergency Visits Day ⁻¹	Confidence Interval
13	6-17	6.24	5.34-7.8
20.3	17-24	6.59	5.71-7.46
29.6	24-36	7.61	6.71-8.50
55.3	36-103	8.00	-

* Adjusted for effect of hospital and day of week.
Age ≤ 65 yr only.

For each day the deviations from the mean visits for each hospital for that day of the week were summed and compared with PM_{10} concentrations. A strong trend was evident by quartile of PM_{10} concentration. This is shown in table 2, where the grand means are added back, to give the mean number of emergency room visits for asthma in each quartile of PM_{10} concentration. A clear dose-related increase is seen.

In initial Poisson regression analyses by age strata, similar regression coefficients for prior days PM_{10} ($\mu\text{g}/\text{m}^3$) ($\beta = 0.00299$, 0.00232 , and 0.00402 , respectively) were found for the first three

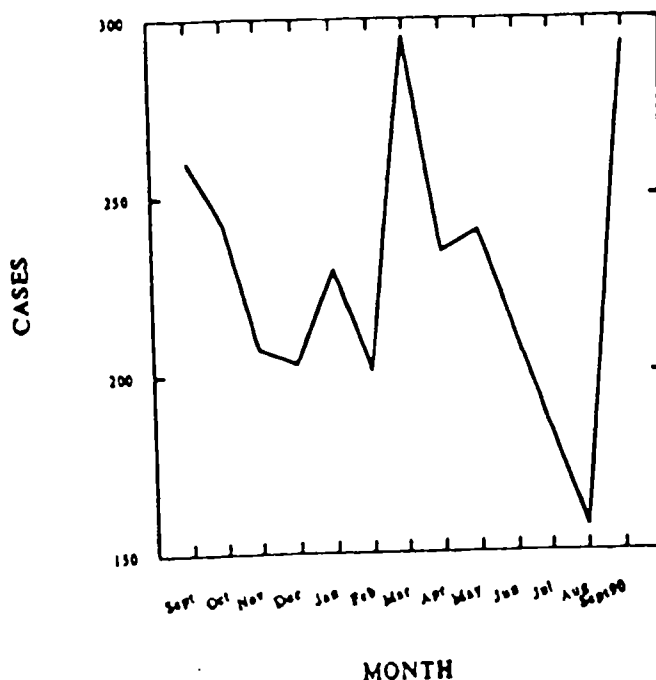


Figure 3. Monthly counts of asthma emergency visits for all ages at the eight study hospitals in Seattle. Note the peaks in March and September.

TABLE 3
ASTHMA EMERGENCY VISITS BY OTHER SELECTED FACTORS*

Hospital	Total Visits	Day of the Week	Total Visits	Age Category	Total Visits
1	102	Sunday	513	< 5	714
2	963	Monday	394	6-20	676
3	472	Tuesday	388	21-65	1,419
4	234	Wednesday	374		
5	357	Thursday	331		
6	285	Friday	346		
7	228	Saturday	463		
8	168				

* Age < 65 yr only

age groups. In contrast, no noticeable association was found between PM₁₀ and asthma emergency visits for the elderly ($p = -0.00271 \pm 0.00548$). Subsequent analyses were restricted to emergency visits by patients under age 65, and all age strata were combined for those analyses. The counts of asthma emergency visits by age, hospital, and day of week are shown in table 3. Asthma emergency visits by season are shown in table 4.

In our basic model controlling for temperature categories (on the previous day), seasons, day of the week, hospital, September time trends, and age strata, PM₁₀ on the previous day was a significant predictor of asthma emergency room visits ($\beta = 0.00333 \pm 0.00126$). PM₁₀ values 2, 3, and 4 days before the visit were also significant predictors of asthma visits. The mean of PM₁₀ on the previous 4 days had slightly better explanatory power ($\beta = 0.00367 \pm 0.00126$, $p < 0.005$) (relative risk = 1.12, 95% CI = 1.04 to 1.20). The relative risk is for a 30 $\mu\text{g}/\text{m}^3$ increase in PM₁₀. Additional lags did not add further information, so the average PM₁₀ concentration for the 4 prior days was used in subsequent analyses. The odds ratio and 95% confidence intervals for a 30- $\mu\text{g}/\text{m}^3$ increase in PM₁₀ (4-day average) for our model and for several sensitivity analyses are shown in table 5. The first examines the impact of using temperature categories on the same day rather than the previous day, the second the impact of controlling for cold, dry days, the third the impact of using categories of mean daily temperature instead of minimum daily temperature, the fourth the use of 48-h temperature categories, and the fifth the use of a continuous term for relative humidity. The relative risk for PM₁₀ shows little sensitivity to the model specification. In addition, an interaction term to test for a different slope of the PM₁₀-asthma visit relationship during the warm months of the year (April through October) was highly insignificant. Pollen levels are highest in March in Seattle. Excluding March from our data had little impact on the PM₁₀ regression (relative risk = 1.10, 95% confidence interval, CI, = 1.02 to 1.20).

To determine whether the relationship exhibited a dose-dependent increase, the continuous PM₁₀ variable was replaced with indicators for quartiles of PM₁₀ and the model reestimated. The relative risk of asthma emergency room visits by quartile of PM₁₀, with the risk in the lowest quartile taken as 1.0, is shown

TABLE 4
ASTHMA EMERGENCY VISITS BY SEASON*

Winter	587
Spring	734
Summer	519
Fall	969

* Age < 65 yr only.

TABLE 5
RELATIVE RISK (95% CI) OF ASTHMA EMERGENCY VISITS FOR A 10- $\mu\text{g}/\text{m}^3$ INCREASE IN PM₁₀ FOR DIFFERENT MODEL SPECIFICATIONS

Model	Relative Risk	95% CI
Base*	1.037	1.064-1.012
Same day temperature†	1.037	1.064-1.012
Cold, dry days‡	1.037	1.064-1.012
Mean daily temperature§	1.033	1.059-1.009
2-Day average temperature	1.037	1.063-1.012
Relative humidity¶	1.037	1.064-1.012

* Controlling for six categories of yesterday's minimum temperature, seasons, hospital, day of week, September, age group, serial correlation, and overdispersion.

† Using six categories of current day's temperature instead of previous day's temperature.

‡ Adding indicator variable for cold, dry days.

§ Using six categories of yesterday's mean temperature.

|| Using the six categories of the mean of today and yesterday's temperature.

¶ Using a continuous term for relative humidity.

in figure 4. A dose-dependent increase is evident at concentrations well below the current air quality standards.

Light scattering (km^{-1}) in the residential neighborhood was also significantly associated with hospital emergency room visits for asthma ($\beta = 0.0145 \pm 0.0045$). For a change in light scattering comparable to the change in PM₁₀ relative risk (7 km^{-1}), an essentially identical risk was seen using this different measure of particulate matter concentration (relative risk = 1.11, 95% CI = 1.04 to 1.18). When SO₂ was examined, no significant associations with asthma emergency visits were found (relative risk = 0.99, 95% CI = 0.94 to 1.05). Ozone was also insignificant as a predictor of asthma attendance (relative risk = 0.97, 95% CI = 0.89 to 1.05). The relative risk is for a 15 ppb change in average ozone concentration.

In contrast to the results for asthma, gastroenteritis visits were not significantly associated with PM₁₀ pollution, and the sign of

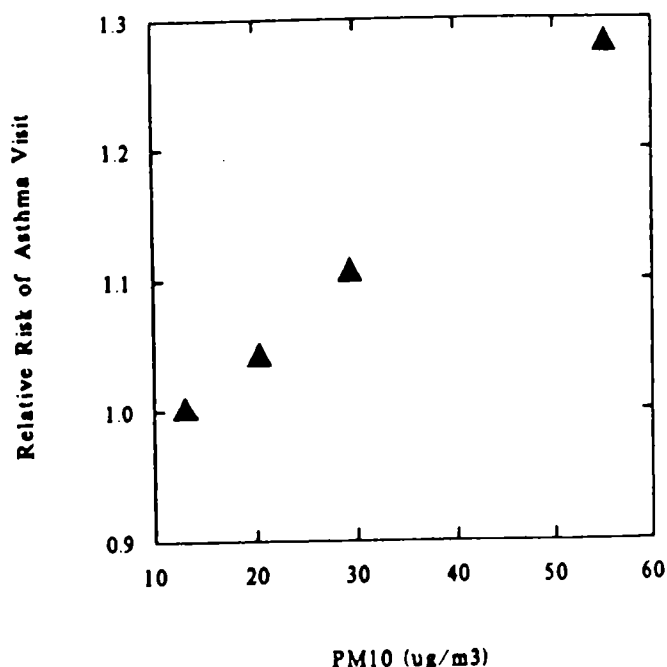


Figure 4. Relative risk of asthma visits by quartile of PM₁₀ concentration, plotted against the mean PM₁₀ concentration in the quartile. The relative risks are adjusted for temperature, seasons, day of week, hospital, time trends, age, and September peak.

the insignificant association was negative (relative risk = 0.96, 95% CI = 0.89 to 1.03).

DISCUSSION

A highly significant ($p < 0.005$) relationship between asthma admissions and PM_{10} concentrations was observed in this study. The association showed clear evidence of a dose-dependent increase and no evidence of a threshold. At the mean concentration ($30 \mu\text{g}/\text{m}^3$) of inhalable particles observed in the Seattle area during the study period, PM_{10} exposure appears to have been responsible for approximately 12% of the asthma emergency visits [$100(e^{0.00347 \times 30} - 1)$]. If this association is causal, it represents a nontrivial concern. Moreover, this association occurred in a community where 24-h PM_{10} concentrations never exceeded 70% of the current ambient air quality standard.

A 4-day average PM_{10} concentration had slightly greater predictive power than the prior days' PM_{10} in this study. Although the within-study evidence for a longer than 24-h average is not strong, the pattern is consistent with other recent studies associating longer term average particle concentration with increased need for asthma medication, decreased peak expiratory flow values, and increased symptom reporting and hospitalization (6, 10, 11).

Asthma emergency visits showed the same peak in September that was observed in Vancouver by Bates and colleagues (9). The PM_{10} association is consistent with the studies of Bates and coworkers (8, 9) and of Pope (10, 11) in that asthma visits were higher during periods of high PM_{10} concentrations. Similar findings have been reported at higher concentrations of total particulate matter (24, 25). Consistent with the results of Goldstein and Weinstein (26), no association was observed with SO_2 . However, our SO_2 monitor was close to an industrial facility and not representative of the general population exposure. Other studies have reported significant relationships between asthma end points and SO_2 (27, 28). An SO_2 association also was reported in Vancouver (9). In the Utah studies, no appreciable concentrations of SO_2 were present.

Changes in diagnostic practices or coding seem an unlikely confounder in this study since the observed correlations occurred in a study whose duration was only 13 months. There is no reason to believe that day-to-day variations in diagnostic practices should vary with air pollution. Similarly, although unequal access to medical care might confound a cross-sectional analysis of air pollution and asthma emergency attendance, there is also no reason to believe that access to medical care fluctuates on a day-to-day basis in a manner correlated with air pollution.

The use of outdoor monitoring data to represent personal exposure introduces error into the exposure assessment and is a limitation of this study. A study comparing indoor and outdoor fine particulate matter concentrations in wood-burning residences reported an average indoor/outdoor ratio of 0.5 (29). Quackenboss and colleagues reported an indoor/outdoor ratio of 0.63 for PM_{10} in homes of nonsmokers in Tucson, Arizona (30), and Dockery and Spengler reported an indoor/outdoor ratio of 0.55 for total suspended particulates (TSP) in Steubenville, Ohio (31). Outdoor PM_{10} measurements appear to be a noisy but reasonable proxy for indoor exposure. In our study, 39% of the asthma visits occurred in people aged 20 or under, a population that spends more time outdoors than the average adult.

The observed association is supported by the associations between PM_{10} and peak flow decrements, symptoms, and increased need of medication that were reported recently (6). Peak flow decrements also were associated with indoor TSP concentrations in a study by Lebowitz and coworkers (32). Whittemore and Korn

(3) reported positive associations of symptoms in a diary study of asthmatic subjects with total suspended particulate matter and ozone. $FEV_{0.75}$ and FVC declines have been noted in episode studies of schoolchildren (33, 34), although the concentrations of airborne particles seen in these episodes were considerably higher than those in this study.

In addition to the symptoms reported in these studies, chronic exposure to PM_{10} has been associated with acute bronchitis rates in the Six City Study (5). Several papers reported an association between PM_{10} and respiratory symptoms in diary studies of preschool children (19) and schoolchildren (7), and particulate matter exposure has also been associated with an increased risk of croup (26). Symptoms in adults have also been noted (35).

Although not identical in all details, the recent studies of hospital visits and admissions show a broad consistency, implicating airborne particles as a risk factor for asthma attacks. This is supported by panel data associating particulate matter exposure with increased response in asthmatic subjects and by the diary data in the general population. Other recent studies suggested that low concentrations of airborne particles increase the risk of acute mortality in sensitive subpopulations (12–14). In the absence of a plausible alternative explanation for these findings, airborne particles at concentrations previously considered safe must be considered a potential risk factor for asthmatic subjects.

The mechanism whereby particles may be triggering or exacerbating asthma attacks remains unclear. In the Seattle area the primary source of fine particulate matter in residential neighborhoods during the winter heating season is from wood burning. We have shown a significant association between measures of this particulate matter and declining lung function in elementary schoolchildren who have asthma (36). Our studies have shown that PM_{10} greater than $50 \mu\text{g}/\text{m}^3$ is found primarily in the winter months, and thus the relationship shown between asthma visits and PM_{10} may in large part reflect the toxicity of wood smoke. However, the relationship in figure 4 continues to much lower PM_{10} concentrations, suggesting that wood smoke is not the only contributing factor. The interaction term testing for a different PM_{10} slope in warm weather, when wood smoke is a lesser factor in PM_{10} , was not significant.

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Increased Mortality in Philadelphia Associated with Daily Air Pollution Concentrations¹⁻⁴

JOEL SCHWARTZ and DOUGLAS W. DOCKERY

Introduction

High levels of particulate air pollution have been associated with excess mortality in anecdotal reports for centuries. Evelyn attributed the rising death rate and increased rates of respiratory illness to the combustion of coal in London in 1661 (1), and Graunt, in a classic study of Bills of Mortality, attributed the high week-to-week variability in mortality to changes in the "airs" (2). Brimblecombe (3) has recently reanalyzed mortality data from this period and compared it with diary accounts of "Great Stinking Fogs." In the fall of 1679 a peak stinking fog period was associated with an increase in both total mortality and mortality from "tissick," a lung disease associated with asthma. The rise seemed greatest in the elderly. More recently, winter smog episodes characterized by high particulate and sulfur dioxide concentrations have been associated with substantial increases in daily mortality in the Meuse Valley, Belgium, in 1930, in Donora, Pennsylvania, in 1948, and in London, England, in 1952. The tracking of mortality increases and decreases during these episodes with the rise and fall of air pollution levels left little doubt that the relationship was causal. The increased mortality in London in 1952 was higher among the elderly, in deaths from respiratory disease, and from cardiovascular disease. More recently, excess mortality has been associated with a smog episode in West Germany (4). Particulate and SO₂ concentrations were lower than in the previous episodes, but high in comparison with concentrations currently observed in the United States and in Western Europe.

Studies of air pollution and mortality during nonepisode periods have shown correlations between increased daily air pollution and increased daily mortality across a wide range of concentrations, with no sign of a threshold (5-7). In London, the relation with particles held independent of sulfur dioxide, but not vice versa (5). Similar findings have been reported in New York City (8-10) and re-

SUMMARY Cause-specific deaths by day for the years 1973 to 1980 in Philadelphia, Pennsylvania, were extracted from National Center for Health Statistics mortality tapes. Death from accidents (International Classification of Disease, Revision 9 ≥ 800) and deaths outside of the city were excluded. Daily counts of deaths were regressed using Poisson regression on total suspended particulate (TSP) and/or SO₂ on the same day and on the preceding day, controlling for year, season, temperature, and humidity. A significant positive association was found between total mortality (mean of 48 deaths/day) and both TSP (second highest daily mean, 222 µg/m³) and SO₂ (second highest daily mean, 299 µg/m³). The strongest associations were found with the mean pollution of the current and the preceding days. Total mortality was estimated to increase by 7% (95% CI, 4 to 10%) with each 100-µg/m³ increase in TSP, and 5% (95% CI, 3 to 7%) with each 100-µg/m³ increase in SO₂. When both pollutants were considered simultaneously, the SO₂ association was no longer significant. Mortality increased monotonically with TSP. The effect of 100 µg/m³ TSP was stronger in subjects older than 65 yr of age (10% increase) compared with those younger than 65 yr of age (3% increase). Cause-specific mortality was also associated with a 100-µg/m³ increase in TSP: chronic obstructive pulmonary disease (ICD9 490-496), +19% (95% CI, 0 to 42%), pneumonia (ICD9 480-486 & 507), +11% (95% CI, -3 to +27%), and cardiovascular disease (ICD9 390-448), +10% (95% CI, 6 to 14%). These results are somewhat higher than previously reported associations, and they add to the body of evidence showing that particulate pollution is associated with increased daily mortality at current levels in the United States.

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cently in Santa Clara, California (11). These studies have used optical measures of particulate concentration that are nonlinearly related to gravimetric particulate mass concentrations in a site-specific manner (12), making comparison with currently monitored particulate concentrations difficult. Studies using direct gravimetric measurement of particulate concentrations in the United States have been limited by the every-sixth-day sampling schedules for most particulate monitors. A recent report has found a significant association between total suspended particulates (TSP) and daily total mortality in Steubenville, Ohio, for the period 1974 to 1984 (13). Again, the TSP association was independent of SO₂, but not vice versa. This report presents an analysis of daily total and cause-specific mortality in Philadelphia, Pennsylvania, compared with daily TSP and SO₂ concentrations for 8 yr.

Methods

Daily deaths in the city of Philadelphia (population, 1,688,710 in 1980) (14) were extracted from mortality tapes from the National Center for Health Statistics for the calendar years 1973 to 1980. Deaths from accidental causes

(International Classification of Disease Revision, ICD9 ≥ 800) were excluded, as were all deaths that occurred outside of the city. Daily counts of total mortality, mortality in persons younger than 65 yr of age, and mortality in persons 65 yr of age and older were

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computed. Total mortality was also subdivided by cause of death. The choice of ICD code categories represents a trade off between specificity and sufficient cases to allow a separate analysis. The causes analyzed were pneumonia (ICD9 480-486 plus 507, ICD8 480-486), chronic obstructive pulmonary disease (COPD) (ICD9 490-496, ICD8 490-493 plus 519.3), cardiovascular disease (CVD) (ICD 390-448), and cancer (ICD 140-208). Cardiovascular disease accounted for 45.9% of the deaths in Philadelphia during this period, cancer for 21.8%, pneumonia for 3.0%, and COPD for 1.9%.

Daily mortality was matched to the 24-h samples (midnight to midnight) of TSP and SO₂ concentrations. All population-based monitors, defined by Environmental Protection Agency (EPA) sampler descriptions (15) within the city of Philadelphia, that is, not including the suburban communities, were included. Data were retrieved from the national aerometric data banks of the EPA (16). For each day, TSP and SO₂ from all available monitors were averaged to produce a citywide mean. For TSP, daily samples were routinely collected at two monitors (1501 East Lycoming and Community Health Services Building) supplemented by sampling every sixth day at several additional sites. SO₂ daily samples were collected at as many as 11 sites. On any given day, an average of more than seven monitoring sites contributed data to the citywide mean. For TSP, citywide means were available for 2,726 days (93.3% of 2,922 total days), and for SO₂, 2,706 days (92.6%).

This analysis sought to replicate the association between particulate air pollution and daily mortality that has been reported on data from Steubenville, Ohio (13). Age-stratified analyses were then performed, along with analyses of cause-specific mortality.

Daily mortality is a count of a rare event and was modeled by Poisson regressions. Daily mortality was fit to a model including seasonal indicators and weather variables that explained as much of the variation as possible. Air pollution variables were then added to this model. Therefore, a more exploratory approach was adopted with respect to model fitting with the season and weather terms since the goal was not to test specific hypotheses about weather but rather to conservatively estimate the association with air pollution.

During the period of study there was a decline in cardiovascular mortality rates in the United States. This was expected to result in a downward trend in mortality over time. There was also a slight drop in the population of Philadelphia during the period. To control for this, indicator variables for each year of the study were included in the models, as well as a continuous time variable to parameterize a continuous decline within year. The initial analysis of weather variables considered 24-h mean temperature and dew-point temperature, indicator variables for hot days, cold days, humid days, and hot and humid days, seasonal indicator variables, and interaction terms between season and the weather

variables. Weather variables on the day of recorded death and the prior day were considered, and the square of temperature and dew point were also considered for each day. The definition of hot, cold, and humid days was initially set at the ninety-fifth percentile (fifth percentile for cold) and then varied to find the definition with the greatest explanatory power.

The Poisson model was estimated using the generalized estimating equations of Liang and Zeger (17, 18). In these models, as in a classic Poisson model, the logarithm of the expected number of deaths Y is given by: $\log[E(Y)] = X\beta$, where X is the matrix of covariates, β is the regression coefficients, and E denotes the expected value. In addition, an autoregressive covariance structure is assumed, modeling the serial correlation often found in long-time series. The approach of Liang and Zeger incorporates the covariance structure in the estimation of the regression coefficients as well as their variances, giving more efficient estimates of the parameters. Because of the computational complexity, models were initially developed using simple Poisson regression, and final models were then estimated using the methodology of Liang and Zeger.

Results

The distribution of air pollution, weather, and daily mortality in Philadelphia during the study period from 1972 to 1982 is shown in table 1. An average of 48 persons died each day in the city. Approximately 65% of the deaths were in those older than 65 yr of age. Except for cardiovascular and cancer disease, counts for the individual causes of death were low.

In initial analyses of weather factors, hot days (mean > 80° F), previous day's mean temperature, mean dew point, and winter temperature were significant predictors of daily mortality.

When TSP was included in the above

model, particulates on both the current and the previous day were highly significant predictors of daily mortality, with approximately equal coefficients. The mean TSP of current and prior days was a stronger predictor than that of either the current or the previous day, and the 2-day mean was used in subsequent analyses. The coefficient of TSP ($\mu\text{g}/\text{m}^3$) was 0.000661 ± 0.000131 . Current day and prior day SO₂ measurements (ppb) were also significant predictors of daily mortality. Again, the 2-day mean was the best predictor ($\beta = 0.00132 \pm 0.000290$). When both pollutants were considered together, TSP remained significant ($\beta = 0.000497 \pm 0.000179$), whereas SO₂ became insignificant and substantially reduced in magnitude ($\beta = 0.000565 \pm 0.000403$). To test the hypothesis that TSP was serving primarily as a vector to deliver SO₂ into the respiratory tract, we divided the sample into days below and days above the median (18 ppb). The coefficient of TSP during the low SO₂ days was 0.000707 ± 0.000238 . When SO₂ was above 18 ppb, the coefficient of TSP was 0.000645 ± 0.000187 . Hence, no evidence of an interactive effect was found. This parallels results from London (19).

The association with TSP was not strongly confounded by variables in season and weather. The estimated coefficient for TSP without controlling for these variables ($\beta = 0.000664 \pm 0.000129$) was only slightly different from the complete model estimates. Similarly, adjustment for day of the week slightly increased the estimate for TSP ($\beta = 0.000725 \pm 0.000135$).

The association of mortality with indicators of quintiles of TSP compared with the lowest quintile were evaluated.

TABLE 1
DISTRIBUTION OF DAILY MORTALITY COUNTS, WEATHER, AND
AIR POLLUTION IN PHILADELPHIA, 1973-1980

	5%	10%	25%	50%	75%	90%	95%	Mean
Weather								
Temperature, °F	25	30	41	56	71	77	80	54.8
Dew Point, °F	9	15	28	44	59	68	70	42.8
Air pollutants								
TSP, $\mu\text{g}/\text{m}^3$	37	43	56	73	94	117	132	77.2
SO ₂ , ppb	6	8	12	18	27	39	46	21.0
Mortality, deaths/day								
Total	35	37	42	48	54	60	64	48.2
Age < 65 yr	10	11	14	17	20	23	25	16.9
Age > 65 yr	21	23	26	31	36	40	44	31.3
Cause-specific mortality, deaths/day								
Cardiovascular	13	15	18	22	26	30	32	22.1
Cancer	5	6	8	10	13	15	16	10.5
Pneumonia	0	0	0	1	2	3	4	1.44
Chronic obstructive pulmonary disease	0	0	0	1	1	2	3	0.89

creased risk of COPD mortality was triple the increase in all-cause mortality. In contrast, the percentage increase in cancer mortality associated with particulate pollution was only half the percentage increase in all-cause mortality (figure 2). The pattern of increased mortality in Philadelphia is also consistent with the pattern in the London smog episode of 1952 (25). Total mortality was elevated 2.6-fold during the smog week, but bronchitis deaths were elevated 9-fold. The increase in total mortality during the episode was also higher for the elderly.

Only a small fraction of deaths have respiratory conditions defined as the primary cause. The physiologic reasons for the associations between total mortality and air pollution in the current or previous day are not obvious. Schimmel and Greenberg (9) have suggested that air pollution acts as an additional stress, similar to other environmental stresses such as heat waves, on subjects with preexisting respiratory or cardiovascular problems. Bates (26) has recently suggested three specific mechanisms by which respiratory conditions associated with acute air pollution exposures could contribute to cardiovascular mortality. First, acute bronchitis and bronchiolitis may be misdiagnosed as pulmonary edema. Second, air pollutants might increase lung permeability and precipitate pulmonary edema in people with myocardial damage and an increased left atrial pressure. Third, acute bronchiolitis or pneumonia induced by air pollution, in the presence of preexisting heart disease, might precipitate congestive heart failure.

Patients with COPD would be expected to be particularly at risk. Such patients almost universally suffer from ventilation-perfusion inhomogeneity. Hence, a disproportionate amount of their respiration occurs in a small part of their lungs, and it is in this portion where the particulate exposure will be concentrated (26). The combination of greater effective dose in the portion of the lung that remains functional and decreased reserve capacity should enhance any response to particulates in subjects with COPD.

If acute exposure to particulates increases mortality, one would also expect to find associations with elevated morbidity. In fact, particulate exposure has been associated with increased hospitalization for respiratory illness, and with other evidence of respiratory morbidity. Pope, in two recent studies (27, 28),

demonstrated an association between inhalable particles and hospital admissions for respiratory illness in Utah. Bates and Sizto (29) have reported that sulfate particulates were associated with hospital admissions for respiratory conditions in southern Ontario. Gross and coworkers (30) found respirable particles associated with hospital admissions in Israel. A weaker association with emergency room visits was reported in Steubenville by Samet and colleagues (31). Wichmann and coworkers (4) reported increased hospitalization and ambulance calls during the European smog episode.

Exposure to particulates has also been associated with increases in respiratory symptoms in a diary study of patients with COPD (32). At lower levels of exposure, a series of analyses of data from the Health Interview Study have reported associations between particulate exposure and respiratory symptoms severe enough to restrict activity (33).

Although associations with illness in children are not directly relevant to health effects in adults, these can provide indirect support by demonstrating the association between low level particulate exposure and increased rates of respiratory illness. Schwartz and coworkers (34) have reported an association between PM_{10} concentrations and daily rates of lower respiratory symptoms in a diary study of school children in which PM_{10} concentrations were well below the ambient standard at all times. Dockery and colleagues (35) have also reported an association between annual average PM_{10} and acute bronchitis rates across six cities. The effect was much greater in children with a history of wheezing. These studies suggest that particulate pollution, even at low concentrations, exacerbates chronic respiratory conditions. This pattern is consistent with the increased relative risk of mortality associated with particulate pollution among persons with COPD in this study.

In summary, the association of particulate air pollution with daily total mortality in Philadelphia is quantitatively similar to results in other communities in the United States and in Europe. Moreover, the association is stronger among the elderly than among younger subjects, and it is stronger for respiratory causes of death compared with total mortality and cancers. Given the consistency of these findings, and the coherence of evidence from morbidity studies, the association reported here is likely to

be causal. Additional studies will remain useful in confirming these associations, particularly in communities with daily measurements of not only the mass concentration of particulates but also chemical characterization of their composition.

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Acute Health Effects of PM₁₀ Pollution on Symptomatic and Asymptomatic Children¹⁻³

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Introduction

Particulate air pollution has been implicated as contributing to the incidence and severity of respiratory disease. Elevated levels of particulate pollution have been associated with increased incidence of respiratory symptoms (1-4), decreased pulmonary function (4-9), increased hospitalization for respiratory disease (10-15), and increased mortality (15-23). National ambient air quality standards have been established for respirable particulate matter with an aerodynamic diameter equal to or less than a nominal 10 μm (PM₁₀). PM₁₀ standards include a 24-h standard of 150 $\mu\text{g}/\text{m}^3$, to exceed this standard no more than once per year, and an annual PM₁₀ standard of an arithmetic mean of less than 50 $\mu\text{g}/\text{m}^3$ (24).

During winter months, Utah Valley has experienced high PM₁₀ pollution episodes with multiple violations of the 24-h PM₁₀ standard. Several studies specific to Utah Valley have been conducted. Strong associations between respiratory hospital admissions, PM₁₀ pollution, and the operation of the local steel mill have been observed (11, 12). Large associations between PM₁₀ pollution and mortality have also been observed in Utah Valley using both cross-sectional and longitudinal studies (17, 23).

A recent study investigated changes in reported respiratory symptoms and changes in lung function as measured by peak expiratory flow (PEF) associated with daily changes in PM₁₀ pollution levels in Utah Valley (4). Participants in this previous study included a sample of fourth- and fifth-grade elementary students who were mildly asthmatic or had a history of wheezing, and included a sample of more severely asthmatic patients. Elevated PM₁₀ pollution was associated with statistically significant declines in PEF and increases in reported incidence of respiratory disease and use of asthma medication. Associations between compromised respiratory health and elevated PM₁₀ pollution were ob-

SUMMARY This study assessed the association between daily changes in respiratory health and respirable particulate pollution (PM₁₀) in Utah Valley during the winter of 1990-1991. During the study period, 24-h PM₁₀ concentrations ranged from 7 to 251 $\mu\text{g}/\text{m}^3$. Participants included symptomatic and asymptomatic samples of fifth- and sixth-grade students. Relatively small but statistically significant ($p < 0.01$) negative associations between peak expiratory flow (PEF) and PM₁₀ were observed for both the symptomatic and asymptomatic samples. The association was strongest for the symptomatic children. Large associations between the incidence of respiratory symptoms, especially cough, and PM₁₀ pollution were also observed for both samples. Again the association was strongest for the symptomatic sample. Immediate and delayed PM₁₀ effects were observed. Respiratory symptoms and PEF changes were more closely associated with 5-day moving-average PM₁₀ levels than with concurrent-day levels. These associations were also observed at PM₁₀ levels below the 24-h standard of 150 $\mu\text{g}/\text{m}^3$. This study indicates that both symptomatic and asymptomatic children may suffer acute health effects of respirable particulate pollution, with symptomatic children suffering the most.

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served even when PM₁₀ levels were below the 24-h national ambient air quality standard. The objective of the present study was to see if similar PM₁₀ pollution effects could also be demonstrated in relatively healthy symptomatic and asymptomatic children.

Methods

Study Area

In 1990 Utah Valley had a population of approximately 188,000 who resided in several contiguous cities including and surrounding Provo and Orem, Utah. The principle source of PM₁₀ pollution in the valley was an integrated steel mill built during World War II (25). The mill was located near the shore of a large freshwater lake on the west side of the populated corridor. The valley has a dry four-season climate; during winter temperature inversions, air pollutants are trapped near the valley floor, often resulting in high concentrations of PM₁₀ pollution.

Subject Selection

In November 1989 a questionnaire requesting information about respiratory health was sent home with all 701 fourth- and fifth-grade students from three public schools in the immediate vicinity of PM₁₀ monitors in Orem and Lindon, Utah. The questionnaire, which was in a format similar to that recommended by the Epidemiology Standardization Project (26), was completed by a parent or guardian and then returned to the school. The questionnaire was completed and returned by 591 children.

The questionnaire identified 129 (22% of the total) children who were mildly symptomatic. These included only children who were not receiving asthma medication but who (1) coughed in the morning or at other times during the day or night for as much as 3 months in a row in the previous 12 months, (2) whose chest ever sounded wheezy or whistling, including times when he or she had a cold, or (3) whose doctor ever said the child had asthma. Of these nonmedicated, symptomatic children, 60 were randomly selected as potential participants in the symptomatic sample. Also, 60 children whose parents did not indicate any of these symptoms on the questionnaire were randomly selected as potential participants in the asymptomatic sample.

In November 1990, potential participants and their parents were contacted by telephone.

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Of the original 120 participants, 2 did not want to participate, and the remainder could not be reached at home, had moved or were moving, or their phone had been disconnected. One child was not included in the final analysis because of failing to record PEF and symptom data properly. Final analysis included a total of 79 subjects – 39 in the symptomatic sample and 40 in the asymptomatic sample. Because the actual study period began approximately 1 yr after the administration of the questionnaire, an abbreviated version of the original questionnaire was administered to each participant and a parent at the beginning of the study period to verify that none of the participants had begun receiving asthma medication and that they were properly assigned to their sample. All the participants were in the fifth or sixth grade during the study period and were 10 to 12 yr old. Summary information comparing the final two samples is provided in table 1.

Materials and Procedure

Research protocols were approved by the Brigham Young University institutional review board for human studies. Informed written consent was obtained, and peak flow meters, health symptom diaries, and instructions were delivered to homes of participants on or about December 1, 1990. Each child was allowed to choose one of three children's science books. These books were ordered and then given to the child at the end of the study period. Participants were provided with Mini-Wright peak flow meters (Armstrong Medical Industries Inc., Lincolnshire, IL), and daily health symptom diaries and were instructed on their proper use. Participants reported the following symptoms: trouble breathing; runny or stuffy nose; wet cough; dry cough; wheezing; fever; rash; burning, aching, or red eyes; and upset stomach.

Participants were instructed to perform the peak flow test three times in the standing position just before bedtime and to record the highest reading along with the symptoms experienced that day. Parents were asked to supervise children's compliance with instructions. Participants were assisted in their homes until they demonstrated they could perform the test and record symptoms properly. Participants were instructed that, if they forgot a day, they should leave that entry blank and go on to the next day. Participants were visited in their homes six times during the 3½-month study period. During these visits participants' performance was observed, any needed retraining or encouragement was given, and results were retrieved.

Pollution and Weather Data

PM₁₀ monitoring was conducted by the Utah State Department of Health in accordance with the U.S. Environmental Protection Agency (EPA) reference method (24). The 24-h samples were collected commencing at midnight at the Lindon and Orem monitoring

TABLE 1
SUMMARY INFORMATION CONCERNING THE SYMPTOMATIC AND ASYMPTOMATIC SAMPLES

	Symptomatic Sample	Asymptomatic Sample
Final sample size	39	40
Average number participating on any given study day	32	33
Mean PEF, L/min	287	308
% Female	46	68
% Lived with parent who smoked*	0	5
% Coughed in the morning or any time during the day or night for as much as 3 months in a row*	31	0
% Chest has sounded wheezy or whistling, including times when he or she had a cold*	82	0
% Doctor ever said he or she had asthma*	28	0
% Reported a wet or dry cough for 20% or more of study period†	33	20
% Reported wheezing for 1 day or more during study period†	33	8
% Reported trouble breathing for 1 day or more during study period†	31	25
% Reported no symptoms of cough, trouble breathing, or wheezing for the entire study period†	5	30

* Based on information provided by parents from the questionnaires administered through the school and at the beginning of the study period.

† Based on symptoms reported on the daily diaries through the study period.

sites. All participants' homes and schools were within 4 km of one of these sites. Mean PM₁₀ levels at these two sites were not significantly different ($p < 0.10$) and were strongly linearly correlated ($R = 0.94$) suggesting that PM₁₀ pollution levels were similar throughout the area where participants lived and attended school. PM₁₀ levels from the Orem site were used in the analysis, except for 4 days when data at the Orem site were not available. For these days data from the Lindon site were used.

During the study period, 24-h PM₁₀ levels averaged 76 $\mu\text{g}/\text{m}^3$ and ranged from 7 to 251 $\mu\text{g}/\text{m}^3$. The 24-h PM₁₀ standard of 150 $\mu\text{g}/\text{m}^3$ was exceeded 14 times, all during three pollution episodes. Violations of the 24-h standards occurred on up to 5 consecutive days (Fig. 1). During one 5-day episode (January 1 to 5) PM₁₀ levels averaged 209 $\mu\text{g}/\text{m}^3$. During another 14-day episode (January 30 to February 12), PM₁₀ levels averaged 154 $\mu\text{g}/\text{m}^3$.

No monitoring of SO₂ was conducted by the state during the study period, because

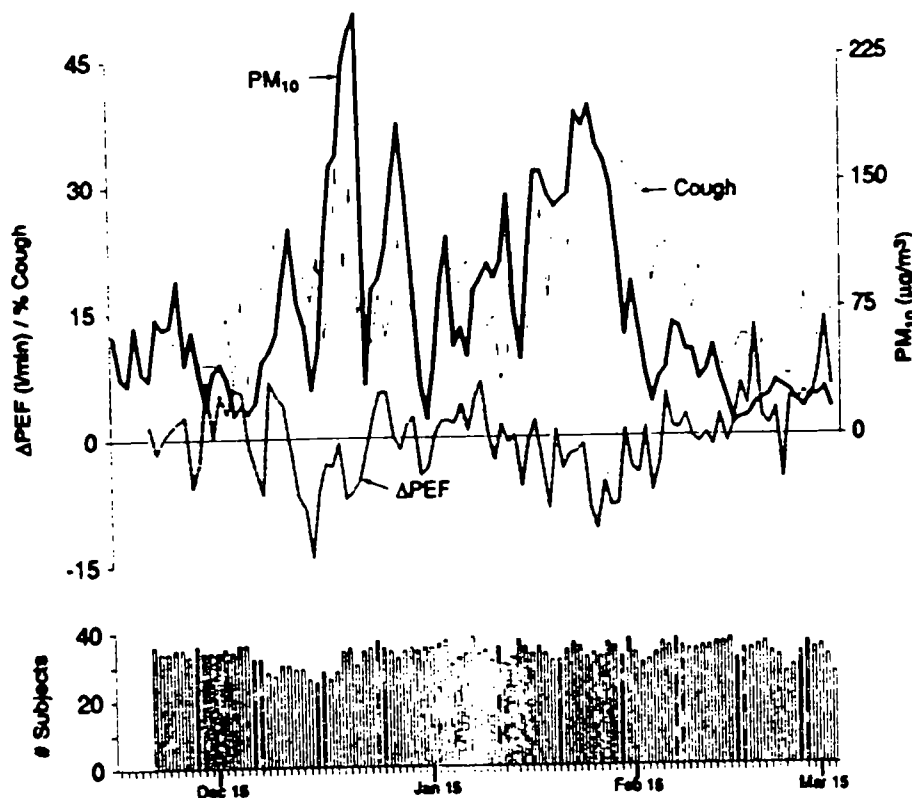


Fig. 1. Daily PM₁₀ levels, mean peak expiratory flow deviations (ΔPEF), percentage who reported cough, and number of participants for the symptomatic sample.

monitoring conducted during preceding winters indicated that SO_2 concentrations were always well below the National Ambient Air Quality 24-h standard of 0.14 ppm. Over a 2-month monitoring period (January and February 1989) the hourly average never exceeded 0.04 ppm. Monitoring of O_3 was discontinued during winter months because conditions necessary for substantial O_3 formation do not exist. Sampling of aerosol strong acidity conducted during the previous winter indicated that particulate acidity was low and never exceeded the equivalence of $0.5 \mu\text{g}/\text{m}^3 \text{H}_2\text{SO}_4$ (4). Daily minimum temperatures were obtained from the Brigham Young University weather station. Mean daily low temperature equaled 20°F , with a range of -16 to 46°F .

Statistical Methods

Statistical analysis was conducted separately for the two samples. The mean PEF (L/min) for each participant was calculated for the 100-day period from December 6, 1990 to March 15, 1991. Individual deviations of daily performance from each participant's mean PEF were calculated. These deviations were averaged across participants to obtain a daily mean deviation (ΔPEF) for each sample. ΔPEF values were plotted with PM_{10} levels, and mean values were calculated within quartiles of PM_{10} . Single-period models, polynomial distributed lag models (27), and 5-day moving average models were estimated by regressing ΔPEF on different combinations of daily low temperature, PM_{10} pollution levels, and a linear time trend variable.

Daily mean deviations (ΔPEF values) were computed with different sample sizes and under different environmental conditions resulting in potential problems of heteroscedasticity, that is, unequal day-specific variance. Such heteroscedasticity can produce biased standard errors of the regression coefficients. Therefore, weighted least-squares regression models (27) were estimated using the inverse of the calculated standard errors of the mean day-specific deviations (ΔPEF values) as weights. Because statistically significant ($p < 0.05$) first-order autocorrelation was observed, weighted least-squares models were estimated using the Yule-Walker estimation method (28).

Three binary response variables indicating daily symptoms of respiratory disease were analyzed. The first variable indicated symptoms of upper respiratory disease: the participant reported having one or more of the following symptoms: runny or stuffy nose; wet cough; or burning, aching, or red eyes. The second variable indicated symptoms of lower respiratory disease: the participant reported having one or more of the following symptoms: trouble breathing, dry cough, or wheezing. Because cough was a common symptom and the children may have had difficulty differentiating between a wet and a dry cough, a third variable that independently indicated cough was the participant's report of either a wet or a dry cough.

These symptom variables were analyzed by

comparing the mean fraction of participants reporting respiratory symptoms across quartiles of PM_{10} levels. These variables were also analyzed by estimating logistic regression models (29). Logistic regressions were conducted for each of the variables and were conducted separately for each sample. The binary response variables that indicated daily symptoms were regressed on PM_{10} , low temperature, and subject-specific indicator variables. Because repeated daily observations were made on each subject, serial correlation needed to be accounted for in the analysis. Two approaches were used to account for this serial dependence. The first approach, described by Liang and Zeger (30, 31), models the marginal expectation of the dependent binary variable as a function of the independent variables, incorporating the autoregressive covariance structure in the estimation of the regression coefficients and their standard errors. Robust standard error estimates, which provide unbiased hypothesis tests even if the covariance has been misspecified, were computed using this approach. The second approach modeled the conditional expectation of the binary-dependent variable given previous observations. This approach used regressive logistic models as described by Bonney (32). Preliminary regressions observed statistically significant ($p < 0.05$) third-order serial correlation; therefore, the pattern of dependence was treated as third-order Markov serial correlation. Observations with missing data were not included in the analysis.

Associations between PEF and PM_{10}

A negative association between ΔPEF and PM_{10} pollution was observed despite much stochastic variability in ΔPEF (figures 1 and 2 and table 2). Associations were observed when both concurrent and lagged PM_{10} pollution levels were considered. The mean ΔPEF values for quartiles of PM_{10} levels, for which the quartiles are based on the average PM_{10} levels of the concurrent and preceding 4 days (5-day moving-average PM_{10} levels), are presented in table 2. ΔPEF was lower when PM_{10} pollution levels were higher. Mean ΔPEF values were approximately 6.5 L/min lower for both samples during days with pollution levels in the highest quartile versus days in the lowest quartile.

The negative relationship between PM_{10} pollution and ΔPEF was confirmed by regression analysis. Regression results for selected models for both the symptomatic and asymptomatic samples are reported in table 3. Several important observations were made from the regression results. First, negative coefficients between ΔPEF and PM_{10} were consistently found. Second, distributed lag models generally performed better than single-period models. As can be seen in

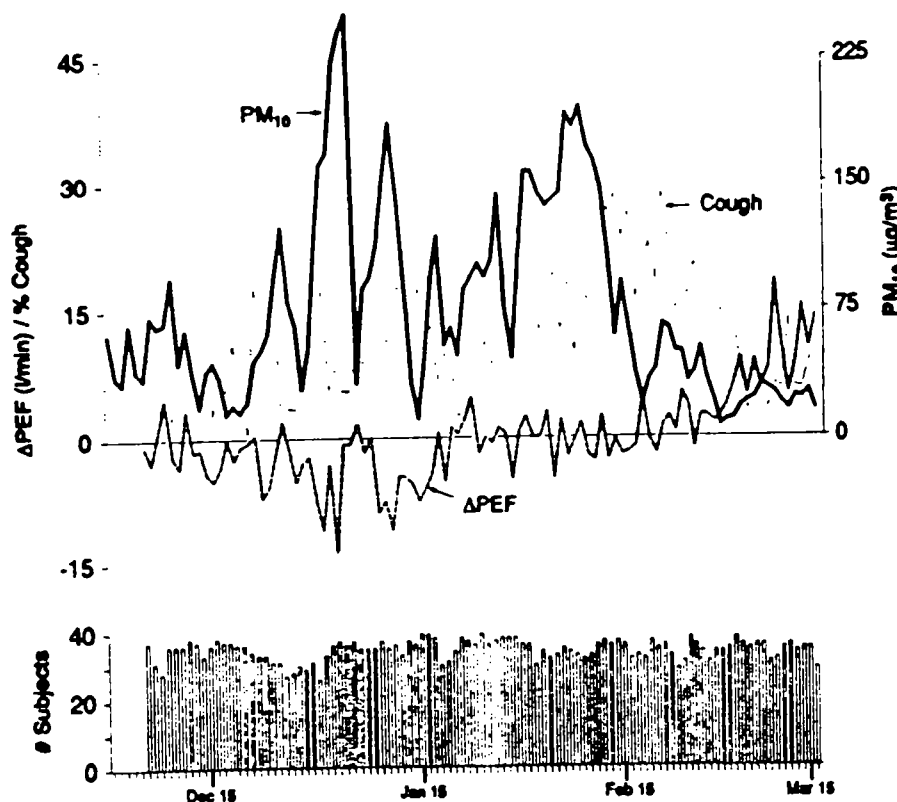


Fig. 2. Daily PM_{10} levels, mean peak expiratory flow deviations (ΔPEF), percentage who reported cough, number of participants for the asymptomatic sample.

TABLE 2
MEAN Δ PEF AND MEAN % REPORTING RESPIRATORY SYMPTOMS FOR QUANTILES
OF PM_{10} LEVELS*

		OF PM_{10} LEVELS*								
		Mean % Reporting								
		Mean Δ PEF			Symptomatic			Asymptomatic		
Quartile	No. of Days	PM_{10} Mean†	Symptomatic	Asymptomatic	Upper	Lower	Cough	Upper	Lower	Cough
1	25	25	3.52	4.45	21	11	12	17	10	9
2	25	55	0.47	-0.15	27	13	16	18	11	11
3	25	89	-1.52	-1.86	27	16	18	15	10	11
4	25	141	-2.86	-2.28	33	20	24	18	14	16

* The quartiles were based on 5-day moving averaged PM_{10} levels, which ranged from 13 to 209 $\mu g/m^3$, with the 1st, 2nd, and 3rd quartiles equal to 39, 67, and 107 $\mu g/m^3$, respectively.
† This equals the mean PM_{10} level for the 25 days in each quartile.

table 3, 5-day moving-average PM_{10} levels (Model II) were more strongly associated with Δ PEF than were concurrent day PM_{10} levels (Model I). Polynomial distributed lagged models (not presented) observed significant lagged effects on PM_{10} for up to 4 or 5 days but generally provided little additional explanatory power over the more simple 5-day moving-average models. Third, the association between Δ PEF and PM_{10} , as estimated from the regression analysis, was larger for the symptomatic sample than for the asymptomatic sample. Finally, no statistically significant correlation between low temperature and Δ PEF was observed. Based on the regression results of Model II, reported in table 3, elevated PM_{10} levels of 150 $\mu g/m^3$ would result in an estimated average reduction in PEF of 5.4 and 3.8 L/min (approximately 1.8 and 1.3%) for the symptomatic and asymptomatic samples, respectively.

Regression models were estimated individually for each participant in both samples. As with the aggregate analysis, the Yule-Walker estimation method (28) was used. Regression coefficients be-

tween PEF and PM_{10} for participants in the symptomatic sample ranged from -0.442 to 0.218, with the lower quartile, median, and upper quartile estimates -0.107, -0.047, and 0.020, respectively. Regression coefficients between PEF and PM_{10} for participants in the asymptomatic sample ranged from -0.278 to 0.164, with the lower quartile, median, and upper quartile estimates -0.074, -0.033, and 0.025, respectively. The mean of the regression coefficients on 5-day mean PM_{10} (Model II) for all participants in the symptomatic sample was -0.0549 (standard error of the mean, SEM = 0.0205), compared with -0.0359 (SEM = 0.0117) in table 3. The mean of the regression coefficients on 5-day mean PM_{10} (Model II) for all participants in the asymptomatic sample was -0.0239 (SEM = 0.0157), compared with -0.0254 (SEM = 0.0095) in table 3.

Associations between PM_{10} and Symptoms

The mean percentage of children reporting symptoms of respiratory disease increased with increased PM_{10} pollution (table 2). For the symptomatic sample,

those reporting upper respiratory symptoms, lower respiratory symptoms, and cough were approximately 57, 82, and 100% higher, respectively, during days with pollution levels in the highest quartile versus days in the lowest quartile. For the asymptomatic sample no association between upper respiratory symptoms and PM_{10} pollution was observed, but lower respiratory symptoms and cough were approximately 40 and 78% higher during days with pollution levels in the highest quartile versus days in the lowest quartile, respectively.

Logistic regression analysis confirmed this association. Regression coefficients on PM_{10} from the Liang and Zeger (30, 31) robust logistic models are reported in table 4. The Bonney (32) regressive logistic models estimated similar results, with nearly identical statistical significance levels for the PM_{10} coefficients. Both approaches observed positive associations between PM_{10} and respiratory symptoms, especially lower respiratory symptoms and cough. The associations were stronger for the symptomatic sample than for the asymptomatic sample. Symptoms were more strongly associated with 5-day moving-average PM_{10} than with concurrent-day PM_{10} levels. Logistic regression coefficients on low temperature (not reported) had inconsistent signs and were not statistically significant ($p < 0.10$).

Results with Violation Episodes Excluded

Additional analysis was conducted to evaluate whether the associations between Δ PEF and respiratory symptoms and PM_{10} pollution could be observed for PM_{10} pollution levels below the 24-h National Ambient Air Quality Standard. Model II as presented in tables 3 and 4 were reestimated for each sample after excluding all observations when PM_{10} pollution of the concurrent day or any of the preceding 4 days exceeded 150 $\mu g/m^3$. By doing so, 30 of 100 days were excluded from the analysis and the highest remaining 24-h PM_{10} level equaled 143 $\mu g/m^3$. For both samples, the estimated regression coefficients between PM_{10} and Δ PEF were approximately 30% larger (in absolute terms) than those reported in table 3. Although this difference was not statistically significant ($p < 0.05$), these results suggest that a PM_{10} pollution effect was observable at PM_{10} levels below 150 $\mu g/m^3$. The logistic regression coefficients for PM_{10} , with the violation episodes excluded,

TABLE 3
REGRESSION COEFFICIENTS FOR Δ PEF (L/min) FOR SELECTED MODELS FOR
SYMPTOMATIC AND ASYMPTOMATIC SAMPLES*

	Symptomatic Sample		Asymptomatic Sample	
	Model I	Model II	Model I	Model II
Intercept	0.6008 (1.7868)	2.0834 (1.7507)	-3.8081 (1.4724)†	-2.5044 (1.4270)†
PM_{10} (concurrent day, $\mu g/m^3$)	-0.0175 (0.0094)	-	-0.0110 (0.0082)	-
PM_{10} (5-day moving average, $\mu g/m^3$)	-	-0.0359 (0.0117)‡	-	-0.0254 (0.0095)‡
Low temperature	0.0464 (0.0498)	0.0887 (0.0456)	0.0046 (0.0456)	0.0146 (0.0426)
Time trend	0.0004 (0.0244)	-0.0078 (0.0230)	0.0824 (0.0196)‡	0.0884 (0.0186)‡

* Absolute values of the standard errors are provided in parentheses. Statistical significance is based on standard t tests.

† $p < 0.05$.

‡ $p < 0.01$.

TABLE 4

PM₁₀ LOGISTIC REGRESSION COEFFICIENTS ($\times 100$) FOR CONCURRENT-DAY PM₁₀ AND 5-DAY MOVING-AVERAGE PM₁₀ FOR RESPIRATORY SYMPTOMS OF SYMPTOMATIC AND ASYMPTOMATIC SAMPLES*

	Symptomatic Sample			Asymptomatic Sample		
	Upper Respiratory Symptoms	Lower Respiratory Symptoms	Cough	Upper Respiratory Symptoms	Lower Respiratory Symptoms	Cough
Concurrent day PM ₁₀	0.384 (0.183) [†]	0.472 (0.188) [‡]	0.508 (0.143) [‡]	-0.022 (0.244)	0.237 (0.218)	0.334 (0.173)
5-Day moving-average PM ₁₀	0.519 (0.203) [‡]	0.658 (0.206) [‡]	0.708 (0.198) [‡]	0.072 (0.325)	0.379 (0.279)	0.606 (0.243) [†]

* Absolute values of the standard errors ($\times 100$) are provided in parentheses.

[†] $p < 0.05$.

[‡] $p < 0.01$.

were nearly identical to the coefficients reported in table 4.

Discussion

Elevated PM₁₀ levels were associated with small but statistically significant reductions in lung function as measured by PEF, and large increases in the frequency of reported symptoms of respiratory disease. These associations were observed at PM₁₀ levels below the 24-h standard of 150 $\mu\text{g}/\text{m}^3$. Observed associations between PM₁₀ and respiratory health were consistent with previously reported associations found in a similar Utah Valley study of symptomatic children and asthmatic patients (4). Given that the primary source of the PM₁₀ pollution was a steel mill, and given that SO₂, aerosol acidity, and ozone levels were low, these results may not be readily extrapolated to other areas. Furthermore, similar studies on other age groups, including adults, have not been conducted. Studies conducted elsewhere, however, have observed similar results in children. Decreases in measurements of FVC and FEV_{0.75} among third- to fifth-grade elementary students were observed in Steubenville, OH following air pollution episodes with maximum 24-h mean particulate (TSP) concentrations up to 312 $\mu\text{g}/\text{m}^3$ (5, 8). Decreases in FVC and FEV₁ pulmonary function measurements of children in IJmond, the Netherlands were associated with maximum TSP levels equal to 200 to 250 $\mu\text{g}/\text{m}^3$ (6). Declines of PEF of children in Tucson were also associated with elevated TSP and ozone levels (9).

This study suggests both an immediate and a longer term effect of PM₁₀ on respiratory health. Respiratory symptoms and PEF were more closely associated with 5-day moving-average PM₁₀ levels than with concurrent-day pollution. In the previously reported Utah Valley

study, which used more severely symptomatic participants (4), significant correlations between PEF and lagged PM₁₀ levels for 4 or 5 days were also observed. A recent reanalysis of the Steubenville study indicated that FVC and FEV_{0.75} in children was more strongly associated with a 5-day moving-average rather than previous-day TSP (8). The deficit in lung function and the increased symptoms of respiratory disease associated with elevated levels of particulate pollution appeared to be mostly transient, yet the impact on the risk of developing chronic respiratory diseases in adulthood is unclear (33). A recent study observed a strong statistically significant relationship between mortality in Utah County and PM₁₀ pollution levels (23). Nonaccidental daily death counts were also most strongly associated with 5-day moving-average PM₁₀ levels.

This study indicates that the respiratory health of a wide range of children may suffer acute effects of respirable particulate pollution, with symptomatic children suffering the most. Associations between PEF and PM₁₀ were observed for both the symptomatic and asymptomatic samples, although the association was strongest for the symptomatic sample. Large associations between respiratory symptoms and PM₁₀ were also observed for both the symptomatic and asymptomatic samples, the association being strongest for the symptomatic sample.

Large differences in response to particulate air pollution were also seen between children within each sample. Individual regressions indicated that more than 25% had a response more than twice as large as the mean value. Although part of this between-subject variation is undoubtedly due to random measurement error, at least part reflects variability of individual response. Children would be expected to vary in the magnitude of their

response to air pollution. They may also vary in timing of the onset of symptoms and remission and in the timing of any drop and recovery of pulmonary function. The net effect of varying response or recovery times in these data would be a dispersion of the association over several days before the pulmonary function measurement. Thus the stronger association with 5-day mean PM₁₀ concentration should not be interpreted to imply short-term, that is, 1 day or less, exposures are not important. Rather, it may imply that response and recovery may even several days and that the timing of response and recovery varies between children.

Acknowledgment

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Respiratory Health and PM₁₀ Pollution

A Daily Time Series Analysis¹⁻³

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Introduction

Many studies have implicated particulate air pollution as contributing to the incidence and severity of respiratory disease (1-15). Decreases in pulmonary function associated with particulate pollution levels have been observed (7, 16, 17). Fine particulate pollution is of specific concern because it contains a higher proportion of various toxic metals and acidic sulfur species (14), and, aerodynamically, it can penetrate deeper into the respiratory system (15).

In recognition of the health risks associated with fine particulate matter, national ambient air quality standards have been set for particulate matter with an aerodynamic diameter (d_a) equal to or less than a nominal 10 μm (PM₁₀). The PM₁₀ standards include a 24-h standard of 150 $\mu\text{g}/\text{m}^3$, with no more than one expected exceedance per year, and an annual PM₁₀ standard of an arithmetic mean of less than 50 $\mu\text{g}/\text{m}^3$ (15).

Utah Valley has experienced high PM₁₀ pollution episodes during winter months. These episodes have been associated with multiple violations of the 24-h PM₁₀ standard. Therefore, studies specific to Utah Valley have been conducted. Archer (18) compared age-adjusted death rates for malignant and nonmalignant respiratory disease across three Utah counties. It was estimated that 30 to 40% of respiratory cancer and nonmalignant respiratory disease deaths in Utah County may be attributable to air pollution. Recent research also has taken advantage of the intermittent operation of the local steel mill, showing large associations between respiratory hospital admissions, PM₁₀ pollution, and the operation of the steel mill (19, 20).

This study investigated changes in lung function as measured by peak expiratory flow (PEF) associated with daily changes in PM₁₀ pollution levels in Utah Valley. Because the effects of particulate pollution on lung function may be felt over several days, distributed lag relationships

SUMMARY This study evaluated changes in respiratory health associated with daily changes in fine particulate pollution (PM₁₀). Participants included a relatively healthy school-based sample of fourth and fifth grade elementary students, and a sample of patients with asthma 8 to 72 yr of age. Elevated PM₁₀ pollution levels of 150 $\mu\text{g}/\text{m}^3$ were associated with an approximately 3 to 6% decline in lung function as measured by peak expiratory flow (PEF). Current day and daily lagged associations between PM₁₀ levels and PEF were observed. Elevated levels of PM₁₀ pollution also were associated with increases in reported symptoms of respiratory disease and use of asthma medication. Associations between compromised respiratory health and elevated PM₁₀ pollution were observed even when PM₁₀ levels were well below the 24-h national ambient air quality standard of 150 $\mu\text{g}/\text{m}^3$. Associations between elevated PM₁₀ levels, reductions in PEF, and increases in symptoms of respiratory disease and asthma medication use remained statistically significant even when the only pollution episode that exceeded the standard was excluded. Concurrent measurements indicated that little or no strong particle acidity was present. *AM REV RESPIR DIS* 1991; 144:668-674

between PM₁₀ pollution and PEF were evaluated. Also, possible associations between reported respiratory symptoms, asthma medication use, and PM₁₀ pollution were examined.

Methods

Study Area

Utah Valley is a mountain valley situated in north central Utah. In 1990 approximately 188,000 people resided in several contiguous Utah Valley cities including and surrounding Provo and Orem (21). These cities are approximately 1,387 m above sea level and are bordered on the west by a large fresh-water lake and on the east by mountains. Most of the population is crowded into a corridor that is approximately 5 to 9 kilometers wide from the east to the west and 30 km long from the north to the south. The valley has a dry four-season climate with low level temperature inversions common during winter months. During temperature inversions, air pollutants are trapped in the valley floor, often resulting in high concentrations of PM₁₀ pollution.

The principal source of PM₁₀ pollution is an integrated steel mill built during World War II. The mill is located near the shore of the lake on the west side of the populated corridor, roughly in the center of the valley from north to south. When in operation, the mill emits 50 to 70% of total Utah valley PM₁₀ emissions (22).

Subject Selection

Two samples of participants were selected, a school-based sample and a patient-based sam-

ple. Participants in the school-based sample were selected from fourth and fifth grade elementary students in three public elementary schools in the immediate vicinity of the PM₁₀ monitors in Orem and Lindon, Utah. In November 1989, a questionnaire requesting information about respiratory illnesses and symptoms was sent home with all 701 students to be completed by a parent or guardian and then returned to school. The questionnaire was in a format similar to that recommended by the Epidemiology Standardization Project (23). The questionnaire was completed and returned by 591 children, 84% of the total.

The questionnaire identified 60 children

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TABLE 1
SUMMARY INFORMATION CONCERNING THE SCHOOL-BASED SAMPLE
AND THE PATIENT-BASED SAMPLE*

	School-based Sample	Patient-based Sample
Original sample size	41	25
Final sample size	34	21
Original participants, %	83	84
Average number participating on any given study day	29 (2.6)	18 (1.6)
Mean age, yr	10.3 (0.7)	28.7 (21.3)
Youngest	9	8
Oldest	11	72
Mean PEF	260 (51)	320 (110)
Female, %	38	52
Smokers, %	0	0
Lives with parent or spouse that smokes, %	15	5
Use of asthma medication on any given day during the study period, mean %	12	67
Reported using asthma medication during study period, %	29	90

Definition of abbreviation: PEF = peak expiratory flow

* Standard deviations are provided in parentheses when appropriate

who had a positive response to one or more of three questions: ever wheezed without a cold, wheezed for 3 days or more out of the week for a month or longer, and/or had a doctor say the "child has asthma." These children (just over 10% of the total) were selected as potential participants in the school-based sample. Potential participants in the patient-based sample consisted of 35 Utah valley residents who were receiving medical treatment for asthma and who were referred to the study by local physicians. Twenty-nine of the potential participants could not be contacted, were planning on moving out of the area, or were otherwise unable or unwilling to participate. This left 66, 41 in the school-based sample and 25 in the patient-based sample, as original participants.

Eleven of these 66 participants were not included in the final analysis for various reasons. Two moved out of town during the study period, one produced unreliable readings because of spitting into the peak flow meter, and eight completed less than 55% of days in the study period. Final analysis included a total of 55 subjects—34 in the school-based sample and 21 in the patient-based sample. On the basis of the responses in the questionnaires, in 38% of the participants in the school-based study asthma had never been diagnosed, but they had "wheezed without a cold"; in 32% asthma had been diagnosed, but they had not been troubled by asthma in the last 12 months; 21% had been troubled by asthma in the last 12 months but did not require medication; and only 9% had asthma that required medication on a routine basis. In contrast, participants in the patient-based sample were all troubled by respiratory problems and generally required asthma medication. Summary information comparing the two samples is provided in table 1.

Materials and Methods

Research protocols were approved by the Brigham Young University institutional review board for human studies. Informed written consent was obtained and peak flow

meters, health symptom diaries, and instructions were delivered to homes of participants from December 13 to 17, 1989. Each participant was provided with a mini-Wright peak flow meter (Armstrong Medical Industries Inc., Lincolnshire, IL) and daily health symptom diaries and were instructed on their proper use. Participants reported the following symptoms: trouble breathing; runny or stuffy nose; wet cough; dry cough; wheezing; fever; rash; burning, aching, or red eyes; and upset stomach. They also reported if they stayed home for the day; saw a doctor or a nurse; were hospitalized; took asthma medication on a given day; took extra asthma medication that day; or were out of town overnight.

Participants were instructed to perform the peak flow test three times in the standing position just before bedtime and record the highest reading along with the symptoms experienced that day. Parents were asked to supervise children's compliance with instructions. Participants were assisted in their homes until they demonstrated they could perform the test and record symptoms properly. Participants were instructed that if they forgot a day they should leave it blank and go on to the next day. Participants were revisited approximately 2 wk after the first visit and every month throughout the study period. During these visits participants' performances were observed, any needed retraining or en-

couragement was given, and the previous month's results were retrieved. Mention of air pollution levels or the steel mill was avoided.

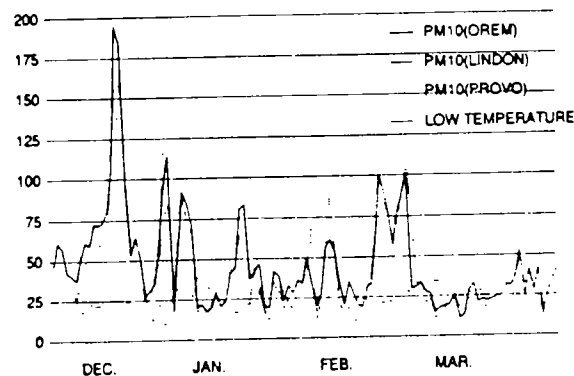
Pollution and Weather Data

PM₁₀ monitoring was conducted by the Utah State Department of Health in accordance with Environmental Protection Agency's reference method for monitoring PM₁₀ (15). Samples for each 24-h period were collected commencing at midnight. PM₁₀ monitoring was conducted at three sites including the Lindon site, approximately 5 km northeast of the steel mill, the Orem site, approximately 1.5 km east of the mill, and the Provo site, approximately 9 km southeast of the mill. PM₁₀ levels from all three sites tracked each other very closely throughout the study period (figure 1). Mean PM₁₀ levels at the Provo site were approximately 14% lower than at the other two sites. Mean PM₁₀ levels at the Lindon and Orem sites were not significantly different ($p < 0.10$) and were strongly linearly correlated ($R^2 = 0.84$). PM₁₀ levels from the most centrally located Orem site were used in the analysis of this study, except for 8 days during the study period for which PM₁₀ data at the Orem site were not available. For these 8 days data from the Lindon site were used.

During the study period 24-h PM₁₀ levels ranged from 11 to 195 $\mu\text{g}/\text{m}^3$, with an average of approximately 46 $\mu\text{g}/\text{m}^3$. The 24-h PM₁₀ standard of 150 $\mu\text{g}/\text{m}^3$ was exceeded twice during the study period. Primarily because of favorable weather conditions, PM₁₀ levels were lower than in recent winters. Over the past three winters when the steel mill was operating, PM₁₀ levels exceeded the 24-h standard 13, 10, and 22 times per winter, and 24-h PM₁₀ levels reached as high as 365 $\mu\text{g}/\text{m}^3$.

Limited monitoring of sulfur dioxide (SO₂), nitrogen dioxide (NO₂), and ozone (O₃) was conducted by the State Bureau of Air Quality. Concentrations of each of these pollutants were well below the ambient air quality standards. During the study period NO₂ levels averaged less than 0.03 ppm (compared with an annual standard of 0.05 ppm), and 24-h NO₂ levels never exceeded 0.07 ppm. No monitoring of SO₂ was conducted by the state during the study period, but monitoring conducted during the preceding winter, when weather conditions resulted in relatively higher pollution concentrations, indicated that SO₂

Fig. 1. Low temperature ($^{\circ}\text{F}$) and PM₁₀ levels ($\mu\text{g}/\text{m}^3$) at the Lindon, Orem, and Provo monitoring sites, December 13, 1989 through March 31, 1990.



concentrations averaged less than 0.01 ppm, and 24-h concentration levels never exceeded 0.02 ppm (compared with the 24-h standard of 0.14 ppm). Monitoring of O_3 was discontinued during winter months because conditions necessary for substantial O_3 formation do not exist during the winter period.

Supplemental 24-h integrated sampling of aerosol strong acidity was conducted daily at the Lindon site between December 28, 1989 and March 19, 1990. A Harvard impactor ($d_a < 2.5 \mu m$) (Harvard Apparatus, Millis, MA) equipped with an ammonia diffusion denuder to protect the acidic sampler from neutralization was used (24, 25). Strong particle acidity never exceeded the detection limit of 8 nmol/m^3 , indicating that particulate acidity was very low and never exceeded the equivalence of $0.5 \mu g/m^3 \text{ H}_2\text{SO}_4$. These low hydrogen ion concentrations are typical of wintertime aerosol acidity reported for St. Louis, Missouri; Portage, Wisconsin; Topeka, Kansas; and Watertown, Massachusetts (26). These measurements do not preclude the possibility that acidic aerosols might be formed during cold winter fog conditions that did not occur during the study period but are common during some winter periods in the study area.

Daily minimum temperatures were obtained from the Brigham Young University weather station, approximately 10 km southeast of the steel mill (figure 1). The study period was unusually warm and dry compared with normal winters in the valley.

Statistical Methods

Statistical analysis was conducted separately for the two samples. The mean PEF (L/min) for each participant was calculated. Individual deviations of daily performance from each participant's mean PEF were calculated. These deviations were averaged across participants to obtain a daily mean deviation (ΔPEF) for each sample. On all days of the analysis, greater than 60% of the respondents provided PEF readings. ΔPEF values were plotted with PM_{10} levels, and mean values were calculated across selected ranges of PM_{10} on the same day. Single period and polynomial-distributed lag models were estimated by regressing ΔPEF on different combinations of daily low temperature, PM_{10} pollution levels, and a linear time trend variable. The time trend variable was defined as 1 to 109 and assigned in order to the 109 days in the study period.

Daily mean deviations (ΔPEF values) were computed with different sample sizes and under different environmental conditions, resulting in potential problems of heteroscedasticity, including biased standard errors of the regression coefficients. To correct for these problems, weighted least-squares regression models (27) were estimated using the inverse of the calculated standard errors of the mean (SEM) deviations (ΔPEF values) as weights. Because statistically significant ($p < 0.05$) first-order autocorrelation was observed, weight-

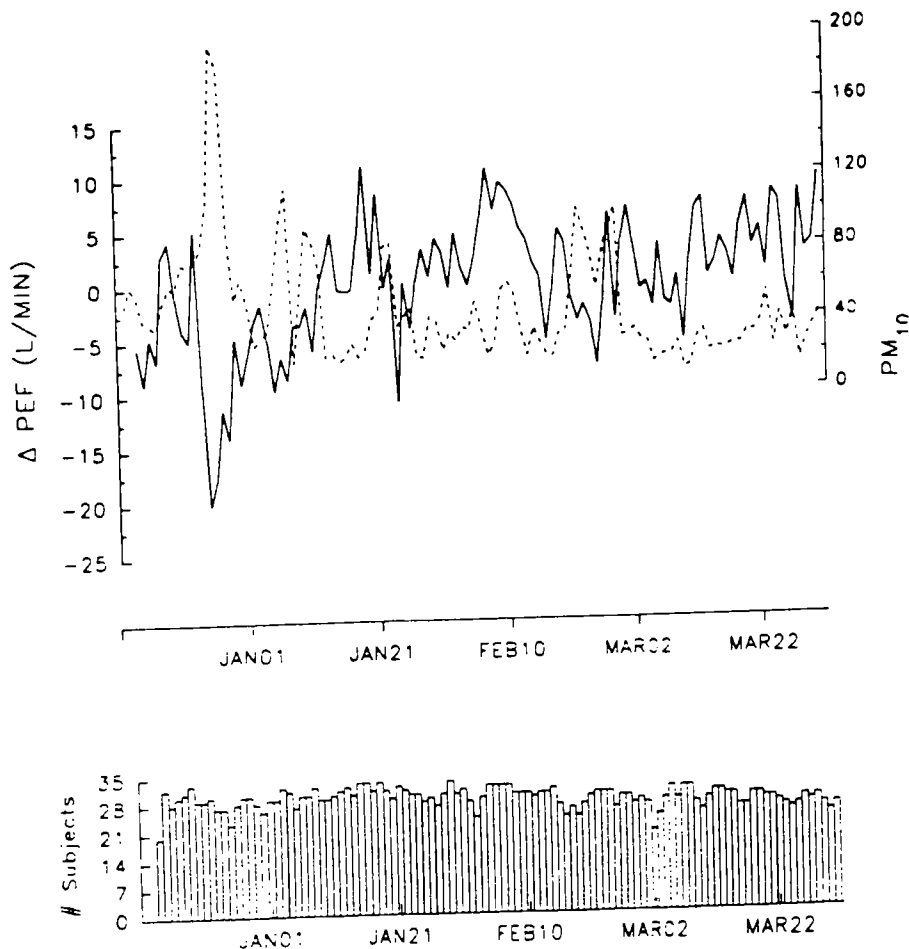


Fig. 2. PM_{10} levels ($\mu g/m^3$) (broken line) at the Orem monitoring site, mean peak expiratory flow deviations (ΔPEF) (solid line), and daily number of participants. School-based sample, December 13, 1989 through March 31, 1990.

ed least-squares models were estimated using the Yule-Walker estimation method (28).

Four binary response variables indicating daily symptoms of respiratory disease and asthma medication use were analyzed. The first variable indicated symptoms of upper respiratory disease and was defined as 1 when the participant reported having one or more of the following symptoms: runny or stuffy nose; wet cough; or burning, aching, or red eyes. The second variable indicated symptoms of lower respiratory disease and was defined as 1 when the participant reported having one or more of the following symptoms: trouble breathing, dry cough, or wheezing. The third and fourth variables were defined as 1 if the participant reported taking asthma medication or taking extra asthma medication, respectively.

These symptoms and medication use variables were analyzed by comparing the mean fraction of participants reporting respiratory symptoms and medication use by level of PM_{10} on the same day. These variables were also analyzed by estimating fixed effects logistic regression models. The models were fitted using the maximum-likelihood method (29). Logistic regressions were conducted for each of the four variables and were conducted separately for each sample. The regressions

estimated logistic regression coefficients for PM_{10} and low temperature along with subject-specific indicator variables.

Results

Associations between PEF and PM_{10}

As can be seen in figure 2 and table 2, a negative relationship between PM_{10} pollution levels and ΔPEF for the school-based sample was observed in spite of much obvious stochastic variability. This negative relationship between PM_{10} pollution and ΔPEF was confirmed by regression analysis. Regression results for two single-period models and two polynomial-distributed lag models for the school-based sample are shown in table 3.

Several important observations were made from the regression results. First, negative correlations between ΔPEF and PM_{10} were consistently found. Second, the current-day PM_{10} levels had the largest effect on ΔPEF . Third, distributed lag models generally performed better than single-period models. Statistically significant lagged effects of PM_{10} were observed

TABLE 2
MEAN Δ PEF AND MEAN PERCENT REPORTING RESPIRATORY SYMPTOMS AND
MEDICATION USE FOR DIFFERENT RANGES OF PM₁₀ LEVELS

	PM ₁₀ Range	PM ₁₀ Mean	Days (n)	Mean Δ PEF	Mean Percent Reporting			
					Respiratory Symptoms		Medication Use	
					Upper (%)	Lower (%)	Regular (%)	Extra (%)
School-based sample	0-50	29	71	1.75	32	15	12	2
	51-100	70	30	-1.87	38	17	12	3
	101-200	134	6	-10.77	41	23	18	6
Patient-based sample	0-50	29	71	1.88	33	38	67	5
	51-100	70	30	-3.68	33	39	67	8
	101-200	134	6	-4.46	33	34	62	10

TABLE 3
REGRESSION COEFFICIENTS FOR Δ PEF (L/MIN) AND SUMMARY INFORMATION
FOR SELECTED MODELS FOR SCHOOL-BASED SAMPLE*

	Single-Period Models		Polynomial-Distributed Lag Models	
	Model I	Model II	Model III	Model IV
INTERCEPT	4.619 (1.043) [†]	3.481 (2.424)	7.232 (1.198) [†]	6.356 (2.503) [‡]
PM ₁₀ (0)	-0.066 (0.019) [†]	-0.064 (0.019) [§]	-0.040 (0.015) [§]	-0.039 (0.015) [‡]
PM ₁₀ (1)	-	-	-0.035 (0.007) [†]	-0.033 (0.007) [†]
PM ₁₀ (2)	-	-	-0.028 (0.007) [†]	-0.026 (0.007) [†]
PM ₁₀ (3)	-	-	-0.020 (0.008) [‡]	-0.018 (0.008) [‡]
PM ₁₀ (4)	-	-	-0.011 (0.006)	-0.009 (0.006)
Temperature	-	-0.099 (0.068)	-	-0.052 (0.066)
Time trend	-	0.063 (0.025) [‡]	-	-0.032 (0.026)

* The absolute values of the standard errors are provided in parentheses beneath the coefficients. The values in parentheses after PM₁₀ indicate the lag values.

[†] Significant at $p < 0.001$ using standard t test.

[‡] Significant at $p < 0.05$ using standard t test.

[§] Significant at $p < 0.01$ using standard t test.

for 2 or 3 days. Fourth, no statistically significant correlation between low temperature and Δ PEF was observed. On the basis of the regression results of Model III reported in table 3, three consecutive days with PM₁₀ levels elevated by 150 $\mu\text{g}/\text{m}^3$ would result in an estimated average reduction of PEF of 15.5 L/min, i.e., approximately 6%.

These results were not highly sensitive to two important changes in the makeup of the sample. Dropping all the participants who took any asthma medication ($n = 10$) during the study period produced nearly identical results to those reported in table 3. The estimated single-period effect of PM₁₀ for Models I and II changed from -0.066 (SE = 0.019) and -0.064 (SE = 0.019) L/min/ $\mu\text{g}/\text{m}^3$ to -0.060 (SE = 0.22) and -0.069 (SE

= 0.022) L/min/ $\mu\text{g}/\text{m}^3$, respectively. When the models were estimated using data from all the original participants—including those who were dropped primarily because of lack of regular or continuous PEF testing—the results were also nearly identical with the PM₁₀ effects, being somewhat larger and more statistically significant.

A negative relationship between PM₁₀ and Δ PEF also existed for the patient-based sample (table 2). The stochastic variability in Δ PEF (figure 3) was larger than for the school-based sample, and the negative association between Δ PEF and PM₁₀ was not as readily apparent. Regression results for two single-period models and two polynomial-distributed lag models for the patient-based sample are shown in table 4.

Several important differences between the two samples existed. The current-day PM₁₀ levels did not have the largest effect on Δ PEF for the patient-based sample, as was the case with the school-based sample. Distributed lag models performed better than did single-period models. Unlike the school-based sample, a positive, statistically significant correlation between low temperature and Δ PEF existed.

Models such as those reported in tables 3 and 4 were estimated individually for each participant. As with the aggregate analysis, the Yule-Walker estimation method (28) was used. Regression coefficients between PEF and PM₁₀ (Model I) for participants in the school-based sample ranged from -0.416 to 0.108 with the lower quartile, median, and upper quartile equal to -0.098, -0.056, and 0.001, respectively. Because of increased stochastic variability associated with individual PEF readings, most of the coefficients were not statistically significant. However, coefficients for 25 (74%) of the participants were negative. On the basis of a modest level of statistical significance ($p < 0.10$), the correlation between PEF and PM₁₀ was negative and significant for eight (26%) of the school-based participants, but it was positive and significant for only one (3%) of the participants. The mean of the regression coefficient on PM₁₀ (Model I) for all participants in the school-based sample was -0.061 (SEM = 0.019) compared with -0.066 (SE = 0.019) in table 3.

Respiratory Symptoms and Asthma Medicine Use

The mean percent reporting symptoms of respiratory disease and asthma medication use increased with increased PM₁₀ pollution (table 2). Logistic regression analysis confirms this association (table 5). For the school-based sample, logistic regression coefficients indicated positive, statistically significant associations between PM₁₀ pollution and reported symptoms of upper respiratory disease, symptoms of lower respiratory disease, and use of asthma medication. On the basis of the logistic regression results, the estimated probabilities of reported symptoms of upper and lower respiratory disease were 1.5 and 2.1 times as high, respectively, when 24-h PM₁₀ levels were at the highest level for the study period (195 $\mu\text{g}/\text{m}^3$) versus the lowest level (11 $\mu\text{g}/\text{m}^3$).

For the patient-based sample, no associations between PM₁₀ pollution and

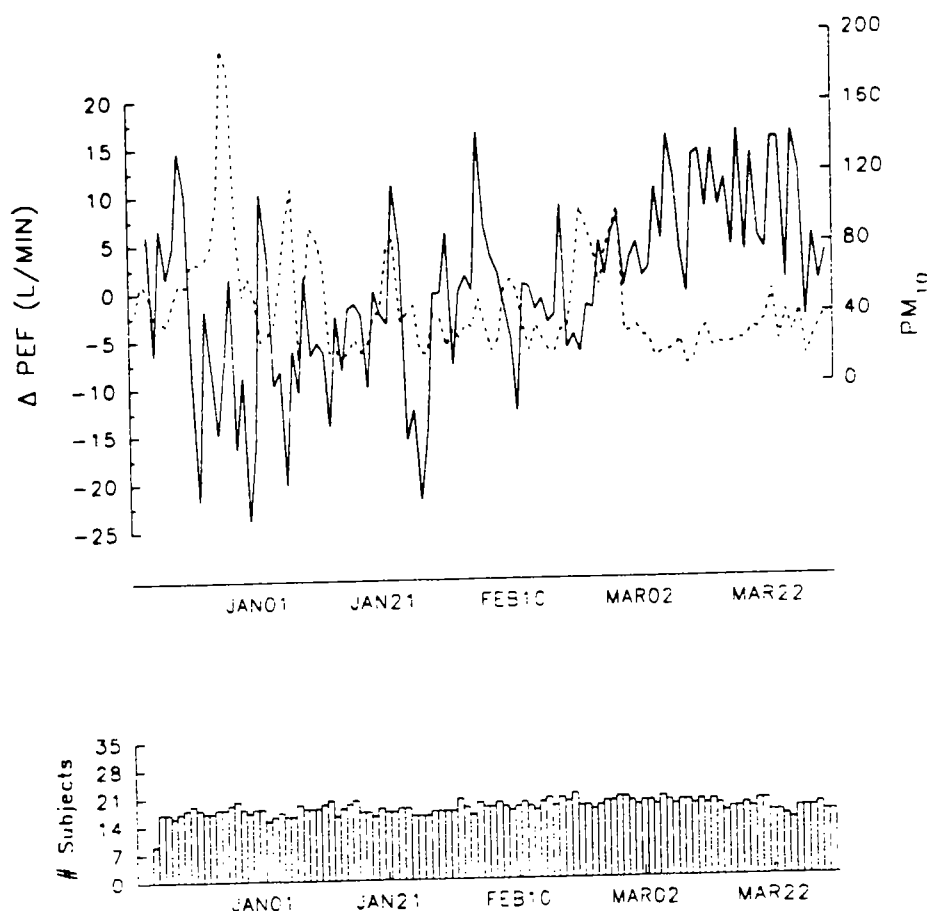


Fig. 3. PM_{10} levels ($\mu g/m^3$) (broken line) at the Orem monitoring site, mean peak expiratory flow deviations (ΔPEF) (solid line), and daily number of participants. Patient-based sample, December 13, 1989 through March 31, 1990

TABLE 4
REGRESSION COEFFICIENTS FOR ΔPEF (L/MIN) AND SUMMARY
INFORMATION FOR SELECTED MODELS FOR PATIENT-BASED SAMPLE*

	Single-Period Models		Polynomial-Distributed Lag Models	
	Model I	Model II	Model III	Model IV
INTERCEPT	3.101 (1.833)	-10.194 (3.712) [§]	6.749 (2.110) [§]	-8.338 (3.761) [‡]
PM_{10} (0)	-0.049 (0.030)	-0.015 (0.029)	-0.014 (0.022)	0.008 (0.019)
PM_{10} (1)	—	—	-0.026 (0.011) [‡]	-0.008 (0.010)
PM_{10} (2)	—	—	-0.031 (0.009) [†]	-0.018 (0.008) [‡]
PM_{10} (3)	—	—	-0.032 (0.011) [§]	-0.023 (0.009) [‡]
PM_{10} (4)	—	—	-0.027 (0.011) [‡]	-0.021 (0.009) [‡]
PM_{10} (5)	—	—	-0.016 (0.007) [‡]	-0.013 (0.006) [‡]
Temperature	—	0.173 (0.116)	—	0.186 (0.112)
Time trend	—	0.118 (0.037) [§]	—	0.117 (0.039) [§]

* The absolute values of the standard errors are provided in parentheses beneath the coefficients. The values in parentheses after PM_{10} indicate the lag values.

[†] Significant at $p < 0.001$ using standard t test.

[‡] Significant at $p < 0.05$ using standard t test.

[§] Significant at $p < 0.01$ using standard t test.

reported symptoms of respiratory disease were observed. A statistically significant positive association between PM_{10} pollution and reported use of extra asthma medication was observed. On the basis of the logistic regression results, the probability of the use of extra asthma medication was approximately 6.2 times as high when 24-h PM_{10} levels were at the highest level for the study period versus the lowest level.

A negative association between low temperature and reported symptoms of upper respiratory disease existed for both samples. For the school-based sample, positive associations between low temperature and both regular and extra asthma medication also existed. None of the subject-specific fixed effects coefficients was statistically significant.

Results with Violation Episode Excluded

The only pollution episode during the study period where the 24-h national ambient air quality standard for PM_{10} of $150 \mu g/m^3$ was exceeded occurred during the latter part of December 1989 (figure 1). ΔPEF was substantially lower during those days when the standard was exceeded. Additional analysis was conducted in order to evaluate whether the statistical association between indicators of respiratory disease and PM_{10} pollution was attributed solely to this single pollution episode. The models presented in tables 3, 4, and 5 were reestimated after excluding this episode, that is, the 2 days that exceeded the PM_{10} standard and the 5 days immediately following.

After excluding this episode, the highest 24-h PM_{10} level included was $114 \mu g/m^3$. The single-period and polynomial-distributed lag models for ΔPEF for both samples were nearly identical to those reported in tables 3 and 4, with no substantial changes in the magnitude or statistical significance of the correlation between ΔPEF and PM_{10} . The logistic regression coefficients for PM_{10} with this episode excluded were 20 to 60% larger than the coefficients reported in table 5.

Discussion

Associations observed in this study between PM_{10} pollution levels and respiratory health were mostly consistent and robust. Elevated PM_{10} levels were associated with statistically significant reductions in lung function as measured by reductions in PEF and increased reported symptoms of respiratory disease and asthma medication use. Previous

TABLE 5
LOGISTIC REGRESSION COEFFICIENTS AND SUMMARY
INFORMATION FOR BOTH SAMPLES*

	Respiratory Symptoms		Medication Use	
	Upper	Lower	Regular	Extra
School-based sample				
PM ₁₀	0.0036 (0.0015) [‡]	0.0050 (0.0020) [‡]	0.0090 (0.0034) [§]	0.0106 (0.0042) [‡]
Temperature	-0.0139 (0.0057) [‡]	-0.0046 (0.0081)	0.0291 (0.0137) [‡]	0.0426 (0.0179) [‡]
Observations	3,096	3,096	3,096	3,096
Patient-based sample				
PM ₁₀	-0.0002 (0.0021)	0.0002 (0.0023)	0.0032 (0.0029)	0.0113 (0.0034) [†]
Temperature	-0.0186 (0.0083) [‡]	0.0034 (0.0093)	0.0108 (0.0113)	0.0088 (0.0151)
Observations	1,912	1,912	1,912	1,912

* The absolute value of the standard errors are provided in parentheses.

† Significant at $p < 0.001$ based on likelihood-ratio goodness-of-fit chi-square test.

‡ Significant at $p < 0.05$ based on likelihood-ratio goodness-of-fit chi-square test.

§ Significant at $p < 0.01$ based on likelihood-ratio goodness-of-fit chi-square test.

studies of the acute effects of particulate pollution on lung function have suggested similar associations. Dockery and coworkers (16) reported a decrease in measurements of FVC and FEV_{0.75} among 335 children in grades 3 to 5 in Steubenville, Ohio after air pollution episodes. Maximal 24-h mean particulate (TSP) concentrations were 312 $\mu\text{g}/\text{m}^3$ and SO₂ concentrations were 455 $\mu\text{g}/\text{m}^3$. The maximal FVC decline of 2.7% was observed 2 wk after the episode. Statistically significant negative associations were found with both SO₂ and TSP on the previous day. A recent reanalysis of these data has shown a stronger statistical association with 5-day mean rather than previous-day mean TSP (30). Dassen and coworkers (7) reported deficits in FVC and FEV₁ pulmonary function measurements of children in IJmond, the Netherlands. These deficits were associated with maximal TSP levels equal to 200 to 250 $\mu\text{g}/\text{m}^3$. Maximal deficits were observed 2 wk after the episode. Lebowitz and coworkers (31) reported an association between deficit of PEF in children in Tucson, Arizona, and TSP and ozone levels.

The present study supports these earlier findings, but it provides new information regarding the structure of association between particulate pollution and lung function. Daily peak flow measurements suggest that the deficit in pulmonary function in response to particulate pollution episodes can be seen immediately but continue to accumulate for several days. This was suggested by the earlier studies, but, because these studies were limited to pulmonary function mea-

surement intervals of a week or more, was not directly testable. The deficit in lung function and the increased symptoms of respiratory disease associated with elevated levels of particulate pollution appeared to be mostly transient. The impact on the risk of developing chronic respiratory diseases in adulthood are unclear (32).

This study also provides limited guidance regarding the portion of the population that may be most responsive to the effects of particulate pollution. In the Steubenville (16) and IJmond (7) studies, general population samples were recruited. In the Tucson study (31), families of asthmatic but not necessarily symptomatic children were recruited. In this study, children with respiratory symptoms determined by questionnaire (the school-based sample) were recruited. Although the number of participants was small compared with that in the previous studies, statistically significant associations were found. In the school-based sample 74% showed a negative response to particulate pollution compared with 59% in the Steubenville study, suggesting that symptomatic children are more susceptible to the effects of particulate pollution.

On the other hand, relatively weaker associations were found with the sample of asthmatic patients (patient-based sample) — except for the use of extra asthma medication. This does not imply that asthmatics are less susceptible to PM₁₀ pollution, but rather that the symptoms and pulmonary function of these diagnosed asthmatics was being managed by medication and life-style changes (e.g., staying indoors). In contrast to partici-

pants in the school-based sample who rarely used asthma medication, participants in the patient-based sample usually used asthma medication. The asthmatic patients may indeed be more susceptible to PM₁₀ pollution, but their response is more readily measured as changes in medication use and not changes in PEF or daily symptom reporting.

In previous studies, high particulate pollution concentrations were accompanied by high concentrations of other pollutants. Although statistical analysis generally suggested stronger associations with particulate pollution, independent or interactive associations with ozone, SO₂, acid aerosols, or other pollutants could not be ruled out. In the present study concentrations of SO₂, NO₂, acid aerosols, and ozone were very low. PM₁₀ pollution, therefore, was more explicitly implicated as the pollutant responsible for the observed associations.

Finally, this study provides no evidence that the 24-h PM₁₀ standard of 150 $\mu\text{g}/\text{m}^3$ represents a threshold pollution level below which adverse respiratory health effects are negligible. In fact, these results suggest that measurable associations between respiratory health and PM₁₀ pollution can be observed at PM₁₀ levels well below the national ambient air quality standard.

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'Best Data Yet' Say Air Pollution Kills Below Levels Currently Considered Safe

RESEARCHERS are reporting "robust" associations between premature mortality and air pollution levels that the US government currently deems safe in what appears to be the best study of its kind to date.

The Harvard Six Cities Study found a 26% higher rate of premature death in the most vs the least polluted cities in which it tracked 8111 people for 14 to 16 years.

"People who live in highly polluted cities die earlier. It's just that simple," says C. Arden Pope, PhD.

What's more, the risk may be highest not from commonly known pollutants like ozone but from respirable particles with a diameter of 2.5 μm or less, small enough to penetrate deep into the lungs, says Pope. He is a visiting scientist at the Harvard School of Public Health, Boston, Mass., and associate professor at Brigham Young University, Provo, Utah.

Particulate matter can include such things as carbon, hydrocarbon, dust, and acid aerosols. Pope says he suspects that the most dangerous components are by-products of burning fuel. The effect is seen primarily in deaths from respiratory disease, he says, including chronic obstructive pulmonary disease, cardiovascular disease, and asthma.

Sulfates, another by-product of combustion, also increase the risk for premature death, according to the data.

Controls for Smoking

Similar studies in the past that attempted to document the dangers of dirty air have been discounted by skeptics for failing to adequately control for smoking, environmental differences between communities, and other possible confounding factors. However, the Harvard Six Cities Study, which Pope presented at the annual meeting of the American Lung Association (ALA), held in San Francisco, Calif., did control for those factors.

"This is the first study to control for individual risk factors, and the link between airborne particles and death rates is still very robust," says Pope. The relative risk for premature death was 1.26 in Steubenville, Ohio, the city with the most respiratory particles, compared with Topeka, Kan., and Portage, Wis., the two cities that tied for the lowest levels, says Pope. (Interestingly, Steubenville is about 20 m from East Liverpool, Ohio, the site of an incinerator recently approved by the EPA despite quite a bit of controversy.) Other cities in the study were Watertown, Mass., St Louis, Mo., and the Kingston-Harriman area in Tennessee.

Danger Below 'Safe' Levels

The increased mortality risk was seen at levels of respirable particles and sulfates well below those deemed safe in current federal air quality standards, says Pope.

"A lot of people still think of air pollution as more a nuisance than a threat. But these data greatly strengthen the view that pollution is not merely dangerous but deadly," says Alfred Munzer, MD, president of the ALA.

The finding that mortality risks are more strongly associated with mean concentrations of respirable particles and sulfates than with total particulate matter or the sulfur dioxide, ozone, and aerosol acidity most commonly associated with air pollution risks could revolutionize thinking about air pollution, and lead to a shift away from the current emphasis on ozone levels in pollution reports and warnings, says Munzer.

Under current regulations, cities are in violation if the 24-hour average concentrations of particles that are 10 μm or less exceed 150 $\mu\text{g}/\text{m}^3$ of air, or if annual averages exceed 5 $\mu\text{g}/\text{m}^3$ —far above the levels in the Six Cities Study. (The 2.5- μm standard was used in the study because it was the only particulate measure made consistently during the entire study period.)

The ALA estimates that 66% of Americans live in areas that fail to meet current air quality standards—up from 60.5% in 1989. An ALA report entitled *Breath in Danger II* states that 31 million children and 18 million elderly Americans in the United States are at risk for lung disease or respiratory irritation because of exposure to unhealthy levels of air pollution. So are some 6 million people with asthma, nearly 9 million with chronic obstructive pulmonary disease, and about 3.5 million with coronary and cerebrovascular disease.

EPA Yet to Begin Review

The Environmental Protection Agency (EPA) has not yet begun any review of its particulate matter standards, says Dennis Kotchmar, MD, a medical research officer with the EPA in Research

Triangle Park, NC. Such a review "will be coming up in the future," he says, noting however that it will entail a "long, involved process" with multiple layers of data analysis, report writing, and public comment.

An EPA senior scientist, Joel Schwartz, PhD, was among the first researchers to document the dangers of particulate matter at currently allowed levels.

In a study submitted for publication to *Environmental Research*, Schwartz found that cardiovascular deaths are 7% higher on days with the highest levels of particulate matter compared with days with the lowest levels. What's more, mentions of both documented respiratory disease and unexplained respiratory symptoms were about 35% higher on death certificates on days when pollution was highest.

Increased cardiovascular mortality may in fact be related to even lower levels, suggests David Bates, MD, University of British Columbia, Vancouver, Canada, since "people in imminent risk of cardiovascular death are not out playing tennis. I can't imagine that their exposures to ambient particulates are more than a fraction of outdoor levels."

Another study by Pope showed that children's use of medication for asthma and other respiratory symptoms increases with particulate levels. And a 2-year study in seven Seattle, Wash, hospitals shows that visits to the emergency department for asthma exacerbations also increase with particulate matter, even at levels below 60 parts per billion—60% less than current regulation allows (*Am Rev Respir Dis*. 1993;147:826-831).

Similar findings for outpatient hospital visits in Beijing, China, and for urgent hospital admissions in Montreal, Canada, were also presented at the meeting.

Acidic particulate matter may be a danger downwind of major pollution sources, according to a study of 22 relatively small towns in the United States and Canada. Small but persistent changes in children's lung function of 3% on average, and as great as 10% in those who already had diminished function, were documented, says Mark Raizenne, air pollution health effects research director for Health and Welfare of Canada, Ottawa.

"They're just small particles that shouldn't be doing anything. But there is lots of evidence at this meeting that particulate matter, irrespective of what's on it—metals, carbon, or acid—adversely affects health," says Raizenne.

The strong correlation between respirable particles and acidity makes it difficult to tell which is primarily re-

sponsible, notes Andrew Damokosh, a biostatistics doctoral student who participated in the analysis of the Six Cities data. "The correlate is so high, on the order of 0.8, that you can't tease it apart."

Different pollutants appear to have synergistic adverse effects, says Kent Pinkerton, PhD, associate professor of anatomy and cell biology at the University of California, Davis. Ozone and/or acid exposure substantially impairs clearance of inhaled particulates from the lungs for as long as 60 days, according to his research in Sprague-Dawley rats. He suspects that even if people adapt to low levels of pollution, their ability to clear fibrinogenic or carcinogenic particles from their lungs may have become impaired, thereby increasing the risk of fibrosis or cancer due to enhanced retention of those particles.

"There can be interactions between gases and particles that lead to greater adverse effects of environmental pollution than with single exposures to one gas or one type of particle," says Pinkerton.

'Remarkable Coherence'

The "remarkable coherence" among all the recent data on particulate matter "enables us to say, even though we're ignorant of the mechanism, that we have to make a causal inference," says Bates. "That is why this particular aspect of pollution is dominating so many people's thoughts at this time."

"We keep seeing these things occurring well below the ambient standard for particulate matter," says Schwartz. "We [the EPA] need to get our act together and start revising that standard."

The ALA's immediate past president, Lee B. Reichman, MD, MPH, notes that his organization has had to sue the EPA in the past to get it to update standards on ozone and sulfur dioxide. "As the guardians of clean air, someone has to say, 'Hey, you guys are damaging the health of people,'" says Reichman.

"The EPA has historically been slow to undertake these reviews," says Paul G. Billings, field services coordinator for the ALA. The standard for particulate matter is "clearly something that needs to be looked at. An increasing body of data is coming out about the health effects of particulates at much lower levels" than are currently allowed. Eventually, says Billings, the EPA "will have to review the standard, whether as a result of litigation or because they just decide to follow the law" that mandates review of standards every 5 years.

Canada's Raizenne says all the new findings "fuel the argument that particulate standards need to be looked at very carefully, both in terms of mass

and chemical composition." However, application of the new findings to regulations in his country is not likely to occur any sooner than in the United States, he says.

Possible Mechanism Studied

Several studies presented at the meeting explored possible mechanisms for damage by particulate matter.

One suggests that the reason these particles are so deadly may be that they remain in the lungs far longer than previously thought. Young healthy volunteers at the University of North Carolina inhaled a bolus of monodisperse aerosols (inert particles 1, 3, or 5 μm in diameter) through a laser aerosol photometer. The students were left with twice as many deposits of particles 3 μm or less in diameter in their upper and conducting airways than was previously observed with less sophisticated techniques.

A study in hamsters found that although macrophages are rapidly recruited to the sites of particle deposits, less than 15% of the macrophages help clear the particles from the airways. Another hamster study found that just a single instillation of urban air particulate causes substantial cell injury, intra-alveolar bleeding, and inflammation.

A computer simulation of particle transport and deposition in alveoli and alveolar ducts, created at Duke University Medical Center, Durham, NC, suggests that such deposition is much greater in alveolated ducts than in similar nonalveolated ducts, and that the deposits remain in alveolated ducts about 30% longer as well. At higher flow rates, the model suggests that particles catch on alveolar septal edges, increasing the deposition of 1.0- μm particles by as much as 70%.

Rx: Get Out of Town

With EPA standards not likely to change in the immediate future, Pope says that physicians in one of the highly polluted cities are already routinely advising patients with severe asthma to leave town during the inversion periods when pollution is at its worst.

When conducting other studies, Pope says, he has had problems with people leaving the cohort because their physicians told them they had to move to a cleaner area.

"Now that we find that fine-particle pollution is a substantial health risk spread across a large segment of our population, physicians on the front lines trying to treat people with respiratory problems certainly ought to be concerned," concludes Pope.

—by Paul Cotton

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July 19, 1993

**METERED DOSE INHALERS:
A SPECIAL CASE**

**Application for the Nomination
of Metered Dose Inhalers (MDIs)
for Exemption as an
Essential Use of Chlorofluorocarbons
(CFCs) Under the Montreal Protocol**

submitted to the

United States Environmental Protection Agency

by the

International Pharmaceutical Aerosol Consortium (IPAC)

and the

American Lung Association (ALA)

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I. Introduction

This document is an application requesting that the United States Government, on or before September 30, 1993, nominate metered dose inhalers (MDIs) for exemption as an essential use of chlorofluorocarbons (CFCs) under the Montreal Protocol on Substances that Deplete the Ozone Layer for the period 1996-1999 in accordance with Decision IV/25 of the Fourth Meeting of the Parties to the Protocol. This document is submitted on behalf of those members of the International Pharmaceutical Aerosol Consortium (IPAC) which currently manufacture MDIs in the United States or otherwise have a commercial interest in MDIs in the United States. It responds to the solicitation of requests for nominations of essential uses published by the U.S. Environmental Protection Agency (EPA), 58 Fed. Reg. 29410 (May 20, 1993).

This application was prepared by IPAC in collaboration with the American Lung Association (ALA), and represents the views of both of those organizations. IPAC is an unincorporated association of eleven corporations which develop, manufacture, market or otherwise have a commercial interest in MDIs in the United States and abroad.¹ The ALA is the oldest voluntary health organization in the United States; its mission is the conquest of lung disease and promotion of lung health.

As with the CFC problem itself, the MDI issue is a global one. For this reason, this document addresses the issue in global terms, in addition to providing information specific to the United States. Following a summary of the position of IPAC and ALA, this document provides background information, an historical overview of MDIs, and a detailed response to each of the eight categories of information solicited in the nomination request (58 Fed. Reg. at 29412).

II. Summary

- A. MDIs are pocket-sized aerosol devices used to deliver precisely measured doses of medicines directly to the pulmonary system. MDIs use CFCs-11, -12 and, in some cases, -114 as propellants in very small quantities. The process of manufacturing MDIs employs CFCs-11, -12 and -113 in even smaller quantities.
- B. MDIs are used primarily to treat asthma and chronic obstructive pulmonary diseases (COPD), such as chronic bronchitis and emphysema. These afflictions are characterized by obstruction of the airways and shortness of breath. They are persistently debilitating and can cause death during severe episodes. An estimated 300 million people suffer from these diseases worldwide. In the United States, the incidence is estimated to be about one in ten, or more than 25-30 million people. Morbidity and mortality from the diseases are rising.
- C. MDIs have become the mainstay of therapy for these diseases, especially in the United States. Virtually all of the drugs important to such therapy are available in MDI form. MDIs are simple to use: they are portable, reliable, safe, efficient and cost-effective. They provide a very consistent dose with extraordinary dependability for patients. They make it possible for millions of people to lead relatively normal lives at work and at school. In many cases, they sustain life itself.
- D. Pharmaceutical companies are striving individually and collectively to develop CFC-free alternatives as rapidly as possible. The leading alternatives are (1) MDIs containing substitute propellants and (2) dry powder inhalers (DPIs). The competitive advantages of being the first to offer suitable alternatives are motivating the companies to work as quickly as ingenuity, good science and government review allow. Various companies are funding multi-million dollar joint programs (IPACT-I and IPACT-II) for the FDA-mandated toxicologic testing of two promising substitute propellants, HFA-134a and HFA-227. These programs are progressing as quickly as possible.
- E. MDIs and DPIs are subject to extensive regulation by national health authorities to ensure safety, efficacy and quality. In the United States, as in most other countries, a company may place an inhalant drug product on the market only in accordance with a specific license issued by the appropriate authority. If a company wishes to alter such a product to a significant degree, it must first obtain an amendment to the existing license. The review by health authorities is rigorous and exhaustive, especially when the product is intended, as here, for chronic use by millions of particularly vulnerable patients (*e.g.*, children and the elderly).
- F. The introduction of CFC-free MDIs and DPIs will occur step-by-step through the rest of the decade and perhaps beyond. Complete substitution with one or more CFC-free MDIs could not occur by 1996.

At present, there are no multi-dose DPIs available to patients in the U.S.; two single-dose products are available, but both of these have been met with very limited patient acceptance. The regulatory approval process for DPIs is similar to that for reformulated MDIs. The development of each of these alternatives requires a certain minimum time for pharmaceutical formulation, safety, efficacy and stability testing as well as for government review and approval. Also necessary is the careful re-education of physicians and patients, as a major cause of morbidity and mortality from these diseases is non-compliance with prescribed treatment. A seamless transition is critical to the welfare of the patient population.

- G. The eventual pace of this transition to CFC-free products is uncertain. But it is certain that CFC-driven MDIs will continue to be needed, albeit in gradually decreasing volumes, through 1999 at least. The medical importance of MDIs is reinforced by a recently-developed international consensus on the appropriate treatment of asthma, which emphasizes the importance of chronic administration of anti-inflammatory drugs via inhalation.
- H. Employing used CFCs (*e.g.*, CFCs from refrigerators and air-conditioners) as propellants in MDIs has been thoroughly examined, but is not a viable option. It would be unprecedented in the industry and in acceptance by the government and would pose serious safety risks for a highly sensitive patient population. It is doubtful that state-of-the-art technologies for purification and quality assurance could ensure an impurity profile that is consistent among batches and essentially similar to previous virgin CFCs and, therefore, reduce those risks to acceptable levels. There is a strong likelihood that health authorities in the United States (*i.e.*, the Food and Drug Administration (FDA)) and elsewhere would not approve the use of used CFCs in MDIs. In any event, the process of developing commercial facilities that would attempt to purify used CFCs to pharmaceutical standards and of obtaining authorizations for their use in MDIs would take at least four years. Moreover, there is grave doubt that sufficient quantities of used CFCs would be available on the open market during 1996-99.
- I. Stockpiling of virgin CFCs is at best only a partial solution. It presents substantial problems of procurement, storage capacity, potential contamination, stability, quality assurance, and security. In addition, stability studies would be required demonstrating that stockpiled CFCs remain comparable to virgin CFCs in order to obtain FDA approval to use stockpiled CFCs in MDIs. It is doubtful that stockpiles of sufficient size and with sufficient quality control could be built quickly enough in the time remaining to cover MDI needs.
- J. To make an accurate forecast of maximum CFC requirement is extremely difficult, largely because of uncertainty about the rate of increase in

patient need for hand-held inhalation devices and the emergence of CFC-free MDIs and DPIs. However, data do exist indicating that the maximum need for MDI propellant and manufacturing purposes worldwide probably is on average 15,000 metric tonnes of virgin CFCs annually for the years 1996-99. 15,000 metric tonnes is less than 1.5 percent of all of the CFCs produced worldwide in 1986, the base year for defining the CFC phaseout schedule in the Protocol. In the United States, the maximum need for virgin CFCs during those years probably is on average 3,600 metric tonnes annually.

- K. The process of manufacturing MDIs and their components currently consumes roughly 15 percent of the total CFCs used in MDIs. About half of that 15 percent is released into the atmosphere, with the balance being captured and either recycled or destroyed. For example, CFC-11 is used by valve manufacturers to extract impurities from the elastomers in the device. MDI manufacturers have worked intensively in recent years to minimize these emissions by improving the manufacturing process and capturing and re-using some CFCs. They are continuing this work.
- L. Exemptions for production and consumption of CFCs for MDIs during 1996-99 therefore are necessary and appropriate in order to ensure continued patient welfare.
- M. More than 60 percent of the asthma and COPD patients in the United States, or roughly 15-18 million people, rely upon MDIs for the delivery of medication necessary to their continued health. Without an exemption to allow continued production of CFCs for use in MDIs during 1996-1999, an essential form of therapy would become unavailable for most, if not all, of these patients. The result would be a health care emergency of significant proportions, as some 15 million patients suddenly would have to be switched to a substitute form of therapy.
- N. In sum, the United States, on or before September 30, 1993, should nominate MDIs for exemption as an essential use of CFCs under the Montreal Protocol for the period 1996-1999.

III. Background

In 1991 the UNEP Technical Options Committee on Aerosol Products, Sterilants, Miscellaneous Uses and Carbon Tetrachloride (the "Aerosol Committee") issued an assessment of MDIs as part of an effort by the Protocol Parties to understand what the implications would be of an acceleration of the CFC phaseout schedule from 2000 to 1997. The Committee concluded that:

The necessary toxicology testing of suitable alternative propellants for inhalant drug products will not be completed until early 1996. Provided there are no adverse findings during the course of these toxicology studies, clinical studies and regulatory approval should be completed for the majority of products by 1999.

An early phase out of CFCs of 1997 will result in the non-availability of life-supporting medication in a form which a large majority of asthmatics and those suffering other respiratory diseases have found effective in stabilizing their illness. It is therefore essential that there should be exemptions for these applications since current alternatives such as powder inhalers and nebulizers cannot substitute existing products for a number of patients.²

Subsequently, the Parties at their Fourth Meeting accelerated the general phaseout of production and consumption of CFCs to a date even earlier than the Aerosol Committee had contemplated, namely, January 1, 1996. At the same time, the Parties made a provision for essential uses. They adjusted the Protocol explicitly to allow the Parties by subsequent decisions to create exemptions for such uses. In addition, the Parties issued Decision IV/25 defining the parameters for such subsequent decisions.³

Decision IV/25 establishes that a use is "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 [.]

The Decision also establishes that production and consumption for an essential use is permissible only if (i) "all economically feasible steps have been taken to minimize" the use and emissions from it and (ii) the substance in question is "not available in sufficient quantity and quality from existing stocks of banked or recycled controlled substances"

Decision IV/25 calls on each Party to nominate to UNEP by a certain deadline any use the Party considers "essential." The Technology and Economic Assessment Panel is then to develop recommendations on any nomination in collaboration with the appropriate Technical Options Committee and to submit those recommendations to the Parties at least three months before the Meeting of the Parties at which a decision is to be made. The Decision indicates that the Parties would not address "essential uses" of CFCs until their Sixth Meeting in 1994.

In May of this year, EPA published a notice in the Federal Register soliciting requests for nominations for essential use exemptions. 58 Fed. Reg. 29410 (May 20, 1993). The notice directs respondents to present information on eight specific topics in support of nomination requests. This information request is intended to provide EPA with the information necessary to evaluate nomination requests and to frame any nominations which might be made by the United States.

IV. Discussion

A. Historical Overview and Conceptual Framework

The pharmaceutical aspects of the treatment of asthma and COPD have changed a great deal over the past fifty years. The incidence and recognition of the diseases has increased dramatically. In addition, the methods for delivering medicines have grown in number and diversity.

At mid-century, the principal pathway for delivering medicines to the lungs was the gastrointestinal tract and, from there, the bloodstream. The pharmaceutical industry offered oral solids, oral liquids, and suppositories. It also offered injectables. These "systemic" forms of delivery had substantial disadvantages, such as the need for relatively high doses as compared to direct pulmonary delivery and hence a relatively greater risk of adverse side effects. Another pathway was the respiratory tract, but the only device available for creating an aerosol cloud was the stationary nebulizer. Unfortunately, it was -- and remains -- cumbersome. A patient cannot carry a nebulizer to work or school.

MDIs came into the marketplace in the 1950s. They represented a significant therapeutic advance, combining highly dependable precision dosing, topical delivery, and extreme portability. Consequently, they quickly became the mainstay of therapy in the United States, as well as in Europe.

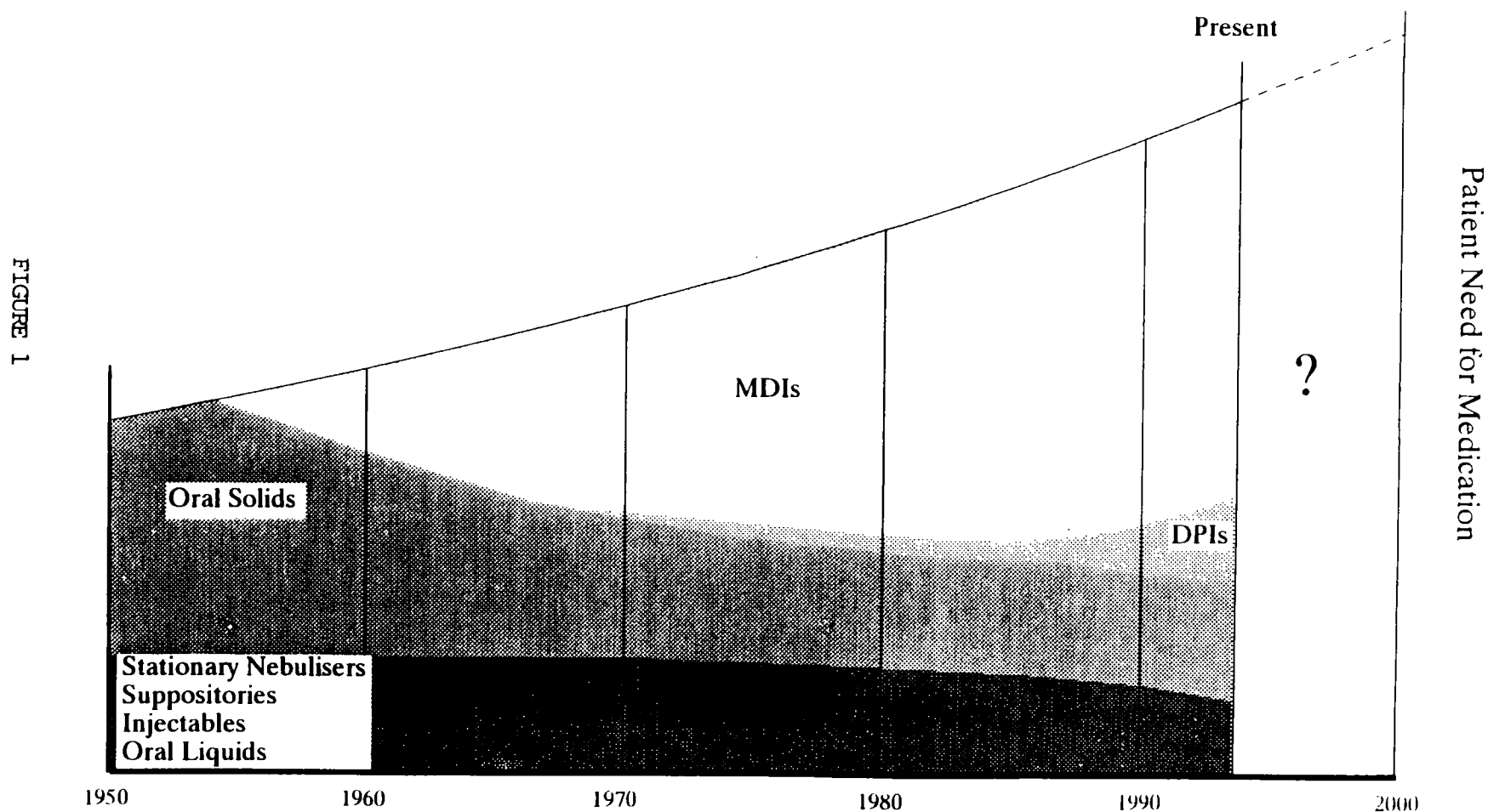
In the late 1960s, DPIs began to appear on the market. Together, MDIs and DPIs have been steadily displacing the systemic forms of administration.

Thus, the demand for hand-held devices has been increasing, not only because the incidence and recognition of the diseases have been increasing, but also because the global medical community has recognized the advantages of pulmonary delivery and thus has been moving away from systemic administration.

A graphical representation of this overall situation appears as Figure 1. It shows the evolution of the diseases and their recognition in terms of a rising curve of patient need for medication. It then presents the various forms of therapy as represented by shaded sub-areas that increase or diminish in size over time.

MEETING THE WORLDWIDE NEED FOR PHARMACOLOGIC THERAPY FOR ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASES:

A GRAPHICAL REPRESENTATION 1950-2000



The future course of this dual evolution of disease and delivery is very difficult to predict, as suggested by the blank space in Figure 1. It depends on many factors, including:

- The global increase in the incidence of and recognition of the diseases;
- The movement away from systemic delivery of medicines, and the increasing preference for chronic pulmonary administration of anti-inflammatories;
- The possible development of new CFC-driven MDIs (e.g., for the delivery of new medicines);
- The progress in development of MDIs containing substitute propellants such as HFA-134a and HFA-227;
- The continuing emergence and broader acceptance of DPIs;
- The extent, if any, of stockpiling of virgin CFCs during 1994-95 for use in 1996-99;
- The potential for developing hand-held nebulizers and other currently-unforeseen devices;
- The potential for employing used CFCs in MDIs; and
- The continuing progress in reducing the consumption of CFCs in the process of manufacturing MDIs.

B. Responses to Specific Information Requests

This section provides detailed information in response to the eight categories of information requested by EPA in its request for nominations (58 Fed. Reg. at 29412). For convenience, each of EPA's eight information requests is reproduced verbatim.

1. *"Description of the specific use of the controlled substance, as well as the annual projected amount required."*

a. The Use of CFCs in MDIs

MDIs are highly sophisticated aerosol devices. This sophistication has two key effects. It allows the delivery of precise amounts of medicines directly to the pulmonary system. It also results in the high degree of dependability and operational simplicity that has made MDIs the mainstay of asthma and COPD therapy. Current examples of medicines that MDIs deliver are:

corticosteroids, adrenergic bronchodilators, anti-cholinergics, sodium cromoglycate, and nedocromil sodium. Currently under development are new drugs, such as anti-infectives, for which the MDI probably would be an excellent form of delivery. In addition, peptides, which cannot be taken by the oral route, are presently being formulated as MDIs. This will avoid the cumbersome use of injection.

An MDI appears outwardly to be a simple device. Its essential components are a storage canister, a medicinal formulation of the drug inside the canister including liquified propellants, a metering valve to control the discharge of precise doses of formulation, and a mouthpiece. When the user actuates the device, the metering valve opens and emits a fine cloud of medication through the mouthpiece.

Inside an MDI there works a complex and delicate interplay of chemical and physical forces. The material in the storage canister consists of several ingredients: (1) a drug, (2) a propellant mixture, and (3) a co-solvent or surfactant. The precise make-up of this formulation depends largely on the physical properties (especially density and solubility) of the drug being delivered.

The basic function of an MDI is the consistent delivery of a specific amount of medication as a very fine mist. The size of the particles in the final aerosol are in the range of 1 to 5 microns. It is this small size of the particles which assures effective deposition in the small passageways of the lungs.

MDIs typically contain as propellants various mixtures of CFC-11, CFC-12 and CFC-114 in liquid form. CFC-12 is usually the major component, providing most of the propellant energy. CFC-11 and CFC-114 are used to moderate pressure and adjust the density and solubility of the propellant mixture. When stored as a liquid in a closed container at room temperature the mixture of these compounds has a pressure greater than one atmosphere. This pressure forces the drug formulation out of an MDI when the valve is triggered.

The propellants also serve a critical role in creating a very fine mist. Upon release from the MDI, the propellant gases suddenly encounter a temperature well above their boiling point. This causes their flash-evaporation. The result is a very fine mist of whatever drug was suspended or dissolved in the liquified gas.

In addition to its role as a propellant, CFC-11 has another important function: it acts as a solubilizing agent for the surfactants used in suspension MDIs. Both CFC-12 and CFC-114 are poor solubilizing agents, and many surfactants do not dissolve well in them. The addition of CFC-11 to the formulation creates a propellant solution in which surfactants can be dissolved.

A detailed description of the functioning of MDIs and the role that CFCs play as propellants is set forth in pages 4-6 of Exhibit A.

CFCs are consumed or emitted in several different ways during the MDI manufacturing process. Small amounts of CFC-11, -12, and -114 are emitted - during material transfer operations, product mixing and canister filling. CFC-11 and, to a lesser extent, CFC-113 are used to clean certain of the manufacturing equipment, particularly mixing vessels and filling machines. The elastomeric components of the MDI valves are prepared in a process that uses CFC-11 to remove extractable contaminants. Finally, after being filled and sealed, each individual MDI unit is actuated three to four times to test the functioning of the valve, resulting in the release of three to four doses of the propellant/drug formulation. A detailed description of the MDI manufacturing process appears in Exhibit B.

b. Annual
Projected
Amount
Required

The Aerosol Committee in 1991 estimated that the worldwide use of virgin CFCs as propellants in MDIs in 1990 was "in the order of 5,000-6,000 tonnes."⁴ This estimate probably is accurate, but it is not indicative of the likely need for virgin CFCs in 1996-99. The volume of that need is likely to be greater, based on the increasing incidence of asthma and COPD and the development of new medications which can only be formulated for delivery by means of an MDI. On the other hand, IPAC has found the task of quantitatively forecasting the need for virgin CFCs for MDI purposes to be extremely difficult. As the above discussion of a conceptual framework shows, the forecast depends on many factors, each of which has an uncertain future.

Nevertheless, a predecessor of IPAC, the Pharmaceutical Aerosol CFC Coalition (PACC), attempted in 1991 to develop a worldwide forecast of propellant (as opposed to manufacturing) needs by means of an industry survey and independent market research. That effort yielded the following estimates of the worldwide and United States need for CFCs for propellants in MDIs (in metric tonnes rounded to the nearest hundred):

<u>Worldwide</u>	<u>United States</u>
1991: 6,500	1991: 1,800
1992: 7,400	1992: 2,200
1993: 8,200	1993: 2,400
1994: 8,400	1994: 2,400
1995: 9,200	1995: 2,600
1996: 10,200	1996: 2,700
1997: 11,800	1997: 2,900
1998: 13,600	1998: 3,300
1999: 15,600	1999: 3,700

CFC-12 accounts for the bulk of these quantities -- roughly 60 percent, on average, in the U.S. (roughly 70 percent worldwide) for 1991-99. CFC-11 accounts for 25 percent on average (both worldwide and in the U.S.), and

CFC-114 for 15 percent in the U.S. (5 percent worldwide). A copy of the relevant pages from the report of this study (the "CFC Volumes Study") describing both the U.S. and worldwide need for CFCs in MDIs appears as Exhibit C.

The PACC estimate for 1991 (*i.e.*, 6,500 metric tonnes) is based mainly on historical data (the survey was completed at the end of 1991) and plainly is in line with the estimate of the Aerosol Committee. The estimates for subsequent years require careful interpretation for the following four reasons:

First, they depict an upper boundary of propellant usage, because the PACC study:

- assumed that no alternatives to CFC propellants would be available for MDIs prior to the year 2000;
- assumed that the MDI industry would neither stockpile virgin CFCs nor employ used CFCs;
- embodied conservative estimates of the extent to which current or emerging alternative delivery systems (*e.g.*, DPIs) might reduce demand for MDIs after 1995; and
- embodied a liberal forecast of the number of new CFC-driven MDI products that will be introduced into the market after 1995.

Figure 2 portrays this plausible case of maximum usage.

MEETING THE WORLDWIDE NEED FOR PHARMACOLOGIC THERAPY FOR ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASES:

A PLAUSIBLE SCENARIO 1990-2000

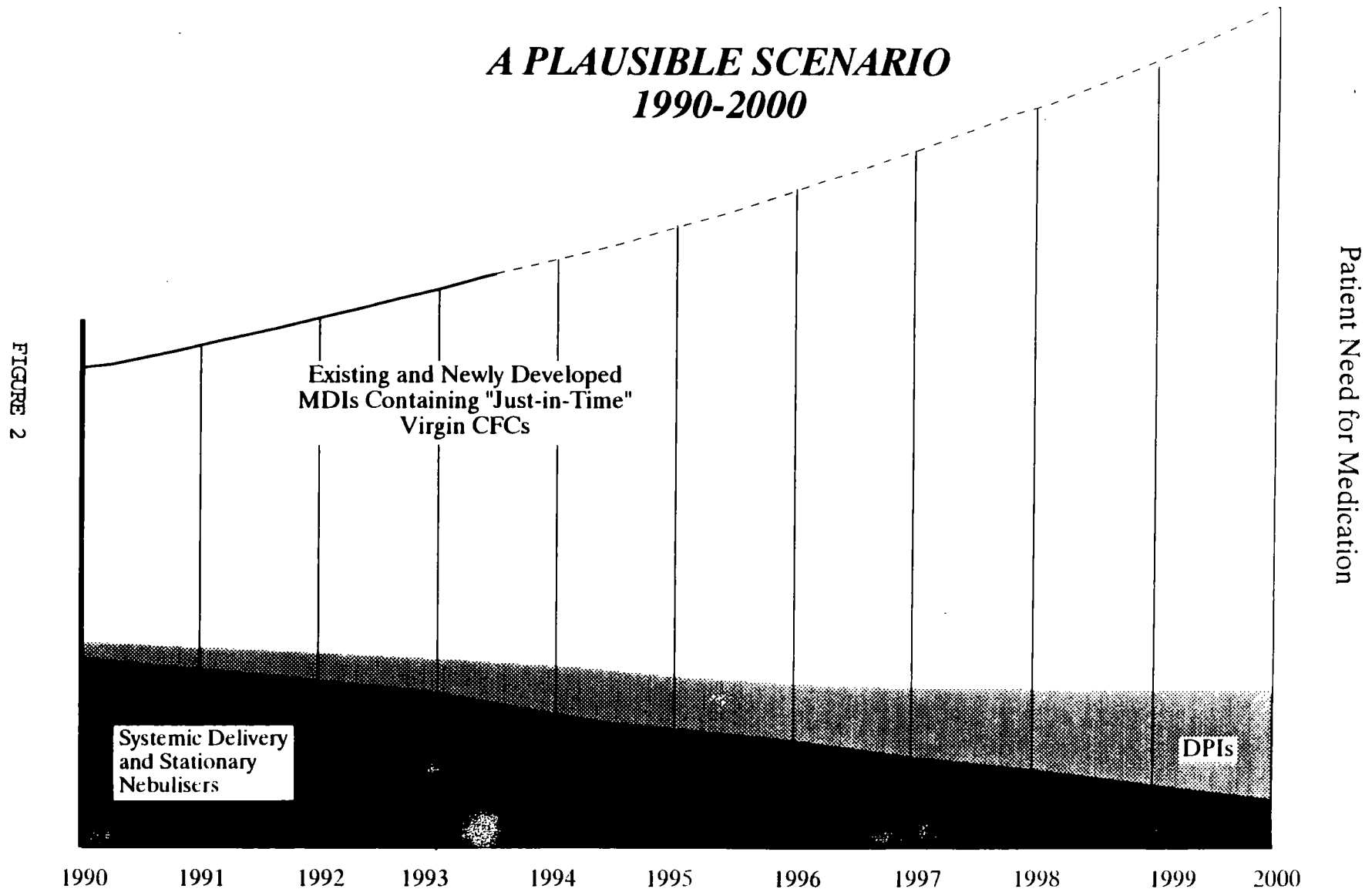


Figure 2

May 1993

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Second, the PACC estimates do not include the CFCs needed for the manufacturing process itself. Those CFCs are in total volume roughly 15 percent of the CFCs needed as propellants, according to the CFC Volumes Study itself (see page 4) and the description of the manufacturing process which appears as Exhibit B (see page 1). The addition of that 15 percent to the propellant volumes yields the following estimates of total need for 1996-99:

<u>Worldwide</u>	<u>United States</u>
1996: 11,700	1996: 3,100
1997: 13,600	1997: 3,300
1998: 15,600	1998: 3,800
1999: 17,900	1999: 4,300

These figures average out to a probable maximum need for virgin CFCs of 3,600 metric tonnes per year in the U.S. (15,000 metric tonnes per year worldwide).

Third, the estimates for areas outside North America and Western Europe are based on a marginal data base (see pages 4 and 113 of the CFC Volumes Study) and therefore are only speculative as to the actual requirements. For example, IPAC does not have fully reliable data for large population areas such as China, India, Latin America, and Eastern Europe, into which areas MDIs might be imported from Europe and North America.

Finally, the Study provides data only on sales of MDIs in a particular region. It does not reflect the sites of MDI manufacturing, nor CFC production. In fact, MDIs and MDI components often are manufactured in one region and sold in another. Similarly, the CFCs often are produced in one country and used for MDIs in another. This pattern, moreover, is likely to change as the MDI and CFC industries adjust to the restrictions on CFC production and importation and as CFC producers relocate production facilities. The outcome is uncertain.

IPAC considered the possibility of attempting to quantify the needs of the industry for virgin CFCs in less conservative scenarios. IPAC believes that the currently ongoing development of CFC-free MDIs is likely (but not certain) to succeed and that such devices may start displacing CFC-containing MDIs on a major scale in 1997-99. Similarly, IPAC believes that DPIs which currently are used by less than 1 percent of the asthma and COPD patients in the United States, are likely to take on an increased market share during the period 1996 to 1999, at least until CFC-free MDIs begin to appear. In the United States, the increase in the use of DPIs is expected to proceed more slowly than in most other countries because of the current lack of availability of multi-dose DPIs in this country. There is, however, no factual basis at present upon which to project the emergence of CFC-free MDIs and only historical trends for DPIs.

2. *"Demonstration that continued use of that substance in that application is necessary for health and safety reasons or is critical to the functioning of society."*

a. Explanation
of MDI
Essentiality

MDIs are at present a mainstay of therapy for asthma and COPD. Millions of people, including children and the elderly, depend on them on a daily basis to cope with their diseases and, in many cases, to sustain life itself. The withdrawal of CFC-driven MDIs prior to the complete substitution of CFC-free devices would force these patients to use systemic forms of delivery with their attendant side effects or cumbersome and expensive stationary nebulizers. In addition, that withdrawal would frustrate the implementation of the recently-developed international consensus on the best form of therapy for asthma -- a program of chronic management emphasizing the prophylactic administration via inhalation of anti-inflammatories.⁵

i. The
Diseases

Asthma and chronic obstructive pulmonary diseases (COPD), such as emphysema and chronic bronchitis, reduce the capacity for respiration. In the United States, about 25-30 million people suffer from these diseases. They inflame the human airway, which becomes hyperreactive and subject to convulsive coughing and wheezing that disrupts breathing. These diseases also produce obstructions, such as swollen tissues and mucus plugs, which block airflow. In addition, they trigger muscular spasms that constrict the airways and impede the flow of oxygen to the lungs. Finally, in the case of emphysema and bronchitis, these diseases gradually destroy the surface area of the lungs, reducing their capacity for the exchange of oxygen and carbon dioxide. In a very real sense, these diseases cause suffocation. They greatly diminish the quality of life for the patient and his or her family and, in severe cases, may cause death.

Asthma

Asthma is a particularly burdensome disease, in part because of its prevalence among children. The victim of asthma may be restricted from normal physical activity, limited in his or her choice of work, afflicted by the side effects of some medications, and subject to unpredictable and sudden asthma attacks which disrupt his or her daily activities and may even threaten his or her life.⁶ As described by John Updike, the prominent U.S. author, and an asthma sufferer, himself:

An asthma attack feels like two walls drawn closer and closer, until they are pressed together. Your back begins to hurt, between the shoulder blades, and you hunch. . . . I felt immensely angry at my own body and at everyone. Like a child blind in his tantrum, I thought, serves them right, and waited to die, standing bent over and gasping, of suffocation.⁷

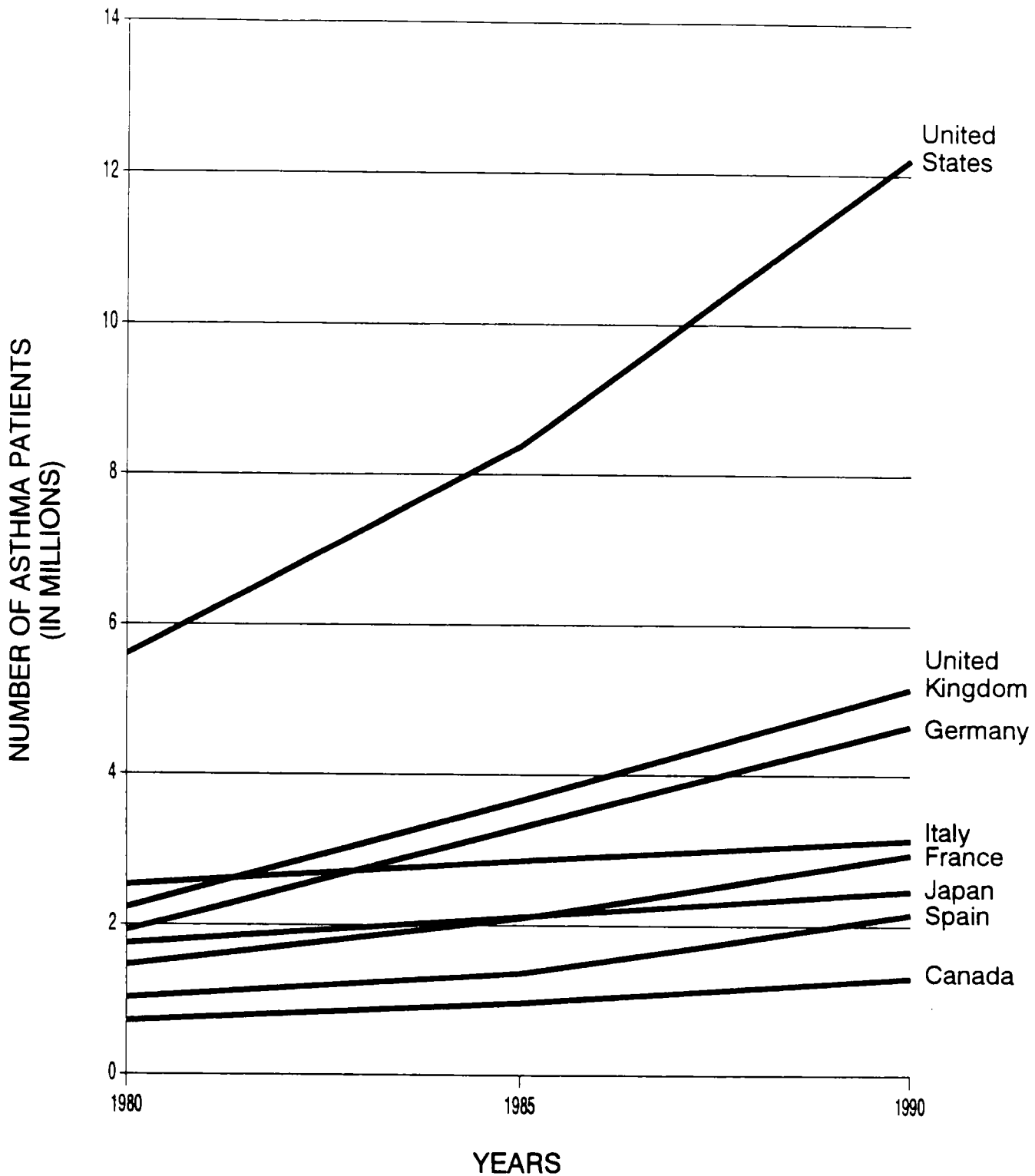
The global incidence of asthma globally is generally accepted to be on the order of 5-8 percent of the population, at least in the developed world. In the U.S. alone, 10-15 million people suffer from asthma, with about 4 million being children and youngsters under the age of 18.⁸ This incidence has risen 70 percent since 1970.⁹ Deaths from the disease in the U.S. have more than doubled since 1979.¹⁰

Indeed, on a global level:

Data from many countries suggest that both asthma morbidity and mortality are increasing, although the reasons for this are not clear. Asthma prevalence has been reported to be increasing in the United States, the United Kingdom, New Zealand, and Australia; asthma mortality rates and mortality trends vary widely but appears to be increasing in many countries where data are available ¹¹

Figure 3 displays the rising incidence of asthma for several developed countries.

INCIDENCE OF ASTHMA IN 8 MAJOR COUNTRIES ON A COUNTRY-BY-COUNTRY BASIS (1980-1990)*



COPD

Emphysema also is debilitating:

The wall between the tiniest air sacs within the lungs breaks down, and those compartments become unnaturally enlarged. Elasticity of the lung tissue is lost, and the lungs become distended, unable to expand and contract normally. Breathing falters and, ultimately, each breath becomes a chore. Meanwhile, the patient grows progressively weaker -- at first experiencing only minimal shortness of breath, soon unable to attempt even minor physical activity, in the end dependent on administration of oxygen, even at rest.¹²

Chronic bronchitis also develops over many years, sometimes in conjunction with emphysema. It produces inflammation and clogging of the lungs and causes periodic attacks of obstructed breathing.¹³

In the U.S., about 2 million people suffer from emphysema and 13 million from chronic bronchitis.¹⁴ Deaths per year in recent years in the U.S. have been about 75,000, reflecting an increase on the order of 30 percent over the 1980s.¹⁵

ii. Medications

The medications developed for treatment of asthma and COPD generally fall into two categories: anti-inflammatory agents and bronchodilators. Anti-inflammatory agents treat inflammation of the airway and reduce its hyperreactivity. They include corticosteroids, such as beclomethasone dipropionate, triamcinolone, flunisolide and budesonide; and non-steroidal anti-inflammatories such as sodium cromoglycate and nedocromil sodium.

Bronchodilators, on the other hand, act to dilate the airways by relaxing bronchial smooth muscle. They also enhance the clearance of mucus and other airway obstructions. Bronchodilators include, among other drug agents, beta-agonists such as albuterol (salbutamol), metaproterenol, pirbuterol, terbutaline, isoprenaline, isoetharine and epinephrine (adrenaline); and anti-cholinergics such as ipratropium. These drug agents provide a broad range of medications from which physicians may choose in developing a program for treatment of asthma and COPD.

In recent years, the medical community has become increasingly aware of the importance in the management of asthma of preventing the onset of bronchoconstriction through the chronic administration of anti-inflammatories, rather than reacting to such onset through episodic administration of bronchodilators.¹⁶ Of course, this form of prophylactic treatment is possible at present only because of the existence of MDIs and, to a lesser extent, DPIs.

iii. Drug
Delivery
Systems

Until the 1950s, medications for asthma and COPD usually were taken orally, absorbed by the bloodstream, and delivered to the airway through the circulatory system. This use of "systemic therapy" requires a relatively long period of time for medication to reach the airway. It also requires the use of relatively large dose amounts since much of the medication is metabolized or diluted by the body before it reaches the airway. For some important therapies, these large dose amounts pose risks of harmful side effects.¹⁷

Inhalation therapy by means of the MDI was introduced in the 1950s as a major advance over systemic therapy. It relies entirely on the airway as its route of administration. It also relies in varying degrees on the available force and direction of inhaled air.

Inhalation therapy delivers drug particles to the diseased airway directly and far more rapidly than systemic therapy and yields more rapid onset of therapeutic effects. Reliance on the airway instead of the bloodstream reduces the amount of medication that is metabolized or diluted by the body before it reaches the disease site. Inhalation therapy therefore is effective with far smaller dose amounts, thus posing (for some important therapies) far smaller risk of harmful side effects. Some of the drugs available today for inhalation, particularly via MDIs, could not be taken orally because the allowable and required dosage is so small; to attain effective treatment through oral administration would require increasing the dose to an unacceptable level.

Inhalation delivery systems perform four separate functions: They hold the drug agent in a reservoir; meter that agent into precise amounts for dosing; release the dose through a valve; and provide for the delivery of the dose to the airway.

Inhalation delivery systems take several different forms including the pressurized MDI, the DPI, and the nebulizer. The design and performance characteristics of each of these systems is discussed below.

*The
Pressurized
Metered
Dose
Inhaler*

As described above, the MDI is capable of releasing precisely calculated and highly reproducible dose amounts since drug particles are evenly distributed in a propellant solution which is released through a metering valve. The MDI provides virtually all of the force required to transport drug particles from the device to the target location in the airways. This force is provided by the propellant that is held under pressure in the canister prior to release. The MDI delivers multiple doses, and is pocket-sized, highly portable, and simple to actuate.

*The Dry
Powder
Inhaler*

In this device, the drug agent is placed in a holding chamber or reservoir as "dry powder." It is metered into dose amounts in one of several ways. A capsule containing a pre-measured dose amount may be inserted into the device. The dose also may be held in a "blistered" disk that is punctured by the device prior to drug release. Finally, dry powder held in bulk may be

metered into a holding cup of precise dimension in preparation for release and delivery.

The DPI is non-pressurized and relies entirely on the inspiratory capacity of the patient for delivery of drug particles. The patient places his mouth on the end of the DPI and inhales. As he or she does so, drug particles are lifted out of the holding chamber, through the device, into the mouth and down through the airways.

Respiratory disease may significantly diminish inhalation capacity in some patients, particularly during severe asthmatic attacks. Without the aid of propellants, these patients may not have sufficient inspiratory strength to draw dose amounts from some DPIs and disperse them properly throughout the airway.

When held as bulk powder, the tiny micronized particles which make up dry powder may aggregate as the result of electrostatic and other interparticle forces. These drug particles also may become enlarged and agglomerate, or stick together, upon exposure to atmospheric moisture. The amount of drug and the particle size of drug exiting DPIs are dependent on how hard, how consistently, and how long a patient breathes in.

Drug particles are larger and heavier in aggregate form. As aggregates, they may interfere with the metering of dose amounts and proper release of medication from the DPI. Aggregates may exceed respirable particle size and hinder the administration of a constant reproducible dose. They require greater inspiratory "lift" from the patient, are more difficult to disperse, and tend to get stuck in the upper airway including the mouth and throat, posing a risk of side effects. The creation of turbulent airflow within the DPI and the use of "carrier" particles help deaggregate micronized powder. The efficacy and safety of devices which hold dry powder in bulk depends in substantial measure on their ability to control the size and manage the separation of drug particles.

DPIs feature a range of technical and design characteristics. The early products must be reloaded after one or several dosings and are generally difficult to actuate. More advanced systems deliver multiple doses and are relatively simple to actuate. A very few multi-dose devices are approved and available to patients in European countries and elsewhere. However, there are no multi-dose DPIs currently approved by FDA for use by patients in the U.S. DPIs are generally pocket-sized and portable.

The Nebulizer

Using either ultrasonic or air-jet technologies, the nebulizer transforms an aqueous solution in which drug particles are dissolved or suspended into an aerosol cloud for inhalation by the patient. The particle size of this cloud may vary significantly from one nebulizer to the next.

Existing nebulizers are large, cumbersome, noisy and awkward to use. Many require an independent power source. Moreover, the mechanics of set-up and administration can consume 10-20 minutes, a period that may be too long for a patient in severe respiratory distress.

While a significant effort to develop a portable, hand-held, multiple-dose nebulizer currently is underway, no such product is expected to be approved prior to 1996.

iv. Current
Pattern of
Use of
Existing
Delivery
Systems

IPAC has analyzed the current worldwide pattern of usage of the various systems for delivery of medicines for asthma and COPD, using audited industry marketing data for the 20 leading markets for hand-held inhalation devices. That analysis appears in Exhibit D. It shows that the delivery of all therapy in the major developed countries of the world was accomplished in 1992 as follows:

<u>DELIVERY SYSTEM</u>	<u>MARKET SHARE (%)</u>
CFC-driven MDIs	55
DPIs	9
Nebulizers	5
Systemic	<u>31</u>
	100

In the United States, the breakdown of usage of the various delivery systems differs somewhat from the worldwide pattern. The use of DPIs in the U.S. accounted for less than 1 percent of all therapy over the past five years, while the use of MDIs accounted for more than sixty percent. This is because multi-dose DPIs are not available in the United States, MDIs are widely accepted by patients and physicians in the U.S., and a wide variety of medications are available in the MDI form. While an increase in the use of DPIs over the next seven years is likely to occur in the U.S., it will involve obtaining requisite regulatory approvals for devices (as well as developing new, multi-dose devices) and massive education of the patient and physician community. A full description of the development process for DPIs appears in Exhibit D.

v. Critical
Importance
of CFC-
Driven
MDIs

Obviously, the United States patient population as well as the worldwide community of asthma and COPD sufferers currently relies heavily on CFC-driven MDIs. Any reduction in the supply of such MDIs prior to the comprehensive substitution of hand-held inhalation devices could have serious consequences. Millions of children and other sufferers would have to use systemic forms of delivery or stationary nebulizers, which could result in a lower risk benefit ratio in treating their disease. In cases of acute severe attacks of bronchoconstriction, some could die, and others would run the risk of serious side effects.

Asthma presents a particularly telling example of the latter point. The rising morbidity and mortality of asthma recently prompted the U.S. National Heart, Lung, and Blood Institute to convene an international group of leading physicians and scientists to develop a consensus on therapy and identify areas for further research. This group produced the *International Consensus Report on Diagnosis and Management of Asthma* in June 1992. This report concluded that:

The major factors contributing to asthma morbidity and mortality are under diagnosis and inappropriate treatment. Most exacerbations reflect a treatment failure because they can be prevented if treatment of the disease is comprehensive and ongoing.¹⁸

The report then lays out what these leading experts regarded as the best treatment regimens, asserting in part that (1) "anything more than mild occasional asthma requires daily therapy with anti-inflammatory agents"¹⁹ and (2) "treatment via inhalation is generally preferable to systemic or oral treatment."²⁰ In fact, the Report emphasizes that "[c]hronic oral corticosteroid treatment should not be used unless other forms of therapy, including high doses of inhaled corticosteroids, have failed to mitigate the patient's asthma."²¹

Full application of this advice to the entire asthma population, however, is dependent at present on the CFC-driven MDI, and will continue to be dependent on it until such time as the CFC-free MDI, the DPI or combinations of the two obtain the necessary government approvals for all of the relevant drugs and then fully penetrate the markets in all countries.

This process of substitution will take many years, likely running at least to the end of the decade as explained below. In the meantime, CFC-driven MDIs will continue to be of critical importance to the global society.

b. MDIs are
Recognized
as "Essential"

The continued use of CFCs in MDIs is widely recognized as necessary for the health and safety of millions of patients suffering from asthma and COPD. For this reason, MDIs are among the few products remaining exempt from the U.S. ban on the use of CFCs as aerosol propellants. That ban was implemented in 1978 under the auspices of an interagency task force, with the prohibition by EPA of CFC-containing aerosols under the Toxic Substances Control Act,²² and the prohibition by FDA of the sale of any food, drug or cosmetic using CFCs as propellants.²³

At the time FDA took steps to ban CFCs from aerosol products coming under its jurisdiction, the Agency listed specific uses of CFCs that are "essential" and therefore exempt from the ban.²⁴ FDA originally listed five uses of CFCs as essential; four of those uses pertained to MDIs.²⁵ Since then, FDA has added

to the list several times; at present, there are thirteen essential uses of CFCs that are exempt from the ban, nine of which pertain to MDIs.²⁶

FDA's essentiality determinations remain current and authoritative. Most recently, FDA added MDIs delivering nedocromil sodium to the list of essential uses, without making any other adjustments. 58 Fed. Reg. 6086 (January 26, 1993). Furthermore, in June of this year, FDA granted a petition to allow investigational studies on a new CFC-driven MDI containing a combination of ipratropium bromide and albuterol sulfate.²⁷

FDA's regulations establish the following criteria that must be met before a product will be added to the list of essential uses:

- (1) There are no technically feasible alternatives to the use of a chlorofluorocarbon in the product,
- (2) The product provides a substantial health benefit, environmental benefit, or other public benefit that would not be obtainable without the use of the chlorofluorocarbon, and
- (3) The use does not involve a significant release of chlorofluorocarbons into the atmosphere or ... the release is warranted in view of the consequence if the use were not permitted.

21 CFR 2.125(f). In creating the original list of essential uses and then each subsequent addition, FDA undertook detailed consideration and analysis of these factors pursuant to a notice-and-comment rulemaking process.²⁸ These factors are similar to those being considered by EPA in connection with the making of essential use nominations under the Montreal Protocol. In particular, FDA's factors require that there be "a substantial health benefit . . . that would not be obtainable without the use of the chlorofluorocarbon."

The health benefit determination is one that FDA is best qualified to make. This was recognized by Congress when it created Title VI of the Clean Air Act, as is evidenced by FDA's primacy in ruling on the essentiality of MDIs for purposes of any exemption under Title VI. Specifically, Congress provided:

The term "medical device" means any device (as defined in the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321)), diagnostic product, drug (as defined in the Federal Food, Drug, and Cosmetic Act), and drug delivery system--

- (A) if such device, product, drug, or drug delivery system utilizes a class I or class II substance for which no safe and effective alternative has been developed, and where necessary, approved by the Commissioner, and

- (B) if such device, product, drug, or drug delivery system, has, after notice and opportunity for public comment, *been approved and determined to be essential by the Commissioner* in consultation with the Administrator.²⁹

And further, as to promulgating an exemption for medical devices, Congress provided:

Notwithstanding the termination of production required by subsection (b), the Administrator, after notice and opportunity for public comment, shall, to the extent such action is consistent with the Montreal Protocol, authorize the production of limited quantities of class I substances solely for use in medical devices if such authorization *is determined by the Commissioner [of FDA]* in consultation with the Administrator, to be necessary for use in medical devices.³⁰

Thus, Congress recognized that FDA is best positioned to decide which medical products are essential, and gave FDA primacy in making that decision.

FDA recently emphasized the medical necessity of MDIs in a letter to EPA, as follows:

The majority of essential use drug products currently formulated with CFC propellants are used to treat asthma, a disease affecting approximately 10 million Americans. Asthma is accompanied by substantial morbidity and an appreciable mortality. Many of the most important therapeutic agents for the treatment of asthma are formulated in metered-dose inhalers (MDIs) with CFC propellants. *FDA's medical experts agree that these groups of drugs are life-saving for many asthmatics.*

These medications are available in other dosage forms, such as oral formulations and liquids for delivery by mechanical nebulizers, but because of the inherent differences in rate and extent of exposure of various body tissues due to the route of administration, these dosage forms differ in their safety and efficacy and are more difficult to use. *These medications are not available in MDIs that do not incorporate CFCs, and because MDIs using new propellants must be tested for their effectiveness and safety in clinical trials, products with these substitute propellants cannot yet be safely marketed.*

There is, for example, no directly comparable therapeutic alternative to CFC-propelled MDIs for administering inhaled corticosteroids, an extremely important group of drugs in the

treatment armamentarium for individuals with severe and chronic asthma. See National Heart, Lung, and Blood Institute, National Institute of Health, *International Consensus Report on Diagnosis and Treatment of Asthma* (March 1992). The alternative dosage forms for cromolyn sodium, another vital asthma medication for many patients, requires more elaborate preparation and a separate bottle of capsules, and is more irritating to some patients. MDIs containing other asthma medications, such as beta adrenergic agonists for acute use, provide prompt relief, can be used more frequently when necessary, and are more portable than the same medication in oral or nebulizer dosage forms, *making MDIs a key part of the management of many asthma patients. Because of these and other advantages, MDIs are the mainstay of asthma therapy, accounting for most first and second line treatments. Other formulations are added as needed in patients who cannot be managed with MDIs alone.*

Letter dated June 15, 1992, to William K. Reilly, Administrator, EPA, from Michael R. Taylor, Deputy Commissioner for Policy, FDA, at 3-4 (footnotes omitted; emphasis added).

EPA as well has recognized several times the essentiality of MDIs and the primacy of FDA's determinations. For example, in publishing its proposed rule to ban the use of class I compounds from nonessential products under CAA section 610,³¹ EPA requested comment on the continued essentiality of continued CFC use in these medical products. In the final rule, EPA exempted MDIs from the class I products ban, relying upon FDA's list of essential uses as being authoritative and current for purposes of defining what uses of CFCs fall outside the ban.³²

More recently, EPA stated in the preamble to its proposal to accelerate the phaseout of ozone-depleting chemicals that MDIs "would clearly qualify under the health and safety criteria established by the Parties"³³ Clearly, the essentiality of MDIs is well recognized.

3. *"Demonstration that no alternatives, including the retrofit of existing equipment, are technically, economically or legally available."*

At present, only two possible alternatives to CFC-driven MDIs have any significant promise of displacing MDIs within the foreseeable future: (a) MDIs driven by HFA-134a or HFA-227; and (2) dry powder inhalers (DPIs). Neither of them, however, could displace MDIs prior to January 1, 1996. In each case, the replacement of existing CFC-driven MDIs entails compliance with lengthy and time-consuming regulatory requirements.

a. CFC-Free MDIs

MDI manufacturers are expending an enormous amount of effort to develop MDIs using the alternative propellants, HFA-134a and HFA-227. The process of re-engineering, safety testing and approval for 134a/227 devices of necessity will run until the late 1990s for some drugs and at least until the end of the century for others. The Aerosol Committee in its 1991 report reached the same conclusion:

The industry has focused attention on HFC 134a and 227 as both have a low order of toxicity in early tests. However, these compounds are not compatible with current surfactants and valve elastomers used in most of the products, and therefore, in most cases, substantial reformulation is necessary. Companies are still searching for a substitute for CFC 11. It is anticipated that in some cases reformulation may be complete by 1993. After that, toxicology and clinical studies will take until mid 1997 to complete, and the regulatory approval process will then take about two more years to complete. Thus CFC free pressurized inhalation aerosol products will not be available until at least mid-1998, and in some cases not until the end of the century.³⁴

The fundamental thrust of this description remains accurate: The substitution of CFC-free MDI products for the current MDI products will extend through the balance of the decade and possibly into the next century. A full and current analysis of the development process appears as Exhibit A.

b. Dry Powder Inhalers

In the United States, DPIs currently account for approximately one percent of patient usage of hand-held inhalation devices. As noted above, there are no multi-dose DPIs currently approved for patient therapy in the U.S. Even with maximum effort, DPIs could not be substituted for MDIs entirely by 1996, or even by the year 2000. At present, various companies are working to develop DPIs, but there are a wide range of difficulties to be surmounted in bringing these efforts to fruition. To begin with, as with MDIs, DPIs tend to be medication-specific, and generally are developed to work with a particular type of drug molecule. In other words, a DPI device that is successful for one type of drug molecule will have to be adjusted and/or redesigned to accommodate a different type of medication, depending on the degree of difference; such changes, of course, will render the device a new drug product for purposes of FDA regulation, hence requiring a New Drug Application and concomitant FDA approval. As a result, a wide variety of different types of DPI devices would be required to satisfy the need for currently-approved MDIs. Each such device would require separate design, testing, FDA approvals, manufacturing and marketing capabilities, and patient and physician education programs. Such educational programs can only begin, of course, subsequent to FDA approval of a new device or product; preapproval activities of this nature would be prohibited by FDA. The transition to DPIs necessarily could only occur over several years.

This is supported by historical patterns in treatment. In the past five years, the worldwide use of therapy for asthma and COPD has increased about 20 percent from approximately 8 billion patient days treatment in 1988 to almost 10 billion days treatment in 1992. In 1988, DPIs accounted for about 4 percent of treatment worldwide. The use of DPIs increased gradually in each succeeding year. In 1992, however, DPIs still only accounted for about 9 percent of total days treatment worldwide. In the United States, of course, the increase in DPI usage has proceeded very slowly, and, due to the unavailability of multi-dose DPIs, can be expected to continue to increase at a slow pace.

The rate of increase in the use of DPIs differs substantially from one major developed country to the next. It varies in accordance with several important factors, including:

- The pace and results of research and development of new dry powder systems;
- The stringency, pace and results of governmental review of these new systems;
- The number of medications approved for use in dry powder systems;
- The availability of more advanced dry powder systems;
- The confidence of general practitioners and their patients in the safety and efficacy of DPIs for particular medications and disease conditions, particularly in comparison to MDIs on which they may have relied for many years; and
- Governmental policies and regulations concerning the use of MDIs and health care cost.

As with any single therapeutic modality, the DPI likely will never be appropriate for all patients, all disease conditions and all medications. Patients whose respiratory capacity is severely impaired may not be capable of "lifting" dry powder from a holding chamber for delivery to their diseased airways. Moreover, many drug agents may not have appropriate physico-chemical properties for use in DPIs.

The use of DPIs both in the United States and worldwide will increase only gradually over time. Their emergence is governed worldwide by a process for development, approval and patient education in the proper use of these systems. This process generally extends over a period of many years.

Developing a dry powder system is complicated and time consuming. Moreover, many of the challenges presented at the development stage will be

critically reviewed at the approval stage. Some of the most difficult issues in the successful development and formulation of dry power systems are the need to: (1) generate the optimum 'respirable dose'; (2) assure consistent reproducible dosing; (3) avoid agglomeration; and (4) incorporate multiple dosing.

Once the development issues have been resolved to the satisfaction of the drug innovator, governmental approval of the product must be obtained. In the United States, dry powder systems designed to deliver asthma and COPD drugs are considered new drugs subject to the new drug approval process. The United States new drug approval process is one of the most rigorous and time consuming in the world.

In this process, DPIs will be subject to the same regulatory hurdles applicable to new or reformulated (CFC-free) MDIs, as described in Exhibit A. In brief, this process includes preclinical testing, stability testing, the filing of an investigational new drug application (IND), Phases I, II and III clinical trials, the filing of a new drug application (NDA), and, finally, regulatory review and approval.

Once approval is obtained the process of educating physicians and patients must begin. In the United States, where current use of DPIs is so limited, most patients and physicians are unfamiliar with them. To facilitate a transition to new DPIs, physicians will require instruction as to their proper use, the doses they deliver, and the clinical profiles of adverse reactions and contraindications of the systems. Educating physicians about changes or advances in treatment regimens can be a difficult and lengthy process. Access to timely and accurate information varies within the medical community; academic researchers and specialists usually receive information long before the general practitioners.

In addition to doctors, a wide variety of healthcare providers including nurses, respiratory therapists, and aides also will need to be educated about the use and functioning of DPIs.

Patients, and in some cases, their families, also must be educated, trained and made to feel comfortable and confident with dry powder systems. The nature of respiratory diseases makes patient knowledge of and confidence in medications critical. More precisely, most of the day to day responsibility for managing asthma falls on the patient and the patient's family. Patients often are called upon to medicate themselves rapidly and while suffering frightening symptoms such as chest tightening, wheezing and shortness of breath. The importance of patient education is highlighted in the International Consensus Report, which contains a six part asthma management program. The first element of the six part program is to educate patients to develop a partnership in asthma management. The report indicates that the goal of patient education is to provide patients with sufficient information to allow for successful self-

management of the disease. Successful self-management depends in part on the patients knowledge of disease symptoms and therapy.

While it is not certain how long a transition to DPIs would take, it seems clear that in the United States very little progress could be made prior to 1996.

Even in those few countries where DPIs are emerging relatively quickly, such as Sweden and Holland, it has taken over five years for them to reach even half of patient treatment days for asthma and COPD. In most other major developed countries of the world, DPIs have achieved only a small fraction of these use levels. It likely will take another five to seven years -- until 1998 to 2000 at the earliest -- before the use of dry powder systems increases from current levels of about 9 percent to even 50 percent of patient treatment days worldwide. This is especially true in the United States. Whether the use of DPIs in the United States or worldwide will ever increase to such levels or beyond is, of course, highly speculative and unknown, and depends entirely on the pace and results of the process for development, approval and patient education. Usage of DPIs may well level off or even decline as CFC-free MDIs are introduced in future years. In any event, it is simply inconceivable that DPIs could displace CFC-driven MDIs by 1 January 1996, that is, within only two and a half years.

c. Effect on Patients

As noted above, some 25-30 million patients in the United States suffer from asthma or COPD. More than 60 percent of these patients, or roughly 15-18 million people, rely upon MDIs for the delivery of medication necessary to their continued health. Without an exemption to allow continued production of CFCs for use in MDIs during 1996-1999, an essential form of therapy would become unavailable for most, if not all, of these patients. The result would be a significant health care emergency, as some 15 million patients suddenly would have to be switched to a substitute form of therapy. In economic terms, the total increase in the cost of asthma and COPD therapy could be expected to exceed \$7 billion annually (based on an estimated \$500 additional cost per patient), for each year that MDIs remain unavailable.

The first step in converting patients from treatment with MDIs to some alternative form of therapy would be to educate the physician community in how to make the transition. Presumably, this process would begin with the establishment of guidelines prepared by physician groups, working in conjunction with other interested parties (e.g., ALA, and the National Heart, Lung, and Blood Institute). These guidelines would then have to be disseminated to physicians. The guidelines would instruct physicians on appropriate substitutes for the various types of MDIs, and how to go about changing patients to alternative therapies.

The choice of alternate therapy would vary from patient to patient. For most patients, oral medication probably would be prescribed. This is because most physicians and patients are familiar with the available oral medications, and

are knowledgeable in their treatment regimen, including dosage titration, and the identification of side effects. DPIs would be an option for only a small percentage of patients, mainly due to unfamiliarity with the devices, and also because they are not widely available in the United States and, pending new regulatory approvals, may not be widely available prior to 1996. In particular, multi-dose devices are not available, and very few medicines are available in DPI form. Certainly, the use of DPIs could be expected to increase, but this increase would be only small. Most importantly, steroid medications, which are a mainstay of therapy, are not available in any DPI form. In the case of very young children and some elderly patients, who may have trouble using oral medication or DPIs (DPIs require significant coordination to operate), the most likely alternate form of therapy would probably be the nebulizer.

Enormous logistics would be involved in the transition process, as some 15 million patients would undergo the conversion simultaneously. For each patient, three to four doctor visits would be required just to establish the new treatment regimen, and to ensure that it is working safely and effectively. During these visits, patients would be required to undergo new pulmonary function tests, instruction in the use of the alternative therapy, monitoring for side effects from the new therapy, and in some cases, such as with patients using theophyllin, blood monitoring for levels of medication in the bloodstream. Significant costs would be incurred during these doctor visits. In addition, because most patients would be switched to oral medication, which can have dangerous side effects, increased monitoring of patients by their physicians over time will be required; bi-monthly visits would probably be recommended. Further, because oral medications generally are not as quick to take effect as MDIs, they are not useful to alleviate severe and sudden episodes of bronchoconstriction. As a result, increased utilization of emergency room treatment could be expected. For patients who are switched to nebulizer therapy, home nebulizer units would have to be purchased; these can cost an average of \$400.

The total costs of this transition process would be enormous. A conservative estimate would be that an additional \$500 cost per patient would be incurred annually (including costs of increased doctor visits, blood monitoring, pulmonary function tests, emergency room treatment, etc.); this amounts to a total of at least \$7 billion per year (at present, the total cost of treating asthma in the United States is roughly \$6.2 billion per year, \$1.1 billion of which is spent on medication).³⁵ Further costs would be incurred as patients could be expected to miss more days at work in cases where they are unable effectively to treat their diseases away from home.

For children who suffer from asthma, the cost of having to switch from MDIs to another form of therapy would be steep. At present, asthma is the number one cause of school absenteeism in the United States.³⁶ The incidence of school absenteeism could be expected to rise if MDIs become unavailable.

Indeed, the primary concern of a physician prescribing asthma medication to a child is how the medication will effect the child's performance in school. Oral liquid and solid medication have two prevalent side effects in children: extreme drowsiness or hyperactivity. Prior to the advent of MDIs, asthmatic children often missed many days of school as a result of the side effects of oral medication. Today, because of the availability of MDIs, which are associated with fewer side effects than the systemic forms of delivery, asthmatic children generally miss less school than they once did. However, the situation will revert if MDIs become unavailable; children once again would be forced to rely mainly upon oral forms of medication. Nebulizers also would be used to fill the gaps, but a child cannot take a nebulizer to school, and hence would be forced to stay home more often for necessary treatment.

MDIs are the mainstay of asthma and COPD therapy in the United States. They allow for sophisticated treatment utilizing state-of-the-art medications. Without them, asthma and COPD therapy could revert to where it was some twenty or thirty years ago. While this would be only a temporary regression (*i.e.*, until reformulated CFC-free MDIs become available) it would have a devastating effect on patients and the healthcare system. For example, many patients would have to refrain entirely from any athletic or physically taxing activities, in order to avoid triggering a severe bronchoconstriction (MDIs allow patients to live far more active lives). It is essential therefore that steps be taken to facilitate a smooth transition to CFC-free MDIs, by allowing an exemption for a period of time from the ban on CFC production.

4. *"Description of the steps taken to date to find alternatives."*

MDI manufacturers have expended an enormous amount of effort to find alternatives to the use of CFCs in MDIs, and to reduce the amount of CFCs needed for MDI production. These efforts for the most part have centered on developing alternative propellants, and also have focussed on developing alternative forms of delivery (*e.g.*, DPIs), as well as reducing usage of CFCs during the manufacturing of MDIs.

a. The Search for Alternatives

Beginning in the late 1980s, the MDI industry, as did many other industries, began searching for appropriate CFC alternatives. By 1990, the industry had narrowed its search to two compounds that were newly available in small commercial scales – HFA-134a and HFA-227. Other CFC alternatives, including various HCFCs, other HFCs and various hydrocarbons, were rejected for a variety of reasons. The 1991 report of the Aerosol Committee addressed this issue, as follows:

Chemicals such as HCFC 123, 141b, HFC 134a, 227, and hydrocarbons have all been mentioned as possible alternatives. HCFC 123 and 141b have shown anesthetic effects and HCFC 123 is a moderate cardiac sensitiser and has been shown to induce benign pancreatic and

testicular tumors in rats. HCFC 141b is a strong cardiac sensitizer, which effectively precludes its use in inhalation aerosol products. Hydrocarbons are highly flammable, have an oily stinging taste and little is known of their long term toxic effects when inhaled regularly.³⁷

The general thrust of this analysis is that only HFA-134a and HFA-227 hold promise as propellants for use in MDIs. Further information on this issue appears at pages 12-14 of Exhibit A.

The members of IPAC both collectively and individually have been working aggressively to develop CFC-free MDIs. Some members of IPAC formed a joint program for the toxicology testing of HFA-134a in May 1990 (IPACT-I) and a joint program for HFA-227 in December 1990 (IPACT-II). These programs exist and operate to facilitate the most rapid completion of safety testing on the two alternative compounds. Both programs are designed to satisfy the safety requirements of FDA and other health authorities around the world at the earliest possible time. A total of about \$35 million is being devoted to the combined effort. The full data package from each program is expected to be available within the next two to three years. In addition to safety testing, these consortia, along with IPAC itself, are working with regulatory agencies, including FDA, to facilitate consideration and approval of the alternative compounds (a process involving, in part, the review by FDA of thousands of pages of reports on safety studies), as well as to establish a program for reviewing and approving reformulated products using these compounds as propellants. These efforts are described more fully in Exhibit A.

Concurrently with the efforts of these consortia, each individual company has been working to reformulate its own products using the new propellants. This requires, in almost all cases, finding wholly new surfactants which will be compatible with both the new propellants and the medication, as well as new valve elastomers for the metering valve. *See, generally, pages 4-6 of Exhibit A.* In addition, companies are performing their own programs of safety and efficacy testing on the new propellants in combination with their individual medicative products. *See, generally, pages 8-14 of Exhibit A.*

In the case of DPIs, various companies are working to develop products in DPI form. Information regarding these efforts is extremely proprietary and therefore we are not able to include any discussion of these efforts. The process for developing DPIs involves as many steps and is at least as time-consuming as the process for developing CFC-free MDIs. However, as noted above, DPI devices tend to be unique to specific medications, and therefore their development cannot be carried out collectively, as is being done for the new propellants.

b. Limiting
Manufacturing
Usage of
CFCs

Individually, the members of IPAC have powerful incentives to develop CFC-free MDIs and DPIs as quickly as human ingenuity and logistics allow. The first companies to be able to market such devices in the U.S. are likely to gain a disproportionate market share. Each U.S. MDI manufacturer, therefore, can be expected to be moving as rapidly as it can to develop substitutes.

The emissions of CFCs which are attributable to MDIs come not only from the activation of the devices themselves by patients, but also from the manufacturing process. Little, if anything, could be done to adjust the design of the MDIs so as to reduce the emissions from activations by the patient. In any event, such an adjustment would require approval by the relevant health authorities, particularly as to continued efficacy, and therefore could entail new testing and the usual lengthy process for completing government review. The reductions from a design adjustment, however, are likely to be extremely small. The more appropriate inquiry concerns the potential for reducing CFCs emissions from the manufacturing process.

About 15 percent of the CFCs required each year for MDIs are consumed (but not necessarily emitted) during the manufacturing process. The main propellants used for MDIs are CFC-11, -12, and -114. Small amounts of these compounds are emitted during material transfer operations, product mixing and canister filling. CFC-11, and to a lesser extent, CFC-113 are used to clean certain of the manufacturing equipment, particularly mixing vessels and filling machines. The elastomeric components of the MDI valves are prepared in a process that uses CFC-11 to remove extractable contaminants before introduction into the final product and delivery to the patient. Finally, after being filled and sealed, each individual MDI unit is actuated three to four times to ensure proper quality of the system, resulting in the release of three to four doses of the propellant/drug formulation.

At present, more than half of the CFCs consumed during the manufacturing of MDIs are captured and either reclaimed or destroyed. The balance, about 7 percent of the overall usage of CFCs for MDIs, is emitted to the environment during the manufacturing process.

Substantial reductions already have been achieved in consumption and emissions of CFCs during MDI manufacturing. Several years ago, manufacturing consumption probably accounted for about 30 percent of the total amount of CFCs used for MDIs, and most of this amount was emitted to the atmosphere. Thus, the industry already has reduced manufacturing consumption by about 50 percent, and manufacturing emissions by more than 75 percent. Both emissions and consumption of CFCs during the manufacturing process are expected to decline further over the next several years as the industry continues to improve control technologies.

To the extent that efforts to control consumption and emissions of CFCs involve significant changes in the manufacturing process, they must be

validated and approved by regulatory health authorities for both safety and efficacy. As a result, the pace at which certain types of improvements can be implemented is constrained by the pace of regulatory review and approval of amendments to previously-filed product and process descriptions. Such review and approval can take several years.

Attached as Exhibit B is a paper which analyzes the usage and emissions of CFCs that occur during the MDI manufacturing process, and describes some of the industry's efforts to minimize such usage and emissions and to enhance the recovery and recycling of CFCs.

5. ***"Description of future steps to be taken to find alternatives."***

The development of alternative propellants and devices, which essentially is an eight to ten year program, is already far along; this development will continue along the lines described above. Over the next three years, each of IPACT-I and IPACT-II will complete its respective safety testing programs and will prepare and file a Drug Master File (DMF) with FDA. IPACT-I and IPACT-II will continue to meet with health authorities to facilitate the most rapid completion and review of these filings. Concurrently, individual companies will continue their efforts to reformulate current products using the new propellants, and to perform safety testing of the reformulated products. Each company, individually, will in time prepare and submit to FDA a separate application for approval of each such reformulated product. In addition, companies will continue to develop DPIs for delivery of current and future medications.

6. ***"Demonstration that steps have been taken to secure existing stocks of the chemicals, either from a bank or from recovery sources, and that necessary quantities of appropriate quality are not available for the potential exempted use."***

It will not be feasible to use recycled CFCs in MDIs during 1996-2000. IPAC commissioned an in-depth peer-reviewed analysis of the potential for employing used CFCs as propellants in MDIs. The report on that analysis which appears as Exhibit E, concluded (at page 4) that:

The use of used commercial material in pharmaceutical products would be unprecedented and pose serious risks for a highly sensitive patient group. It is highly doubtful whether state-of-the-art technologies for purification and quality assurance could reduce these risks to acceptable

levels. There is a strong likelihood that health authorities would not approve of the use of used CFCs in MDIs.

In any event, developing commercial facilities for the purification of used CFCs and obtaining authorization for their use in MDIs would take at least 4 years. Assuming that this program did not start until after the Sixth Meeting of the Parties in 1994, it would take until mid-1998 and probably longer to complete an effort of this kind.

By this time, the MDI industry will be nearing completion of its transition to non-ozone depleting substitute propellants and likely require only a few thousand additional metric tons of virgin CFCs. The ozone protection benefits of preventing production of this relatively small amount of CFCs would be marginal at best and clearly outweighed by the risks to patient health from material once used for commercial and industrial purposes.

On this basis, IPAC regards the use of used CFCs as not being a viable option for assuring a seamless transition from current MDIs to substitute devices.

IPAC also has considered the potential for meeting the needs of the MDI industry during 1996-99 through the stockpiling of virgin CFCs during 1994-95. It concluded that such stockpiling is at best only a partial and, even then, dubious solution. First, it is doubtful that stockpiles of sufficient size and subject to sufficient quality control could be built quickly enough in the time remaining to cover MDI needs. The major producers of CFCs (*e.g.*, DuPont and ICI) are exiting the marketplace at least a year ahead of the 1 January 1996 deadline. Thus, the supply of CFCs will be diminishing at a time when major users (*e.g.*, refrigeration and air-conditioners) will be placing more demand on the producers in order to satisfy their "just-in-time" supply needs. But beyond that, it takes considerable time to secure the necessary storage capacity and establish sufficient quality control programs to satisfy the health authorities. Even then, those authorities may stand in the way of an approval, or the stockpile may escape due to a leak. In the meantime, the capacity for "just-in-time" production of CFCs may have withered.

Nevertheless, it is possible that some companies may find some amount of stockpiling to be a useful hedge against the uncertainties of the exemptions and procurement processes. However, it is unlikely that any stockpiled amount would suffice until adequate substitutes are approved and fully enter the marketplace.

7. *"The expected time period for which this exemption is required."*

An exemption to allow production of CFCs for use in MDIs is required for 1996 through 1999, and possibly for subsequent years. A timetable demonstrating how long it will take to develop and obtain regulatory approvals for CFC-free MDIs appears at the end of Exhibit A.

8. *"Consistency with CAA provisions on essential uses."*

The nomination of MDIs for an essential use exemption and implementation of the exemption in the United States would be consistent with the Clean Air Act. As EPA noted in its request for essential use applications, exemptions allowed up to the year 2000 would be governed by the Montreal Protocol and the general phaseout schedule established in sections 604(a) and (b) of the Clean Air Act, while exemptions beyond January 1, 2000 would also have to comply with the limitations on allowable exemptions established by Congress in section 604(d). The needed exemption for MDIs would comply with all of these requirements.

For the years 1996 through 1999, the issue is straight forward. The only conceivable limitation on the allowance of such an exemption under the Clean Air Act would be the allowable production percentages established in section 604(a) (40 percent of 1986 levels for 1996, and 15 percent of such levels for the years 1997 through 1999). It is extremely unlikely that the demand for CFCs for MDIs would outstrip these allowable production percentages. Indeed, it is almost inconceivable that such demand could even reach 5 percent of 1986 levels.

As for the years 2000 and beyond, the needed exemption for MDIs still would be consistent with the Clean Air Act. Section 604(d)(2) specifically contemplates such an exemption. That section provides:

Notwithstanding the termination of production required by subsection (b), the Administrator, after notice and opportunity for public comment, shall, to the extent such action is consistent with the Montreal Protocol, authorize the production of limited quantities of class I substances solely for use in medical devices if such authorization is determined by the Commissioner, in consultation with the Administrator, to be necessary for use in medical devices.

Thus, for an exemption to be allowed, the Clean Air Act requires that the Commissioner of the FDA must determine, in consultation with the EPA Administrator, that an exemption for MDIs is necessary. Such an essentiality determination already has been made by the Commissioner in the case of all

MDIs currently available for patient therapy in the U.S. See 21 CFR 2.125(e). The FDA's determinations remain valid and establish clearly that MDIs are "medical devices," as that term is defined in section 601(8) of the Clean Air Act, and that CFCs are "necessary" for use in MDIs.

EPA must respect the essential use determinations that have been made by FDA. FDA is plainly the agency that has responsibility for such determinations. In addition, the determinations FDA has made so far have undergone notice-and-comment rulemaking, were based on much the same analytical framework that Title VI employs (*i.e.*, an examination of the harm to the environment that might be caused by a particular use, the benefit to health or safety of the use, and availability of alternatives), and are part of a well-established and on-going system of regulating CFC-containing medical products.

Section 604(d)(4) puts a 10 percent cap on any MDI exemption (*i.e.*, production of CFCs for MDIs under any section 604(d)(2) exemption cannot exceed 10 percent of 1986 production levels). As discussed above, it is nearly inconceivable that demand for MDIs could cause this limit to be exceeded.

V. Conclusion

CFC-driven MDIs plainly are "essential" within the meaning of Decision IV/25, and there is strong justification for authorizing production and consumption of virgin CFCs for MDIs for 1996-99, and possibly beyond, without limitation. EPA should nominate MDIs for exemption by the Parties as soon as possible, but not later than the end of September 1993, in order that the Parties might be able to consider it during their Sixth Meeting.

IPAC requests an opportunity to meet with EPA to discuss this application.

Endnotes

1. The members of IPAC are Abbott Laboratories; Armstrong Pharmaceuticals, Inc.; ASTA Medica AG; Boehringer Ingelheim Pharmaceuticals, Inc.; Fisons plc, Pharmaceutical Division; Glaxo, Inc.; Hoffmann-LaRoche Inc.; 3M; Norton Healthcare; Rhone-Poulenc Rorer Pharmaceuticals, Inc.; and Schering Corporation.
2. Report of the Technical Options Committee on Aerosol Products, Sterilants, Miscellaneous Uses and Carbon Tetrachloride, at 43 (December 1991) ("1991 Report of the Aerosol Committee").
3. The text of Decision IV/25 appears at pages 24-26 of the Report of the Fourth Meeting of the Parties to the Montreal Protocol on Substances That Deplete the Ozone Layer (UNEP/OzL.Pro.4/15, 25 November 1992).
4. Report of the Technical Options Committee on Aerosol Products, Sterilants, Miscellaneous Uses and Carbon Tetrachloride, at 34 (December 1991) ("1991 Report of the Aerosol Committee").
5. National Heart, Lung, and Blood Institute, International Consensus Report on Diagnosis and Management of Asthma, Pub. No. 92-3091, vii (June 1992) (hereinafter "International Consensus Report").
6. NIAD Task Force Report, National Institute of Allergy and Infectious Diseases, PB-297601, Asthma and the Other Allergic Diseases 10 (1979) ("Asthma Task Force Report"); see also C. Feldman, N. Clark, and D. Evans, The Role of Health Education in Medical Management of Asthma, Some Problem Applications, Clin. Rev. Allergy 195 (1987).
7. Zamula, "Childhood Asthma," FDA Consumer (July 1990), at 10, citing J. Updike, Self-Consciousness (1989).
8. ALA 1993 Data, 7-8, 34; News Release ("Asthma Not Adequately Treated in United States"), dated April 15, 1993, by National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services.
9. Ibid.
10. Ibid.
11. International Consensus Report, supra n. 5.
12. ALA 1993 Data, 5-6.
13. Ibid. at 6.
14. Ibid. at 5, 33; see also R.C. Bone, J. Respiratory Dis., v. 12, n. 8, p. 1 (August 1991) (hereinafter "Bone").
15. ALA 1993 Data, 33; see also Bone, 1.
16. International Consensus Report, xi-xii.
17. L. Henley, et al, Asthma Market: Pharmaceutical -- Industry Report (March 25, 1991) (LEXIS, Nexis Library, Investext File); N. Sander, A Parent's Guide to Asthma, 89 (1989).
18. International Consensus Report, xi.
19. Ibid. at xii.
20. Ibid. at 28.
21. Ibid. at 30.
22. 15 U.S.C. 2601 (see 40 CFR Part 762).
23. See 21 CFR 2.125.
24. 21 CFR 2.125(e).
25. 43 Fed. Reg. 11316 (March 17, 1978).
26. Specifically, FDA's regulations currently exempt the following MDI products: "(1) Metered-dose steroid human drugs for nasal inhalation; (2) Metered-dose steroid human drugs for oral inhalation; ... (5) inhalation; (3) Metered-dose adrenergic bronchodilator human drugs for oral inhalation; ... (5) Metered-dose ergotamine tartrate drug products administered by oral inhalation for use in humans; ... (9) Metered-dose nitroglycerin human drugs administered to the oral cavity; (10) Metered-dose cromolyn sodium human drugs administered by oral inhalation; (11) Metered-dose ipratropium bromide for oral inhalation; (12) Metered-dose atropine sulfate aerosol human drugs administered by oral inhalation; (13) Metered-dose nedocromil sodium human drugs administered by oral inhalation." 21 CFR 2.125(e).
27. See letter dated June 24, 1993 from Carl C. Peck, M.D., Director, Center for Drug Evaluation and Research, to Martin Kaplan, M.D., J.D., Director, Drug Regulatory Affairs, Boehringer Ingelheim Pharmaceuticals, Inc. (Docket No. 93P-0110/CP).

Conclusion

28. 43 Fed. Reg. 11301 (March 17, 1978); 44 Fed. Reg. 3960 (January 19, 1979); 44 Fed. Reg. 30334 (May 26, 1979); 45 Fed. Reg. 22902 (April 4, 1980); 51 Fed. Reg. 4590 (February 6, 1986); 52 Fed. Reg. 15716 (April 30, 1987); 54 Fed. Reg. 9033 (March 3, 1989); 55 Fed. Reg. 39266 (September 26, 1990).
29. CAA section 601(8), 42 USC 7671(8) (emphasis added).
30. CAA section 604(d)(2), 42 USC 7671c(d)(2) (emphasis added). *See also* section 605(d)(1).
31. 57 Fed. Reg. 1992, 2002 (January 16, 1992).
32. See 58 Fed. Reg. 4768, 4794 col. 3 (January 15, 1993).
33. 58 Fed. Reg. 15014, 15026 col. 1 (March 18, 1993).
34. Ibid.
35. Weiss, et. al., "An Economic Evaluation of Asthma," New England Journal of Medicine (March 26, 1992).
36. Department of Health and Human Services Report, "Healthy People 2000" (1990).
37. Ibid. at 33-34.

PHOTOCOPY
PRESERVATION

IPAC

Statement to the Parties to the
Montreal Protocol on Substances
that Deplete the Ozone Layer

May 12, 1993

The Likely Availability
of CFC-Free Metered Dose
Inhalers

Note

This report was prepared by the International Pharmaceutical Aerosol Consortium (IPAC), an association of manufacturers and marketers of metered dose inhalers. The members of IPAC are: Abbott Laboratories; Armstrong Pharmaceuticals, Inc.; ASTA Medica AG; Boehringer Ingelheim Pharmaceuticals, Inc.; CIBA-GEIGY Corporation; Fisons plc, Pharmaceutical Division; Glaxo, Inc.; Hoffmann-LaRoche, Inc.; Merck & Co., Inc.; 3M; Norton Healthcare; Rhone-Poulenc Rorer Pharmaceuticals, Inc.; Schering Corporation; and SmithKline Beecham Pharmaceuticals. Contacts are as follows:

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Endnotes

Exhibits

Exhibit A: Timetable for Completing Development of
CFC-Free MDIs

Exhibit B: Comparison of Physical Properties of CFCs
and Possible Substitutes for MDI
Purposes

I. Introduction

This paper analyzes the likely availability of metered dose inhalers ("MDIs") that use substances other than chlorofluorocarbons ("CFCs") as propellants. MDIs are pocket-sized aerosol devices used to deliver accurately measured doses of medicines directly to the pulmonary system. Millions of asthmatics and other sufferers of lung disease depend upon MDIs. The medicines that MDIs deliver are often critical to the maintenance of a normal life; in many cases, they sustain life itself.

In 1991, the UNEP Technical Options Committee on Aerosol Products, Sterilants, Miscellaneous Uses and Carbon Tetrachloride issued the following assessment:

The industry has focused attention on HFA 134a and 227 as both have a low order toxicity in early tests. However, these compounds are not compatible with current surfactants and valve elastomers used in most of the products, and therefore, in most cases, substantial reformulation is necessary. Companies are still searching for a substitute for CFC 11. It is anticipated that in some cases reformulation may be complete by 1993. After that, toxicology and clinical studies will take until mid 1997 to complete, and the regulatory approval process will then take about two more years to complete. *Thus CFC free pressurised inhalation aerosol products will not be available until at least mid 1998, and in some cases not until the end of the century.*¹

In effect, this paper provides an update on the Committee's assessment.

Following an "Executive Summary," this paper gives a background on MDIs, describing what their medical uses are and how they function. It then describes the steps a manufacturer must take to develop an MDI that does not use CFCs; the current status of development, including the current availability of CFC substitutes; and the prospects for successful reformulation of MDIs.

The reader should be aware that this paper is based on information that the members of IPAC hold in common -- for example, the sorts of testing that health authorities require and the length of time that those authorities generally take to review applications. The paper, of necessity, cannot detail the actual progress and plans of individual companies since such information is proprietary. The group as a whole nevertheless regards this paper as being an accurate reflection of the future availability of CFC-free MDIs.

II. Executive Summary

MDI manufacturers are moving rapidly to develop MDIs that do not use CFCs. The industry has identified two promising substitutes for CFCs and has begun joint multi-million-dollar programs of safety testing for those compounds.

Those substitutes, however, are not compatible with most of the current drug formulations and the materials used in MDI devices. Intensive testing and research has been underway to identify and develop compatible formulations and materials. Once pharmaceutical reformulation for a particular MDI product is complete, the new formulation must undergo further toxicology, stability and clinical studies, and review and approval by appropriate governmental authorities worldwide.

MDI products are subject to extensive regulation by national health authorities to ensure safety, efficacy and quality. In virtually all countries, a company may place an MDI on the market only in accordance with a specific license issued by the appropriate authority. If a company wishes to alter an MDI to a significant degree, it must first obtain an amendment to the existing license. The review by health authorities typically is rigorous and searching, especially when the product is intended, as here, for chronic use by millions of particularly vulnerable patients (e.g., children and the elderly). Across the MDI industry, the redevelopment of all MDI products will be a massive undertaking, costing on the order of \$250-500 million.

For the majority of MDI products, the entire development process will proceed into 1998 in most countries, especially the United States. For a few MDIs the process may take even longer. On the other hand, for some MDI products (*i.e.*, those few that are relatively easy to reformulate and that have clear and smooth testing and approval pathways) the process may take less time in a few European countries, possibly coming to completion in 1995. *Thus, CFC-free MDI products will not be available by 1 January 1996 to satisfy the vast bulk of worldwide patient need, and likely will continue to be unavailable for that purpose for several years beyond that time. In this regard, the fundamental thrust of the 1991 report of the UNEP Technical Options Committee remains accurate.*

III. Background

A. Uses of MDIs

MDIs are used primarily to treat asthma and chronic obstructive pulmonary disease (COPD), which includes chronic bronchitis and emphysema. These diseases are characterized by obstruction of the airways and shortness of breath. They are persistently debilitating and can cause death during severe episodes. Approximately 5-10% of the world's population suffers from these diseases. Moreover, the incidence of asthma and COPD is rising.

Since the 1950s, when MDIs were first introduced, they have become the most popular and effective means of delivering medication for the treatment of these diseases. MDIs are safe, reliable, portable, efficient, and cost effective. They are used to deliver various types of medication, including: (i) beta-agonists and anti-cholinergics, which work to open air passageways; (ii) sodium cromoglycate and nedocromil sodium, which act as anti-inflammatories; (iii) corticosteroids, which function also as anti-inflammatory agents and are becoming a primary tool in preventative therapy for asthmatics; and, to a lesser extent, (iv) inhaled xanthines.

A significant amount of new drug development is centered on MDIs. Indeed, a recent survey of more than 60 pharmaceutical companies worldwide revealed that many new drugs may be introduced in MDI form between now and the year 2000.² Improving therapy for asthma and COPD sufferers continues to be the primary focus of this MDI activity, with the development of several new anti-inflammatory drugs as well as long-acting bronchodilators. In addition, certain anti-infectives are being clinically tested which combat infections of the lungs, especially those infections suffered by AIDS patients. MDIs also are viewed increasingly as a way to deliver some drugs systemically. For some drugs, appropriate treatment levels can be achieved in this manner with a much lower dose than might otherwise be required when the drug is taken orally. This can be important with drugs that might produce adverse side effects when taken orally in larger doses. Another benefit of MDI delivery is that therapeutic response is very fast, matching that of intravenous injection.

In 1991, there were approximately 330 million MDI units produced worldwide (about 180 million for the European market, 90 million for the U.S. market, and 60 million elsewhere). More than 200 different MDIs are currently marketed worldwide. The demand for currently produced MDIs is expected to grow by about 3.5% in the United States each year between the present and 2005, and by about 7.5% in Europe each year over the same period. The demand for new MDI drugs is expected to grow substantially as well.

In contrast to the huge numbers of patients relying on MDIs, the volumes of CFCs involved are very small. For example, the total amount of CFCs used in MDIs as propellants in 1991 was only about 6,500 metric tonnes. This quantity is less than one percent of total worldwide production of CFC's in 1986, the base year used in the Protocol for structuring the phaseout schedule.

B. Regulation of MDIs

The conversion of MDIs is subject to extensive regulation by health authorities to ensure safety and efficacy. In virtually all countries, a company may place an MDI on the market only in accordance with a specific license issued by the appropriate national authority. If a company wishes to alter an MDI to a significant degree, including changes in components or the manufacturing process, it must first obtain an amendment to the existing license. In addition, the company with a license typically is subject to oversight and periodic inspection by the authority.

The review by health authorities typically is rigorous and searching, especially when the product, as here, is intended for chronic use by millions of particularly vulnerable patients (e.g., children and the elderly). The sciences of analytical chemistry and toxicology have become increasingly sophisticated, allowing very fine-grained analyses. Evaluation of clinical efficacy in patient populations have become sophisticated and exacting as well, requiring the administration of test products to large numbers of patients prior to approval. Overall, entry to the marketplace in the 1990s is much more difficult and time-consuming than it was in the 1950s when MDIs first appeared.

C. How An MDI Functions

I. Overview

An MDI appears to be a simple device. Its essential components are a storage canister, a medicinal formulation of the drug inside the canister including liquified propellants, a metering valve to control the discharge of precise doses of formulation, and a mouthpiece. When the user actuates the device, the metering valve opens and emits a fine cloud of medication through the mouthpiece.

Inside an MDI, however, there works a complex and delicate interplay of chemical and physical forces. The material in the storage canister consists of several ingredients: (i) a drug, (ii) a propellant (usually a mix of two to three CFCs: CFC-11, CFC-12 and CFC-114), and (iii) a co-solvent or surfactant. The precise make-up of this formulation depends largely on the physical properties (especially density and solubility) of the drug being delivered.

The predominant goal in designing an MDI is the consistent delivery of a specific amount of medication as a very fine mist. The size of the particles in the final aerosol are preferably in the range of 1 to 5 microns to ensure effective deposition in the small passageways of the lungs. The precise repeatable delivery of medication as a fine mist is a major technological achievement.

2. Propellants

Propellants are key ingredients of MDIs. They are what make MDIs work so well. MDIs typically contain as propellants various mixtures of CFC-11, CFC-12 and CFC-114 in liquid form. CFC-12 is usually the major component, providing most of the propellant energy. CFC-11 and CFC-114 are used to moderate pressure and to adjust the density and solubility of the propellant mixture. When stored as a liquid in a closed container at room temperature the mixture of these compounds has a pressure greater than one atmosphere. This pressure forces the drug formulation out of an MDI when the valve is triggered.

The propellants also serve a critical role in creating a very fine mist. Upon release from the MDI, the propellant gases suddenly encounter a temperature well above their boiling point. This causes their flash-evaporation. The result is a very fine mist of whatever drug was suspended or dissolved in the liquified gas.

3. Surfactants and Co-Solvents

There are two basic types of MDI formulations: solution and suspension. In the first type, the medication being delivered is actually dissolved in the liquid contents of the storage canister. In the second type, the medication is suspended. Most MDIs are suspensions.

MDI solutions are less common because most MDI drugs cannot be completely dissolved in a propellant formulation. The propellants themselves are poor solvents. Incomplete solubility leads to uneven dispersion of the drug in the propellant formulation, resulting in the delivery of uneven doses of medication. In those MDIs that are formulated as solutions, it is generally necessary to use a co-solvent, such as ethanol, to increase the solvent capabilities of the propellants. Even with a co-solvent, however, most medications still will not dissolve adequately.

MDIs also contain, in addition to the drug and the propellants, a surface active agent or surfactant. Surfactants are used to create a stable suspension of drug particles, and to provide lubrication for the aerosol metering valve so that it will function effectively without sticking. The physical properties of surfactants also allow them to control the size of the droplets in the final mist by preventing aggregation (clumping) of the small particles. Formulations vary in the surfactant used and its concentration. These variations are necessary to ensure accurate dose delivery of the active ingredient.

The choice of surfactant is an important and difficult step in designing an MDI. The surfactant must be completely soluble in the propellant mix. Furthermore, to ensure uniform suspension of the medication, the medication itself must be completely insoluble in the solution formed by combination of the surfactant and propellants. Any deviation from these conditions will result in unsatisfactory formulations. In practice, there are few surfactants available for use in MDIs which satisfy all the necessary criteria, including lack of

toxicity. The use of other or as yet unidentified surfactants will require lengthy and costly toxicological and clinical evaluations.

4. CFC-11

Along with the medication, propellants CFC-12 and/or -114 and a surfactant (or co-solvent), an important component of many MDIs is CFC-11. In addition to its propellant function, CFC-11 acts as a solubilizing agent for the surfactants used in suspension MDIs. As noted above, both CFC-12 and CFC-114 are poor solubilizing agents, and many surfactants do not dissolve well in them. The addition of CFC-11 to the formulation creates a solution in which surfactants can be dissolved.

In some MDIs CFC-11 also acts to adjust the vapor pressure of the final propellant mixture. CFC-12 has such a high vapor pressure that it is not always ideally suitable for use by itself in MDIs.

CFC-11 also is critical to the manufacturing process, as described in detail in a separate IPAC analysis of that process.

5. The Valve

The type of valve used in an MDI is a "metering" valve, designed to measure each dose precisely. The valve is equipped with a metering tank that surrounds the valve stem and spring. This tank serves to measure each puff precisely. At each end of the tank there is a seal made of an elastomer. When the MDI is used, it is held with the valve pointing downward. This allows liquid to enter the metering tank through its top end. On actuation of the device, the top end of the metering tank is closed off by the elastomeric seal, an opening at the bottom end is unsealed, and the liquid held in the metering tank is released through the valve. The elastomers used to seal the tank must be compatible (*i.e.*, completely nonreactive) with the substances contained in the storage canister.

IV. Development of a CFC-Free MDI

MDIs constitute a highly successful balance of complex forces. The achievement of a similarly successful balance with substitute propellants will take considerable time and effort. A change in one element of the design requires changes in varying degrees in others.

The industry has found two hydrofluoroalkane (HFA) compounds that may serve as replacements for the CFC propellants in MDIs. It is in the midst of testing the safety of these compounds and of trying to combine them with the necessary surfactants, co-solvents and elastomers. But how long the overall process will take no one can predict accurately, largely because the periods of time required for product development and then review by regulatory agencies are highly variable.

Current estimates of the shortest possible time needed for conversion worldwide shows conversion occurring for the bulk of MDIs in 1998. A chart depicting this conversion process is attached as Exhibit A. An explanation of this estimate follows. It first describes the development process in the abstract and then turns to the status of industry's efforts to complete the process.

The description that follows discusses the regulatory review process in the United States by way of illustration. The review process, including timetables, is comparable in other countries, except that in some countries the periods for clinical trials and governmental review are often shorter.

A. The Development Process in General

The major steps in the conversion process are roughly as follows:

- Toxicology studies on alternative HFA propellants
- Formulation development using toxicologically-safe HFA propellant
- Toxicology studies of new formulation using HFA propellant (tests in animals)
- Obtaining government clearance for clinical studies (IND filing)
- Clinical studies of the new formulation (tests in humans)
- Stability testing of the finished MDI product
- Obtaining final government approvals (NDA filing and agency review)
- Market introduction

Some of these steps can be taken concurrently. For example, a company could, and likely would, conduct the costly clinical studies roughly in parallel with the full-blown stability and extended toxicity tests required for final

government approval. In doing this, however, the company runs the risk that the product might fail the formal stability or toxicity tests and have to be reformulated, thus requiring a whole new set of toxicology and clinical studies.

Indeed, many factors work against compression of the development process, and these interact to define a point at which further foreshortening becomes infeasible or impossible. First, certain steps can begin only when another step is completed. For example, toxicology studies cannot begin until a formulation has been identified, and clinical trials cannot begin until a dose range based on pre-clinical studies has been established. Another factor is cost-effectiveness. As described above, companies will sometimes initiate certain steps on the basis of promising preliminary data from an earlier step. However, the more this is done, the more there will be missteps and hence the higher will be the costs of development. At some point, the benefits of schedule compression are outweighed by these inefficiencies. A third factor is logistics. Designing and conducting tests in both the formulation and toxicology stages, identifying patients for clinical studies and then working with those patients, assembling and analyzing data, writing reports for submission to the government, and designing and setting up manufacturing capabilities, among other tasks, all demand a certain minimum amount of time, especially when patient lives and welfare are at stake. The final and most immutable factor is regulatory oversight and approval. The amount of time that this takes is largely in the hands of the relevant agencies worldwide.

B. Making a New MDI -- the Development Process in Detail

1. Formulation Development

The first stage in the formulation process is to identify a non-ozone depleting propellant. None of the MDI makers produce their own propellants; instead, they acquire them from third-party producers. Hence, an alternative propellant must be chosen from among the potential CFC replacements that are or are going to be produced on a commercial scale by third parties.

Once a company has identified a propellant candidate, it must determine the chemical and physical compatibility of the propellant with the other elements of the MDI -- the drug, the surfactant or co-solvent, any other propellant and excipient, and the elastomers in the valves. It must work to resolve any incompatibilities by experimenting with available alternatives to the other elements. Conceivably, the company might have to find an entirely new substitute element, for instance, a new elastomer to go with the new propellants. A company might invent such a substitute itself, or might have to rely on another supplier of components to create such an invention.

How long this reformulation process will take is uncertain. Obviously, it will vary among the many different MDIs currently on the market. In the final analysis, reformulation efforts alone of a given MDI are expected to take anywhere from two to four years, with the average time required to complete the process being about three years.

Companies generally will begin designing and evaluating possible changes in the manufacturing process simultaneously with reformulation. This makes it possible to begin full-scale production at the earliest possible date, and also to identify any unusual manufacturing problems that may accompany a new formulation and therefore impinge on the design of the formulation itself.

2. Toxicology Studies

In order to market a new MDI, a company will have to show that each ingredient, and the combination of ingredients present in the final product, is safe for human use. This requires toxicity testing of both the new ingredient, as well as the final product, in animals. Upon establishing the safety of the new ingredient in an extensive battery of toxicity tests, the safety of the final product also will be tested, albeit to a lesser extent, to assure that no new or increased incidence of toxicities result from the combination of products found in the final formulation.

The rate-limiting pathway for toxicology testing and evaluation of a new propellant consists of three separate consecutive stages of testing performed in two species of animals (usually mice and rats). These stages are: (i) acute studies, (ii) subchronic studies, and (iii) carcinogenicity studies. The acute studies are designed to establish the lethal limits of toxicity of the compound. Based on the results of the acute studies, doses are selected for the testing of long-term tolerance in subchronic studies. These studies generally last three months. One aim of the subchronic studies is to use doses high enough to establish a maximum tolerated dose (MTD) or maximum feasible dose (MFD) for subsequent use in the carcinogenicity studies. The purpose of these studies is largely to determine whether the substance tested is carcinogenic. This requires daily exposure to the propellant at an MTD or MFD (and one or more lower doses) for a period of up to two years. Following the completion of the in-life portion of the carcinogenicity study, an additional year or more is required for pathological evaluation of the data resulting from the study.

Thus, the time required for conducting toxicity studies breaks down approximately as follows:

Acute Studies	1 - 2 mos.
Subchronic Studies	8 - 10 mos.
Chronic Studies	<u>3 - 4 yrs.</u>
Total	3.75 - 5 yrs.

(Additional non-rate-limiting testing required for approval of the propellant includes, but is not limited to, genetic toxicity testing; reproductive toxicology testing; and acute, subchronic and chronic testing in a non-rodent species.)

This entire spectrum of testing may not be necessary for all additional individual components that might be needed to prepare an acceptable MDI formulation. The degree of required testing depends upon whether the substance has previously been approved for inhalation use or is GRAS ("generally regarded as safe" for pharmaceutical uses). Similarly, the entire range of studies may not be necessary to establish the safety of the combination of ingredients; subchronic studies might well suffice. Therefore, it is likely that supplemental studies, required to establish the safety of the completely reformulated product, would not be a time-limiting factor in completion of the development process.

3. IND Filing

Before any new drug formulation can be tested in humans in the United States, a completed IND (Investigational New Drug) application must be filed with FDA. The IND report may include acute toxicity data from at least two species, at least 30 days of subchronic toxicity data from two species (one rodent and one non-rodent) and genotoxicity studies. These tests may have to be conducted on individual, previously untested components of the reformulation, as well as on the complete reformulation as it is intended to be administered. Preparing a report for a 30-day toxicity study usually takes about 6 months and is the rate-limiting step in this filing process. Therefore, upon product reformulation and successful production of an acceptable MDI device for administration of the product, a minimum of 6 months usually is required prior to filing an IND to allow for safety testing in animals. Assuming that the IND report is found acceptable, clinical studies on humans can begin 30 days later.

4. Stability Testing

The purpose of stability testing is to determine whether a product will remain stable throughout its indicated shelf life. The tests look for any deterioration or breakdown of the formula, the storage canister, or the valves over time. FDA regulations require that a new pharmaceutical product cannot be approved for sale until it undergoes stability testing for a period of time equal to its stated shelf life. FDA requires that the tests must be carried out on three full-scale production batches of the product, manufactured in the actual plant that will be used for commercial production after approval is obtained.

This formal testing can begin only after reformulation and retooling of the manufacturing process is complete. Due to the logistics of production, distribution, sale and consumption, the minimum practical shelf life for MDIs is two years. Thus, stability tests have to continue at least for two years, plus several months for data evaluation and report generation.

5. Clinical Studies

Clinical trials are clearly the most critical and difficult step in the drug development process. If the drug survives the rigors of clinical testing, the FDA's ultimate approval decision will be based primarily upon data derived from these studies. FDA estimates that as much as 80 percent of the average NDA (New Drug Application) consists of clinical data alone.

Generally, clinical studies begin and proceed cautiously. As long as the results are favorable, an investigational drug is tested in progressively larger population groups and, in some cases, over longer periods and in higher doses. Although there is no statutory requirement dictating clinical trial structure and design, a clinical drug development program most often proceeds in at least three phases:

Phase I: This is the cautious use of a drug in a few normal human volunteers (usually 20 to 80 subjects) to gain basic safety and pharmacological information. Specifically, these pharmacology studies help the sponsor to determine toxicity, metabolism, absorption, elimination, and other pertinent pharmacological actions, and to find a preferred route of administration and safe dosage range. Phase I studies last an average of six months to a year. [Mean duration of phase development: 14 months.]

Phase II: This is the use of the compound in a small number of patients (100-200) who suffer from the disease or condition that the drug is proposed to treat, prevent or diagnose. Phase II trials give additional safety data and provide the first indication of a drug's clinical effectiveness in its proposed use. [Mean duration of phase development: 24 months.]

Phase III: This is use of the drug in a significantly larger group of patients who suffer from the disease or the condition in question. Phase III trials are designed to assess a drug's safety and effectiveness and to help determine the best dosage in a larger and more varied patient population. The trials may involve several hundred to several thousand patients, enrolled at several sites and treated for a period of several months or longer, especially in the case of asthma. [Mean duration of phase development: 38 Months.]

Thus, the total time needed to conduct clinical studies in the United States normally ranges from 3 to 6 years. In the case of some reformulated MDIs, the clinical program requirements may be less.

Some countries, notably some European countries, do not require as much clinical testing as does the United States. Hence, the total time needed to meet the requirements of those countries in the case of MDIs would be shorter, possibly on the order of 2 years.

6. Final
Approval --
The NDA
Process

Once all the pharmaceutical formulation toxicology and clinical studies have been completed, and all reports have been assembled, an NDA can be filed. This initiates formal government review of a new product. FDA review of a NDA generally takes between 2 and 3 years. Review by authorities in other countries generally takes considerably less time.

Although some companies normally try to complete all stability testing prior to filing the NDA, this is not absolutely necessary. Stability testing can continue during the NDA review process, and the NDA can be updated once testing is complete. Nevertheless, at least some stability testing will be required prior to filing the NDA. Toxicology and clinical studies, however, must be completed along with full reports prior to filing the NDA.

C. Where the Industry
Stands

MDI manufacturers are moving as quickly as possible to develop CFC-free MDIs and have taken substantial strides in that direction. They have identified two new potential compounds -- HFA-134a and HFA-227 -- each of which appear to meet the physical property requirements for liquid gas propellants within an MDI. Companies have entered into cooperative agreements in two separate joint ventures (IPACT-I and IPACT-II) to facilitate the rapid completion of inhalation toxicology testing on these compounds. The testing for HFA-134a started in mid-1990. The longest and therefore rate-limiting study in that program is a 24-month carcinogenicity bioassay in the mouse. The final report, including histopathology, for that study will not be available until Spring 1994. The testing for HFA-227 started in March 1991. The rate-limiting 24-month bioassays in rodents will be available in early 1995. These timeframes are reflected in Exhibit A. At least one company is performing inhalation toxicology testing of HFA-134a independently of the joint program. However, the data from its testing will not likely be available to the industry as a whole significantly prior to the availability of data from the joint program.

Manufacturers have been seeking individually to devise workable formulations with these compounds as propellants. There remains great uncertainty as to when this process will be complete. For a few products, this reformulation process may have been completed already with enough toxicology testing to allow filing of an IND. For other products, this process is expected to take up to one more year to complete (*i.e.*, early to late 1994). For this reason, it is not possible to ascertain a date by when the industry as a whole will be done with the reformulation process.

Once IND reports are filed, the timetable for completing the development process is relatively constant. Exhibit A shows IPAC's best estimate of the shortest timelines for each separate stage in the process in the United States. Completion of government review likely will occur for those MDIs which are easiest to develop in mid-1997; for the bulk of MDIs in 1998; and the rest in 1999. Of course, the process could take more or less time. It may take less time in Europe for the MDIs that are relatively easy to reformulate and have

clear, smooth clinical and regulatory pathways, possibly resulting in the issuance of marketing authorizations somewhat earlier by one or two countries. Whether such early completion will occur is highly speculative. Likewise, it is highly speculative what acceptance the new devices may come to enjoy among physicians and patients.

At this time, uncertainty in development arises largely in two areas: the reformulation stage and the toxicology testing stage. The following discussion focuses on the reformulation process. Of course, if any problems arise during toxicology testing of any compound chosen for use during the reformulation stage, then manufacturers will have to return to this stage and re-conduct the formulation development processes described above.

1. Alternative Propellants

Chemical producers offer a wide range of CFC substitutes, principally for refrigeration, air-conditioning, foam blowing, and cleaning. However, of these compounds, only HFA-134a and HFA-227 hold promise for MDI use.

None of the other CFC alternatives offered to date is appropriate. While some of these substances have suitable density and vapor pressures, they each present problems. A chart comparing all available CFC substitutes for MDI purposes appears as Exhibit B to this paper.

HCFCs are being considered as CFC substitutes by a number of different industries. None of these substances offers any advantages over HFA-227 and HFA-134a; nor do they have all the properties necessary to qualify as suitable replacement candidates for CFC-11. As a starting point, HCFCs include chlorine and therefore have ozone-depletion potential. HFA-134a and HFA-227 do not contain chlorine and therefore do not have any such potential. HCFCs are expected to be phased-out not long after the final ban on CFCs becomes effective. In view of the lengthy time period (*i.e.*, 8-12 years) and high cost for developing a new MDI product, HCFCs are very unattractive candidates. Furthermore, of the five HCFCs that are expected to be commercially available, only HCFC-124, HCFC-142b and HCFC-22 have vapor pressures possibly suitable for use as propellants (although that of HCFC-142b is too low and that of HCFC-22 is far too high for either compound to be used by itself). Moreover, both HCFC-124 and HCFC-142b have been shown to be moderate cardiac sensitizers, HCFC-142b is flammable, and the chronic toxicology profiles of HCFC-22 and HCFC-123 are of concern for chronic use in patients.

The available non-chlorinated compounds besides HFA-227 and HFA-134a also offer no advantages. HFA-152a is flammable and has been shown to have undesirable anesthetic effects. HFA-125 has an extremely high vapor pressure, and has been shown to generate a low order of acute inhalation toxicity.

Hydrocarbons also are being considered as CFC substitutes by a number of industries. However, they present two significant problems. First, they are very flammable. Hence, in some formulations they would present a hazard

to patients, in particular, their mouths and hands. The second problem presents a more difficult hurdle to surmount -- the very real problem of taste. Simply put, hydrocarbons have a poor taste. While adjuvants are available to mask the taste they present risks of toxicity which should be avoided if possible, especially in patients with allergic asthma, and in any event would require testing in their own right. Moreover, every such substance may increase pulmonary irritation, thus undermining the effectiveness of MDI treatment.

2. Surfactants

Studies to date indicate that HFA-134a and HFA-227 are not generally compatible with the surfactants currently used in MDIs. Thus, it appears that either new surfactants or novel co-solvents will have to be used. Either approach could lengthen the development and testing phases.

3. CFC-11

To date, there is no suitable replacement candidate for CFC-11 in MDIs. The only potential alternatives are the HCFCs and hydrocarbons. Of the HCFCs, only HCFC-123 and HCFC-141b have suitable vapor pressures. However, HCFC-141b is flammable and has been shown to be a strong cardiac sensitizer and HCFC-123 has been shown to be a moderate cardiac sensitizer.

As for the hydrocarbons, n-butane, isopentane and n-pentane have vapor pressures relatively similar to that of CFC-11. However, they have very low densities and, as discussed above, are extremely flammable, making them much less desirable alternatives. In addition, each would have to undergo extensive inhalation toxicity testing as none have a history of chronic inhalation for medical purposes.

4. Valve
Elastomers

Another critical element in the reformulation process is elastomer compatibility. New elastomers have to be found and tested that are compatible with the reformulated MDI products. This is a difficult task. The valve, and hence the elastomer it uses, are critical to the achievement of an accurate, reproducible and effective dose. Moreover, the valve and elastomer must work properly throughout the life of the product. Finally, it must be possible to remove any extractables in the elastomer to acceptable levels. Thus, the design specifications for the elastomer are demanding and narrowly defined.

D. Challenges
Remaining

Despite aggressive action by MDI manufacturers, there is still generally a long way to go before CFC-free MDIs will be commercially available. The industry, for example, still must complete toxicology, stability and clinical testing and validation of final production facilities. Finally, it must undergo the intensive and potentially lengthy review of new products that FDA and other health

authorities conduct. The chances are fair that the industry as a whole may succeed by 1998-1999. But many problems could arise that would slow the development process -- the safety or stability studies, for instance, could produce adverse results.

V. Conclusion

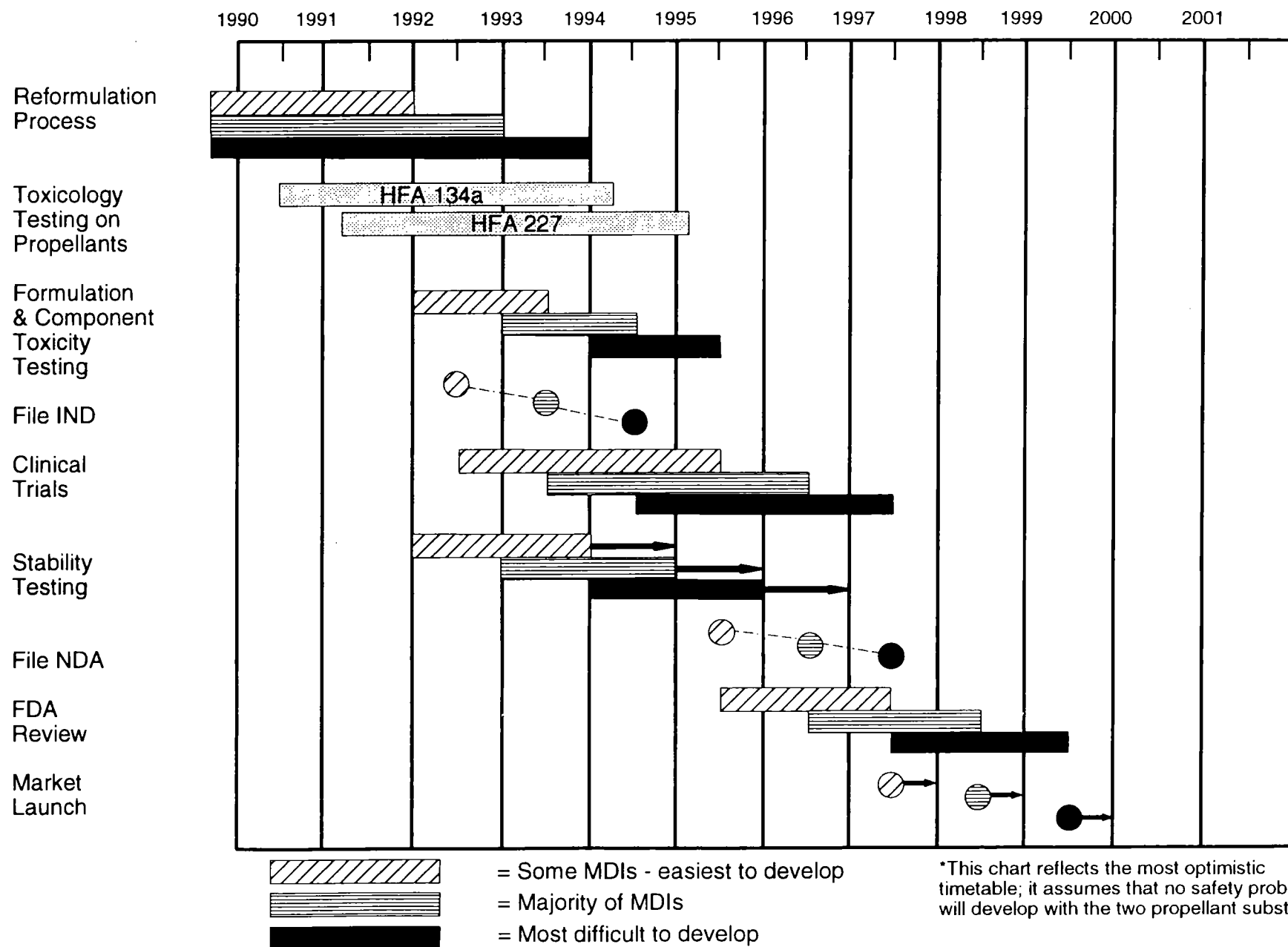
MDI makers are following the most expedited course of development, accelerating or overlapping steps in the process whenever possible. Even so, the majority of MDIs likely will not be available to the worldwide public in a CFC-free form until 1998-1999 at the earliest, although a few may be available in a few European countries at a somewhat earlier time. The early introduction of some, but not all, reformulated MDIs will not provide physicians with the full range of drug choices now available. The access to a full variety of drug types must be maintained to help insure the effective management of asthma and related respiratory diseases. No single pharmaceutical company provides the full range of current drug types. Thus, the general thrust of the 1991 report of the UNEP Technical Options Committee on Aerosol Products remains valid today.

Endnotes

1. Report by the Technical Options Committee on Aerosol Products, Sterilants, Miscellaneous Uses and Carbon Tetrachloride, 34 (December 1991)(emphasis added).
2. Pharmaceutical Aerosol CFC Coalition (PACC), An Analysis of Present and Future Worldwide Usage of Chlorofluorocarbons in Metered Dose Inhalers (June 1992).

TIMETABLE FOR COMPLETING DEVELOPMENT OF CFC-FREE MDIs IN THE UNITED STATES*

Exhibit A



Comparison of Physical Properties of CFCs and Possible Substitutes for MDI Purposes

	Density (g/ml, 20°C)	VP (PSIG, 20°C)	BP (C)	Flamma- bility	ODP	Comment
<u>CFCs</u>						
CFC-11	1.79	-1.8	24	none	1.0	
CFC-12	1.33	67.6	-30	none	1.0	
CFC-114	1.47	11.9	4	none	1.0	
<u>MDI Formulation</u>						
CFC-11,12&114	1.4	50	--	none	1.0	
<u>HCFCs</u>						
HCFC-22	1.21	121	-41	none	0.05	very low acute toxicity
HCFC-123	1.47	0	28	none	0.02	moderate cardiac sensitiser; anesthetic property; effect on liver enzymes
HCFC-124	1.38	46	10	none	0.02	moderate cardiac sensitiser; very low acute toxicity
HCFC-141b	1.26	0	32	yes	0.1	strong cardiac sensitiser; low acute toxicity
HCFC-142b	1.12	29.1	-10	yes	0.06	moderate cardiac sensitiser; very low acute toxicity
<u>HFCs (HFA)</u>						
HFA-125	1.23	165	-55	none	0	some acute inhalation toxicity
HFA-134a	1.22	81	-27	none	0	very low acute toxicity
HFA-152a	0.91	62	-25	yes	0	has an anesthetic effect; very low acute toxicity, weak cardiac sensitizer
HFA-227	1.41	59	-17	none	0	very low acute inhalation toxicity
<u>Hydrocarbons</u>						
n-Butane	0.58	17	0	high		flammable, poor taste, lack of full toxicity data
n-Pentane	0.63	-23	36	high		
n-Propane	0.50	108.1	-44	high		
Isobutane	0.56	31.1	11	high		
Isopentane	0.62	-3.2	82	high		
Dimethyl Ether	0.66	63	-12.7	high		low order of both acute and chronic toxicity

**PHOTOCOPY
PRESERVATION**

IPAC

Statement to the Parties to the
Montreal Protocol on Substances
that Deplete the Ozone Layer

May 12, 1993

Consumption and Emissions
of CFCs During the
Manufacturing of Metered
Dose Inhalers

Note

This report was prepared by the International Pharmaceutical Aerosol Consortium (IPAC), an association of manufacturers and marketers of metered dose inhalers. The members of IPAC are: Abbott Laboratories; Armstrong Pharmaceuticals, Inc.; ASTA Medica AG; Boehringer Ingelheim Pharmaceuticals, Inc.; CIBA-GEIGY Corporation; Fisons plc, Pharmaceutical Division; Glaxo, Inc.; Hoffmann-LaRoche, Inc.; Merck & Co., Inc.; 3M; Norton Healthcare; Rhone-Poulenc Rorer Pharmaceuticals, Inc.; Schering Corporation; and SmithKline Beecham Pharmaceuticals. Contacts are as follows:

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I. Introduction

About 85 percent of the CFCs required each year for metered dose inhalers (MDIs) are contained in the MDI canisters used by patients; the balance, about 15 percent of the total, do not reach the patient community, but are consumed or emitted during the MDI manufacturing process. Companies are working hard to reduce this amount.

CFCs are consumed or emitted in several different ways during MDI manufacturing. The main propellants used for MDIs are CFC-11, CFC-12 and CFC-114. Small amounts of these compounds are emitted during material transfer operations, product mixing and canister filling. CFC-11 and, to a lesser extent, CFC-113 are used to clean certain of the manufacturing equipment, particularly mixing vessels and filling machines. The elastomeric components of the MDI valves are prepared in a process that uses CFC-11 to extract/remove extractable contaminants before introduction into the final product and delivery to the patient. Finally, after being filled and sealed, each individual MDI unit is actuated three to four times to ensure proper quality of the system resulting in the release of three to four doses of the propellant/drug formulation.

At present, more than half of the CFCs consumed during the manufacturing of MDIs are captured and either reclaimed or destroyed. The balance, about 7 percent of the overall usage of CFCs for MDIs, are emitted to the environment during the manufacturing process. During 1992, such emissions amounted to less than 500 tons of CFCs, or less than 0.1 percent of worldwide CFC emissions.

Substantial reductions already have been achieved in both consumption and emissions of CFCs during MDI manufacturing. Several years ago, manufacturing consumption probably accounted for about 30 percent of the total amount of CFCs used for MDIs, and most of this amount was emitted to the atmosphere. Thus, the industry already has reduced total manufacturing consumption by about 50 percent, and manufacturing emissions by more than 75 percent. Both emissions and consumption of CFCs during the manufacturing process will decline further over the next several years as the industry continues to improve control technologies.

To the extent that efforts to control consumption and emissions of CFCs involve changes in the manufacturing process or in product formulation, they must be validated and approved by regulatory health authorities for both safety and efficacy. As a result, the pace at which certain types of improvements can be implemented is controlled by the pace of regulatory review and approval of amendments to previously-filed product and process descriptions. Such review and approval can take several years.

This paper analyzes in a general manner the consumption and emissions of CFCs that occur during the MDI manufacturing process, and describes some of the industry's efforts to minimize such consumption and emissions and to enhance the recovery and recycling of CFCs. This paper, including the estimates of manufacturing consumption and emissions, is based on

Introduction

information obtained from various members of the International Pharmaceutical Aerosol Consortium (IPAC) through interviews with in-company experts.

II. Discussion

For purposes of this discussion, the various uses of CFCs during the MDI manufacturing process can be classified into several general categories, in accordance with the following different stages of the process: (i) material handling and transfer processes; (ii) blending and filling operations; (iii) product testing; (iv) cleaning operations; and (v) component manufacture. Each of these general stages and its concomitant CFC usage is described separately below. The discussion herein is necessarily somewhat general, as each company has designed and developed its own distinct methods of operation, and details of such processes are proprietary.

The term "consumption" is used in this paper to denote the usage of CFCs stemming directly from the manufacture of MDIs; all CFCs required for making MDIs, apart from the amount actually contained in canisters delivered to patients, are, for the purpose of this paper, considered "consumed" during manufacturing. This includes all CFCs disposed of or destroyed as waste, recycled for use in other industries, or emitted to the environment during MDI manufacturing.

A. Material Handling and Transfer Processes

The first step in the manufacturing process is, of course, the delivery of raw material to the manufacturing facility. CFCs usually arrive in tank trucks, and also may be delivered in large canisters. The different types of CFCs may be delivered separately or pre-blended to product specification. Upon arrival, the materials are transferred from the delivery vehicle to large, permanent, on-site storage tanks. A small amount of material is emitted to the environment during this transfer operation.

These emissions are minimized in a number of ways. Most importantly, a vapor return hose is used during the transfer operation so that, as the storage tank is filled, vapor from the top of the tank flows back into the delivery vehicle rather than being vented to the atmosphere. In addition, delivery trucks and canisters often are dedicated to a single type of material, and therefore do not need to be vented and cleaned between deliveries. Further, companies have begun to use permanent in-line filters during the transfer operation, rather than disposable filters, thus reducing the potential for leakage.

The transfer of raw material from the delivery vehicles to the storage tanks generally is made via flexible, temporary hoses. Upon completion of the transfer, these hoses are pumped dry of any liquid material, valves on the delivery and storage tanks are shut, and the hoses are disconnected, thus releasing to the atmosphere the CFC vapor remaining in the hose after it is drained of liquid. This release of vapor constitutes the majority of material emitted during the transfer operation. The hoses are not pumped free of vapor because the amount of material left in the hoses is negligible. During the transfer of a twenty-ton load, for example, less than twelve pounds of material might be lost as vapor.

Once in the storage tanks, material is held until needed. There is virtually no leakage of material from storage tanks. This is monitored by frequent recording of gauge readings.

From the storage tanks, material is transferred to blending or mixing vessels, and thence to the filling lines. During these transfer operations, there is, as with any transfer procedure, some small loss of material. Steps are being taken to minimize such losses. For example, where once it may have been the norm to use temporary, flexible hosing to carry out these transfer procedures, companies have, wherever possible, installed permanent, hard piping. This has reduced vapor emissions, as the permanent transfer conduits do not need to be drained, disconnected and vented between runs.

A main potential leakage point in the transfer network is the pumps; if a pump breaks, the liquid contents of the transfer conduit may be vented to the atmosphere. Although such an occurrence is rare in the first instance, companies have reduced the potential for losses from pump failure by installing on either side of the pumps electronic sensors and automatic valves which act immediately to close off and isolate a pump in the event of a sudden loss in pressure or increase in flow rate. In addition, listening devices have been attached to pumps in order to detect the change in sound that occurs when a pump is about to fail; this allows for the pump to be replaced prior to actual failure.

Even with hard piping, there may be some leakage of material at connection points, valves and elbows in the piping. Such leakage can be minimized by keeping the number of connection points to a minimum. Companies are acting to minimize losses by installing new transfer piping networks with fewer elbows and connection points, redesigning fittings and seals to operate more efficiently, and by installing in-line sensors and shut-off valves adjacent to connection points to prevent catastrophic losses. All Companies have inspection and maintenance programs to detect, prevent and remedy leaks, even small ones, as quickly and effectively as possible.

B. Blending and Filling Operations

During both blending and filling operations, CFCs are maintained in a liquid state. This is accomplished either by keeping the propellants pressurized, or by chilling them to temperatures below their respective boiling points. The blending and filling procedures differ somewhat depending on the method used to keep the CFCs in a liquid state.

1. Formulation Blending

Formulation blending (*i.e.*, the blending of pharmaceutical active ingredient(s), CFC-11, other excipients, and, in the case of cold filling and certain pressure filling operations, the higher pressure CFC propellants) takes place in sealed compounding vessels (the different cold filling and pressure filling procedures are discussed in detail below). These vessels are much smaller than the on-site storage tanks; they may hold, for example, only about 150 gallons of material.

Liquid CFCs are transferred from the storage tanks directly into the compounding vessels, generally through a system of hard piping. With cold filling operations, the CFCs may be chilled prior to being put into the compounder, or the chilling might take place once they are already in the compounder. The chilled compounding vessels do not need to be pressurized, as the CFCs are maintained at temperatures below their boiling points; hence, the refrigeration system itself acts as a vapor control system. With pressure filling, formulation blending takes place in pressurized storage tanks.

From the compounding vessels, the blended formulation is pumped through conduits to the filling line. The vessels themselves, however, are not pumped dry of formulation. Instead, about one or two gallons of the liquid formulation remain in the bottom of the blending vessel after each run. This residual amount becomes waste. It cannot be used because of technical difficulties in pumping the vessel dry and because it is difficult to ensure the consistency of the formulation once the level of liquid in the vessel drops below a certain point.

After each production run, the waste material in the bottom of the mixing vessel is drained off and pumped into sealed drums or tanks for disposal. The liquid CFCs contained in this waste are not allowed to evaporate to the atmosphere. Instead, companies generally pay a waste disposer to carry the material away for destruction through thermal oxidation. Recently, there has been increasing interest in recycling some of the CFCs contained in this waste material, and processes are beginning to be commercialized for doing so. This recycled material is inappropriate for use in pharmaceutical products as it is not pure enough to meet product specifications and regulatory requirements; it can, however, be used for cleaning purposes and by other industries.

Once the compounding vessel is drained of all liquid waste, it is opened for cleaning in preparation for the next production run. A small amount of vapor may be released as the vessel is opened. Because the temperature in the vessel is well below the boiling point of any propellants, the amount of vapor released in this way is very small. It is difficult to capture this vapor. To some extent carbon absorption equipment is used generally within manufacturing facilities to capture streams of fugitive emissions which may arise during the various stages of the manufacturing process. This method of recovery does not work efficiently, however, particularly when pharmaceutical actives and other ingredients are present in the emissions. Companies are taking other steps to minimize emissions during the formulation blending process. For example, seals on blending vessels have been redesigned and improved to minimize any losses. In addition, the industry is moving towards the use of completely hermetically sealed vessels, which can be drained and cleaned without ever being vented to the environment.

2. Filling the Canisters

Pressurised vs. Cold Filling

As noted above, there are two different methods for filling MDIs. The first method, known as "pressure filling," utilizes a process whereby liquid propellants are injected under pressure into the sealed canister; hence, the term "pressure filling." With pressure filling, either a one-step or two-step process can be used for filling the canisters. With a two-step process, canisters first are filled with medication (usually a mixture or suspension of the pharmaceutical active ingredient(s), various excipients, and CFC-11, a low pressure CFC) and immediately sealed with the crimping on of the metering valves; subsequently, the higher pressure propellants (CFC-12 or a blend of CFC-12 and CFC-114) are injected into the MDI canister through the valve stem at about 300 to 400 pounds of pressure. With a one-step pressure filling process, the entire formulation (including propellants, pharmaceutical actives, etc.) is pre-blended and injected into an empty sealed canister all at once.

The other filling method is known as "cold filling." In this process, the CFC propellants are chilled to a temperature far below their boiling points and blended together with the pharmaceutical active(s) in solution or suspension and other ingredients of the product formulation. The blended formulation then is transferred to the filling line through a system of insulated pipes and cryogenic pumps and, while still being kept chilled, is filled into the MDI canisters, whereupon the canisters immediately are sealed with the crimping on of the metering valves. Although less common, some cold filling procedures utilize a two-step filling process, whereby the chilled propellants are filled into the canister separately from the rest of the formulation; the choice between one or two-step filling depends on the low temperature stability of the pharmaceutical active ingredient(s). Because the formulation ingredients are kept chilled during the cold filling process, it is not necessary that this process be performed under pressure, although enclosed systems are used.

Releases During Canister Filling

With cold filling, as described above, although the lines to the filling head and the filling head itself are enclosed, a small amount of formulation is released to the atmosphere as each canister is filled. During the cold filling process, the filling head delivers a precise amount of chilled liquid formulation into each canister. The canisters are at room temperature (about 55° F) prior to being filled. As the chilled formulation comes into contact with the canister, the first part of the liquid to make contact is vaporized and released to the atmosphere, and the canister is cooled to the temperature of the formulation. The amount of CFCs released in this manner is very small. As soon as the canister is filled, it is sealed with the crimping of a metering valve.

With pressure filling, as noted above, either a one or two-step filling process can be used. If a two-step filling process is used, the first step (*i.e.*, the filling of the canister with a formulation of pharmaceutical active(s), CFC-11, and excipients) is carried out in a manner similar to the cold filling process, except the temperature at which the process is performed does not need to be so low because CFC-11 is not very volatile. The injection into the canister of the liquid propellant or, if a one-step filling process is used, the entire formulation,

is carried out as follows: a gassing adapter attaches to the top of the metering valve on the sealed canister; a precisely measured amount of propellant (CFC-12 or a blend of CFC-12 and CFC-114) or blended formulation is injected into the canister; a filling valve within the gassing adapter closes; and the gassing adapter releases itself and moves away from the canister. As the gassing adapter releases and moves away from the valve stem, a small puff of propellant or formulation is released to the atmosphere. This occurs because inside the gassing adapter there is a tiny cavity between the filling valve and the top of the canister. This space remains filled with liquid propellant after the filling of the canister is completed and the filling valve has closed. This cavity space is a necessary element of the design of the machinery, as it allows for the movement of the filling valve within the gassing adapter. About 0.1 to 0.25 ml. of liquid propellant is emitted to the atmosphere in this manner each time a canister is pressure filled.

On a per-canister basis, the two different filling processes consume a roughly equivalent amount of CFCs. Companies are taking steps to reduce consumption of CFCs at the filling stage. For example, instead of using off-the-shelf gassing adapters which are commercially available for aerosol canister filling generally, the industry has begun using gassing adapters that are designed and built especially for MDIs. These special gassing adapters have a cavity of minimal size within the mechanism, and thus they minimize the release of propellant. It is difficult, to capture the vapor lost at the point of filling. To ensure formulation consistency and efficacy, it is necessary to maintain precise environmental conditions at the filling head, particularly as to temperature, pressure and humidity. The use of control equipment tends to alter these conditions in an unacceptable manner. Any changes in process would, of course, have to be validated and approved by regulatory authorities.

C. Product Testing

Each MDI canister is actuated three to four times after it is filled and sealed to ensure that the metering valve functions in accordance with established parameters. The formulation released during these activations is vacuumed and vented to the outside atmosphere. This constitutes the largest single source of CFC emissions during the manufacturing process. Companies are exploring ways to capture these emissions, but there are technical difficulties in doing so, particularly due to the presence of active medication and excipients.

The formulation itself is tested at various stages during the manufacturing process to ensure compliance with product specification, in accordance with regulatory requirements. At the beginning of each production run, a number of canisters also are tested for the purpose of validating that canisters are being produced in accordance with production specifications set forth in regulatory filings and approvals. Further canister testing is conducted periodically during a production run. In addition, a number of canisters from each production batch are retained for stability testing.

Any rejected batches are disposed of in the same manner as are other captured waste materials. They are placed in sealed containers and taken away by a waste disposer. There is ongoing investigation of ways to recycle the contents of these waste canisters, rather than merely destroying them, and methods are beginning to be commercialized for doing so.

D. Cleaning Processes

CFCs are used in cleaning equipment used for MDI production, particularly the formulating vessels and lines. CFC-11 is used for this purpose not only because it is a very good solvent, but also because it is already present in the final formulation and therefore its use diminishes the risk of product contamination by extraneous substances. To a small extent, CFC-113 is also used by some companies for cleaning purposes.

Companies are taking steps to reduce the use of CFCs for cleaning purposes. Both consumption and emissions of CFCs from cleaning processes have been reduced substantially. For example, companies have begun to use other solvents in the cleaning process, and generally now use CFC-11 only as a final rinsing agent. Of course, any change of this nature in the manufacturing process requires regulatory approval. In addition, companies have improved their techniques for recapturing the CFC-11 used during the cleaning process, through the use, for example, of enclosed cleaning systems and hermetically sealed vessels.

Waste CFCs from the cleaning process are sent for recycling, and generally used subsequently in other industries. MDI manufacturing companies have taken steps to initiate their own on-site recycling processes, whereby these waste CFCs can be cleaned sufficiently for re-use as cleaning agents within the MDI production process itself.

E. Component Manufacturing

CFCs are used to some extent in the manufacture of the mechanical components of MDIs. These mechanical components generally are manufactured and supplied to the pharmaceutical company by independent suppliers; most MDI manufacturers do not make their own components. The major use in this area is the use of CFC-11 to leach out extractables from the elastomeric seals used in the MDI metering valve. These extractables include contaminants present in the actual raw materials used to make the rubber seals, as well as lubricants and oxidants that are infused into the material during the molding process. CFC-11 is used because it is a good solvent, and also because, since CFC-11 may already be present in the final formulation, its use in component preparation does not lead to the introduction of any new excipient into the final formulation. The removal of the extractables is a necessary step in the manufacturing process. If the extractables were not removed from the seals prior to their insertion in the metering valve, and thence into the filled canister, the contaminants in the seals would be leached

into the drug formulation by the CFC-11 present in the canister, and would thus be administered to patients upon use of the MDI device.

During the extraction process, the rubber seals are placed into an enclosed extraction chamber, and vapor phase or liquid CFC-11 is circulated past the seals until the majority of contaminants have been removed. The CFC-11 used in this process is recirculated in a continuous loop, first past the seals, then through a filter and a fractional distillation column, where the contaminants leached from the seals are collected, and finally the repurified CFC-11 is circulated back through the extraction chamber. When the process is complete, the seals are removed from the chamber and set aside to dry. The seals actually absorb CFC-11 and swell during the extraction process, and it takes about three weeks for them to dry out and revert to their original size and shape, so that they can be fitted into the metering valve.

Because the CFCs used to perform the extraction are repurified and recycled in a continuous enclosed loop, only a small amount actually are consumed or used up during the process. CFCs are so consumed in two different ways. First, the CFCs infused into the seals during the extraction process evaporate and are vented into the environment as the seals dry. This material is very difficult to capture, as it comes out of the seals so slowly, *i.e.*, over a three-week period. Efforts currently are underway to develop systems for preventing this loss of material to the environment; such systems are expected to be commercialized within the industry in the near future. Second, a certain amount of CFC-11 is consumed also as a result of the fractional distillation procedure, and is lost as part of the contaminant sludge that is a waste product of the procedure. This sludge is sealed in waste containers and taken away by a waste disposer for destruction; hence, these CFCs do not enter the environment. Methods currently are being commercialized for the reclamation of the CFCs contained in this sludge.

Alternative extraction methods, which would not use CFCs, are being considered by the industry. These include extraction by ethanol, super critical carbon dioxide, or HFA-134a. None of these alternative methods is yet close to being commercialized. Any such change would require regulatory approval.

Alternative rubber compounds, which would contain fewer extractables, also are being investigated. These too have not yet reached a stage where they can be commercialized. Use of an alternative compound in the seal of any individual type of MDI would require regulatory approval and amendment of the product description on file with regulatory agencies. Any such changes therefore require a number of years to implement.

As the metering valves are produced, a sampling of valves from each production run is performed to ensure proper function and delivery. The valves being tested are crimped onto empty MDI canisters, which are then pressurized with a mixture of a number of propellants. The valves are then

actuated to ensure that they are metering properly, and the filled canisters are retained for stability testing. The CFCs released during this testing procedure are vented to the environment. Only a small amount of CFCs are used in this way.

The total amount of CFCs consumed during MDI component manufacturing accounts for less than 5 percent of overall CFC usage for MDIs. This amount is expected to decline as new control and recycling technology comes into use.

III. Conclusion

Efforts are underway to minimize the amount of CFCs consumed or emitted during the manufacturing process. Substantial reductions already have been achieved, and further reductions are expected over the next several years.

**PHOTOCOPY
PRESERVATION**

**AN ANALYSIS OF PRESENT AND FUTURE WORLDWIDE USAGE OF
CHLOROFLUOROCARBONS IN METERED DOSE INHALERS**

Prepared on behalf of the

PHARMACEUTICAL AEROSOL CFC COALITION

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- Appendix A - Sample Questionnaire (United States)
- Appendix B - Study Protocols
- Appendix C - MDI Products Overview

INTRODUCTION

This report provides an assessment of the amount of chlorofluorocarbons (CFCs) that will be needed worldwide for the production of oral pressurized metered dose inhalers (MDIs) through the year 1999. It has been prepared on behalf of the Pharmaceutical Aerosol CFC Coalition, a group of the 14 largest producers and marketers of MDIs in the United States^{1/}, by The Dunn Group in conjunction with the law firm of Gardner, Carton & Douglas and the accounting firm of Deloitte & Touche. The Dunn Group, located in Wayne, New Jersey, is an independent consulting organization specializing in providing strategic business advice on the respiratory care marketplace.

The objective of this report is to provide information on the amount of CFCs that will be needed for use as propellants in MDI products between now and the end of the century, assuming that no alternative propellants will be available and approved for use in patient therapy before that time.

The study focuses on both present and future usage of CFCs in MDIs. It provides these usage estimates both on a worldwide basis, and also separately for each of the following five geographic regions:

- United States
- Europe
- Canada
- Japan
- Rest of World

Further, the report also differentiates between presently marketed MDI products and MDI products that are forecast to be introduced to market sometime before the year 2000, and provides separate estimates of CFC usage in each of these two categories of products (as well as overall usage estimates).

^{1/} These companies are Abbott Laboratories; Armstrong Pharmaceuticals, Inc.; Boehringer Ingelheim Pharmaceuticals, Inc.; CIBA-Geigy Corporation; Fisons Corporation; Glaxo Inc.; Hoffmann-LaRoche, Inc.; ICI Pharmaceuticals Group; Merck & Co., Inc.; Minnesota Mining & Manufacturing Company; Rhône-Poulenc Rorer Pharmaceuticals, Inc.; Schering-Plough Corporation; SmithKline Beecham Pharmaceuticals; and Whitehall Laboratories. Beginning May 1, 1992, the Pharmaceutical Aerosol CFC Coalition was dissolved formally as a group and these companies joined with a number of European pharmaceutical companies to form a new industry group having a purpose similar to that of the old group but one that is more international in scope.

The data for this report was gathered from two separate sources of information: (i) a worldwide survey of companies that market MDIs; and (ii) research conducted by The Dunn Group.

To conduct the survey, a questionnaire directed at MDI marketing companies was designed to solicit information about current and forecast MDI sales and CFC usage in MDIs. A copy of the questionnaire appears as Appendix A. Questionnaires were distributed on October 31, 1991 to 61 different companies around the world. Companies that are active in more than one of the five separate geographical regions were asked to complete a separate questionnaire for each such region. Of the 61 companies that were asked to participate in the survey, 33 responded. A total of 145 questionnaires were completed and returned.

The survey was designed to develop the following information for each separate region:

- Total number of different MDI products or active formulations marketed during 1991 as well as the total number of new products expected in the future.
- Historical growth rate in total amount of CFCs used in MDIs (1986 - 1999);
- Total number of MDI units produced during 1991, by product type;
- Average quantity of CFCs used per MDI unit, by product type and type of CFC (i.e., CFC-11, -12 or -114);
- Estimates of future CFC usage in MDIs by product type and type of CFC for both presently marketed and forecast new MDI products.

The questionnaire requested information for the years 1991 through 2005. However, in preparing this report, a determination was made that the data for the years 2000 through 2005 should not be included based on the difficulty of making forecasts so far into the future and the fact that the final phaseout of CFC production under the Montreal Protocol is currently scheduled to occur at the end of 1999 (in developed countries).

Because the questionnaire requested company specific information, including certain information which may be considered proprietary, guidelines were developed to protect the confidentiality of data from each individual company (see

Appendix B), and the independent accounting firm of Deloitte and Touche was retained to review and summarize the results of the survey. The summary results were used by The Dunn Group to prepare this report. Stuart Friedman was the project supervisor at The Dunn Group in charge of preparing this report.

The second source of information utilized in producing this report was assembled by the independent research of The Dunn Group. Approximately 45 interviews were conducted by The Dunn Group with representatives of a variety of companies in the United States, Canada and Europe, including representatives of CFC propellant manufacturers, MDI marketers, MDI manufacturers, and MDI component suppliers. The intent of these interviews was to validate survey data and quantify independently historic, present and future estimates of MDI sales and CFC usage. The Dunn Group also conducted a review of secondary information sources including trade and business publications and other publicly available data.

The final report is based on a synthesis of both survey data and the data independently generated by The Dunn Group; however, information on future CFC usage in forecast new MDIs is based exclusively on survey data.

In designing the survey and preparing this report, the following assumptions were made:

- that no alternative propellants will be available for use in MDIs marketed to the patient population prior to the year 2000;
- that any future approvals of generic MDI products will have a minimal impact on the overall market for such products;
- that respondents have, as requested in the instructions to the questionnaire, taken into account the future impact that alternative delivery methods (e.g., dry powder inhalers, nebulizers) may have on future MDI unit volumes; and
- that information provided by respondents regarding new products forecast to be introduced during 1992 through 1999 is based on accurate estimates of: (i) dates for completing new product development efforts, (ii) timing for submission of regulatory data packages and receipt of regulatory approvals, and (iii) unit volume usage by patients.

The methodology for this study was verified by comparing data generated by means of the study for the year 1991 (for the United States region) with actual

available figures on total CFC usage in MDIs during 1991. The results of this comparison showed the study methodology to be more than 97% accurate. Of course, the accuracy of the figures reported for each separate region corresponds to the number of respondents and their market shares for each such region. The total response in the United States, Europe and Canada was very high, and thus the reported figures for those regions should be considered to be very accurate (i.e., 90% accurate). For Japan and the Rest of World the response was less, but still quite satisfactory, and therefore the data for these regions should be viewed as relatively accurate.

In assessing the accuracy of the data reported in this study, two other factors are also important. First, the survey solicited information on the amount of CFCs actually used in MDIs, but did not account for additional CFCs used during the production of MDIs (CFCs are used to clean MDI components and a certain amount of CFCs are lost during the filling of MDIs). The figures on CFC usage set forth in this report should be increased by 10% to 15% to account for these additional amounts.

Second, it is not easy to forecast accurately markets for products while they are still under development. Such predictions are difficult at best with new products having an expected market launch date that is still a number of years away. In addition, the questionnaire was designed to generate the most optimistic estimates of the markets for these new products (and hence, the outside upper range of CFC requirements for these new products) and the figures reported herein represent direct input from the questionnaires, without any adjustment. Therefore, the purported new product figures represent the highest possible expected needs for new products. More accurate figures can be obtained if appropriate adjustments are made for likelihood of successful market introduction (only about 1 in 4 products that go into development ever get to market) and the degree to which new products will erode market shares of existing products. These factors can be expected to reduce the CFC needs for new products by up to one-half of the amounts reported herein. Thus, for each year from 1992 through 1999, a range of possible CFC needs for new products can be developed with the respective upper limit equaling the amount set forth herein, and the respective lower limit being equal to one-half of that amount.

This report provides a great deal of detailed information. In order to make this information easily accessible to the reader, the succeeding sections of this report are all structured according to a set pattern to provide information with regard to each respective region on: (i) overall CFC usage; (ii) CFC usage in presently marketed MDIs; and (iii) CFC usage in forecast new MDIs. This pattern has been

designed to provide for consistency between the various sections in order to allow the reader quickly to locate information and identify trends in CFC usage.

Some of the information provided herein is repeated in more than one of the various sections. This has been done intentionally to allow the reader to locate key information without having to study the entire report.

The following people may be contacted to obtain more information about the study:

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WORLDWIDE SUMMARY

I. OVERVIEW OF BOTH PRESENTLY MARKETED AND FUTURE MDI PRODUCTS (1991 through 1999)

A. THE PRESENT WORLDWIDE MDI/CFC PROPELLANT MARKET

- MDIs are the dispensing method of choice to deliver therapeutic actives to treat asthma and chronic obstructive pulmonary disease.
 - MDIs have worldwide acceptance. There are over 210 brands of MDI products sold worldwide by an estimated 50 companies.
 - Total worldwide MDI production was estimated at 337.8 million units in 1991. MDI production volume has grown at a strong rate during the past several years based on consumer and professional acceptance of the MDI and an increasing incidence of respiratory disease.
 - Blends of CFCs are used as propellants for all MDI active formulations.
 - Total worldwide consumption of CFCs used in MDI products was 6,450 metric tons in 1991.
 - The major MDI unit growth trends observed during the past several years are expected to continue in the future.
-

B. NEW MDI PRODUCTS LAUNCHES (1992 through 1999)

- New MDI product activities are targeted to deliver both respiratory care and non-respiratory care active formulations.
 - These activities in the respiratory care area are directed at developing more effective and longer-acting products. Non-respiratory care development is designed to utilize the lung to administer actives to the systemic circulation.
 - Significant company and product activity is ongoing. A total of 58 respondents plan to be active marketers, during the period 1992 through 1999, introducing 115 new MDIs to the market.
-

C. CFC PROPELLANT REQUIREMENTS

1991 through 1999

- In 1991, total CFC propellant consumption in MDI products totaled 6,450 metric tons.
 - During the next eight years (1992 through 1999), this total is forecast to increase at an average annual rate of 11.7% per year, growing to 15,615 metric tons in 1999.
 - This strong growth reflects both the assumed continuation of the need for CFCs by presently marketed MDIs (forecast to grow at 6.9% per year through 1999) combined with major new MDI product efforts.
 - Blends of CFC propellants will be required, with CFC 12 being the single largest propellant type consumed. By year 1999, 73% of total CFC requirements for MDIs will be CFC 12.
 - A summary breakdown of future CFC propellant needs is shown in Table 1. The Table first displays the data in matrix charts by CFC compound and by present and new products. The Table then reformats the data into bar charts, the first two distinguishing between present and future products and the last one giving totals.
-

TABLE 1
FORECAST OF WORLDWIDE CFC PROPELLANT USAGE

Metric Tons

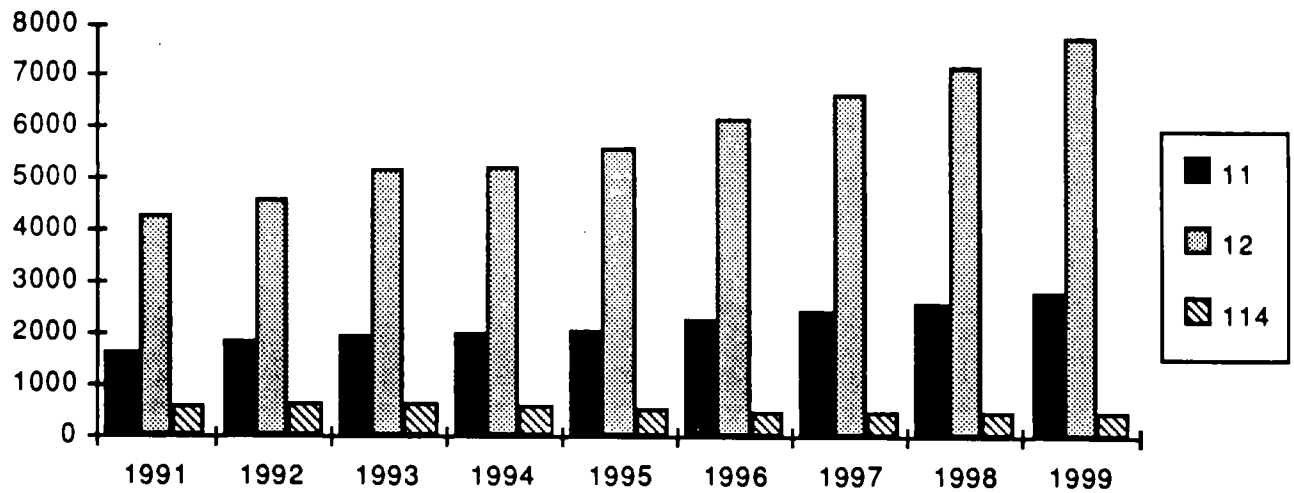
Year	CFC 11		
	Present	New	Total
1991	1,642.1	—	1,642.1
1992	1,817.1	135.1	1,953.2
1993	1,964.2	161.4	2,125.6
1994	1,970.3	216.5	2,186.8
1995	2,056.9	302.4	2,359.3
1996	2,252.1	369.3	2,621.4
1997	2,411.8	496.8	2,908.6
1998	2,598.8	636.7	3,235.5
1999	2,801.2	746.6	3,547.8

Year	CFC 12		
	Present	New	Total
1991	4,267.2	—	4,267.2
1992	4,578.4	157.1	4,735.5
1993	5,166.6	211.0	5,377.6
1994	5,240.2	296.4	5,536.6
1995	5,608.1	481.0	6,089.1
1996	6,172.4	779.5	6,951.9
1997	6,640.5	1,608.5	8,249.0
1998	7,191.8	2,498.1	9,689.9
1999	7,744.6	3,582.2	11,326.8

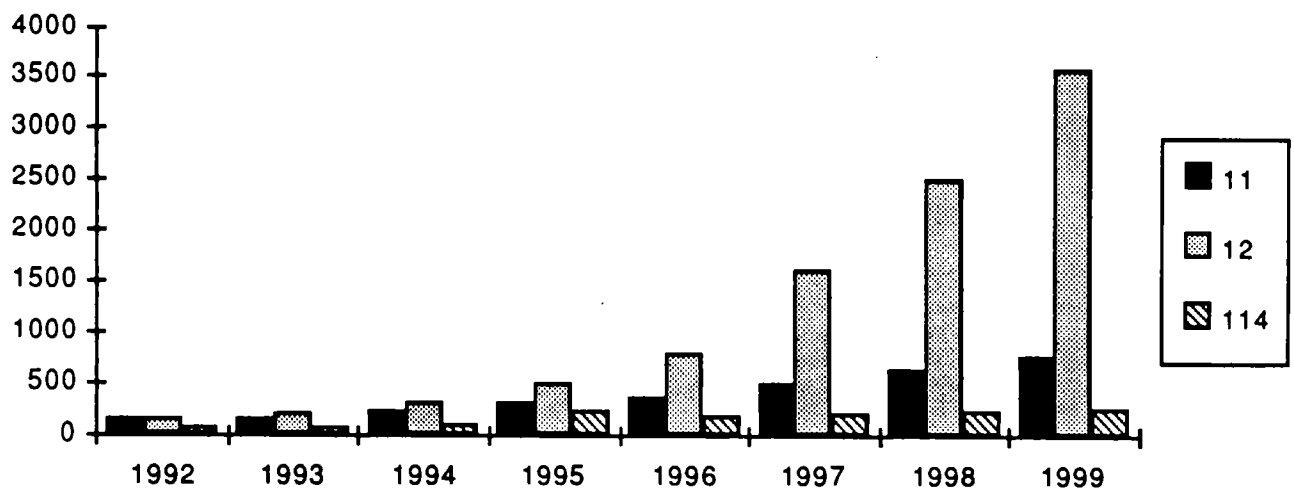
Year	CFC 114		
	Present	New	Total
1991	542.0	—	541.9
1992	632.9	62.8	695.7
1993	620.1	75.1	695.2
1994	560.9	101.4	662.3
1995	497.2	237.4	734.6
1996	468.6	181.1	649.7
1997	451.4	212.6	664.0
1998	447.3	235.3	682.6
1999	480.6	259.7	740.5

Year	Total		
	Present	New	Total
1991	6,451.3	—	6,451.3
1992	7,028.4	355.0	7,383.4
1993	7,750.9	447.5	8,198.4
1994	7,771.4	614.3	8,385.7
1995	8,162.2	1,020.8	9,183.0
1996	8,893.1	1,329.9	10,223.0
1997	9,503.5	2,317.5	11,821.0
1998	10,237.9	3,370.5	13,608.4
1999	11,026.6	4,588.5	15,615.1

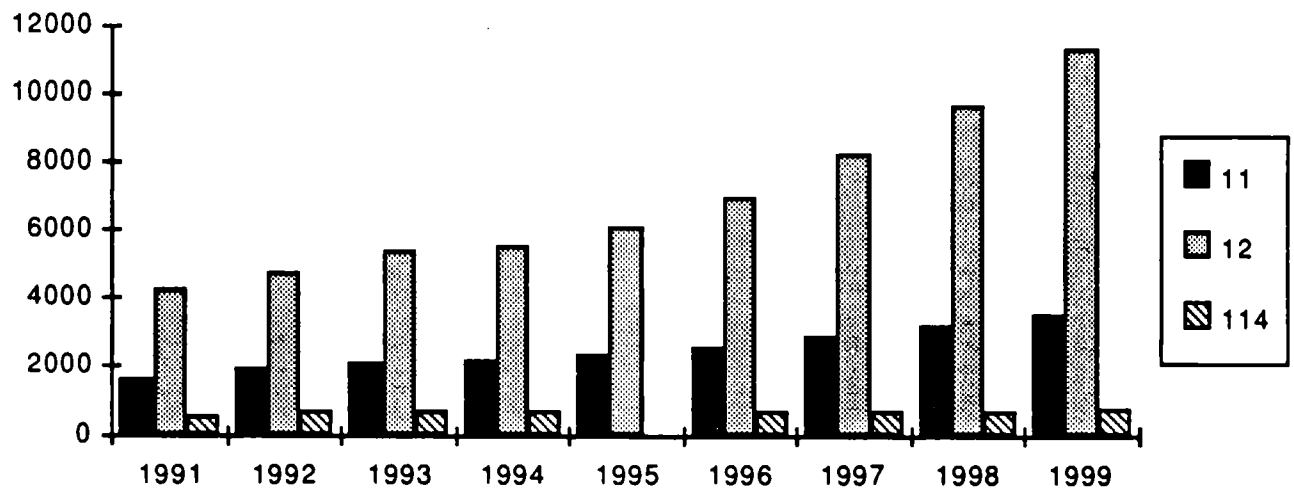
Worldwid Usag of CFC in Pre ent MDIs (1991-1999)



Worldwide Usage of CFCs in New MDIs (1992-1999)



Total Worldwide Usage of CFCs in MDIs (1991-1999)



II. SUMMARY OF PRESENTLY MARKETED MDI PRODUCTS

A. BACKGROUND

- Presently marketed MDIs are used throughout the world to dispense active formulations to treat respiratory disease.
 - Product types do not differ on a regional basis. Each region utilizes beta-agonist bronchodilators, steroids, cromolyn sodium and anti-cholinergics in MDI form.
 - Within each product category, there is consistency among the active ingredients. Minor variations in products approved for human use by government agencies can be noted on a regional basis. However, the leading actives have worldwide acceptance.
 - The MDI package itself is almost identical in physical design and structure throughout the world. Regional preferences can be noted in package size and material of choice for the storage vial or canister.
 - The metering valve responsible for delivering precise dosage is a universal component. Design modifications in the valve reflect differences in formulation and manufacturer specifications.
-

B. REGIONAL MDI PRODUCTS

- In 1991, there were an estimated 210 brands of MDI products produced and marketed throughout the world.
- This total includes both prescription and over-the-counter products.
- Of this total, 125 of the brands were produced for the European market, which ranks as the largest market for MDIs. The United States ranks second, with 32 brands of MDIs being sold, as shown below:

TABLE 2

<u>Region</u>	<u>Number MDIs</u>	<u>% of Total</u>
Europe	125	60
United States	32	15
Canada	20	10
Japan	12	6
Rest of World	<u>21</u>	<u>9</u>
TOTAL	210	100%

C. PRODUCT TYPES AND NUMBER OF MDIs MARKETING

- Beta-agonist bronchodilators, steroids, cromolyn sodium and anti-cholinergics are the leading types of actives dispensed by MDIs.
- Of the 210 MDI brands produced and marketed in 1991, beta-agonists were the leading active type, accounting for 115 different products. Steroids ranked second, as shown below:

TABLE 3

<u>Product Type</u>	<u>Number of Products</u>	<u>% of Total</u>
Beta-Agonist Bronchodilators	115	55
Steroids	45	22
Other*	<u>50</u>	<u>23</u>
TOTAL	210	100%

* Includes Cromolyn Sodium and Anti-Cholinergics

D. TOTAL MDI UNITS PRODUCED BY PRODUCT TYPE AND REGION

- Total worldwide MDI production in 1991 is estimated at 337.8 million units.
- This total includes MDI units produced both for marketing and sampling purposes.
- Europe is the leading region accounting for 187 million units. This rate reflects a long history of MDI usage combined with strong acceptance of MDIs as the therapy of choice to treat asthma and other respiratory diseases.
- The United States ranks as the second leading region with total domestic consumption estimated at 92.8 million units in 1991.
- Of the 337.8 million MDI units produced, 201 million incorporated beta-agonist bronchodilators.
- Steroids ranked as the second leading MDI product accounting for 88.5 million units.
- A detailed breakdown of MDI unit consumption by region and product type is shown in Table 4.

TABLE 4

Product Type	Million Units						% of Total
	United States	Europe	Canada	Japan	Rest of World	Total	
Beta-Agonists	58.5	109.0	10.0	3.0	20.5	201.0	60
Steroids	22.0	50.0	3.0	3.0	10.5	88.5	26
Other	12.3	28.0	3.0	1.0	4.0	48.3	14
TOTAL	92.8	187.0	16.0	7.0	35.0	337.8	100

E. 1991 CFC PROPELLANT USAGE IN MDIs

By CFC Type and Region

- CFC propellants are used exclusively throughout the world in the production of MDIs.
- In 1991, 6,450 metric tons of CFCs were used in MDIs; a total of 337.8 million units were produced.
- These totals compute to an average of 19.1 grams of CFC propellant in each MDI unit.
- For all MDIs, blends of CFCs are incorporated into the formulation. Specific CFC types used include: CFC 11, CFC 12 and CFC 114.
- CFC 12 was the leading individual propellant consumed accounting for 4,267.2 metric tons in 1991, or 66% of total MDI usage. CFC 12 provides the propellant force for all MDI product types. CFC 11 and CFC 114, which are important to adjust propellant force and to provide the needed solubility to the final formulation, were consumed at lower levels.
- A breakdown of regional consumption by CFC propellant type is shown in Table 5.

TABLE 5

Metric Tons

Type CFC	United States	Europe	Canada	Japan	Rest of World	Total
CFC 11	443.8	918.0	72.4	33.2	174.7	1,642.1
CFC 12	1,110.5	2,436.0	191.7	72.3	456.7	4,267.2
CFC 114	214.8	236.0	35.0	14.2	42.0	542.0
TOTAL	1,769.1	3,590.0	299.1	119.7	673.4	6,451.3

1991 CFC PROPELLANT USAGE IN MDIs (cont.)

Respiratory Care by Product Type and Region

- Beta-agonist MDIs were the leading users of CFC propellants. Worldwide usage totaled 3,940.9 metric tons in 1991.
- Steroids ranked second, employing a total of 1,687.4 metric tons of CFC propellants.
- A breakdown of CFC propellant consumption by product type and region is shown in Table 6.

TABLE 6

Metric Tons

Product Type	United States	Europe	Canada	Japan	Rest of World	Total
Beta-Agonists	1,161.0	2,143.0	187.9	49.5	399.5	3,940.9
Steroids	397.1	971.0	60.2	53.2	205.9	1,687.4
Other	211.0	476.0	51.0	17.0	68.0	823.0
TOTAL	1,769.1	3,590.0	299.1	119.7	673.4	6,451.3

F. FORECAST CFC PROPELLANT USAGE IN MDIs

Annual CFC Propellant Requirements

- Worldwide CFC usage in MDIs is forecast to increase from 6,451.3 metric tons during 1991 to reach 11,026.0 metric tons in 1999.
- These propellant totals reflect MDI usage levels increasing at an average annual rate of 6.9% per year.
- Requirements for CFC 12 will grow at a somewhat higher rate than for CFC 11 or CFC 114.
- CFC 11 usage will grow at the current usage ratio while CFC 114 needs will rise at a much lower rate during the period, as shown in Table 7.

TABLE 7

CFC PROPELLANT USAGE IN MDIs 1991 through 1999

By CFC Type

Year	Metric Tons			
	11	12	114	Total
1991	1,642.1	4,267.2	541.9	6,451.3
1992	1,817.1	4,578.4	632.9	7,028.4
1993	1,964.3	5,166.6	620.1	7,750.9
1994	1,970.3	5,240.2	560.9	7,771.4
1995	2,056.9	5,608.1	497.2	8,162.2
1996	2,252.1	6,172.4	468.6	8,893.1
1997	2,411.8	6,640.5	451.4	9,503.7
1998	2,598.8	7,191.8	447.3	10,237.9
1999	2,801.2	7,744.8	480.8	11,026.6
Average Annual Increase	6.9%	7.7%	1.5%	6.9%

FORECAST CFC PROPELLANT USAGE IN MDIs (cont.)

Annual Propellant Requirements by Region (Table 8)

- On a regional basis, the Rest of World is forecast to have the greatest growth rate in total CFC propellant usage in MDIs.
- Rest of World CFC usage in MDIs is forecast to grow from 673 metric tons in 1991 to 1,353.6 metric tons in 1999, with an average annual increase of 9.1%.
- Strong usage growth estimates are also forecast in Europe and Canada.
- United States CFC usage is forecast to increase at a rate below the overall industry average. These totals reflect moderate MDI unit growth.
- A summary of regional CFC propellant need is shown in Table 8.

TABLE 8
REGIONAL CFC PROPELLANT USAGE IN MDIs
1991 through 1999
Metric Tons

Year	United States	Europe	Canada	Japan	Rest of World	Total
1991	1,769.1	3,590.0	299.1	119.7	673.4	6,451.3
1992	1,929.0	3,914.0	326.3	123.3	735.8	7,028.4
1993	2,102.0	4,340.0	363.7	128.5	816.7	7,750.9
1994	1,953.0	4,472.0	372.9	132.4	841.1	7,771.4
1995	1,922.0	4,800.0	402.6	135.6	902.0	8,162.2
1996	1,935.0	5,362.0	445.6	145.7	1,004.8	8,893.1
1997	1,968.0	5,808.0	481.9	153.0	1,092.8	9,503.7
1998	2,012.0	6,300.0	530.3	158.9	1,236.7	10,237.9
1999	2,104.0	6,836.0	567.0	166.0	1,353.6	11,026.6
Average Annual Increase	2.2%	8.4%	8.3%	4.2%	9.1%	6.9%

III. SUMMARY OF MDI PRODUCTS FORECAST TO BE INTRODUCED (1992 through 1999)

A. BACKGROUND

- During the period 1992 through 1999, it is anticipated that many new products will be introduced into the world healthcare market in MDI form.
- These therapeutic actives will fall into two primary segments:
 - Respiratory care - Introducing new, more effective, and longer acting formulations that complement present MDI products.
 - Non-respiratory care - The MDI dosage form has been identified as a method to deliver selected drugs systemically, via the lungs. Benefits presumed for MDI systemic delivery include the ability to obtain therapeutic treatment levels at a much lower dose, minimal side effects, and quick onset of action.

B. COMPANIES

- In 1991, over 50 companies worldwide were active in marketing MDIs.
- Of this total, the 10 largest producers were responsible for over 80% of total MDI units produced. These companies can be described as multinational organizations with broad regional distribution and multiple MDI manufacturing locations.
- During the period 1992 through 1999, these companies will continue to be the major force in the MDI market. In addition, based on questionnaire responses, there will also be a significant number of new companies marketing MDIs in the future. Their primary product thrust will be systemic delivery via the lungs.
- According to the questionnaire responses, a total of 58 respondents plan to introduce new MDIs during 1992 through 1999. Of this total, 19 are present MDI marketers, while 39 will be introducing their first MDI products.

C. NEW MDIs TO BE INTRODUCED BY PRODUCT TYPE

- Based on questionnaire responses, a total of 115 MDI products are expected to be introduced during 1992 through 1999.
- Major new MDI product activity will be focused on systemically delivered actives, which will account for 51 new MDIs. Within the respiratory care sector most new effort will focus on steroids and beta-agonists:

TABLE 9

<u>Product Type</u>	<u>Number New MDI Entries</u>
Respiratory Delivery	64
Systemic Delivery	51
TOTAL	115

D. NEW MDIs TO BE INTRODUCED BY REGION

- New MDI product activity is forecast to take place throughout the world between 1992 to 1999.
- Estimates are that the United States will be the most active region, with 40 new product introductions. Primary U.S. efforts will be focused on MDIs to deliver drugs to the systemic circulation via the lungs.
- Europe will rank second after the U.S. with 26 new MDI entries followed by Canada, as shown in the regional breakdown in Table 10.

TABLE 10

TOTAL NUMBER OF MDI PRODUCTS FORECAST TO BE INTRODUCED 1992 through 1999

By Product Type

<u>Product Type</u>	<u>Number Products to be introduced</u>					<u>Total</u>
	<u>United States</u>	<u>Europe</u>	<u>Canada</u>	<u>Japan</u>	<u>Rest of World</u>	
Systemic Delivery	17	10	13	4	7	51
Respiratory Delivery	23	16	9	7	9	64
TOTAL	40	26	22	11	16	115

E. DATES FOR MARKET INTRODUCTION OF NEW MDIs

- The world marketplace for new MDI products will be extremely active with a total of 115 new entries during 1992 through 1999.
- In any given year a minimum of 7 new products will be brought to market, with the most activity taking place in 1997 when the launch of 24 new MDIs is anticipated.

TABLE 11

NUMBER OF MDI PRODUCTS FORECAST TO BE LAUNCHED 1992 through 1999

Year	Total Number Products					Total
	United States	Europe	Canada	Japan	Rest of World	
1992	7	4	4	0	0	15
1993	2	4	3	0	0	9
1994	8	4	4	0	0	16
1995	4	4	2	2	3	15
1996	7	4	3	3	4	21
1997	5	5	2	5	7	24
1998	3	1	1	1	1	7
1999	4	0	3	0	1	8
TOTAL	40	26	22	11	16	115

F. ANNUAL PROPELLANT REQUIREMENTS BY CFC TYPE

- Based on questionnaire responses, total CFC propellant needs for new MDI product launches is forecast at 355 metric tons in 1992. This total will grow to 4,588.5 metric tons in 1999.
- Blends of CFC propellants will be required in all new product efforts.
- Ratio differences by CFC type will relate to the specific active formulation being dispensed by the MDI. Overall CFC 12 will remain the main type of CFC required for MDIs. By the year 1999, CFC 12 will represent 70 to 80 percent of total propellant requirements.
- CFC 11 will remain an important component in all formulations, while CFC 114 will find somewhat lesser use, as shown in Table 12.

TABLE 12

FORECAST CFC USAGE IN NEW MDI PRODUCT LAUNCHES

1992 through 1999

By CFC Type

Year	Metric Tons			
	11	12	114	Total
1992	135.1	157.1	62.8	355.0
1993	161.4	211.0	75.1	447.5
1994	216.5	296.4	101.4	614.3
1995	302.4	481.0	237.4	1,020.8
1996	369.3	779.5	181.1	1,329.9
1997	496.8	1,608.5	212.6	2,317.5
1998	637.7	2,498.1	235.3	3,370.5
1999	746.6	3,582.2	259.7	4,588.5

G. ANNUAL PROPELLANT REQUIREMENTS FOR NEW PRODUCTS BY REGION

- Regional CFC propellant consumption will closely parallel the number of new product entries that are anticipated to be launched in each region.
- As shown in Table 13, by the year 1999, new products introduced in the United States will consume the largest propellant volumes. These totals are based on 40 new product entries.
- Europe, with an estimated 26 new MDI products to be launched during the period, will rank behind the United States in total propellant requirements, followed by Japan and Canada.

TABLE 13
FORECAST CFC USAGE IN NEW
MDI PRODUCT LAUNCHES

1992 through 1999

By Region

Year	Metric Tons					Total
	United States	Europe	Canada	Japan	Rest of World	
1992	266.0	5.0	84.0	0	0	355.0
1993	299.5	16.0	132.0	0	0	447.5
1994	406.4	32.0	175.9	0	0	614.3
1995	686.2	57.1	237.4	6.8	33.3	1,020.8
1996	741.2	119.9	371.7	28.4	68.7	1,329.9
1997	967.1	553.0	423.0	222.3	152.5	2,317.5
1998	1,282.7	940.6	489.0	385.9	272.3	3,370.5
1999	1,597.0	1,422.0	532.7	630.7	406.1	4,588.5

UNITED STATES

**I. OVERVIEW OF BOTH PRESENTLY MARKETED AND
FUTURE MDI PRODUCTS
(1991 through 1999)**

A. THE PRESENT MDI/CFC PROPELLANT MARKET

- In 1991, there were a total of 18 companies marketing 32 brands of MDIs in the U.S.
 - Of the 32 products, 21 were beta-agonist bronchodilators and 8 were steroids.
 - A total of 92.8 million MDI units were produced.
 - CFC propellant consumption in 1991 totaled 1,769.1 metric tons.
 - The average unit size of a single MDI produced was 19.1 grams.
 - CFC 11, 12, and 114 were used in various ratios. CFC 12 was the leading propellant accounting for 1,110.5 metric tons or 62% of the total volume, followed by CFC 11 with 26% and CFC 114 representing the balance or 12%.
 - DuPont and Allied-Signal were the primary CFC propellant suppliers.
-

B. NEW MDI PRODUCT LAUNCHES (1992 through 1999)

- Based on questionnaire responses a total of 17 companies are planning new MDI product efforts in the future.
- It is predicted that 40 new MDIs will enter the U.S. market by the end of the 1990s. Of this total, 23 will deliver respiratory products, with the balance intended for systemic drug delivery via the lungs.
- All products being developed are forecast to utilize blends of CFC propellants to dispense their actives.

C. FUTURE CFC USAGE IN MDIs 1992 through 1999

Overall Requirements (Table 14)

- CFC propellant requirements for MDI products are forecast to double during the next 8 years.
- These high CFC propellant expectations reflect:
 - Continued consumer acceptance and market growth of presently sold MDI products, and
 - Aggressive introduction of new MDI products during the period.
- Total CFC usage in U.S. MDIs will grow from 1,769.1 metric tons in 1991 to 3,701 metric tons in 1999.
- During 1999, presently marketed products are forecast to consume an estimated 57% of the volume, with new MDIs accounting for the balance.

TABLE 14
 FORECAST TOTAL U.S. CFC PROPELLANT USAGE IN
 BOTH PRESENTLY MARKETED AND NEW MDI PRODUCTS

Year	Metric Tons		
	Present Products	New Products	Total
1991	1,769.1	--	1,769.1
1992	1,929.0	266.0	2,195.0
1993	2,102.0	299.5	2,401.5
1994	1,953.0	406.4	2,359.4
1995	1,922.0	686.2	2,608.2
1996	1,935.0	741.2	2,676.2
1997	1,968.0	967.1	2,935.1
1998	2,012.0	1,282.7	3,294.7
1999	2,104.0	1,597.0	3,701.0
Average Annual Increase	2.2%	--	9.7%

By CFC Type (Table 15)

- Blends of CFCs will continue to be needed in the future. CFC 12 will be the dominant CFC propellant required. CFC 11, which is forecast to be used extensively in new products is also an important factor, as shown in Table 15.

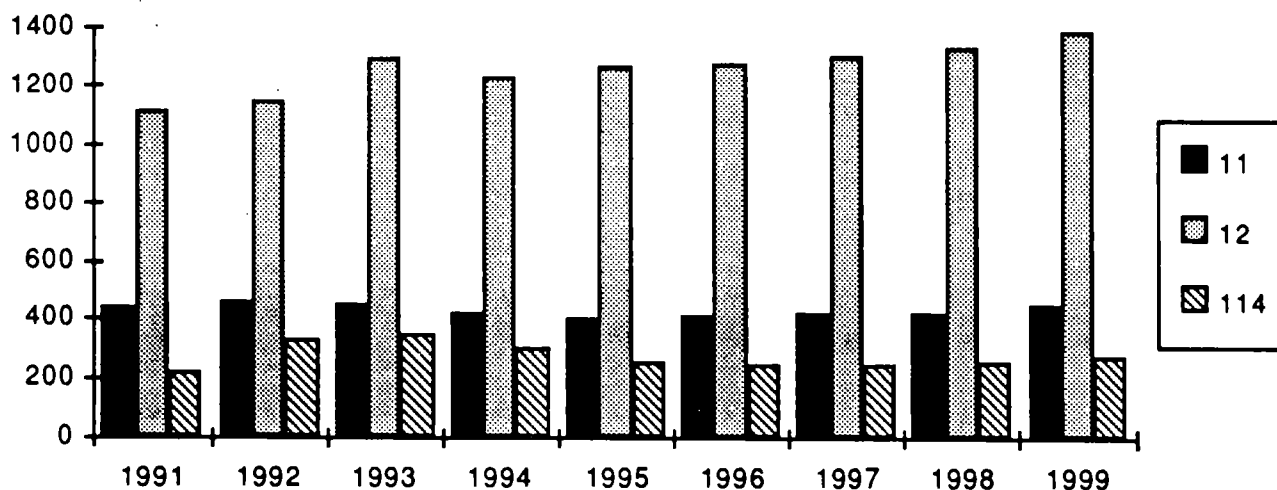
TABLE 15
FORECAST U.S. CFC PROPELLANT CONSUMPTION FOR BOTH PRESENTLY
MARKETED AND NEW MDI PRODUCTS BY CFC TYPE

Metric Tons

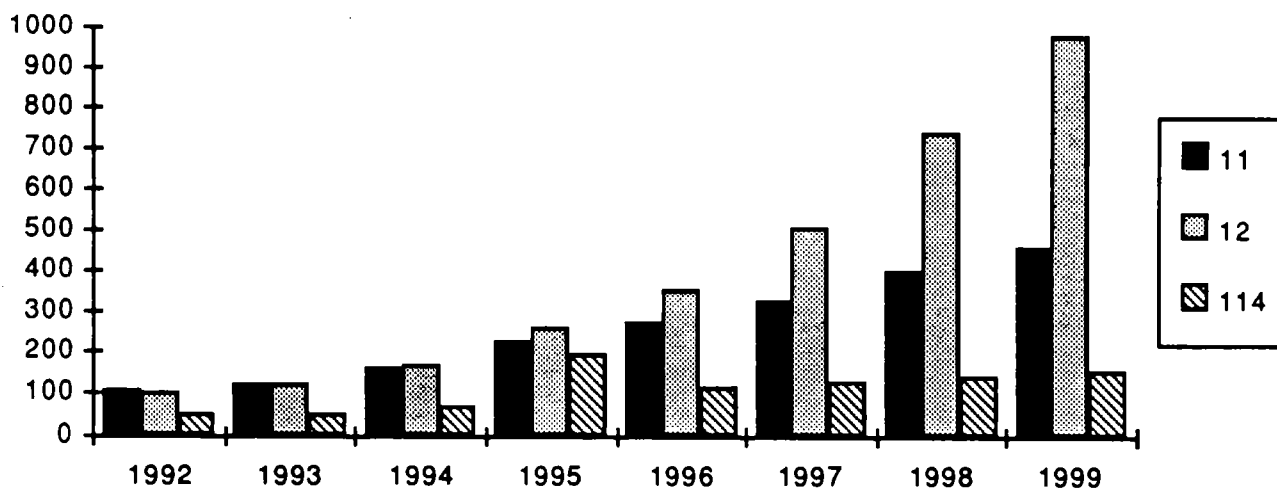
Year	Present Products				Year	New Products			
	11	12	114	Total		11	12	114	Total
1991	443.8	1,110.5	214.8	1,769.1	1991	—	—	—	—
1992	457.0	1,143.0	329.0	1,929.0	1992	110.1	105.3	50.6	266.0
1993	446.0	1,292.0	344.0	2,102.1	1993	122.2	124.9	52.4	299.5
1994	424.0	1,227.0	302.0	1,953.0	1994	162.9	170.3	73.2	406.4
1995	403.0	1,264.0	255.0	1,922.0	1995	227.9	259.7	198.6	686.2
1996	411.0	1,277.0	247.0	1,935.0	1996	273.2	352.6	115.4	741.2
1997	419.0	1,302.0	247.0	1,968.0	1997	331.6	504.0	131.5	967.1
1998	427.0	1,328.0	257.0	2,012.0	1998	402.7	739.0	141.0	1,282.7
1999	449.0	1,382.0	273.0	2,104.0	1999	462.4	975.1	159.5	1,597.0

Year	Total			
	11	12	114	Total
1991	443.8	1,110.5	214.8	1,769.1
1992	567.1	1,248.3	379.6	2,195.0
1993	588.2	1,416.9	396.4	2,401.5
1994	586.9	1,397.3	375.2	2,359.4
1995	630.9	1,523.7	453.6	2,608.2
1996	684.2	1,629.6	362.4	2,676.2
1997	750.6	1,806.0	378.5	2,935.1
1998	829.7	2,067.0	398.0	3,294.7
1999	911.4	2,357.1	432.5	3,701.0

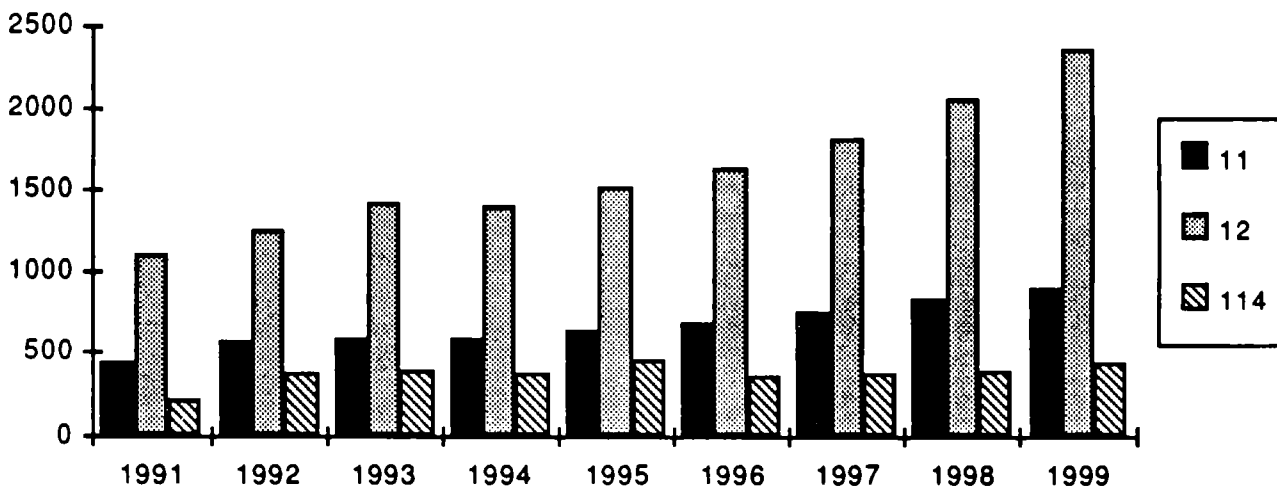
U.S. Usage of CFCs in Present MDIs (1991-1999)



U.S. Usage of CFCs in New MDIs (1992-1999)



Total U.S. Usage of CFCs in MDIs (1991-1999)



II. SUMMARY OF PRESENTLY MARKETED MDI PRODUCTS

A. COMPANIES

- In 1991, a total of 18 companies marketed MDI products in the United States.
- This total reflects companies selling MDIs via prescription along with companies that market such products over-the-counter.
- 11 of the 18 companies responded to the survey.

B. PRODUCT TYPES

- In the United States, MDIs are used primarily to deliver respiratory care active formulations. Leading product types include:
 - Beta-agonist bronchodilators (both prescription and over-the-counter)
 - Steroids
 - Cromolyn sodium
 - Anti-cholinergics

C. NUMBER OF MDIs MARKETED

- Of the estimated 32 different MDI products being marketed in the U.S., 66% are beta-agonists, followed by steroids at 25%, as shown below:

TABLE 16

<u>Product Type</u>	<u>Number MDIs</u>	<u>% of Total</u>
Beta-Agonist	21	66
Steroids	8	25
Other	<u>3</u>	<u>9</u>
TOTAL	32	100%

D. TOTAL MDI UNITS PRODUCED BY PRODUCT TYPE

- In 1991, a total of 92.8 million MDI units were produced for the U.S. market.
- This total reflects products produced for both sales and sampling.
- Beta-agonist bronchodilators accounted for 58.5 million units or 63% of the total number of units produced, followed by steroids which totaled 22 million in 1991, as shown below:

TABLE 17

<u>Product Type</u>	<u>Million Units Produced</u>	<u>% of Total</u>
Beta-Agonist	58.5	63
Steroids	22.0	24
Other	<u>12.3</u>	<u>13</u>
TOTAL	92.8	100%

E. AVERAGE QUANTITY OF CFC GRAMS PER MDI UNIT

- Based on questionnaire responses and interviews, the average amount of CFCs per MDI unit varies.
- Critical variables include:
 - Type of active product being delivered
 - Type of storage vial/canister used to hold the liquid active formulation (metal vial or glass bottle)
 - Capabilities of filling equipment
- Included in the average grams per MDI unit totals are:
 - CFCs used in production runs, but which did not make it to market because of quality issues
 - Amount of CFCs used to clean MDI filling equipment and tanks
- The following provides a breakdown of average CFC grams consumed by product type:

TABLE 18

<u>Product Type</u>	<u>Average Number CFC Grams per Unit</u>
Beta-Agonist	19.2
Steroids	18.6
Cromolyn Sodium	17.0
Anti-Cholinergics	16.9

F. TOTAL CFC PROPELLANT USAGE IN MDIs

- In 1991, a total of 1,769.1 metric tons of CFC propellant were consumed for MDI production in the U.S.
- Beta-agonist bronchodilators accounted for the major share of usage, followed by steroids, as shown below:

TABLE 19

<u>Product Type</u>	<u>CFC Propellant Consumed Metric Tons</u>	<u>% of Total</u>
Beta-Agonist	1,161.0	66.0
Steroids	397.1	22.0
Other	<u>211.0</u>	<u>12.0</u>
TOTAL	1,769.1	100%

G. HISTORICAL GROWTH OF CFC PROPELLANT USAGE IN MDIs BY PRODUCT TYPE

- During the past 5 years, the total amount of CFC propellants used in MDIs increased from 1,053.0 metric tons in 1986 to 1,769.1 metric tons in 1991. This growth reflects an average annual increase of 10.9% per year.
- While beta-agonist bronchodilators accounted for most of the CFCs used in MDIs over the past five years, the market for these MDIs showed the lowest growth rate. Steroid consumption showed considerable growth as these products gained broader consumer and professional acceptance. The highest growth rate occurred among the category of other products. A breakdown of historical CFC propellant volumes is shown in Table 20.

TABLE 20
HISTORICAL CFC PROPELLANT USAGE
1986 through 1991
By Product Type

Product Type	CFC Metric Tons Consumed						Avg. Annual Increase
	1986	1987	1988	1989	1990	1991	
Beta-Agonists	775.0	821.0	887.0	940.0	1,072.0	1,161.0	2.4%
Steroids	216.0	205.0	228.0	298.0	351.0	397.1	12.9%
Other	62.0	95.0	128.5	155.0	187.5	211.0	27.8%
TOTAL	1,053.0	1,121.0	1,243.5	1,393.0	1,610.5	1,769.1	10.9%

**H. TOTAL 1991 CFC USAGE IN MDIs
BY PRODUCT TYPE AND CFC TYPE**

- Of the 1,769.1 metric tons of CFC propellants used in MDIs during 1991, CFC 12 was the leading type.
- Total usage of CFC 12 in MDIs during 1991 is estimated at 1,110.5 metric tons, or 63% of the total.
- A breakdown of consumption by product type and type CFC follows:

TABLE 21

Product Type	CFC Metric Tons Consumed			
	11	12	114	Total
Beta-Agonists	298.0	735.0	128.0	1,161.0
Steroids	115.8	249.5	31.8	397.0
Other	30.0	126.0	55.0	211.0
TOTAL	443.8	1,110.5	214.8	1,769.1

I. FORECAST OF CFC PROPELLANT USAGE IN MDIs

Annual Usage by Product Type (Table 22)

- MDIs will continue to be an important therapy in the treatment of asthma and respiratory diseases.
- During the forecast period:
 - Beta-agonist bronchodilator usage will exhibit a minimal decline.
 - The use of steroid MDIs is forecast to grow at high rates. It is estimated that by the late 90's, steroids will be consumed at a rate equal to that for beta-agonist bronchodilators.
- Total CFC propellant usage for current MDIs is forecast to increase from 1,769.1 metric tons in 1991 to 2,104.0 metric tons in 1999, an average annual increase of 2.2% per year.
- Steroid usage will exhibit the fastest growth, increasing from 397.1 metric tons in 1991 to 939 metric tons in 1999, an average annual total increase of 11.4% per year. Beta-agonist bronchodilators, currently the leading overall consumer, will have a smaller usage increase, as shown in Table 22.

TABLE 22
FORECAST OF CFC USAGE IN PRESENTLY MARKETED MDIs
By Product Type

Year	Metric Tons			
	Beta-Agonists	Steroid	Other	Total
1991	1,161.0	397.1	211.0	1,769.1
1992	1,230.0	476.0	223.0	1,929.0
1993	1,304.0	562.0	236.0	2,102.0
1994	1,082.0	658.0	213.0	1,953.0
1995	974.0	782.0	166.0	1,922.0
1996	935.0	853.0	147.0	1,935.0
1997	910.0	921.0	137.0	1,968.0
1998	961.0	920.0	131.0	2,012.0
1999	1,028.0	939.0	137.0	2,104.0
Average Annual Increase	(1.5%)	11.4%	(5.3%)	2.2%

CFC PROPELLANT USAGE IN MDIs
1991 through 1999 (cont.)

Annual Requirements by CFC Type (Table 23)

- CFC usage in MDIs is forecast to increase from 1,769 metric tons in 1991 to 2,104 metric tons in 1999, for an average annual increase of 2.2%.

TABLE 23

FORECAST OF CFC USAGE IN PRESENTLY MARKETED MDIs

By Type of CFC

Year	Metric Tons			
	11	12	114	Total
1991	443	1,110	214	1,769
1992	457	1,143	329	1,929
1993	466	1,292	344	2,102
1994	424	1,227	302	1,953
1995	403	1,264	255	1,922
1996	411	1,277	247	1,935
1997	419	1,302	247	1,968
1998	427	1,328	257	2,012
1999	449	1,382	273	2,104
Average Annual Increase	0.2%	2.8%	3.0%	2.2%

III. SUMMARY OF MDI PRODUCTS FORECAST TO BE INTRODUCED 1992 through 1999

A. COMPANIES

- Based on the questionnaire responses, 17 companies are planning to introduce new MDI products during 1992 through 1999.
- Of this total, 8 companies are present marketers of MDI products and 9 will be making initial entry into the MDI market.

B. NEW MDIs TO BE INTRODUCED BY PRODUCT TYPE

- Based on questionnaire responses, a total of 40 new MDI products will be introduced during 1992 through 1999.
- New product activity will be focused equally on MDIs for respiratory therapy and those delivering drugs to the systemic circulation via the lungs.
- A breakdown of new product introduction by MDI type follows:

TABLE 24

<u>Product Type</u>	<u>Number New MDI Entries</u>
Respiratory Delivery	23
Systemic Delivery	<u>17</u>
Total	40

C. DATES FOR MARKET INTRODUCTION OF NEW MDIs

- New MDI product launches are forecast to take place in each year from 1992 through 1999.
- During this seven year period, annual activity will be fairly uniform. Significant new product efforts are anticipated in 1992, 1994 and 1996 with 7, 8 and 7 new product entries, respectively.
- A breakdown of calendar year efforts is shown in Table 25.

TABLE 25

NUMBER OF MDI PRODUCTS FORECAST TO BE LAUNCHED 1992 through 1999

By Product Type

Year	Metric Tons		
	Respiratory Delivery	Systemic Delivery	Total
1992	6	1	7
1993	2	0	2
1994	6	2	8
1995	2	2	4
1996	3	4	7
1997	1	4	5
1998	0	3	3
1999	3	1	4
TOTAL	23	17	40

**D. FORECAST OF CFC PROPELLANT USAGE IN
NEW MDIs - 1992 through 1999**

Annual CFC Propellant Requirements

- Based on the introduction of 40 new MDI products to be launched from 1992 through 1999, the need for CFCs to fulfill propellant requirements is significant.
- CFC usage for new MDI products is forecast to increase from 1992 requirements of 266 metric tons to 1,597 metric tons in 1999, as shown below:

TABLE 26

<u>Year</u>	<u>CFC Requirements Metric Tons</u>
1992	266.0
1993	299.5
1994	406.4
1995	686.2
1996	741.2
1997	967.1
1998	1,282.7
1999	1,597.0

E. FORECAST OF CFC PROPELLANT USAGE IN MDI PRODUCTION - 1992 through 1999

Annual CFC Usage by CFC Type

- Blends of CFC propellants will be required in the future.
- CFC 12 will continue to be the dominant propellant used in MDIs.
- On average, 60 to 70% of total annual new product CFC requirements will be CFC 12.
- CFC 11 is forecast to represent 25 to 30% of the total, with CFC 114 accounting for the balance.
- Annual CFC propellant needs for MDI usage is shown in Table 27.

TABLE 27

FORECAST OF CFC PROPELLANT USAGE IN NEW MDI PRODUCTS

1992 through 1999

By CFC Type

Year	Metric Tons			Total
	11	12	114	
1992	110.1	105.3	50.6	266.0
1993	122.2	124.9	52.4	299.5
1994	162.9	170.3	73.2	406.4
1995	227.9	259.7	198.6	686.2
1996	273.2	352.6	115.4	741.2
1997	331.6	504.0	131.5	967.1
1998	402.7	739.0	141.0	1,282.7
1999	462.4	975.1	159.5	1,597.0

**FORECAST OF CFC PROPELLANT USAGE IN NEW
MDI PRODUCTS - 1992 through 1999 (cont.)**

Annual CFC Usage by Product Type

- CFC consumption requirements will parallel new product launch activity.
- New respiratory care MDIs will be the leading category of new products to be launched from 1992 through 1999, dominating the need for CFCs. New MDIs for systemic delivery of drugs via the lungs also are expected to require significant CFC propellant for production, as shown in Table 28.

TABLE 28

**FORECAST OF U.S. CFC PROPELLANT USAGE IN NEW
MDI PRODUCTS**

By Product Type

Year	Metric Tons		
	Respiratory Delivery	Systemic Delivery	Total
1992	266.0	0	266.0
1993	299.5	0	299.5
1994	405.9	0.5	406.4
1995	618.7	67.5	686.2
1996	608.2	133.0	741.2
1997	712.7	254.4	967.1
1998	902.8	379.9	1,282.7
1999	1089.2	507.8	1,597.0

**PHOTOCOPY
PRESERVATION**

IPAC

Statement to the Parties to the
Montreal Protocol on Substances
that Deplete the Ozone Layer

May 12, 1993

The Likely Availability of
Alternatives to Pressurised
Metered Dose Inhalers

Note

This report was prepared by the International Pharmaceutical Aerosol Consortium (IPAC), an association of manufacturers and marketers of metered dose inhalers. The members of IPAC are: Abbott Laboratories; Armstrong Pharmaceuticals, Inc.; ASTA Medica AG; Boehringer Ingelheim Pharmaceuticals, Inc.; CIBA-GEIGY Corporation; Fisons plc, Pharmaceutical Division; Glaxo, Inc.; Hoffmann-LaRoche, Inc.; Merck & Co., Inc.; 3M; Norton Healthcare; Rhône-Poulenc Rorer Pharmaceuticals, Inc.; Schering Corporation; and SmithKline Beecham Pharmaceuticals. Contacts are as follows:

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I. Introduction

In November 1992 the Parties to the Montreal Protocol recognized "essential uses" of chlorofluorocarbons as possible exceptions to the worldwide phaseout of these compounds. The Parties defined an "essential use" as one which is necessary for the health of society and for which no "feasible alternatives" are presently available. The European Community and other nations around the world have adopted basically the same standard in their administration of the phaseout process.

The purpose of this paper is to examine whether dry powder inhalers ("DPIs") or other inhalation delivery systems are, or may become, "feasible alternatives" worldwide to the CFC-driven metered dose inhaler ("MDI"). The question of whether the MDI is necessary for the health of society will be addressed elsewhere.

This paper discusses the critical advantages of inhalation therapy in the treatment of asthma and chronic obstructive pulmonary disease ("COPD"); the safety and efficacy of existing inhalation delivery systems; the worldwide process for development, approval and patient education in the use of inhalation delivery systems; and the likely worldwide use of alternatives to the pressurised MDI.

The paper also discusses the public health consequences, worldwide, of a decision not to designate MDIs as an "essential use" under the Montreal Protocol.

II. Summary of Position

The principal findings of this paper are summarized as follows:

The pressurised MDI is the first line of therapy for tens of millions of asthma and COPD patients around the world. It has been proven safe, effective and reliable for over forty years and accounts today for 55% of total therapy for those diseases in the major developed countries of the world. In many large nations, it accounts for over 60% of total therapy for asthma and COPD.

By contrast, in 1992, DPIs accounted for only about 9% of total therapy in the major developed countries. Even in those countries where use of DPIs has increased most rapidly, it still has taken over five years for dry powder to be accepted for even half of total patient care. In most developed countries, the use of the DPI still accounts for only a small fraction, in some cases less than 1%, of total therapy for asthma and COPD. It likely will take another five years - until 1998 - before DPIs could account for even half of total therapy in the developed world.

A decision not to designate MDIs as an "essential use" of CFCs would disrupt worldwide treatment of asthma and COPD. It would force many patients to resort to systemic delivery, an inferior therapy in many instances. It would force many other patients to resort to medications they have never tried and inhalation delivery systems they are not trained to use. Finally, it would reduce the range of medications from which physicians may now select for treatment of respiratory disease. The public health consequences of these developments would almost certainly be significant, namely: declines in levels of patient care and recovery; prolonged and aggravated illnesses; decreased patient quality of life; increased hospitalizations and healthcare costs; and increased mortality caused by asthma and COPD. All of these compromises would have a much greater negative impact on human health than continued use of CFCs in MDIs could ever have.

A. Treatment Of Asthma And COPD

Asthma is a chronic and debilitating respiratory disease with sudden, unpredictable and potentially life-threatening effects. The treatment of asthma requires constant vigilance and the active involvement of patients, families, physicians and other care givers in a comprehensive programme to monitor, anticipate and promptly respond to the onset of asthmatic attacks.

Chronic obstructive pulmonary diseases such as emphysema and bronchitis produce inflammation, swelling and mucus in the human airway and gradually destroy the surface area of the lung. COPD is inexorably progressive and generally irreversible, and severely restricts the capacity for respiration.

A broad range of over twenty medications worldwide has been developed for treatment of asthma and COPD. These medications differ in terms of the biological influences they exert; relative potency; the speed, duration and extent of therapeutic affect; and side effect profiles. The relief they provide may vary significantly according to a patient's age, weight, sex, genetic make-

up and physiological idiosyncracies. In developing a treatment programme, physicians seek to match a patient with one or more medications that will produce the quickest, most long lasting and comprehensive therapeutic relief, with minimum side effects. In view of the variables involved, patient care is generally far more successful where a broad range of alternative medications is available. Even then, it may take several years of treatment experience to establish which medication, or combination of medications, yields consistent relief with minimum side effects for particular patients.

B. Drug Delivery Systems

Until the 1950s, the only means of delivering these medications -- aside from cumbersome stationary nebulisers -- was "systemically" through oral liquids and solids (capsules), injections and suppositories.

The MDI was introduced in the 1950s as a major advance over systemic therapy. It relies on the human airway, rather than the blood stream, as its route of administration. It requires low dosage amounts, delivers a precisely measured therapeutic dose, greatly minimizes the risk of adverse side effects, and produces rapid onset of therapeutic relief. The MDI is a pocket-sized, hand-held, pressurised multiple-dose inhalation delivery system. It is portable, easy to actuate and convenient to use. It requires no reloading of dose amounts since medication is suspended or dissolved in the propellant solution.

The MDI gained rapid acceptance among physicians and their patients as a superior means of drug delivery. Today the MDI is approved for virtually all medications for asthma and COPD in the major developed countries of the world. It has proven safe, effective and reliable for virtually all patients, and is the mainstay of successful asthma therapy worldwide. In 1992, MDIs accounted for 55% of total asthma and COPD therapy in the major developed countries of the world.

The patient's quality of life is enhanced through benefits provided by a portable, effective, and reliable means of delivering medication. The patient affected by asthma or COPD is free to pursue activities, knowing that, should a respiratory incident occur, relief is at hand.

The use of systemic therapy has declined significantly since the MDI was first introduced over 40 years ago. In 1992, systemic therapy accounted for only about 32% of asthma and COPD therapy in the major developed countries of the world.

An alternative inhalation delivery system -- the dry powder inhaler, or "DPI" -- was introduced shortly after the MDI became available for patient care. DPIs provide for the delivery of drug particles as dry powder and, since they are not pressurised, rely entirely on the inspiratory capacity of the patient for drug delivery.

The early DPIs generally deliver a single pre-measured dose that is held in a gelatin capsule. They require reloading after each use and are difficult to actuate. Later products use a disk that holds several doses in "blisters" which are punctured by the device prior to delivery. Recently, an advanced version of the DPI has been approved for delivery of one or two specific medications in some major developed countries of the world. This advanced device administers multiple doses and is relatively easy to actuate.

The tiny micronized particles which make up dry powder tend strongly to aggregate and will adhere and cohere under a variety of influences. Large aggregates may (1) interfere with the proper performance of the device itself; (2) require greater inspiratory force from the patient; (3) hinder administration of constant and reproducible dose amounts; and (4) exceed the maximum particle size necessary to reach the narrow lower airways. The safety and efficacy of devices which hold dry powder in bulk depend in substantial measure on the ability of these devices to control the size and manage the separation of drug particles.

As noted, DPIs rely on the inspiratory capacity of patients for the energy required to deliver drug particles to their destination within the human airway. This capacity can be diminished in those suffering from disease-related respiratory attacks and may not be sufficient for effective use of DPIs by many patients, particularly the very young and the very old.

Advanced nebulisers are also under development as portable inhalation delivery systems. These systems mechanically transform an aqueous solution or suspension into an aerosol cloud for inhalation by the asthma or COPD patient. Existing nebulisers are too large and cumbersome to serve as alternatives to the MDI. While a significant effort to develop a hand-held, multiple-dose nebuliser currently is underway, no such product has been approved to date.

C. Development,
Approval
And Patient
Education

In the treatment of asthma and COPD, the inhalation delivery system is as critical as the medication itself. Medication is of little value unless it can be delivered properly to the disease site. Inhalation delivery systems therefore are required to meet the same high standards of safety and efficacy which apply to the medications they administer.

The process of conceiving a new inhalation system, transforming that idea into a design and producing a novel product is lengthy and inherently uncertain. Once developed, moreover, that product is subject to extensive testing, first in animals, and subsequently in human volunteers. The results of these tests are carefully weighed by health authorities in each country during their review of the safety and efficacy of new products. In the case of DPIs, this review would focus in particular on the effects of particle aggregation and consistent dose accuracy, and on whether the inhalation capacity of diseased patients is

sufficient in every case for delivery of drug particles to the lower airway. The development of new products may require at least five years, while government review of new product applications may take an average of two-to-three years in many countries.

Governmental approval of a new product provides no guarantee that the product ultimately will be prescribed by physicians or accepted by their patients. A concerted effort is required to advise doctors of a new product's availability and to demonstrate its safety and effectiveness in patient care. Once a new product is accepted by prescribing physicians as a viable therapeutic mechanism, a further significant effort is required to educate nurses, respiratory therapists, family members and patients themselves in its proper use. In the case of DPIs, this education would focus in particular on the safety consequences of circumstances in which this system might malfunction. In addition, information on the medical conditions in which inhalation capacity may fall below levels required for effective use of DPIs would have to be provided.

D. Use of Dry Powder Inhalers

For purposes of comparison, the use of drug delivery systems can be measured in terms of "patient days treatment." A single "patient days treatment" is the amount of therapy required to treat one patient for asthma or COPD for one day.

In the past five years, the use of therapy for asthma and COPD has increased in the major developed countries by more than 20% from approximately 8 billion patient days treatment in 1988 to almost 10 billion in 1992. In 1988, DPIs accounted for about 4% of treatment. The use of DPIs increased gradually in each succeeding year. However, in 1992, DPIs still only accounted for about 9% of total days treatment in those countries.

The rate of increase in the use of DPIs differs substantially from one major developed country to the next. For example, in Japan DPIs never have accounted for more than about 2% of patient days treatment for asthma and COPD. By contrast, the use of DPIs in Holland has increased from 42% of patient days treatment in that country in 1988 to 57% in 1992. The rate of increase in the use of DPIs in these and other countries varies in accordance with several important factors including:

- The pace and results of research and development of new dry powder systems;
- Enrollment of patients into clinical studies to evaluate safety and efficacy;

- The stringency, pace and results of governmental review of these new systems and the deference accorded decisions of health authorities in each of these countries;
 - The number of medications approved for use in dry powder systems;
 - The availability of more advanced dry powder systems;
 - The number, diversity, literacy, attitudes, cultural preferences and geographical dispersion of patients and the physicians responsible for their care;
 - The confidence of physicians and their patients in the safety and efficacy of DPIs for particular medications and disease conditions, particularly in comparison to MDIs on which they may have relied for many years; and
 - Governmental policies and regulations concerning the use of MDIs and health care costs.
-

**E. Essential
Nature
of Pressurised
Metered Dose
Inhalers**

In all likelihood, current DPIs never will be appropriate for all patients, all disease conditions and all medications. Patients whose inspiratory capacity is severely impaired probably are not capable of "lifting" dry powder from a holding chamber for delivery to their diseased lower airways. Moreover, many drug agents do not have the appropriate physico-chemical properties for use in DPIs.

The use of DPIs worldwide will increase only gradually over time. As noted, their emergence is governed worldwide by a process for development, clinical testing, approval and patient education. This process generally extends over a period of many years. It is impossible to predict, with assurance, just how long the process may take for particular medications and delivery systems in particular countries and how quickly it may lead, if at all, to an increase in the use of DPIs.

Even in those few countries where DPIs are emerging relatively quickly, such as Sweden and Holland, it has taken over five years for them to gain a 50 percent share of patient days treatment for asthma and COPD. In most other major developed countries of the world, DPIs have achieved only a small fraction of these use levels. It likely will take another five years -- until 1998 at the earliest -- before the use of dry powder systems could increase from current levels to even 50% of patient days treatment, worldwide. Whether the use of DPIs worldwide will ever increase to these levels or beyond is, of course, unknown, and depends entirely on the pace and results of the process for development, regulatory agency approval and patient education. The use

of DPIs may well level off or even decline as CFC-free MDIs are introduced in future years.

A decision not to designate the MDI as an "essential use" of chlorofluorocarbons would deprive millions of patients worldwide of the only available means of delivering inhaled medications on which they now rely and may have used successfully for many years. Similarly, it would greatly reduce the range of medications from which physicians may now select to treat asthma and COPD. Even where DPIs are available, some patients would be forced abruptly to resort to medications which they never have tried and inhalation delivery systems that they are unprepared to use. The consequences for many patients, however, could be far more severe. Since DPIs will not emerge rapidly enough or on a scale sufficient to fill the void created by an elimination of MDIs, many patients using MDIs today would be left without any form of inhalation therapy at all. This in turn would inevitably force increased reliance on systemic delivery, an inferior therapy in many instances.

Pharmaceutical firms have a major interest in the DPI market and are making every effort to accelerate the emergence of these products. The pharmaceutical industry has been a leader in the design of new products and is applying the full measure of its ingenuity to the development of new inhalation delivery systems. It is estimated, for example, that since 1989 the industry has secured the grant of approximately 50 new patents for inhalation delivery systems in the United States. Worldwide it is estimated that approximately 250 different pending applications and granted patents have been published over the same period. The forced elimination of MDIs would not appreciably accelerate this development process.

III. Background

A. The Treatment of Asthma and COPD

1. Nature of the Disease

Asthma and chronic obstructive pulmonary diseases such as emphysema and bronchitis attack the capacity for respiration. They inflame the human airway, which becomes hyperreactive and subject to convulsive coughing and wheezing that disrupts breathing. These diseases also produce physical obstructions such as swollen tissues and mucus plugs which block airflow. In addition, they trigger muscular spasms that constrict the airways and impede the flow of oxygen to the lung.¹ Finally, in the case of emphysema and bronchitis, these diseases gradually destroy the surface area of the lung, reducing the lung's capacity to exchange oxygen and carbon dioxide.²

In a very real sense these diseases result in suffocation. They greatly diminish the quality of life for patients and their families and in severe cases may result in death.³

2. Medications

The medications developed for treatment of asthma and COPD generally fall into two categories: anti-inflammatory agents and bronchodilators. Anti-inflammatory agents treat inflammation of the airway and reduce its hyperreactivity. They include corticosteroids, such as beclomethasone dipropionate and triamcinolone acetonide; and non-steroidal anti-inflammatory agents such as sodium cromoglycate and nedocromil sodium.⁴

Bronchodilators, on the other hand, "act principally to dilate the airways by relaxing bronchial smooth muscle."⁵ They also enhance the clearance of mucus and other airway obstructions. Bronchodilators include, among other drug agents, beta-agonists such as albuterol (salbutamol), metaproterenol, pirbuterol, terbutaline, isoprenaline (isoproterenol), bitolerol, isoetharine and epinephrine (adrenaline); and anti-cholinergics such as ipratropium.⁶ These drug agents provide a broad range of medications from which physicians may choose in developing a treatment programme for treatment of asthma and COPD.⁷

3. Drug Delivery Systems

Until the 1950s, medications for asthma and COPD usually were taken orally, digested, absorbed by the bloodstream, and delivered to the airway through the circulatory system. This use of "systemic therapy" requires a relatively long period of time for medication to reach the disease site. It also requires the use of relatively large dose amounts since much of the medication is processed or absorbed by the body before it reaches the airway. Systemic therapy relies on the blood stream as its route of delivery, and for some

therapies increases the risk of adverse side effects, and yields only a slow onset of therapeutic relief.⁸

Inhalation therapy was introduced in the 1950s as a major advance over systemic therapy. Inhalation therapy takes full advantage of the respiratory function for direct delivery of medication to the affected airways. It relies entirely on the airway as its route of administration. It also relies in varying degrees on the available force and direction of inhaled air.

Inhalation therapy delivers drug particles to the diseased airway far more rapidly than systemic therapy and yields a more rapid onset of therapeutic effects. In addition, reliance on the airway instead of the bloodstream greatly reduces the amount of medication that is absorbed or processed by the body before it reaches the disease site. Inhalation therapy is therefore effective with far smaller dose amounts, thus posing for some important therapies a far smaller risk of harmful side effects.

B. Inhalation Delivery Systems

Inhalation delivery systems perform four separate functions: They hold the drug agent in a reservoir; meter that agent into precise amounts for dosing; release the dose through a metering system; and provide for the delivery of the dose to the airway.

Inhalation delivery systems take several different forms including the pressurised metered dose inhaler, the dry powder inhaler and the nebuliser.⁹ The design and performance characteristics of each of these systems is discussed below.

The Pressurised Metered Dose Inhaler

In the MDI, the drug agent is suspended or dissolved in a liquified chlorofluorocarbon propellant held under pressure in the reservoir of a small canister. The drug agent is distributed uniformly throughout the product. The contents are released from the canister through a valve in precisely measured amounts. Drug particles or droplets are projected forward as the propellant "explodes" from the canister and evaporates on contact with air.¹⁰

The MDI is capable of releasing precisely measured and highly reproducible dose amounts since the drug is evenly distributed in the propellant solution which itself is metered carefully by a valve. The MDI provides virtually all of the force required to transport drug particles from the device to the target location in the airways. This force is provided by the propellant that is held under pressure in the canister prior to release. The MDI delivers multiple doses. Finally, it is pocket-sized, highly portable and simple to actuate.

The Dry Powder Inhaler

In this device, the drug agent is placed in a holding chamber or reservoir as "dry powder." The early products deliver a single pre-measured dose that is held in a gelatin capsule. These devices require reloading after each use. Later products rely on a "blistered disk" that contains several doses. The

"blisters" on these disks are punctured by the device to release the drug for delivery. More advanced dry powder systems hold the drug as a bulk powder and have multiple dose capacity. The bulk powder in these more advanced systems is metered into a holding cup of precise dimension in preparation for release and delivery. This bulk powder is leveled and compacted by a scraping device to ensure proper loading.¹¹ These devices may hold a pure drug or a drug diluted with a bulking agent such as lactose.

Delivery of medication from the dry powder inhaler to the airways relies, in a complex way, on the inhalation capacity of the patient, involving both inhalation volume and suction power for the energy required to generate and deliver drug particles to active sites in the airways. This capacity varies in those suffering from respiratory disease and in some cases will not be sufficient for effective use of powder devices.¹²

The tiny micronized particles of drug substance which make up dry powder formulations tend strongly to aggregate, or stick to the inside of the device. These drug particles may also become enlarged and agglomerate upon exposure to atmospheric moisture. In some instances, desiccant cartridges may be needed to help prevent problems caused by moisture exposure.¹³ The amount of drug and the particle size of the drug exiting DPIs are highly dependent on how hard, how consistently, and how long a patient breathes in.

Drug particles are larger and heavier in aggregate form. As aggregates, they may exceed the maximum particle size that can reach the lower airways and hinder the administration of a constant reproducible dose. They require greater inspiratory "lift" from the patient, are more difficult to disperse, and tend to get stuck in the upper airway, posing a risk of side effects. The creation of turbulent airflow within the DPI and the use of "carrier" particles help deaggregate micronized powder. In some instances, small amounts of dry "lubricant" may be employed to assist smooth flow through the DPI device.¹⁴ The safety and efficacy of devices which hold dry powder in bulk depend in substantial measure on their ability to control the size and manage the separation of drug particles.

DPIs feature a range of technical and design characteristics. As noted, the early products must be reloaded after one or several dosings and are generally difficult to actuate. More advanced systems deliver multiple doses and are relatively simple to actuate.¹⁵ DPIs are generally pocket-sized and portable.

The Nebuliser

Using either ultrasonic or air-jet technologies, the nebuliser mechanically transforms an aqueous solution in which drug particles are dissolved or suspended into an aerosol cloud for inhalation by the asthma or COPD patient. The particle size of this cloud may vary significantly from one nebuliser to the next. While a pharmaceutical firm retains total control over drug formulations for use in nebulisers, it has no control over which of the many nebulisers may be prescribed by a particular doctor for use with its

formulation. The variations in design and performance of nebulisers have led to major variations in the amount of drug delivered to patients.¹⁶

Existing nebulisers are large, cumbersome, noisy and awkward to use. Many require an independent power source. While a significant effort currently is underway to develop a portable, hand-held, multiple-dose nebuliser, no such product has been approved to date.

C. Development, Approval And Patient Education

Development

The process of launching a new inhalation delivery system proceeds from a novel idea, to design, testing, clinical evaluation, governmental approval and, ultimately, patient education in its proper use. This process is driven by considerations of safety and efficacy. It is complex, time-consuming and uncertain. While this process will differ in implementation from one country to the next, it generally involves at a minimum the following steps:

Development begins with a promising concept and proceeds to research, design, manufacture and laboratory testing of prototypes. A critical challenge in developing a DPI is control of particle size and management of particle separation. Another is the achievement of accurate reproducible dosing. Technologies such as laser light scattering, laser photometry and cascade impactors may be employed to evaluate the size and dispersion of particles delivered by a prototype DPI. Because the size, texture, dimensions, density and shape of drug particles may differ from one active agent to the next, the performance of each prototype must be evaluated separately for each compound that it may be designed to deliver.¹⁷

Preclinical testing is generally required as a prerequisite for government review. Preclinical testing is performed on laboratory animals to evaluate the safety and efficacy of drug agents and excipients.¹⁸ In the case of new agents or excipients, or new combinations of agents and excipients, relatively extensive studies may be required. Where approved drug agents and known inhalation excipients are involved, studies of only a few months may be sufficient.¹⁹

Stability testing is required to evaluate any deterioration or breakdown in drug formulations over time and under typical storage conditions. Stability testing generally is begun in the development phase and extends into the period of government review and approval.²⁰

Review and Approval

Assuming the results of preclinical and initial stability testing are satisfactory, an application for authority to conduct clinical trials is required in most countries.²¹

Clinical trials are designed to measure the safety and efficacy of inhalation therapy in human beings. These trials generally are conducted in several phases. In the United States, Phase I involves 20 to 80 healthy volunteers and

may take one year to complete. Phase II involves approximately 100-300 people and may extend over a period of two years. Phase III studies may include 1,000-3,000 patients and involve treatment for a period of 3 years.²²

Clinical trials for a new inhalation delivery system with a new drug agent would take at least 4-6 years in most major developed countries of the world. Where an approved drug agent and known inhalation excipients are involved, the process may require only about 2-3 years.

Taken together, preclinical and stability testing and clinical trials provide the basis for evaluating the safety and efficacy of new inhalation systems and the drug agents which they are designed to deliver. The results of these studies are weighed carefully by health authorities in deciding whether to approve a new system for use in their countries.²³ From start to finish, the process of testing, clinical evaluation and government review and approval often can take as many as 8-10 years in the major developed countries of the world.²⁴

Education

Depending on their proximity to urban centres, and access to current medical information, it may take physicians a period of many months or even years to become aware of new therapies. Even then, they may not be inclined to experiment with new products, particularly where they have developed high levels of confidence in existing ones. Should they nevertheless recommend a new medication or drug delivery system, physicians may well encounter resistance from patients who feel secure with existing therapies on which they have relied for years. This is particularly true of asthma patients who must count on their therapy to relieve sudden, unpredictable and potentially life-threatening attacks.

Within the past year, participants in the International Asthma Management Project released the *International Consensus Report on Diagnosis and Management of Asthma* ("the Report"). This Report, which was prepared under the auspices of the U.S. National Institutes of Health by a working group of physicians and scientists representing 11 nations around the world, underscores the importance of patient education in the diagnosis and management of asthma. According to the Report,

The aim of patient education -- which is a continual process -- is to provide the asthma patient and the patient's family with suitable information and training so that the patient can keep well and adjust treatment according to a medication plan developed with the clinician

Information improves knowledge and satisfaction (and possible confidence) but does not by itself lead to behavior change and a reduction in morbidity. Patients also need to develop the skill and confidence to follow the clinician's medical advice in their home environments. The information required by individual patients varies, and each patient's ability or

willingness to take responsibility similarly differs. Thus, all individuals require certain core information and skills, but most education must be personalized and given to the patient in a number of steps. Social and psychological support may also be required to maintain positive behavioral change. Further, the patient's understanding of the information and management skills should be assessed periodically so that educational steps may be repeated or added as appropriate

...²⁵

Patient education is a painstaking and time-consuming process. It adds yet another step in the emergence of new inhalation systems. In the case of a new DPI, for example, a patient must be (1) taught how to hold, actuate and reload the DPI; (2) cautioned against its misuse; (3) alerted to signs of breakage or malfunction; and (4) advised of potential side effects.

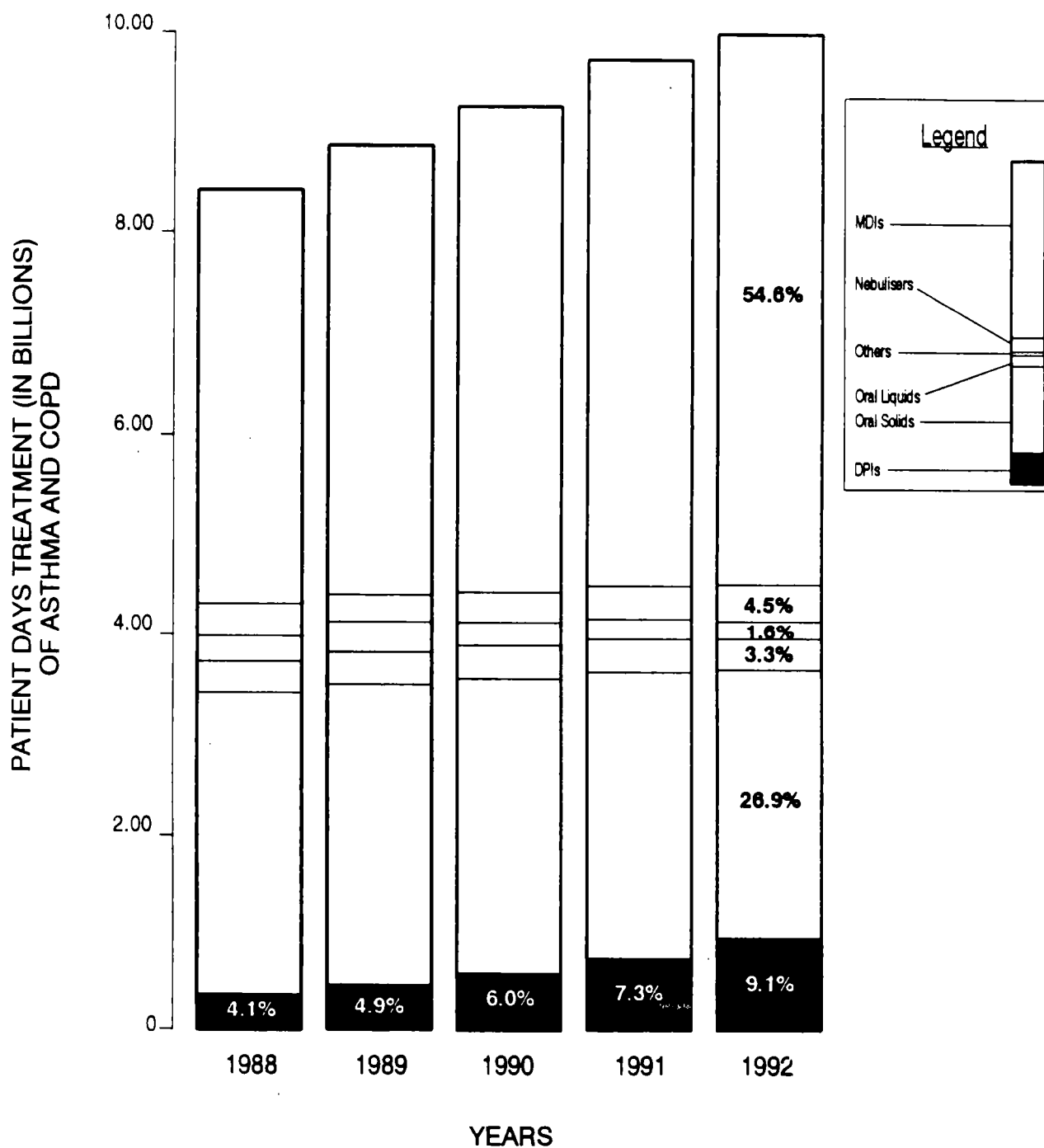
In sum, the process of gaining acceptance for new inhalation delivery systems among physicians and their patients is lengthy and highly uncertain. For example, despite the fact that inhalation therapy is clearly superior to systemic delivery in most cases, after 40 years fully 31% of patients in the major developed countries of the world continue to rely on systemic dosing.

D. Use Of Drug Delivery Systems Worldwide

In the past five years, asthma and COPD morbidity and mortality rates have risen steadily in the major developed countries, resulting in a substantial increase in the use of asthma and COPD medication. The use of asthma and COPD medication in those countries increased from approximately 8 billion patient days treatment in 1988 to over 10 billion in 1992. This period has also witnessed a trend towards inhalation therapy in general and away from the use of systemic delivery. (These trends are reflected on Figure 1 which appears on page 14 of this Report.²⁶)

In 1988, dry powder inhalers accounted for only about 4% of patient days treatment for asthma and COPD in the major developed countries. The use of DPIs increased in each succeeding year. However, in 1992, the DPI still only accounted for about 9% of patient days treatment. (See Figure 1.) By contrast, use worldwide of the pressurised metered dose inhaler rose from about 49% of patient days treatment in 1988 to almost 55% in 1992. (In the meantime, the use of systemic therapy declined from about 43% of patient days treatment in 1988 to about 32% in 1992.) The use of non-portable nebulisers increased from about 3.5% to approximately 4.5% of patient days treatment over this same period. (See Figure 1.)

TOTAL USE OF DRY POWDER INHALERS IN 20 MAJOR DEVELOPED COUNTRIES (1988-1992)*



12 May 1993

* Industry Estimates Based on Audited Market Sales Data

Figure 1

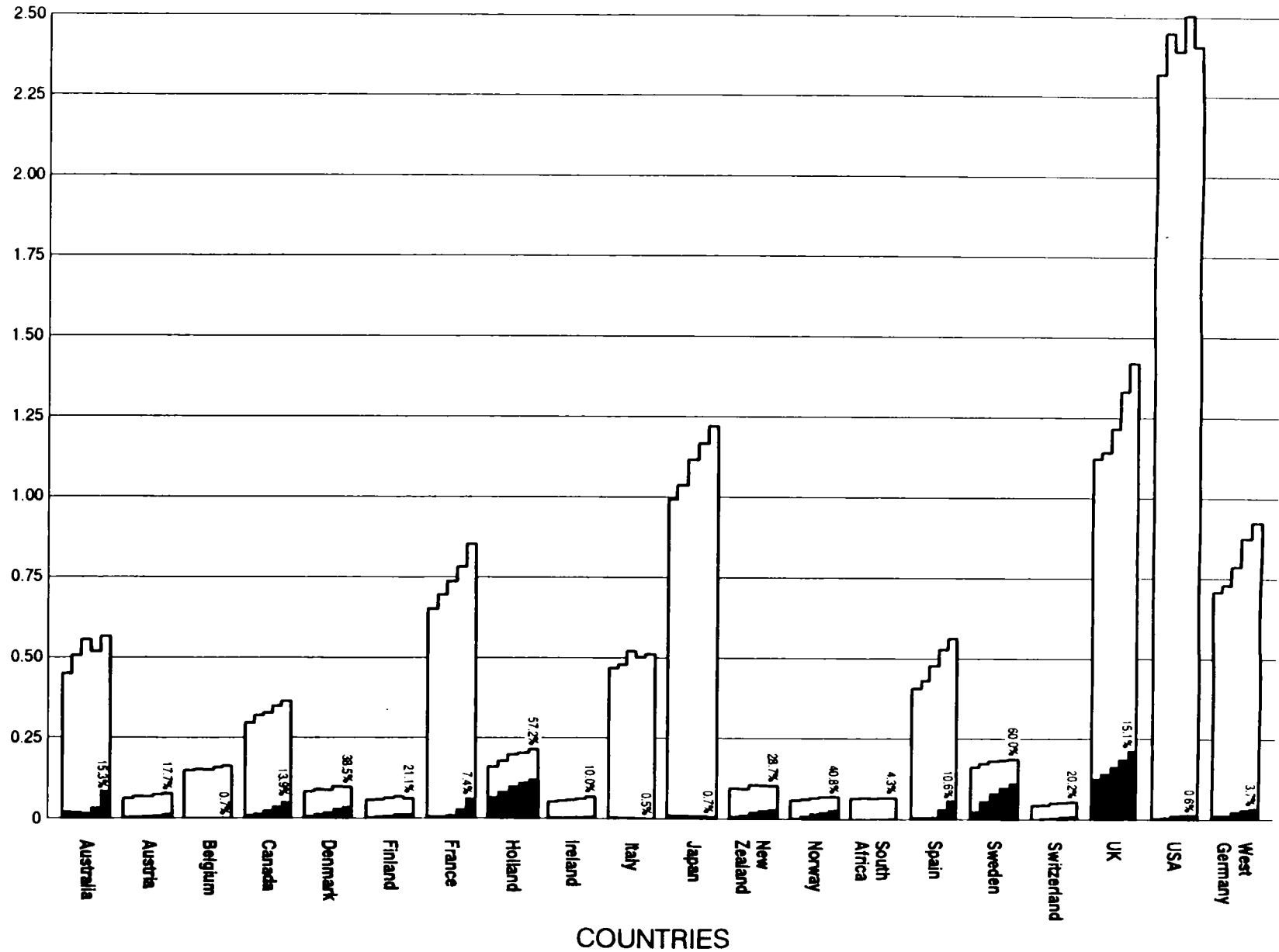
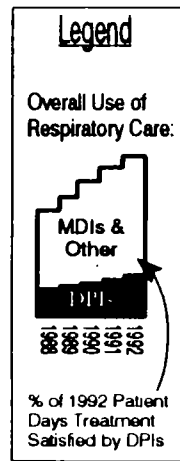
The extent of use of dry powder inhalers differs substantially from one major developed country to the next. (These differences are reflected in Figure 2 which appears on page 16 in this Report.) In Japan and the United States, for example, DPIs never have accounted for even 2% of patient days treatment for asthma and COPD. By contrast, the DPI increased in use in Holland from about 42% of patient days treatment in 1988 to about 57% in 1992, leaving the MDI with a smaller but still significant share of the market. Similarly, in Sweden, use of the DPI increased from about 16% to 60% patient days treatment over this same period of time.

Several important factors account for the different levels of use in these countries. In the United States and Japan, for example, a more advanced dry powder system still has not been approved for any asthma or COPD medication. The only DPIs on the market in the United States generally are disfavored by most physicians and their patients because they are capable of only a single or a very few doses, require frequent reloading, and are relatively difficult to actuate.

USE OF DRY POWDER INHALERS IN EACH OF 20 MAJOR DEVELOPED COUNTRIES (1988-1992)*

PATIENT DAYS TREATMENT (IN BILLIONS)
OF ASTHMA AND COPD

Figure 2



12 May 1993

* Industry Estimates Based on Audited Market Sales Data

IV. Conclusion: MDIs Will Remain Essential for the Foreseeable Future

A. Use Of DPIs Will Increase Only Gradually

As noted, the use of DPIs has increased from only about 4% to approximately 9% of patient days treatment in 20 major developed countries over the past five years. Even in those countries (such as Sweden and Holland), where the DPI has emerged most rapidly it has taken over five years for use to reach 50-60% of patient days treatment.

In most of the major developed countries of the world, the use of DPIs falls far below these levels. Indeed, in many major countries such as Japan, the United States, Austria, Italy and West Germany, the DPI accounts for only a very small fraction, in some cases less than 2%, of patient care.

In these circumstances, it likely will take at least another five years -- until 1998 at the earliest -- for the dry powder inhaler to reach even 50% of patient days treatment, worldwide. Whether the use of the dry powder inhaler ever reaches this level is, of course, highly speculative and depends entirely on the process for development, approval and patient education in each country of the world. As noted, the pace and results of this process are unpredictable and occur gradually over a period of many years.

B. The Dry Powder Inhaler Likely Never Will Be A Feasible Alternative For All Patients

The dry powder inhaler likely never will be safe and effective for all patients, all disease conditions and all medications. Patients whose inspiratory capacity is severely impaired probably are not capable of "lifting" dry powder from a holding chamber for delivery to their diseased airways. Moreover, many drug agents do not have the appropriate physico-chemical properties for use in the dry powder inhaler.

C. Shortages in MDIs Would Severely Compromise Asthma and COPD Treatment

A decision not to designate MDIs as an "essential use" of CFCs would disrupt worldwide treatment of asthma and COPD. It would force many patients to resort to systemic delivery, an inferior therapy in many instances. It would force many other patients to resort to medications they have never tried and inhalation delivery systems they are not trained to use. Finally, it would reduce the range of medications from which physicians may now select for treatment of respiratory disease. The public health consequences of these developments would almost certainly be significant, namely: declines in levels of patient care and recovery; prolonged and aggravated illnesses; decreased patient quality of life; increased hospitalizations and healthcare costs; and increased mortality caused by asthma and COPD. All of these compromises would have a much greater negative impact on human health than continued use of CFCs in MDIs could ever possibly have.

Endnotes

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5. Executive Summary: Guidelines for the Diagnosis and Management of Asthma, National Asthma and Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health (Bethesda, Maryland June 1991) Chap. 2, 10.
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14. See generally Atkins, 4-7; see also Hickey, 180.
15. See generally Hickey, 178-179; see also Atkins, 4.
16. Hickey 162-167; see also Atkins, 7-10.
17. See generally Hickey, 156-157.
18. Pharmaceutical Manufacturers Association, "New Drug Approvals in 1992" (Newsletter distributed by the Pharmaceutical Manufacturers Association, January 1993) (hereinafter "PMA Report"), 10.
19. IPAC Report, 9-10.
20. Ibid., 10.
21. PMA Report, 10.
22. PMA Report, 10.
23. See e.g., 21 Code of Federal Regulations §314 (1992). (Requirements of a New Drug Application in the U.S.).
24. See generally PMA Report, 10.
25. International Consensus Report, Chap. 1, 10.
26. The estimates reflected in Figure 1 and Figure 2 are based on audited proprietary market sales data obtained from within IPAC.

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**Statement to the Parties to the
Montreal Protocol on Substances
that Deplete the Ozone Layer**

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**The Likely Availability
of Used CFCs for Use in
Metered Dose Inhalers**

Note

This report was prepared by the International Pharmaceutical Aerosol Consortium (IPAC), an association of manufacturers and marketers of metered dose inhalers, under the Co-Chairmanship of Dr. John G.D. Carpenter and Mr. Harvey Mintzer. Contacts are as follows:

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No copying of this work or any part hereof is permitted without the prior written consent of an authorized representative of the International Pharmaceutical Aerosol Consortium. Requests for copies of this report and questions should be directed to the above individuals or to Ballard Jamieson, Jr., Esq. Mr. Jamieson may be contacted at Gardner, Carton & Douglas, 1301 K Street, N.W., Suite 900E, Washington, D.C. 20005; telephone: (202) 408-7189; facsimile: (202) 289-1504.

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Acknowledgments

The International Pharmaceutical Aerosol Consortium (IPAC) is an unincorporated special purpose association of companies which manufacture and market metered dose inhalers (MDIs) in Europe and the United States. Its purpose is to address policy and regulatory issues related to MDIs arising from restrictions on the production of chlorofluorocarbons under the Montreal Protocol. The companies which comprised this Consortium during the preparation of this paper include Abbott Laboratories; Armstrong Pharmaceuticals, Inc.; ASTA Medica AG; Boehringer Ingelheim Pharmaceuticals, Inc.; CIBA-GEIGY Limited; Fisons plc; Glaxo Inc.; Hoffmann-LaRoche, Inc.; Merck & Co., Inc.; Minnesota Mining & Manufacturing Company; Norton Healthcare Ltd.; Rhône-Poulenc Rorer Pharmaceuticals, Inc.; Schering Corporation; SmithKline Beecham Pharmaceuticals; and Whitehall Laboratories.

In July 1992 IPAC established a Committee on Used CFCs under the Chairmanship of Dr. Ernest Kelly, Senior Director of Quality Operations for the North American Operations of Rhône-Poulenc Rorer Pharmaceuticals, Inc. The members of this Committee include Mr. Brendan Barnes, Glaxo Holdings plc; Mr. Robert Jones, Head, Corporate Policy Unit, Glaxo Holdings plc; Mr. Harvey Mintzer, President and Chief Operating Officer, Armstrong Pharmaceuticals, Inc.; and Mr. Peter Newman, Manager, Regulatory Systems, Fisons plc. This Report was prepared under the direction of the Committee on Used CFCs.

The Committee wishes to acknowledge the contributions of Dr. John Daly, Dr. James Stevenson, Mr. C.N. Masten and Mr. Paul Farrow in the preparation of this Report. Dr. Daly received his Ph.D. in Organic Chemistry from the University of Maryland in 1955. He spent 37 years with Du Pont before retiring this year as Development Manager and Toxicology Coordinator for Fluorochemicals. Dr. Daly spent 32 years with Du Pont's Freon Products Division and Du Pont Fluorochemicals where he was involved in product research and development, market development, coordination of toxicity studies, planning and product management. Dr. Daly brought years of experience and in-depth knowledge to this effort and the Committee greatly appreciates his contribution.

Dr. James Stevenson received a Ph.D. in Chemical Physics from Harvard University in 1975. He is Section Leader in the Analytical Sciences Department of Boehringer Ingelheim Pharmaceuticals, Inc. where he is responsible for issues of physical chemistry and bio-physics. In prior years, Dr. Stevenson has dealt with the characterization of drug substances and ingredients, methods validation, chemical manufacturing and controls, and regulatory submissions such as Investigational New Drug filings and New Drug Applications. Dr. Stevenson's insight into the regulatory process and issues of purification and quality assurance were invaluable to this effort and the Committee greatly appreciates his contribution.

Mr. C.N. Masten received a B.A. in Chemical Engineering from the University of Delaware in 1950 and a Masters in Chemical Engineering from the

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University of Michigan in 1951. He spent 40 years with Du Pont. From 1970 to 1991 Mr. Masten was responsible for the operation of major Du Pont divisions including the Polyester and Acrylics Division, the Explosives Products Division, the Freon Products Division, and the White Pigments and Mineral Products Division, from which he retired as Vice President and General Manager in 1991. As head of these major divisions, Mr. Masten was responsible for total financial performance, manufacturing, research, marketing and capital projects. Mr. Masten's broad knowledge of corporate planning, manufacturing, capital projects and marketing played a vital role in this analysis and the Committee greatly appreciates his contribution.

Mr. Paul Farrow received a Higher National Certificate in Chemistry from Cambridge University in the United Kingdom in 1977 and is a graduate of the Royal Society of Chemistry at Hatfield Polytechnic. As an analytical chemist at Schering A.G., Mr. Farrow gained experience in managing the analytical services department, providing analytical services such as GC/MS and HPLC. While working for VG Instruments, Mr. Farrow helped to set up analytical service departments and customized software for specialized applications. Mr. Farrow joined Arthur D. Little as manager of their mass spectrometry group and later became a director of the Environmental, Health and Safety Practice at the firm. When IPAC engaged Arthur D. Little to conduct chemical analyses of used refrigerant, Mr. Farrow's breadth of experience and knowledge proved invaluable in his role as Project Coordinator for this effort. The Committee greatly appreciates his contribution.

Following the preparation of a final draft of this Report, the Committee selected five individuals with extensive knowledge and experience in the manufacture and analysis of chlorofluorocarbons to participate in "peer review" of the document. Each of these individuals devoted substantial efforts to evaluating the Report and offering their comments on how it might be improved. Their review of the document provided invaluable assistance in confirming and strengthening the analysis of this critical subject. The Committee wishes to recognize the contributions of Mr. R.E. Boberg, Dr. Hans Deger, Mr. Douglas Gehring, Dr. Timothy Noakes and Mr. F.A. Vogelsberg, Jr.

Mr. R.E. Boberg received a Bachelor's Degree in Chemical Engineering from Clarkson College of Technology in 1950 and has spent over 40 years with AlliedSignal Chemicals and its predecessor, Allied Chemical and Dye Corporation. Mr. Boberg has been engaged actively in the fluorochemical field since 1970 and is currently Manager of Process Technology at AlliedSignal. Mr. Boberg is an active participant in the Air Conditioning and Refrigeration Institute (ARI) and in the Program for Alternative Fluorocarbon Toxicity Testing (PAFT).

Dr. Hans Deger received a Ph.D. in Organic Chemistry. Mr. Deger is Vice President of Research and Technology For Specialty Chemicals in the Chemical Division of Hoechst AG.

Acknowledgments

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I. Introduction

The purpose of this paper is to describe the likely availability of used chlorofluorocarbons (CFCs) for use in metered dose inhalers (MDIs) after 1 January 1996.

MDIs are pocket-size aerosol devices that deliver medicines directly to the lungs in precisely measured doses. Many millions of people in Europe and the United States currently rely on MDIs for the prevention and treatment of asthma and other respiratory diseases. Five percent or more of the world's population suffers from asthma, and the incidence is rising.¹

MDIs use CFCs 11, 12, and 114 as propellants.² The international community, however, has resolved to phase out the production and usage of CFCs in general by 1 January 1996. It has done so through recent adjustments to the Montreal Protocol on Substances That Deplete the Ozone Layer.

The major producers of MDIs have been working intensively to develop CFC-free MDIs for several years. They have identified HFA-134a and HFA-227 as promising non-ozone depleting substitute propellants and are now jointly conducting extensive programs to study the toxicology of each of these compounds.³

Nevertheless, the overall process of redevelopment, including the necessary review and approval by health authorities, will extend at least into the late 1990's for most MDIs, according to the most recent (December 1991) report of the Technology and Economic Assessment Panel convened by the Parties to the Protocol.⁴ Consequently, the Parties may need to create an exemption from the phase-out schedule for MDIs.

Recognizing this possibility, the Parties at their Fourth Meeting in November 1992 resolved in broad outline to (1) conduct during 1993 an assessment of the potential need and (2) consider exemptions at their Sixth Meeting in 1994.

With regard to the 1993 assessment, the Parties:

1. stipulated that production for a particular essential use should be allowed only if:
 - "there are *no available technically and economically feasible alternatives* or substitutes that are acceptable from the standpoint of environment and health;" and
 - "the controlled substance is not available in sufficient *quantity and quality* from existing stocks of banked or *recycled* controlled substances";"

2. directed the Technology and Economic Assessment Panel to provide by early 1994 a report and recommendations on the following subjects, among others:
 - "[s]ources of already produced controlled substances for the proposed essential use (*quantity, quality, timing*);" and
 - "[s]teps necessary to ensure that alternatives and substitutes are available as soon as possible for the proposed essential use;" and
3. further directed the Panel in making its recommendations to take into account, among other factors, the "health effects, economic feasibility, availability, and *regulatory status* of alternatives [to] and substitutes" for the controlled substances in question (emphasis added).⁵

In effect, the Parties through these terms of reference have asked the Panel to study and form an opinion on whether the MDI industry could satisfy the demand for MDIs during the post-1995 period by using used CFCs instead of "virgin" CFCs. Further, the Parties have directed the Panel to examine that issue from the standpoints of quality, quantity and timing, taking into account the "steps necessary" to satisfy the applicable "regulatory regimes."

In response to the dual imperative to both protect the ozone layer and assure an adequate supply of MDIs, the International Pharmaceutical Aerosol Consortium (IPAC) has examined the same issue from the same standpoints by asking: (1) what are the sources of used CFCs, and (2) what would a company actually have to do in order to use CFCs from those sources in its MDIs?

The result of that examination is this paper. It starts with an identification of the likely sources of used CFCs. Then, recognizing that those used CFCs would be inhaled repeatedly by millions of patients, it describes the process and timeline that a company would have to follow in order to protect health and secure the necessary approvals of authorities in Europe and the United States.⁶ The paper then turns to the other practical question, namely: how might a company obtain the used CFCs in sufficient quantity? Finally, against that background, the paper evaluates the likely availability of used CFCs for use in MDIs after 1 January 1996.

II. Executive Summary

The principal findings of this paper are summarized as follows:

The use of used commercial material in pharmaceutical products would be unprecedented and pose serious risks for a highly sensitive patient group. It is highly doubtful whether state-of-the-art technologies for purification and quality assurance could reduce these risks to acceptable levels. There is a strong likelihood that health authorities would not approve the use of used CFCs in MDIs.

In any event, developing commercial facilities for the purification of used CFCs and obtaining authorization for their use in MDIs would take at least 4 years. Assuming that this program did not start until after the Sixth Meeting of the Parties in 1994, it would take until mid-1998 and probably longer to complete an effort of this kind.

By this time, the MDI industry will be nearing completion of its transition to non-ozone depleting substitute propellants and require only a few thousand additional metric tons of virgin CFCs. The ozone protection benefits of preventing production of this relatively small amount of CFCs would be marginal at best and clearly outweighed by the risks to patient health from material once used for commercial and industrial purposes.

The conclusions and analysis which support these findings are summarized below.

A. Potential Sources of Used CFCs

The MDI industry is using approximately 8,500 metric tons of pharmaceutical grade CFC per year worldwide at present and its usage probably will remain in this general range (6-15 thousand) after 1995. According to one major study, CFC-11 represents about 25% of this total usage, CFC-12 about 70% and CFC-114 about 5%.

The principal commercial uses of CFC-11, 12 and 114 are foam products, aerosol products, cleaning agents and refrigerants. Of these, used refrigerant is the only source of CFCs potentially recoverable in sufficient quantity to meet the requirements of the MDI industry.

B. Program For Authorization

The substitution of used refrigerant for virgin CFCs in MDIs would require approval of health authorities in virtually every major country. It would be unlawful to make this substitution without governmental safety review and authorization in these major countries.

The presence of contaminants in MDIs may have severe adverse effects on asthma patients. Health authorities have placed stringent controls on impurities and contaminants in these drug products.

Health authorities require the origins of drug product ingredients to be well-known and continuously monitored. Where an ingredient's provenance is unclear there is risk that it may contain unknown and harmful contaminants.

Health authorities insist on consistency in drug ingredients and are intolerant of material whose impurities vary from one batch to the next. Such "variability" greatly reduces the reliability of controls on impurities during the drug manufacturing process.

Chlorofluorocarbon refrigerants are used in a vast array of refrigeration and air conditioning equipment. They are exposed to a large number of chemical substances and a wide range of operating conditions in millions of individual units worldwide.

Chemical analysis of used refrigerant has disclosed a large number of contaminants that vary substantially from one sample to the next. Some of these contaminants are extracted from lubricants, gaskets, seals and other components of refrigeration equipment. Others are produced by complex organic reactions capable of generating an almost infinite range of additional impurities, depending on the mix of compounds and operating conditions present in individual refrigeration and air conditioning units.

Manufacturers of pharmaceutical grade CFCs have established stringent quality specifications for these drug ingredients. These specifications set minimum levels of organic purity and strictly limit the presence of volatile and non-volatile organic impurities in virgin CFCs.

Used refrigerant reclaimed by distillation fails to meet these specifications because it contains volatile organic impurities in concentrations that exceed the limits established by suppliers for pharmaceutical grade material. In addition, chemical analysis has disclosed that used refrigerant reclaimed by distillation contains a large number of high-boiling organic contaminants which, although present in small concentrations, may pose unacceptable safety risks in the pharmaceutical context.

Large numbers of contaminants, which vary from sample to sample and whose identity is not always known, present severe technical obstacles to purification and quality assurance of drug products. It is highly doubtful that state of the art production technologies (such as fractional distillation) and analytical technologies (such as gas chromatography and gas chromatography/mass spectrometry) could routinely provide sufficient assurance that contaminants have been appropriately characterized and eliminated from used refrigerant.

The reuse of commercial and industrial material for pharmaceutical purposes is without precedent. It would be contrary to the pharmaceutical industry's Code of Good Manufacturing Practice and the continuing trend toward increasingly stringent requirements of purity in drug ingredients.

Under principles of common law, many states in the U.S. impose strict liability on corporations for the sale of pharmaceutical products whose design is "unreasonably dangerous per se." In other words, a company may be liable for harm caused a patient regardless of whether it was negligent in the

manufacture of the product involved. The fact that the product was approved by health authorities is no defense in an action of this kind. There is a very real risk that the use of used refrigerant would be found "unreasonably dangerous" in view of the highly sensitive patient group involved, the types and concentrations of contaminants found in used refrigerant, and the uncertainties surrounding purification and quality assurance.

A program for seeking authorization to employ used refrigerant in MDIs would require, among other things, the development of purification facilities, rigorous validation of analytical procedures to an unprecedented degree, the development of carefully controlled processes for purification and quality assurance, safety testing, and regulatory review, including Good Laboratory Practice and Good Manufacturing Practice certifications for testing laboratories and manufacturing sites. Three separate programs would be required – one each for CFC 11, CFC 12, and CFC 114. It would take at least four years to implement these programs, even assuming all questions of provenance, variability, purification and quality assurance were readily resolved.

C. Adequacy of Supply

Several major firms in the United States and Europe have instituted programs for the reclamation of used refrigerant to commercial standards. However, virtually all reclaimed material is returned to service existing refrigeration and air conditioning units. No reclaimed refrigerants are available for other uses (such as MDIs) today.

There are significant costs involved in retrofitting existing equipment for substitute refrigerants. In some cases, they may range up to \$150,000 per unit. For many firms, millions of dollars may be involved.

Used refrigerant has a long useful life and may be recycled and reclaimed at modest expense. It affords industry the means to extend the transition to new refrigerants and defer the cost of retrofit over a period of years.

In these circumstances, it is extremely unlikely that used refrigerant will be made available for other uses, such as MDIs, under current market conditions. According to industry officials, unless they are persuaded to do otherwise, users will continue to use this material in existing equipment until it is lost to leakage and evaporation.

A program for attempting to purchase an adequate supply of used CFCs for use in MDIs would require, among other things, forming an organization to acquire the material; developing a purchasing strategy; surveying potential sellers; and negotiating the purchase of used CFCs. Users, if any, prepared to sell used refrigerant would demand a significant premium for this material to cover the costs of conversion to substitute refrigerants. It would take several years and millions of dollars to implement a program for the purchase of adequate supplies of used refrigerant for use in MDIs.

D. Likely Availability of Used CFCs

Because of the very long odds against success, and the legal liabilities that could result, no MDI company or group of MDI companies would undertake a used CFC program until it became the option of last resort, if then. The MDI industry will not face this decision unless the Parties to the Protocol reject its request for an exemption from the phase-out deadline. Under current schedules, the Parties will not act on this request until Spring 1994, at the earliest.

The use of used commercial material in pharmaceutical products would be unprecedented and pose special risks for a highly sensitive patient group. There is a strong likelihood that health authorities would not approve this approach.

Even assuming regulatory approvals would be granted, it would take at least four years to implement a used CFC program, assuming all issues of provenance, variability, quality assurance and purification were quickly resolved. Since such a program would not be initiated until mid-1994, the very earliest that used CFC would be available for use in MDIs would be mid-1998. There is every possibility that this program deadline could slip into late 1998, 1999 or beyond.

The MDI industry has forecast that non-CFC substitute propellants probably will be available by the year 2000. Even assuming used CFCs could be made available by mid-1998, it would be needed for only a brief period, probably 18 months. If implementation of the program took longer, the period of need would be shortened.

The best guess of the MDI industry is that it would need somewhere on the order of 10,000 metric tons, and probably much less, during those few months. The ozone protection benefits of preventing the production of this small amount of virgin CFC are marginal and outweighed by the health risks, uncertainties, potential legal liabilities and costs described above.

III. Potential Sources

The purpose of this section is to describe (1) the potential need for CFCs in MDIs after 1995 and (2) the potential sources of used CFCs that possibly could meet this requirement.

A. Projected Usage of CFCs

In 1992, the U.S. MDI industry published an assessment of current and projected usage of CFCs in MDIs. This assessment is entitled "An Analysis of Present and Future Worldwide Usage of Chlorofluorocarbons in Metered Dose Inhalers."⁷

The industry's analysis was designed to project a reasonable upper-bound or maximum on CFC usage after 1995. For that reason, it was based on (1) the assumption that no alternatives to CFC propellants would be available for MDIs prior to the year 2000; (2) a conservative estimate of the extent to which alternative delivery methods such as dry powder inhalers might reduce demand for MDIs after 1995; and (3) a liberal forecast of the number of new MDI products that will be introduced to the market after 1995.⁸

The study projects that worldwide usage of CFCs as propellants in MDIs at the very most will average 10,000 metric tons per year during this decade, and not exceed 15,000 metric tons in any given year.⁹ On a percentage basis, CFC-11 represents about 25% of total MDI propellant usage, CFC-12 about 70%, and CFC-114 about 5%.¹⁰ The study also estimated that the MDI manufacturing process consumes additional amounts of those CFCs at a rate of 10-15 percent of propellant usage.

In a dynamic and evolving market, these projections must be viewed in terms of probabilities. The industry generally believes that actual usage of CFCs will fall below the maximum forecast in its usage study, perhaps substantially so. The actual level of CFC usage after 1995 will depend on many factors including when alternatives to CFC propellants are announced, the usage of alternative delivery methods and the number of new MDI products introduced to the market.

B. Potential Sources

The principal uses of CFCs 11, 12 and 114 are as expanding agents for foam products, propellants in selected aerosol products, cleaning agents and solvents, and refrigerants (including air conditioning fluids). This section discusses whether CFCs could be recovered from any of these products in sufficient quantity to meet the needs of the MDI industry after 1995. It concludes that used refrigerant is the only potential source of used material for the MDI industry.

1. Foam Products

At one time, CFCs 11, 12 and 114 were widely used as expanding agents for foam products. During the manufacturing process they were incorporated in the foam matrix.¹¹

CFC-12 was used as an expanding agent in extruded polystyrene, polyethylene, and polypropylene thermoplastic products such as foam containers for fast food and shipping insulation. CFC-114 was used in small specialty foams.¹²

CFC-12 and CFC-114 have been almost completely phased out of these uses. In addition, virtually all the foam products in which they were used have been discarded, disposed as waste in landfills and elsewhere, or incinerated. There is no practical way to recover these discarded materials for purposes of CFC reclamation and no effort is being made to do so.¹³

CFC-11 is still used as an expanding agent for polyurethane thermoset pour-in-place foams in appliances (e.g., refrigerators), in water heaters, tank cars and trucks, and in construction panels. However, this use is being phased out as a result of significant increases in the excise tax on CFCs in the United States and decreases in CFC production worldwide under government restrictions. After 1995 CFC-11 will not be used for these purposes.¹⁴

Several companies in the United States and Europe have installed equipment capable of recovering CFC-11 from the foam insulation in some appliances. Typically, this foam insulation is removed manually and crushed and shredded in a closed environment. As the CFC-11 is released from the foam as vapor, it is recovered through condensation and carbon absorption.¹⁵

The effort to reclaim CFCs from foam insulation in appliances is in its infancy. The yield of CFCs from this effort will be marginal, relative to the requirements of the MDI industry. The used CFC recovered from foam products is generally sold to firms engaged in the reclamation of this material for commercial and industrial purposes, as discussed below.¹⁶

2. Aerosol Products

The use of CFCs in aerosol products has been prohibited in many countries except for designated "essential uses."¹⁷ There are very few commercial aerosol products now on the market which contain CFCs. The CFCs contained in these products are emitted to the atmosphere during use. After use under normal conditions, there are no CFCs which remain in the product container.¹⁸

As with any product, there are a small number of CFC-containing aerosols which fail to meet product specifications and are withheld from the market. Several companies have developed a process for recovering CFCs from these "off-spec" products.¹⁹ However, the amount of CFCs recovered from these products will be marginal because the number of such products and the amount of CFCs they contain is generally very small. It is estimated that less than 50 metric tons is available for recovery from this source. Recovered product is being sold to firms engaged in the reclamation of used CFCs for commercial and industrial purposes, as discussed below.²⁰

3. Cleaning Agents
and Solvents

CFC-11 is an effective solvent and is used as a cleaning agent. However, less than 250 metric tons of CFC-11 were sold for this purpose in the United States last year. Most CFC-11 is used for "cold cleaning" in uncovered containers from which most of the CFC-11 escapes to the atmosphere. There is no practical opportunity to reclaim CFC-11 in this use. In addition, the use of CFCs as cleaning agents is being phased out and will be discontinued after 1995.²¹

4. Refrigerants

In the refrigeration and air conditioning industry, CFC-11 is referred to as R-11, CFC-12 as R-12 and CFC-114 as R-114. R-11 is a primary refrigerant in large centrifugal compressors used to provide air conditioning for office buildings, hotels and warehouses. R-12 is used primarily in automotive air conditioning. R-12 is also used in household and commercial refrigeration and to some extent in residential air conditioning. It is used in home freezers, water coolers, vegetable display cases and walk-in freezers. R-114 is employed primarily in small refrigeration systems with rotary compressors and in large industrial process cooling and air conditioning systems with centrifugal compressors.²²

Very substantial quantities of R-11, R-12 and R-114 are currently in use worldwide. These quantities could be sufficient to meet the requirements of the MDI industry. Several major companies in the United States and Europe have instituted programs for reclamation of these used refrigerants to commercial and industrial standards.²³ However, these programs are not designed to produce pharmaceutical grade CFC.

IV. Authorization Program

Metered dose inhalers are subject to intense, stringent regulation. As for all approved drug products, manufacturers have filed applications and received marketing authorization for each MDI product. The substitution of used refrigerant for virgin CFCs in MDIs would represent a change in these products requiring reauthorization by health authorities. It would be unlawful to make this substitution without governmental safety review and approval.²⁴ Each company is also subject to the law of product liability, which in effect generates its own legal requirements.²⁵

This section reviews by way of background the pharmaceutical safety standards emanating from drug regulation. It then describes what is known about the contamination of used refrigerant and the potential for its purification. Finally, it sets out a program for seeking regulatory approval for the use of used refrigerant in MDIs.

A. Pharmaceutical Safety Standards

A transcendent responsibility of public health authorities is the "safety" of the patient group for which a new drug product is intended. They discharge this responsibility by balancing the "risk" posed by such a product against its "effectiveness" in promoting human health.²⁶

1. Control of Impurities

One source of risk to patient safety is impurities which are inevitably present in all drug products. Impurities are foreign compounds or substances which are present in addition to prescribed drug constituents. Some impurities are relatively benign; others may be toxic. It is the level and nature of these impurities which determine the risk to the patient and, hence, are of prime importance to drug manufacturers and health authorities.

Impurity Profiles and Specifications

As part of every application for approval of a new drug, the drug manufacturer is required to submit an "impurity profile."²⁷ A separate impurity profile also may be required for individual drug components, such as propellants.²⁸

An impurity profile lists the contaminants which the manufacturer believes possibly may occur in the final drug product, or in any of its components. This list is based generally on chemical analysis performed by the manufacturer during development of the drug or drug component.

The drug manufacturer also must propose specifications for new drugs and drug components.²⁹ These specifications establish upper limits on the permissible concentrations of each major impurity listed in the profile. The specifications are based largely on the toxicology of individual impurities.

The manufacturer sometimes may incorporate the specifications published in pharmacopeia or medical monographs. Where no such published specification

exists (as in the case of new material), or the one that does is outdated, the manufacturer must itself develop a specification for the new ingredient.³⁰

In developing a specification, the manufacturer may turn first to existing information – "the toxicology profile" – on the impurity involved. Where the toxicology of the impurity is unknown, the manufacturer may be required to conduct a battery of tests to measure its effects on animals and humans.³¹

Good Manufacturing Practice

The manufacturers of drug products and their ingredients also must comply with standards of Good Manufacturing Practice ("GMP").³² These standards require a comprehensive range of controls designed to ensure that a product is always manufactured to a consistent quality. GMP requires, among other things, that each process step be monitored continuously batch by batch throughout the manufacturing process and analyzed periodically with state-of-the-art technology. It further requires that the effectiveness and consistency of this technology and all analytical protocols be validated separately through a series of demonstrations conducted prior to their use.

In the United States, for example, GMP requires that analytical testing be conducted in light of "component variability, confidence levels, degree of precision desired and past quality history of the supplier."³³ It also requires "laboratory controls" which incorporate "scientifically sound and appropriate specifications, standards, and test procedures"³⁴ These laboratories must be separately certified under standards established for Good Laboratory Practice.³⁵

For manufacturing equipment, GMP requires that surfaces which contact components "shall not be reactive, additive, or absorptive"³⁶ Under GMP, "[a]ny substances required for operation, such as lubricants or coolants, shall not come into contact with components"³⁷ Moreover, "equipment and utensils shall be cleaned, maintained and sanitized at appropriate intervals to prevent malfunctions or contamination"³⁸ Similar standards apply in Europe and all major countries.

2. Safety Review of
Drug Ingredients

In reviewing the safety of drug ingredients, health authorities normally weigh the following considerations:

Provenance

The origins of the constituents in a drug product have a major bearing on their impurity profiles. The effort to control impurities depends on a combination of technology-based and human resources. It is axiomatic that these controls are imperfect.

For example, pharmaceutical controls will not be effective for impurities whose presence is not anticipated. They are not designed for an undifferentiated mass of impurities whose separate identities have not been established.

Rather, they are specifically tailored for a discrete number of listed compounds.³⁹

Health authorities are therefore wary of drug ingredients whose origins are not fully known or well-understood.⁴⁰ There is no basis for confidently predicting the quality of an ingredient whose origins are ambiguous.

Variability

Similarly, health authorities emphasize "predictability" in drug ingredients and seek guarantees that they will contain only a confirmed list of identified impurities. They are intolerant of "variability."⁴¹ They believe that the risk to patient safety greatly increases where impurities vary from one batch of an ingredient to the next, presenting a "moving target" for pharmaceutical controls.

Safety

In their review of drug specifications, health authorities must confirm that the upper limits on concentrations of particular impurities are sufficient to assure public safety. This determination will be based on known toxicological data or on the results of safety studies conducted by the manufacturer in support of its application for approval of the drug ingredient.

Technical Feasibility

Health authorities must be assured that the purification technology utilized in the manufacturing process is capable of reducing impurities to levels established in the specification. In addition, they must be assured that methods of quality assurance employed by the manufacturer reliably guarantee that these limitations on impurities are met consistently. As noted, questions of provenance and variability bear directly on the technical feasibility of purification and quality assurance.

3. Safety Standards

This section discusses the particular sensitivity of asthma patients to foreign substances. It also discusses specifications established by major suppliers for pharmaceutical grade CFC, and recent actions by health authorities to control impurities in MDIs. Finally, this section describes the process which health authorities would follow in any safety review of used refrigerant.

Patient Sensitivity

A presenting feature of patients who suffer from asthma and related diseases of the lung is hyperreactive airways which are highly sensitive to the presence of foreign substances in minute quantities. Substances which have no effect on the general population possibly may induce idiosyncratic bronchospasms in asthmatics and can cause or aggravate an asthma attack. Consistency of quality and the avoidance of contamination is a prerequisite for anti-asthmatic medication. Doctors go to great lengths to avoid exposing their patients to new foreign substances in their food, medication and environment.

*Pharmaceutical
Standards For Virgin
CFCs*

CFCs 11, 12 and 114 were first used in MDIs in the 1950s. At that time, neither impurity profiles nor quality specifications were required for these propellants. The technology of analysis by, for example, gas chromatography, was then quite primitive.

Specifications for these propellants have been established in major countries in officially recognized pharmacopeia. In the United States, for example, these specifications are contained in the United States Pharmacopeia - The National Formulary.⁴² In regard to impurities, however, the United States Pharmacopeia provides only that "high-boiling residues" (i.e., non-volatile organic compounds) may not exceed 0.01% of CFCs 11, 12 and 114 by volume. It does not list the specific impurities which may comprise this residue and does not prohibit or limit concentrations of any particular substance. More significantly, volatile organic impurities are not addressed. Nor does this monograph establish a minimum level of organic purity of the final product.

Manufacturers of CFCs themselves have established more detailed specifications for pharmaceutical grade CFCs. These specifications typically establish minimum organic purity and contain various limits on volatile and non-volatile organic compounds, non-absorbable gases, water, acidity and particulate matter. (These limitations are described in more detail on page 19 below.) Pharmaceutical firms have relied on consistent quality from the manufacturers of pharmaceutical grade CFCs.

In recent months, public health authorities have indicated that the product specifications in the United States Pharmacopeia for CFCs 11, 12 and 114 are no longer adequate for their purposes.⁴³ They have indicated that in the future separate specifications will be required for CFC propellants whenever they are proposed as inactive ingredients in new drug formulations. In addition, the authors of the United States Pharmacopeia have undertaken an effort to develop new and more stringent specifications for CFCs.⁴⁴

*Recent Actions By
Health Authorities*

The drug formulations which are delivered by metered dose inhalers are each subject to a detailed product specification. These specifications are evaluated by health authorities during the drug approval process.

The possibility that impurities or contaminants not listed in these specifications somehow may occur in MDIs is an issue of concern to health authorities. These authorities monitor product quality during the drug approval process and as the drug product is marketed. Regulatory approvals are delayed if health authorities are not assured of quality; product withdrawals are demanded when continued quality is in doubt. For example, the U.S. Food and Drug Administration delayed approval of new MDI elastomers until components that might leach into the propellant had been identified; required an extensive investigation to establish the precise identity of an unknown compound leached from MDI components that appeared in a liquid chromatogram for an MDI product;⁴⁵ and reversed a substitution of an excipient when taste differences apparently led to product complaints including the exacerbation of an asthma attack.⁴⁶

*Safety Review of Used
Refrigerant*

Health authorities have confirmed that reclaimed CFCs would be regarded as new ingredients for purposes of pharmaceutical safety review.⁴⁷ They have stated that any proposal to use reclaimed CFCs in MDIs would require the

submission of a new drug application or a supplement to a new drug application. In either case, health authorities would require the submission of a detailed impurity profile and quality specifications. They would conduct a full review of the provenance and variability of used refrigerant, the technologies employed for its purification, and the analytical means of assuring that limits on impurities are met consistently. In addition, they would require absolute assurance that unexpected contaminants could be identified and controlled in all sources of reclaimed material.⁴⁸ Depending on the identity and concentration of impurities found, extensive toxicology testing also could be required to demonstrate that used material is not a source of risk to the patient.

B. Contamination of Used Refrigerant

This section discusses the operating environment in which chlorofluorocarbon refrigerants are used. It describes in particular the enormous variety of compounds to which refrigerants are exposed and the wide range of temperatures that it may experience over its useful life.

This section also describes the results of chemical analyses performed on used refrigerant prior to reclamation and discusses the chemical reactions which produce contamination of this material. Finally, this section sets forth the results of chemical analyses on used refrigerant that has been reclaimed to commercial standards and discusses the quality of this material in relation to supplier specifications typically established for pharmaceutical grade CFC.

1. Operating Environment For CFC Refrigerants

Chlorofluorocarbon refrigerants are used in a vast array of refrigeration and air conditioning units including, among many others, household refrigerators, ice machines, automobile air conditioners, truck and railway car refrigeration units, large chillers for industrial refrigeration and commercial air conditioning systems. There are millions of such units and systems now in operation worldwide.⁴⁹

Chlorofluorocarbon refrigerants are exposed to an enormous variety of other compounds. Depending on the make and model of the refrigerator or air conditioning unit involved, refrigerant will contact metals such as steel, cast iron, brass, copper, tin, lead, magnesium and zinc.⁵⁰ As it circulates through these units, the refrigerant dissolves lubricants which contain paraffinic, aromatic and naphthenic compounds and a variety of organic additives.⁵¹

In addition, refrigerants will contact polymers, elastomers, resins, plastics and varnishes. These materials, which themselves are composed of many different chemical compounds, are used in the manufacture of gaskets, gauges, seals, valves, coatings and solder found on the internal surfaces and structures of refrigeration and air conditioning equipment.⁵²

Finally, chlorofluorocarbon refrigerants are exposed to an extremely wide range of operating conditions. In some cases, they will be used as

recommended, within prescribed ranges of temperature (e.g., -10° to +200°F; about -25° to +95°C) and periodically removed and recycled to extend their useful life. In other cases, they may be exposed to extremely high temperatures ranging up to 1000°F (about 540°C) caused by burn-outs of refrigeration motors. They may be recycled only infrequently or not at all.⁵³

2. Contaminants In
Used Refrigerant
Prior To
Reclamation

The refrigerant industry has sponsored a series of "sealed-tube tests" to simulate the operating conditions in which refrigerants are used. Refrigerant, lubricating oils and metals are sealed in heavy-walled glass tubes and heated to the high temperatures produced by motor burn-out. After the test, the types and concentrations of contaminants are measured. This information is used in the evaluation of recycling techniques and procedures.⁵⁴

Sealed-Tube Tests

These sealed-tube tests have indicated the presence of numerous contaminants which do not occur in fresh material. These contaminants include volatile organic compounds (such as related chlorofluorocarbons) and non-volatile organic compounds (such as tar, coke and sludge).

The Kauffman Report

In 1989, the American Society of Heating, Refrigerating and Air-Conditioning Engineers sponsored an empirical study of contaminants in used refrigerants. The study was conducted by Robert E. Kauffman, under the auspices of the University of Dayton Research Institute.⁵⁵ The results of the study were published in 1990 in a written report entitled "Chemical Analysis and Recycling of Used Refrigerant From Field Systems."

Kauffman removed samples of chlorofluorocarbon refrigerants, including R-11 and R-12, from a small number of refrigeration and air conditioning units located at the Dayton Research Institute. Some of these systems had experienced motor burn-outs. Others had not.⁵⁶ Kauffman filtered some of these samples using filter-drier technology.

Kauffman conducted his study of used refrigerant using gas chromatography. His report contains the chromatograms which resulted from this analysis. The chromatograms for samples of CFC 11 and CFC 12, even after filtration, indicate the presence of less volatile organic compounds such as substituted phenols, trichlorotrifluoroethane, toluene, chloroform, carbon tetrachloride, xylene, compressor oil, benzene and tetrachloroethylene.⁵⁷ They also indicate the presence of such volatile organic compounds as R-22, R-23, R-32 and ethylene, as well as organic acids, hydrochloric and hydrofluoric acids, water and particulate matter. In addition, the chromatograms indicate the presence of numerous other contaminants -- as indicated by dozens of chromatographic peaks -- which could not be identified specifically by the testing methodology which Kauffman used.⁵⁸ Finally, the chromatograms indicate that the types and concentrations of contaminants found in used refrigerant vary substantially from one sample of refrigerant to the next.

*Chemical Analysis By
Arthur D. Little*

IPAC retained the independent consulting laboratories of Arthur D. Little to perform a chemical analysis on used and reclaimed refrigerant for purposes of this paper. The results of this analysis are contained in a report entitled "Characterization of Recovered and Reclaimed CFCs by GC/MS," dated March 31, 1993, (hereinafter "Arthur D. Little Report"). A copy of this report is attached as Exhibit A.

Arthur D. Little performed its analysis on samples of used R-11 and R-12 that were provided by a major supplier engaged in reclamation of used refrigerant by distillation. Some of these samples were taken before the used material was reclaimed. Others were taken after reclamation and will be discussed in the next section. The methodology used for this analysis was gas chromatography - mass spectrometry (GC-MS).

The results of the Arthur D. Little analysis generally confirm and amplify the findings of the sealed-tube tests and the Kauffman Report. In particular, this analysis indicates that used refrigerant contains a large number of contaminants in substantial concentrations and hundreds of others in smaller amounts; that these contaminants include both volatile and non-volatile organic compounds; and that the types and concentrations of contaminants vary substantially from one sample to the next, both before and after reclamation, so that no two samples are alike.

The Arthur D. Little Report specifically identified only a small percentage of the organic compounds whose presence was detected by GC-MS. Further analysis and the use of additional analytical techniques would be required to identify the many other organic compounds in these samples.

The Arthur D. Little analysis was performed on a very few samples. These samples were taken from only two or three different sources. These sources featured only a tiny fraction of the very large number of operating environments in which refrigerant is used. It seems safe to assume that chemical analysis of a larger number of samples from many different sources would disclose additional contaminants not indicated in the Arthur D. Little analysis.

The results of Arthur D. Little's analysis are reflected in tables and chromatograms contained in its final report. The results of the analysis of used refrigerant, prior to reclamation, are discussed below. The results of the analysis of reclaimed refrigerant are discussed in the following section of this report.

The Arthur D. Little analysis identified 26 selected compounds in three samples of used R-11, prior to reclamation, including, among others, toluene, nonane, trimethyl heptane, methyl heptanone and dimethyl octene (Table 4). Not all of the compounds were found in each sample. Many of them occurred in only one of the three samples. For example, toluene was found in Sample #1 (mechanical) but not in the other two. Similarly, octyl cyclohexane was

found in Sample #2 (TK Electric) but not in Sample #1 (Mechanical) or Sample #3 (Boland) (Table 4).

Likewise, the concentrations of these compounds often differed markedly among samples where they were found in more than one. For example, the estimated concentration of trimethyl dodecane in Sample #3 (Boland) was 24,000 ppb. By contrast, the estimated concentration of the same compound in Sample #1 (Mechanical) was 175 ppb (Table 4).

This variability in contaminants is graphically portrayed by the chromatograms for the three samples contained in Figure 1 of the Arthur D. Little Report. A copy of Figure 1 appears on page 18. Each peak on these chromatograms represents a different compound. The height of the peak indicates the concentration of the compound. The dissimilarity in these three chromatograms reflects significant variation in the types and concentrations of contaminants in the samples of used R-11 that were analyzed.

The Arthur D. Little Report contains similar findings for samples of used R-12, prior to reclamation. These findings are reflected in Table 7 and 8 and Figures 7-12.

*Organic Reactions and
Other Sources of
Contamination*

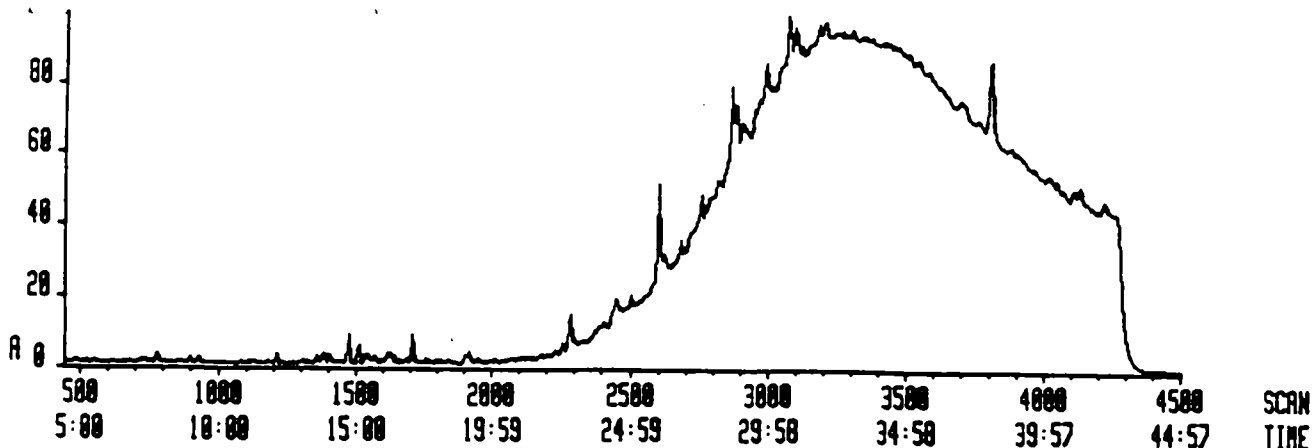
The contaminants found in used refrigerant are produced by complex organic reactions, including reduction, catalysis, disproportionation, halogenation, dehydrohalogenation, pyrolysis (thermal cracking) and polymerization, among others. These reactions lead to the decomposition of the refrigerant itself and/or the decomposition of oil. The unpredictable course of these reactions and related side-reactions is capable of producing an almost unknowable range of contaminants depending on the compounds present and range of temperatures involved.⁵⁹ In addition, contaminants may be introduced from outside sources during, for example, "on-line" recycling of used material. Extraction of impurities from refrigeration materials of construction also account for contamination of used refrigerant. The sealed-tube tests, Kauffman Report and Arthur D. Little Report provide only a small survey of the range of contaminants that may be found in used refrigerant.

3. Contaminants In
Used Refrigerant
After Reclamation
to Commercial
Standards

As previously noted, several major firms in the United States and Europe engage in the reclamation of used refrigerant to commercial standards. These standards require, among other things, that contaminants in reclaimed refrigerant not exceed certain prescribed percentages by weight or volume.⁶⁰ For example, specifications established by the Air Conditioning and Refrigeration Institute limit volatile organic compounds to 0.5% by weight and non-volatile organic compounds to 0.01% by volume.⁶¹ There are no published reports (other than the Kauffman Report) describing the specific contaminants which remain in used refrigerant after it has been reclaimed to commercial and industrial standards.

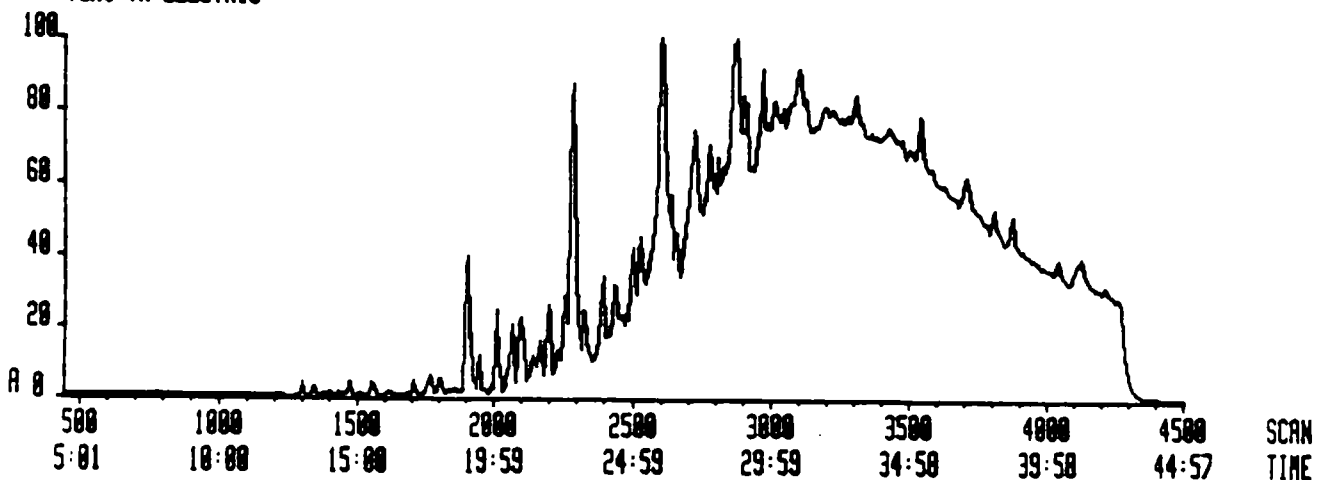
10152A05 #450-4500 15-OCT-92 16:23 TR10-2 (EI+)
 Chromatogram Identifiers : A :ATIC
 Text:MECHANICAL MAINT.

IHP
 A: 14100



10152A04 #450-4500 15-OCT-92 14:54 TR10-2 (EI+)
 Chromatogram Identifiers : A :ATIC
 Text:TK ELECTRIC:

IHP
 A: 19600



10162A01 #450-4500 16-OCT-92 09:46 TR10-2 (EI+)
 Chromatogram Identifiers : A :ATIC
 Text:RECOVERED BOLAND R11

IHP
 A: 3362

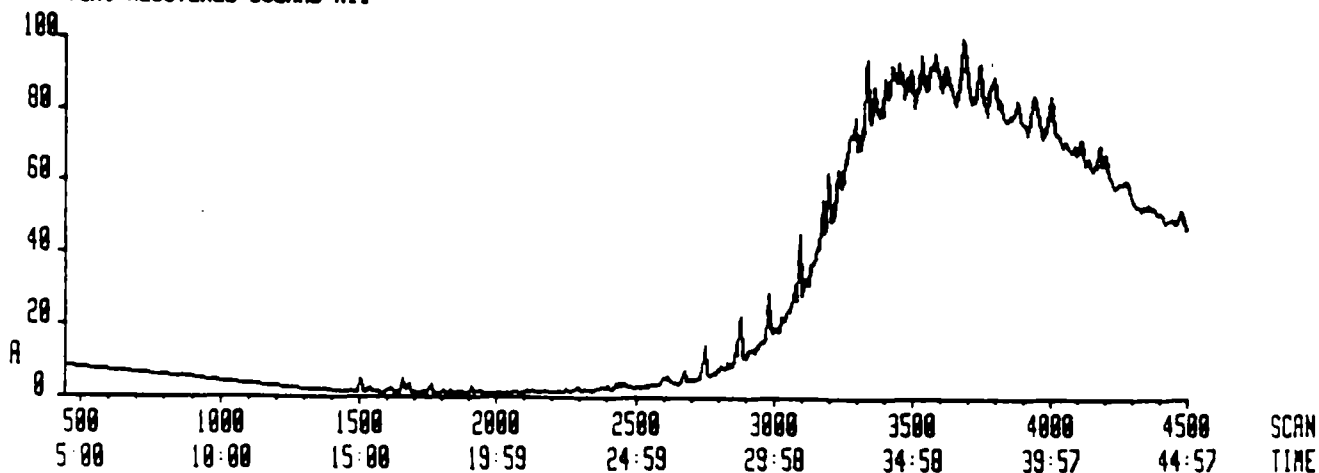


Figure 1 Total Ion Chromatograms for R-11 Recovered Samples (semi-volatile)

Arthur D Little

*Quality of Used
Refrigerant for
Pharmaceutical
Grade CFC*

Manufacturers of CFCs have established their own internal specifications for pharmaceutical grade CFC which are more restrictive than the industry standards listed above. These specifications typically contain the following kinds of limitations:⁶²

1. Organic Purity

- Organic purity of the final product must be equal to or greater than 99.8%

2. Volatile Organic Compounds

The volatile organic compounds most likely to occur in the final product are listed by specific chemical identity. These compounds may include chlorocarbons, other CFCs, HCFCs and HFCs including saturated and unsaturated compounds.

- These identified compounds are limited in the aggregate to 200 parts per million or less by weight; and/or
- Certain ones of these identified compounds are limited to particular concentrations in parts per million by weight; and/or
- Other volatile organic compounds and "unknowns" are limited in the aggregate to a very low level (e.g., 20 parts per million or less by weight). (Unknown compounds are those whose presence can be detected but whose specific chemical identity cannot be determined by the particular analytical method employed for measuring product quality.)

3. Non-Volatile Organic Compounds

- These compounds are limited in the aggregate only to 0.01% (100 PPM) by volume.

Supplier specifications also place limits on non-absorbable gasses (NAG), water, acidity and particulate matter.

Against these specifications, reclaimers perform chemical analyses on samples of reclaimed material.⁶³ IPAC's review of their analyses indicates that distilled reclaimed refrigerant consistently meets their product specifications for commercial refrigerant. However, our review also indicates that in virtually every case refrigerant reclaimed to commercial standards fails to meet the product specifications typically established for pharmaceutical grade CFCs for the following reasons:

- Reclaimed product fails to meet minimum organic purity; or
- Reclaimed product contains concentrations of identified volatile organic compounds which either individually or as a group exceed specification limitations; or

- Reclaimed product contains other identified volatile organic compounds which are not listed in the specifications and therefore are not permitted in the product; or
- Reclaimed product contains concentrations of other volatile organic compounds and "unknowns" which as a group exceed specification limitations.

The failure of reclaimed refrigerant to meet quality specifications for pharmaceutical grade CFC results from the presence of volatile rather than non-volatile compounds. Historically, the primary non-volatile fraction found in virgin CFCs is compressor oil present in very small concentrations not exceeding specifications. By contrast, volatile compounds are more common in virgin CFCs. The quality specifications for virgin CFCs therefore are designed primarily to control these volatile compounds. Similarly, the chemical analyses conducted by CFC manufacturers are designed primarily to disclose the presence of volatile compounds.

The Kauffman Report illustrated the presence of numerous non-volatile compounds in used refrigerant which had been reclaimed by filter-drier techniques. These analyses raised the possibility that non-volatile compounds as well as volatile compounds might remain in used refrigerant after distillation. If present, these compounds could pose unacceptable safety risks in the pharmaceutical context or require some more stringent control than presently provided by pharmaceutical grade specifications.

IPAC engaged the independent consulting laboratories of Arthur D. Little to evaluate the presence of non-volatile compounds in reclaimed distilled refrigerant which might have escaped detection in chemical analyses performed by reclaimers. Arthur D. Little employed analytical techniques specifically designed for that purpose.

*Chemical Analysis By
Arthur D. Little*

Arthur D. Little's analysis indicates that even after reclamation by distillation used refrigerant contains a large number of non-volatile contaminants and that the types and concentrations of these contaminants vary substantially from one sample to the next. For example, the Arthur D. Little analysis identified 21 selected compounds in three samples of reclaimed R-12 including, among others, butanol, methyl heptane, ethylhexyl oxy-methyl oxirane, methoxy propyl phenol and octadecyne (Tables 9 and 10). Many of these compounds occurred in only one of the three samples. For example, butanol was found in Sample #2 (FT-689) but not in the other two (Table 9). Similarly, decahydro dimethyl naphthalene was found in Sample #3 (FT-445) but not in the other two (Table 9).

Likewise, the concentrations of these compounds often differed markedly among samples where they were found in more than one. For example, the concentration of unsaturated hydrocarbon in Sample 2 (FT-689) was 1500 parts per trillion. By contrast, its concentration in Sample #3 (FT-445) was only 170

parts per trillion (Table 9). These variations are reflected on chromatograms appearing as Figures 13, 14 and 15 in the Arthur D. Little Report.

Similar findings were recorded for two samples of reclaimed R-11. See Tables 5 and 6, and Figures 3-6.

It should be noted that many volatile organic compounds identified in chemical analyses performed by reclaimers (see previous section) were not listed in the Arthur D. Little Report even though commercial reclaimed refrigerant was analyzed. This is because: (i) the Arthur D. Little system was not optimized to look for volatiles in the vicinity of the parent compound and thus compounds like HCFC 21 and 22 were not reported; (ii) the gas chromatography/mass spectrometry technique scanned for fragments greater than mass 50 thereby discriminating against the identity of compounds like HCFC 21 and 22; and (iii) these compounds were in effect eluted before identification.

Summary

Refrigerant reclaimed by distillation to commercial standards fails to meet supplier specifications for pharmaceutical grade CFC and contains large numbers of high-boiling organic contaminants which may pose unacceptable safety risks. The question remains whether further purification of this refrigerant, through additional fractional distillation, could render it fit for pharmaceutical use.

C. Feasibility of Purifying Used Refrigerant

This section describes the purification process of fractional distillation. It also discusses the technical obstacles to purification created by the large number and variability of contaminants found in used refrigerant and by the possibility that unknown impurities may be present.

1. Fractional Distillation

Fractional distillation is a process used to separate a mixture of compounds into its pure components. The process of separation is based on the differences in the vapor/liquid equilibria of individual compounds at different temperatures and pressures. In a general way, these differences are indicated by the differences in the boiling points of the compounds involved.

Fractional distillation is ideally suited to volatile materials such as CFCs and is the main purification process used in its manufacture and reclamation. Distillation is performed in equipment that includes a reboiler to supply heat to the mixture, a column of calculated height and a condenser typically cooled with water to condense the vapors. The column contains a series of separation units such as perforated plates or packing consisting of hollow cylinders.

The mixture is heated in the reboiler to vaporize the components which flow up the column. The relative concentrations of the components at any point in

the column depend on their relative vapor pressures at the varying temperatures in the column. The components that boil at the lower temperatures are more concentrated in the vapor as they rise up the column and the higher boiling components are more concentrated in the lower part of the column. The components (or streams) are withdrawn at varying locations from the column as vapor, and condensed and collected.

As the vapor rises in the column, it is continuously condensed by exposure to cooler liquid streams flowing downward and then revaporized by exposure to hotter vapor streams rising from below. This continuous process of condensation and revaporization increases the purity of vapor components and enriches the low-boiling components as they rise in the column. Higher levels of purity are achieved through "reflux" or recirculation of a purified component through the column.

2. Azeotropes

While the process of fractional distillation can in theory separate components which differ in their individual boiling points, it is not always effective in practice, for example when azeotropes are formed. The term azeotrope refers to a complex molecular interaction in which two or more compounds interlink and cannot be separated into pure components through a process of distillation. Azeotropes are not an uncommon phenomenon. For example, R-12 forms an azeotrope with R-22.⁶⁴ Where an azeotrope occurs, further purification by distillation is difficult and may even be impossible.⁶⁵

3. Technical Considerations

In designing a distillation column, the following questions, among many others, must be addressed:

- What are the types and concentrations of chemicals contained in used refrigerant?
- What are the physical properties and vapor/liquid equilibria of each chemical contained in used refrigerant?
- How many separation units must be used to reduce the concentration of these chemicals to prescribed levels?
- How should "purge streams" be managed to achieve desired quality in view of feedstock impurity composition?
- What temperatures are required to produce the necessary vaporization of these chemicals?
- What is the appropriate amount of reflux or recirculation of used refrigerant through the distillation column?
- Are azeotropes present?

As discussed above, the possibility exists that some or many contaminants whose identity is unknown may occur in used refrigerant. To the extent that they do, it is not possible to address the critical questions which must be answered in the design of any distillation column.

The possible presence of unknown contaminants substantially reduces confidence levels in fractional distillation. From an engineering standpoint, it is uncertain whether a distillation column reliably will remove an impurity whose identity is unknown.

The fact that impurities in used refrigerant may vary dramatically from one batch to the next is also a serious obstacle to purification. Where variability exists, there can be no assurance that a distillation column designed for one batch of refrigerant will be capable of purifying another. In other words, variable composition reduces the effectiveness of distillation columns.

A very large number of contaminants makes it more probable that one or more of them will have a vapor/liquid equilibria that is very close to the compound being purified. It also makes it more likely that azeotropes will occur. In either case, separation of compounds becomes more difficult and in some cases impossible beyond a certain point. In these circumstances, the reliability of fractional distillation in achieving pharmaceutical standards may decrease significantly.

D. Feasibility of Quality Assurance

In order to be assured of the quality of the CFC propellants used in MDIs it is necessary to have rigorous analytical techniques which can determine whether impurities exceed prescribed limits. Gas chromatography (GC) and gas chromatography/mass spectrometry (GC/MS) are principal techniques for analyzing volatile materials. They are employed to assess the types and concentrations of volatile organic impurities in CFCs. This section discusses the feasibility of using these techniques to assess the quality of used refrigerant before and after purification.

1. Chemical Analysis by Gas Chromatography

Gas chromatography (GC) is a means of separating and measuring the concentrations of impurities in drug ingredients.⁶⁶ In GC, the substance to be analyzed is injected into an inert gas stream which flows through a thin tube or "column" made of metal, glass and fused silica. The gas itself passes freely through the column without obstruction. The substance and its impurities are impeded, however, by "substrates" within the GC column.

Substrates exhibit a variety of chemical properties and interact somewhat differently with each of the components and impurities passing through. These interactions slow the passage of each compound to varying degrees. As a result, compounds flow through the column at different rates and "elute" or

exit the column at different times. The time required for a compound to complete this passage is called its "retention time."

As the molecules of an impurity exit the GC column, they can be detected by various means such as "flame ionization." In flame ionization, the molecules are converted into electrically charged species which produce an electronic response. This response produces a "peak" on a gas chromatogram which records the strength of the electrical impulse and the time at which it occurred. The height of the peak is proportional to the number of molecules present.

The molecules of each impurity actually exit the end of the column over a short period of time rather than all at once. There is a "leading edge" of these molecules and a "tail." There is a brief moment that elapses between the point at which the leading edge reaches the end of the column and is detected and the point at which the tail has completely cleared it.

Uncertainty arises where the leading edge of one impurity overlaps the tail of another. In these circumstances, it becomes more difficult to identify and measure the concentrations of impurities involved.

In some cases, for example, a relatively small concentration of one impurity can "sneak" through under cover of a larger concentration of a second impurity whose leading edge exits before, and tail exits after, the first impurity has passed completely through. In these situations, the first impurity is hidden by the second and escapes separate detection by gas chromatography. In the vernacular of analytical chemists, the first impurity is "buried" under the "big peak" created by the second. Where this occurs, the two impurities are referred to as "coelutants."

The chromatograms in the Arthur D. Little report illustrate some of the concepts discussed above. Figure 1 in the Report, which appears on page 18, contains three chromatograms. One can identify various peaks which correspond to specific compounds which are coming off the column at a certain (retention) time. The scan number indicates the relative retention time. For example, the peak which corresponds to scan 1901 at about 19 minutes is identified by its mass spectrum as nonyl cyclopropane. The height of the various peaks indicate the relative amounts of various components.

All three chromatograms have a very broad feature which indicates the presence of numerous species with very close retention times that are coeluting. As a result only the components present as relatively larger amounts, which produce the spikes above this feature, can be identified. Arthur D. Little estimates that there are probably 100 or more compounds which were not specifically identified from their analysis.

GC is used typically to measure the concentrations of impurities whose identities and retention times are known. It provides a means to determine whether the concentrations of these impurities fall below (or exceed) the limits

set in the specifications for the substance. Assuming problems of co-elution can be overcome, GC provides an appropriate analytical method for detecting and identifying known impurities in CFCs. However, it cannot guarantee the absence of unknown impurities nor can it identify them if they are detected. For the latter, techniques which can aid in elucidating the structure of the impurities, such as mass spectrometry, are required.

2. Mass Spectrometry

A molecule is comprised of atoms bonded together in a particular configuration. Mass spectrometry ("mass spec") provides a means for identifying an unknown molecule by deducing its atomic composition and arrangement of atoms.⁶⁷

The process begins by establishing the "mass" of the molecule involved. The mass of a molecule is the combined weight of the atoms arranged within it. When the mass of a molecule is known, it is often possible to determine its atomic composition. This is done by investigating the combination of atoms whose combined weight totals the mass of the unknown molecule.

In most cases, however, more than one configuration of atoms could account for total mass. In these situations, additional information can be obtained from the fragmentation of the molecule.

In mass spec, the molecules are split apart into fragments. The mass of each fragment is separately established. From its mass and magnitude, the atomic composition of each fragment is deduced. It is generally possible to determine the way in which the atoms of a molecule are connected from the atomic compositions of the fragments.

When mass spectrometry is coupled to GC (GC/MS), it becomes the detector. As molecules elute from the GC column, they are fragmented and analyzed by the mass spectrometer. The fragmentation spectrum can be compared to known spectra to identify the molecule or a structure can be proposed based on the spectrum. In cases where two or more components elute from the GC column at the same time ("coelute"), the pattern becomes complicated by the presence of fragments from more than one type of molecule. In some cases, the identity of different coeluting species can be determined. However, where several species are coeluting analysis can become ambiguous. The fact that the mass spectrum is complicated is, however, useful in establishing that coelution is occurring and that another GC column should be used to facilitate the separation.

3. Technical Considerations

The whole purpose of quality assurance is to guarantee that impurities do not exceed prescribed limits. As with distillation, this is difficult to accomplish where unknown compounds may be present, where large numbers of contaminants are involved, and where the types and concentrations of impurities vary substantially from one batch of refrigerant to the next.

As noted, gas chromatography is not capable of reliably measuring the presence of impurities unless their identities and retention times are already known. In addition, the risk that some contaminants -- whether known or unknown -- will "sneak" by GC increases significantly where large numbers of impurities are involved.

Gas chromatography coupled to mass spectrometry is capable of detecting and identifying unknown compounds. At the very least, it would be needed to determine the range of contaminants in used refrigerant. The variability of the sources of used material may also require that it be used in quality assurance to identify unknown impurities. However, the capacity of GC/MS may be substantially limited where large numbers of impurities are involved.

E. Program For Seeking Authorization

This section describes a program for seeking authorization for the use of used refrigerant in MDIs. Any such program would proceed down two interrelated tracks. The first track would involve the development of a purification facility through concept design, bench scale development, pilot plant testing and finally, design and construction of a commercial facility. The second track would involve the development and implementation of pharmaceutical safety standards and programs including an impurity profile for used refrigerant, product specifications and a program for quality assurance that complied with Good Manufacturing Practices. While much of this work could be done concurrently, the program would involve several discrete stages that proceeded sequentially, one after the other.

To provide used CFCs for the manufacture of MDIs worldwide, purification facilities probably would have to be located in several major countries, e.g., the United States, Germany and the United Kingdom. In addition, a separate purification technology and probably separate facilities would be required for each of the three CFCs involved -- CFCs 11, 12 and 114.

Since these activities would proceed concurrently, the description of the steps involved in the development of pharmaceutical safety standards and programs is at points intermingled with the description of the stages in development of a purification facility, and vice versa. An estimated timetable for completion of each stage is also set forth. The timetable is based on the assumption that technical questions of purification, quality assurance, impurity profiles, product specifications and safety testing are quickly resolved. In that event, it will take at least 4 years to complete the program. If any one of these questions proved difficult to overcome, the effort could take substantially longer.

The several stages of a used refrigerant program are described below.

Concept Design

- Assemble teams of qualified personnel including broadly experienced project managers with engineering backgrounds; analytical chemists; process engineers; production engineers and financial analysts.

- Assess contaminants contained in used CFCs 11, 12 and 114 including the types and concentrations of contaminants and their variability from one sample to the next. To meet pharmaceutical standards, virtually all "unknowns" would have to be identified. A very large number of samples would have to be assessed in view of the wide range of operating conditions from which used refrigerant would be recovered.
- Commence development of pharmaceutical safety standards and programs based on the results of the chemical assessment. Meet with health authorities to discuss issues of provenance, variability, impurity profiles and product specifications.
- Determine the physical properties of contaminants including boiling points at various pressures, densities, heat of vaporization, vapor densities, vapor pressures and corrosion rates, among others.
- Establish vapor/liquid equilibria of contaminants. In many cases this information will be known. In others, it may be necessary to turn to a consulting laboratory for experimentation and testing. This data serves as a critical basis for concept design.
- Design purification facilities for CFCs 11, 12 and 114. For fractional distillation, this would include, among other things, selecting materials and designing columns with reboilers, heat exchangers, condensers and separation units.

It is estimated that concept design would take approximately 15 months.

*Bench Scale
Development*

- Design laboratory glassware demonstration and test performance of purification concepts in laboratory setting.
- Continue development of impurity profiles and product specifications for CFCs 11, 12 and 114 based on results of laboratory testing.
- Continue chemical analyses of used CFCs 11, 12 and 114 to confirm the range of contaminants it may contain.

It is estimated that bench scale development and laboratory testing would take at least three months, and probably longer.

Pilot Plant

- Demonstrate commercial viability of design concepts through construction and operation of pilot plants. A pilot plant provides operating experience, reliable performance data and personnel training for development of a commercial facility.
- Meet with health authorities to discuss projected levels of CFC purity, pharmaceutical safety programs and standards and appropriate safety testing for each CFC.

- Based on performance of purification technologies and results of discussions with health authorities, reach "go/no go" decision on commercial development.

It is estimated that the pilot plant stage would take at least six months, and probably longer.

*Commercial Plant
Design and
Construction*

- Assuming a decision to go forward is reached, retain design and construction firm; assemble project personnel; select sites or acquire existing buildings; obtain necessary permits; set up laboratories; purchase instrumentation; implement programs for quality assurance and GMP; start up and operate purification facilities; and conduct final prove-out of purification technology and product quality.

It is estimated that this stage would take two years to complete.

Safety Testing

- Assuming a decision to go forward is reached, conduct necessary safety testing on CFCs 11, 12 and 114 in accordance with understanding reached with health authorities. Testing would involve at a minimum animal toxicological studies. Health authorities might also require carcinogenicity tests and tests for variations in taste, odor or smell, depending on the types and concentration of impurities which persist in used material. As safety testing is underway, conduct necessary tests on the stability of drug formulations using used CFCs.
- Commence preparation of "Drug Master Files" for CFCs 11, 12 and 114 for submission to health authorities. These files would describe the used refrigerant program and address issues of provenance, variability, contaminants, purification, quality assurance, safety testing, impurity profiles and specifications.
- Commence preparation of New Drug Applications for submission to health authorities.

Shorter term toxicological studies would take approximately one year. Carcinogenicity tests such as those required for CFC substitutes now under development would take approximately three years.

Drug Application

- Complete preparation of Drug Master Files for submission to health authorities based on results of safety testing.
- Complete preparation of New Drug Applications for submission to health authorities in market countries. There are approximately 50 such products for which new applications would have to be filed.

It is estimated that it would take approximately three additional months to complete the preparation of Drug Master Files and New Drug Applications for submission to health authorities.

Authorization
Program

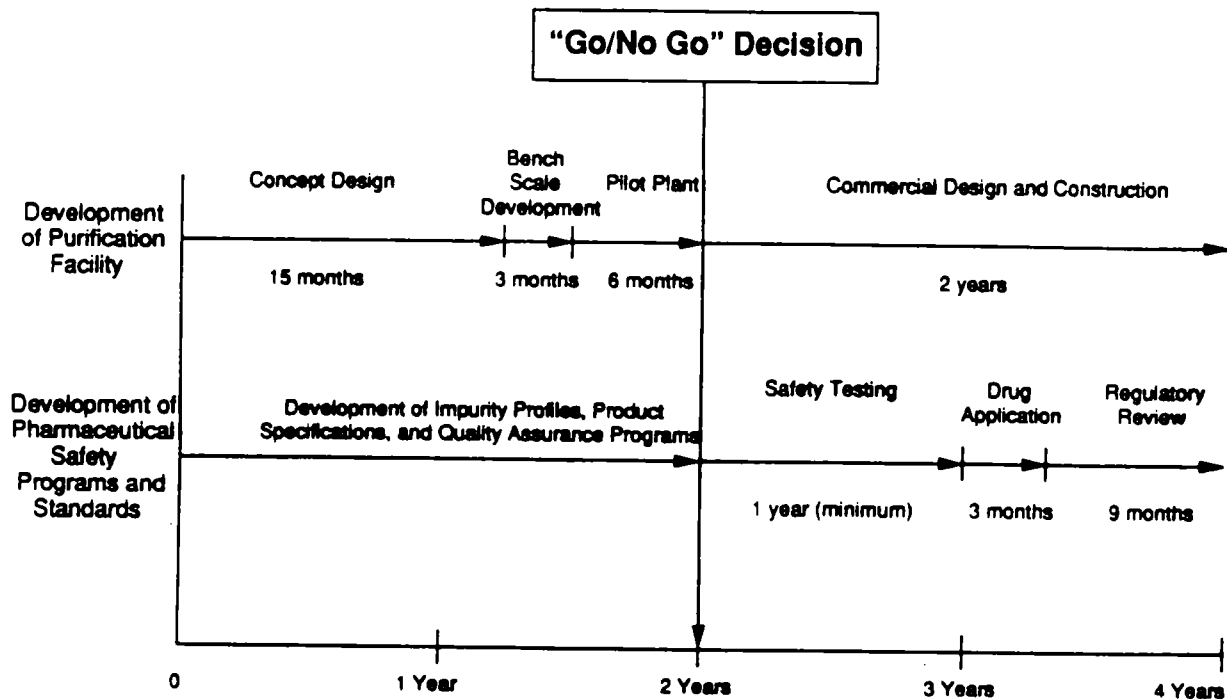
Regulatory Review

It is estimated that review and approval of new drug applications by health authorities would take on average six months. The amount of time required for this review would vary somewhat from one country to the next.⁵⁸

The stages of a used refrigerant program are depicted on Figure 2 on page 30.

Figure 2

An Estimated Timetable For Seeking Authorization for the Use of Used CFCs in MDIs



V. Acquisition Program

A. Availability of Used Refrigerant

This section first defines "recovery," "recycling" and "reclamation" as these terms are used in the refrigerant industry. It then discusses the potential availability of used refrigerant for other uses, such as MDIs, under existing market conditions. It further describes the exceptional value of used refrigerant to its current users (owners of existing refrigeration and air conditioning equipment) as a means of deferring the cost of the transition to substitute refrigerants, especially the cost of retrofitting existing equipment or purchasing new equipment.

1. Clarification

The terms "recovery," "recycling" and "reclamation" are sometimes used interchangeably in discussions of used refrigerant. As used by industry, however, these terms refer to very different activities.

Recovery

The "recovery" of used refrigerant simply means its removal from refrigeration and air conditioning equipment and storage in an external container. It does not suggest that any testing or processing of the used material has occurred.⁶⁹

Recycling

"Recycling," on the other hand, usually refers to a process for cleaning the used refrigerant for immediate reuse in the equipment from which it is removed. Recycling almost always occurs on the premises, at the job site or at a local service shop. It generally involves the separation of oil and the removal of moisture, acidity and particulate by passing the used material through core filter dryers or similar devices. In recycling, there is usually no analysis performed to ensure that the cleansed material meets the specifications for new product.

In recycling, ownership or possession of the refrigerant does not usually change hands. It is generally returned for reuse as a refrigerant in the equipment from which it was removed. By definition, recycled material is not available for other uses (such as MDIs).⁷⁰

Reclamation

By contrast, reclamation means the processing of used material to new product specifications through the use of more sophisticated cleansing techniques such as filter-drying and distillation. Chemical analysis is employed to ensure that these specifications have been met. Used refrigerant almost always is reclaimed at a reprocessing or manufacturing plant where facilities for distillation and chemical analysis are available.⁷¹

In many cases, ownership of the used refrigerant is retained by users or wholesalers who pay a fee for reclamation. In other cases, the user or wholesaler returns used refrigerant for a credit towards purchase of an equal quantity of reclaimed or virgin material.

2. Availability of
Reclaimed R-11,
R-12 and R-114 for
Other Uses

As noted, several major firms in the United States and Europe have instituted programs for the reclamation of used refrigerant. Together these firms reclaim most of the used material which is processed.⁷²

According to industry officials, only about 1000-1500 metric tons of R-11 and R-12 (and far smaller amounts of R-114) will be reclaimed by these firms in the United States in 1992. Industry officials believe these amounts possibly could increase to 3000-4500 metric tons in 1995.⁷³

However, the current owners of R-11, R-12 and R-114 (including users and wholesalers) almost always arrange for reclamation of used material on condition that they be permitted to buy back an equivalent amount of reclaimed material. Very often these owners will receive a credit for the value of their used material which is applied toward the purchase of reclaimed material.⁷⁴

The practical result of these arrangements is that virtually all reclaimed refrigerant is repurchased for use in refrigeration and air conditioning equipment rather than made available for other purposes. There was virtually no reclaimed R-11, R-12 or R-114 available for other uses (such as MDIs) in 1992, according to industry officials.⁷⁵

3. Exceptional Value
of Reclaimed
Refrigerant to
Current Users

As virgin production of R-11, R-12 and R-114 for sale in the developed countries declines significantly and ceases altogether at the end of 1995 under government restrictions, the owners of existing air conditioning and refrigeration equipment must replace these materials with substitute refrigerants. In many cases, this will require expensive retrofit of existing equipment or the purchase of new equipment. For example:

- In the case of large chillers, retrofit may involve the replacement of housing, impellers, gears and motors at a one-time cost of up to \$150,000 for a single unit. By contrast, it would cost only several thousand dollars to recycle or reclaim used refrigerant for reuse in these chillers. There are approximately 80,000 such chillers in use in the United States today. It is estimated that 75% - 85% of these chillers use CFC-11. For major firms with many such chillers, the cost of retrofit may total many millions of dollars.⁷⁶
- In the case of automobile air conditioners which use R-12, the cost of retrofit may run as high as \$300 per unit, according to industry officials. For a major change in some cars the cost could reach \$1,000. By contrast, it would cost only a fraction of this amount to recycle R-12 for reuse in existing automobile air conditioning units.⁷⁷
- In the case of a household refrigerator, the conversion to substitute refrigerants may require the purchase of a whole new unit at a cost of

\$1,000 or more. By contrast, it would cost only a small fraction of that amount to recycle and reuse R-12.⁷⁸

Refrigerants are exceptionally stable materials and have a useful life of many years if they are recycled or reclaimed on a regular basis. The equipment and facilities required for recycling and reclamation are now readily available to the current users of R-11, R-12 and R-114.⁷⁹

By recycling and reclaiming these materials for reuse in existing equipment, the owners of refrigeration and air conditioning units may extend the transition to substitute refrigerants and defer the expense of retrofit for at least several years. There is a consensus among industry officials that, under existing market conditions, users generally will follow this course and only very limited if any supplies will become available for non-refrigerant use.⁸⁰

B. Purchase Of Used CFCs

This section sets forth the program that would be required in any effort to purchase an adequate supply of used CFCs for use in MDIs. The necessary steps include forming an organization to acquire the material; developing a purchasing strategy; surveying potential sellers; and negotiating the purchase of used CFCs. These steps are described in more detail below:

Organization

Form an organization to plan and implement an acquisition strategy; assemble team of marketing and purchasing specialists.

Strategy

Develop strategy for assessing the availability of used CFCs, contacting potential sellers, negotiating price, and acquiring material.

User Survey

Where possible, negotiate arrangements with existing wholesalers and reclaim firms to survey potential sellers.

As necessary, contact directly potential sellers. For R-12, contact car garages that service automobile air conditioning units and contractors that service residential air conditioning units and household refrigerators. For R-11, contact the owners of centrifugal compressors for air conditioning and office buildings, hotels and warehouses. For R-114, contact the owners of both small refrigeration systems and large industrial process cooling and air conditioning systems.

Purchase

Negotiate purchase of used CFCs. In the case of large users, retrofit and conversion to substitutes may take many months. Substantial lead time for acquisition would be required.

Arrange for transportation of used CFCs to purification facilities.

**Acquisition
Program**

It is estimated that an effort of this kind would take approximately 2 years. The effort probably could be staged in such a way that used material would be available for purification at about the time that it was approved by health authorities for use in MDIs, under the 4 year timetable for that process described above.⁸¹

VI. Conclusion:

Likely Availability of Used CFCs for Use in MDIs

The use of used commercial material in pharmaceutical products would be unprecedented and pose serious risks for a highly sensitive patient group. It is highly doubtful whether state-of-the-art technologies for purification and quality assurance could reduce these risks to acceptable levels. There is a strong likelihood that health authorities would not approve the use of used CFCs in MDIs.

In any event, it would take at least four years to develop commercial facilities for purifying used CFCs and to obtain authorization for their use in MDIs, assuming all questions of safety and technical feasibility were quickly resolved. Health authorities might take even more time to complete this process in view of the special risks involved in exposing millions of highly sensitive asthmatics to material already used for commercial and industrial purposes. Authorities especially would be concerned about the possibility of unknown impurities that escaped detection in the manufacturing process.

Aside from protecting patients from impurities in used refrigerants is the practical problem of purchasing an adequate supply of this material. The best one can say at present is that current owners of refrigerant are choosing to conserve it for their own use. Users are greatly concerned about the cost of converting to substitute refrigerants and are planning to defer this expense by continuing to use the material they now own. Any effort to entice current users to part with existing supplies of refrigerant would take a great deal of time and money. Even then there would be problems of stockpiling, pooling, storage, collection and transportation.

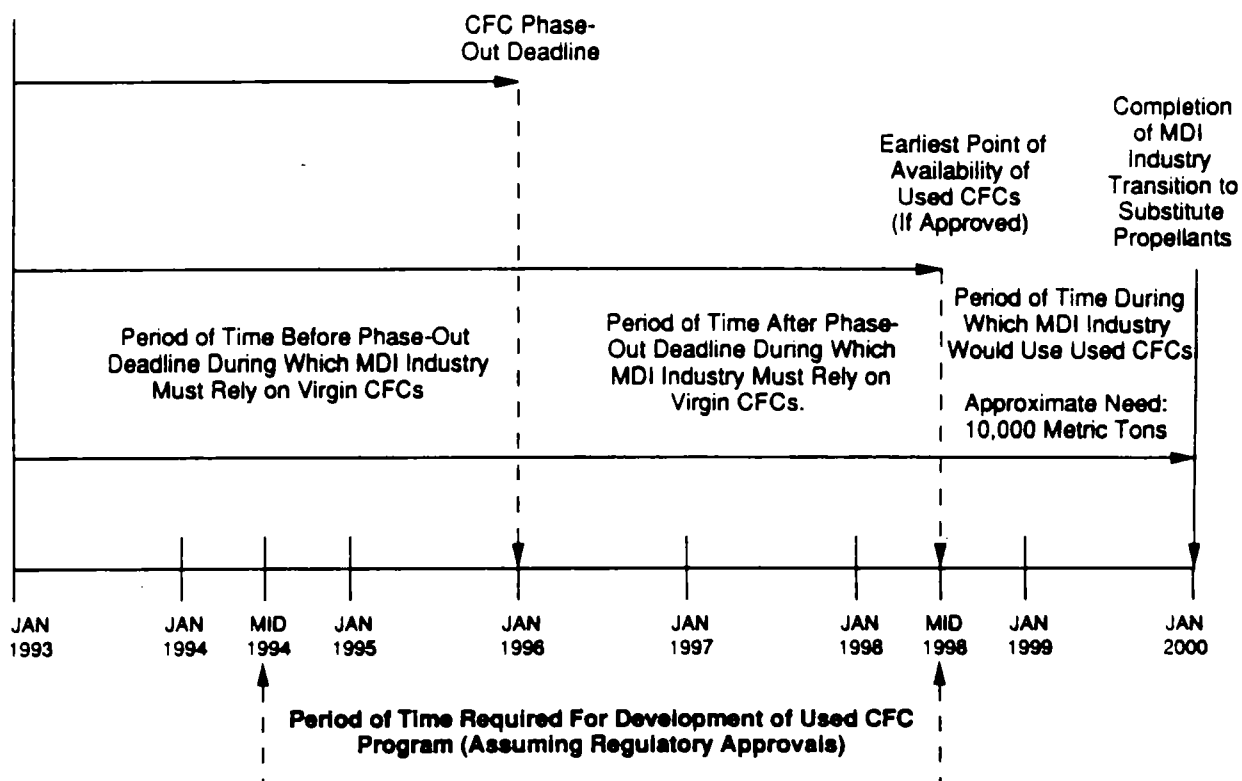
In addition, the use of used CFCs in MDIs would expose pharmaceutical firms to risks of large judgments in product liability litigation. Moreover, the costs of any used CFC program would be large, would dilute the on-going program of the MDI industry to find a permanent solution, and would divert R&D resources from truly innovative projects.

Finally, a used CFC program would be undertaken, if at all, only if the Parties to the Protocol refused at their Sixth Meeting in 1994 to grant exemptions for the MDI industry. The risks of failure and legal liabilities are simply too great to incur unless there is no other choice.

Assuming, however, that a used CFC program was initiated in mid-1994 after the Sixth Meeting of the Parties, it would not be completed for four years, until mid-1998, at the earliest. By this time, the MDI industry would be nearing completion of its transition to substitute propellants and require somewhere on the order of 15,000 additional metric tons of CFCs (and probably much less), assuming that only 18 months remained in the transition. (The limited period of time for usage of used CFCs in MDIs is depicted diagrammatically in Figure 3 on the following page.) The ozone protection benefits of preventing the virgin production of this small amount of CFCs are negligible and outweighed by the costs and risks described above.

Figure 3

The Limited Period of Time for Usage of Used CFCs (Assuming Regulatory Approvals)



Endnotes

1. Montreal Protocol: 1991 Assessment; Report of the Aerosol Products, Sterilants, Miscellaneous Uses and Carbon Tetrachloride Technical Options Committee (hereinafter "1991 Technical Assessment"), 33.
2. Ibid., 33.
3. Ibid., 34.
4. Ibid., 34.
5. Report of the Fourth Meeting of the Parties to the Montreal Protocol (UNEP/OzL. Pro. 4/L.1/Rev. 2) (November 1992), 19-20.
6. Every country in the world regulates the manufacture and sale of drug products. This report focusses primarily on the regulations of the United States and the European Community (EC). These regulations are essentially similar to those found elsewhere in the world.
7. The Dunn Group, "An Analysis of Present and Future Worldwide Usage of Chlorofluorocarbons in Metered Dose Inhalers," (Pharmaceutical Aerosol CFC Coalition, August 1992) (hereinafter "The Dunn Group").
8. The Dunn Group, 2-3.
9. Ibid., 10.
10. Ibid., 11.
11. Daly, John J., Wilmington, Delaware, to International Pharmaceutical Aerosol Consortium, November 1992, A Report on the "Potential for the Use of Reclaimed Chlorofluorocarbons (CFCs) in Metered Dose Inhalers (MDIs)," Part I, 2.
12. Ibid., Part I, 2-3; Part III, 2-3.
13. Ibid., Part I, 2-3; Part III, 2-3.
14. Ibid., Part I, 2-4; Part III, 2-3. See generally J.M. Blessing, "A Unit for the Recovery of CFC-11 from Rigid Polyurethane Foams," in Polyurethanes World Congress 1991-September 24-26 (1991), 366; N.C. Vreenegoor, "Environmental Considerations in the Production of Flexible Slabstock," in Polyurethanes World Congress 1987-September 29-October 2 (1987), 178; R. Hurd, "Scrubbing of Isocyanate and CFC Emissions in Flexible Foam Plants," in Polyurethanes World Congress 1987-September 29-October 2 (1987), 173; E.I. du Pont de Nemours, Freon Products Division, "Limitations of Carbon Adsorption for Solvent Conservation and Recovery", FREON Solvents & Chemicals: Technical Report RP-5, (Delaware: E.I. du Pont de Nemours & Co.); "Control Technology Overview Report: CFC-11 Emissions from Flexible Polyurethane Foam Manufacturing", (Washington, D.C.: U.S. Environmental Protection Agency, Draft Report DCN #86-203-023-61-06, EPA Contract No. 68-02-3994, December 17, 1986); and "Method and Apparatus for Recovering Blowing Agent in Foam Production" (Washington, D.C.: U.S. Patent Office, United States Patent 4,531,951; Patent Inventor: James G. Burt, July 30, 1985).
15. Blessing, 366-69.
16. Daly, Part I, 2-4.
17. See, e.g., 21 Code of Federal Regulations § 2.125; 1991 Technical Assessment, 33.
18. Daly, Part I, 2; Part III, 1.
19. Losora Systems, Inc., General Information: The U.S. Aerosol Market and It's Practices, 1992; Letter from F. Dean, President of Enviro-American, Inc., to T. Freeman, Fisons Corporation, February 28, 1992.
20. Daly, Part I, 2; Part III, 1.
21. Ibid., Part I, 4.
22. A. Althouse, C. Turnquist, and A. Bracciano, Modern Refrigeration and Air Conditioning (South Holland, Ill.: The Goodheart-Willcox Company, Inc., 1988), 299; Daly, Part I, 5.
23. Du Pont Fluorochemicals, "Du Pont Refrigerant Reclamation Program" (brochure distributed by Du Pont Fluorochemicals, Inc., March 1991); National Refrigerants, Inc., "Guaranteed Quality Control Sets Us Apart" (brochure distributed by National Refrigerants, Inc., n.d.).
24. See, e.g., 21 United States Code § 321 et seq.; Commission of the European Communities, The Rules Governing Medicinal Products for Human Use in the European Community, January 1989; Council Directive 65/65 EC.
25. For example, under principles of common law in the United States, many states impose strict liability on corporations for sale of pharmaceutical products whose design is "unreasonably dangerous per se." Reyes v. Wyeth Laboratories, 498 F.2d 1264 (5th Cir.) (1974). In other words, a company may be liable for harm caused a patient regardless of whether it was negligent in the manufacture of the product involved. The fact that the product was approved by health authorities is no defense in an action of this kind. See generally Note, "A Question of Competence: The Judicial Role in the Regulation of Pharmaceuticals" 103 Harv. L. Rev. 773 (1990).

Whether a drug is deemed "unreasonably dangerous" turns in substantial measure on the "inherent risks" involved. Brochu v. Ortho Pharmaceutical Corp., 642 F.2d 652 (1st Cir.) (1981). The issue before the jury in this case would be the inherent risks of used refrigerant.

The factors involved in calculating that risk would almost certainly include the sensitivity of the patient group involved, the contaminants found in used refrigerant, and the reliability of efforts to remove them. It is noteworthy that both major reclaimers in the United States have declined to provide used refrigerant for pharmaceutical purposes in part because of concern over legal liabilities. Daly, Part II, 6.

26. See, e.g., 21 United States Code, § 355.
27. See, e.g., Department of Health and Human Services, Food and Drug Administration, Center for Drugs and Biologics, Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances (Washington, DC: U.S. Government Printing Office, February 1987) (hereinafter "Drug Applications"), 38.
28. See, e.g., Ibid., 39.
29. See, e.g., Ibid., 39.
30. See, e.g., Ibid., 39.
31. G. Burke, G. Poochikian, and P. Botstein, "Regulatory Science of Inhalation Aerosols," Journal of Aerosol Medicine Vol. 4, no. 3 (1991) 265-68.
32. 21 Code of Federal Regulations § 211; Council Directive 91/356/EEC.
33. 21 Code of Federal Regulations § 211.84(b).
34. Ibid., § 211.160(b).
35. Ibid., § 58.1 et. seq.
36. Ibid., § 211.65(a).
37. Ibid., § 211.67(a).
38. Ibid., § 211.67(a).
39. See discussion of pharmaceutical controls at pages 19-23 below.
40. Consultation with Dr. James Stevenson. Health authorities require exhaustive information on the provenance of drug ingredients for their review and continuous monitoring of safety and efficacy. See e.g., 21 Code of Federal Regulations § 314.50(d)(1)(i).
41. Consultation with Dr. James Stevenson. See also, HHS, Drug Applications, Section II.E.2, 33, which requires additional and more stringent analytical testing where indications of variability are present.
42. See, e.g., United States Pharmacopeial Convention, Inc., Committee of Revision, 1990 USP XXII, NF XVII The United States Pharmacopeia, The National Formulary (Rockville, MD.: United States Pharmacopeial Convention, Inc., 1985), 1926. Similar specifications have been established in Europe and elsewhere.
43. Consultation with Dr. James Stevenson.
44. Consultation with Dr. Ernest Kelly, Member of U.S.P. Advisory Panel on Aerosols.
45. J. L. Hopkins, et al., "Pharmaceuticals," Analytical Chemistry 59, no. 6 (1 June 1987): 784A.
46. P. Marks, "Boehringer Recalls Aerosol Asthma Drug," The News-Times, 31 October 1989; "Boehringer Ingelheim's Alupent Will Return to Sorbitan Trioleate," F-D-C Reports: Pharmaceuticals, 6 November 1989.
47. See, e.g., "Chlorofluorocarbons in Medicinal Products," Mail 72 (Medicine Control Agency, UK, July/August 1992), 6.
48. B. Matthews, "CFCs and Portable Therapy," The Regulatory Affairs Journal Vol. 3, no. 10, (October 1992), 805.
49. Althouse, 305, 397, 475, 633, 679, 949.
50. R. Downing, Fluorocarbon Refrigerants Handbook (Englewood Cliffs, N. J.: Prentice Hall, 1988), 302-303.
51. Ibid., 206-270.
52. Ibid., 271-285.
53. Consultation with Dr. John Daly.
54. See generally G. C. Doderer and H. O. Spauschus, "A Sealed Tube-Gas Chromatograph Method for Measuring Reaction of Refrigerant 12 with Oil," ASHRAE Trans., Vol. 72, No. 2, Paper No. 2008, (1966); G. C. Doderer and H. O. Spauschus, "Chemical Reactions of Refrigerant 22," ASHRAE Trans., Vol. 71, No. 1, Paper No. 1925 (1965); G. C. Doderer and H. O. Spauschus, "Reaction of Refrigerant 12 with Petroleum Oils," ASHRAE Trans., Paper No. 1743; D. E. Kvalnes, "The Sealed-Tube Test for Refrigeration Oils," ASHRAE Trans., Paper No. 1921, (1965); W. O. Walker and S. Rosen, "Stability of Mixtures of Refrigerants and Refrigerating Oils," ASHRAE Journal, Vol. 4, (1962).

55. R. Kauffman, Chemical Analysis and Recycling of Used Refrigerant from Field Systems (Dayton: University of Dayton Research Institute, 1990).
56. Ibid., 5-7.
57. Ibid., 9-32.
58. Ibid., 13, 24; Daly, Part I, 4. Kauffman also confirmed that filter-drier technology had only a limited capacity to remove contaminants from used refrigerant. Filter-driers are effective in removing some oil, water, chlorides and particulates from used refrigerant. However, this technology is not capable of removing volatile and non-volatile organic compounds.
59. Daly, Part I, 12-16.
60. See, e.g., Air-Conditioning & Refrigeration Institute, 1988 Standard for Specifications for Fluorocarbon Refrigerants (Arlington, VA: Air-Conditioning & Refrigeration Institute, 1988), (hereinafter "1988 Specifications for Fluorocarbon Refrigerants") 4.
61. See, e.g., 1988 Specifications for Fluorocarbon Refrigerants, 4.
62. Dr. John Daly, a consultant to IPAC, was permitted to review these supplier specifications. IPAC has been authorized to provide the description of these specifications contained in the text above. However, IPAC has not been authorized to disclose any further detail concerning these specifications because they are considered confidential business information.
63. Dr. Daly was permitted to review the chemical analyses performed by major suppliers on samples of distilled reclaimed refrigerant.
64. Downing, 143-44.
65. Ibid., 139-144.
66. See generally, J. Bobbitt, A. Schwarting and R. Gritter, Introduction to Chromatography, (New York: D. Van Nostrand, 1968); H. Willard, et. al., Instrumental Methods of Analysis, (Belmont, CA: Wadsworth Publishing, 1988).
67. See generally, Willard, 465.
68. This discussion of an authorization and development program for used CFCs was developed in consultation with Mr. Peter Newman, Manager, Regulatory Systems, Fisons plc; Mr. C.N. Masten, a former senior executive of Du Pont and consultant to IPAC; and Dr. James Stevenson, Section Leader in the Analytical Sciences Department of Boehringer Ingelheim Pharmaceuticals, Inc.
69. Althouse, 979; Daly, Part I, 5.
70. Ibid., 979; Daly, Part I, 5-6.
71. Althouse, 979; Daly, Part I, 6.
72. Daly, Part I, 6-11.
73. Ibid., Part II, 3-4.
74. Ibid., Part II, 3-6.
75. Ibid., Part II, 3-4.
76. Ibid., Part III, 3-5.
77. Ibid., Part II, 4-5.
78. Ibid., Part II, 5.
79. Althouse, 977-988; Daly, Parts I, II and III.
80. Daly, Parts II and III; See March Consulting Group, CFCs in the UK Refrigeration and Air Conditioning Industries: Usage and the Scope for Substitution A Study for the Department of the Environment carried out by March Consulting Group (October 1992). The pace of conversion could conceivably be effected by the introduction of so-called "drop-in" substitutes that do not require retrofit of existing equipment. However, officials of at least one leading manufacturer have stated that "no perfect drop-in product" exists or is likely to be developed. "Time's Running Out, But Some CFC Users Slow to Switch," Global Environmental Change Report Vol. IV, no. 20, ed. Bradford J. Hurley (October, 1992,) 6-7.
81. This discussion of a program for the purchase of CFCs was developed in consultation with Mr. C.N. Masten, a former senior executive with Du Pont and consultant to IPAC. Mr. Masten's professional experience and background is described in the Acknowledgments preceding this report.

Exhibit A: Characterization of Recovered and Reclaimed CFCs by GC/MS

Arthur D Little

**Characterization of
Recovered and
Reclaimed CFCs by
GC/MS**

Final Report

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March 31, 1993

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1.0 Scope of Work

The following report describes a study performed by Arthur D. Little to characterize recovered and reclaimed chlorofluorocarbons (CFCs) by gas chromatography-mass spectrometry (GC-MS). Two separate sampling methods were used to identify volatile and semi-volatile organic contaminants. The identification of contaminants was carried out by computer matching with library spectra. A quantitative estimate of the concentrations of significant compounds in representative samples was made.

2.0 Introduction

The use of CFCs is being phased out worldwide under the Montreal Protocol on Substances that Deplete the Ozone Layer. The pharmaceutical industry uses these compounds as propellants and excipients in metered dose inhalers.

Exemptions from the phaseout schedule may be available where a particular use of a CFC is deemed "essential" and, among other things, used CFC is unsuitable for reuse in the product involved.

The purpose of this study is to identify contaminants in used chlorofluorocarbon refrigerant both before and after it has been reclaimed. The information generated by this study will be used in assessing whether used refrigerant is suitable for reuse in pharmaceutical products.

3.0 Objectives

Our objectives were to analyze both R-11 and R-12 CFCs in order to identify volatile and semi-volatile contaminants from randomly supplied lots of recovered and reclaimed material. A qualitative comparison was made in order to assess the reproducibility of the reclamation process. In this study, the term "recovered" is used to describe used CFCs which are collected for processing; "reclaimed" is used to describe used CFCs which have been processed for reuse.

4.0 Sample Preparation and Analysis

Samples of R-11 and R-12 were provided by National Refrigerants, Inc. R-12 samples were received in lecture-tank cylinders while R-11 samples arrived in polyethylene screw-capped bottles. Sample sets consisted of representative samples of recovered and reclaimed CFCs.

4.1 Volatile Organic Analysis (VOA)

4.1.1 R-11 Samples

A 3 liter Tedlar gas sampling bag was connected to the UHP Helium manifold which provided carrier gas for the GC-MS with an approximately 20 cm length of teflon tubing. The bag was flushed with helium in a manner similar to that used for R-12 samples. After seven flushes, the bag was disconnected from the manifold, and 100 μ l of an R-11 sample was introduced with a 250 μ l gas-tight syringe. The sampling bag was then sealed and gently kneaded to ensure the volatilization necessary for a homogeneous sample. The bag was then connected to the sample concentrator.

4.1.2 R-12 Samples

R-12 samples cylinders were connected to 3 liter Tedlar gas sampling bags with an approximately 20 cm length of teflon tubing. The tank was inverted, and the bag was filled by briefly opening the tank valve. After filling, the bag was disconnected, and its contents expelled by squeezing. The bag was re-connected and refilled. This process was repeated for a total of seven flushes, after which the filled bag was connected to the sample concentrator in preparation for GC-MS analysis.

4.1.3 Control Samples

Control samples consisted of flushing a 3 liter Tedlar gas sampling bag with UHP Helium seven times. The bag was then connected to the sample concentrator for GC-MS analysis.

4.1.4 GC-MS Conditions for VOA Analysis

The VOA GC-MS system consisted of a VG Trio-II quadrupole mass spectrometer interfaced to a HP 5890 gas chromatograph. In place of a conventional injection port was a Chemical Data Systems model 330 sample concentrator. This system utilizes two traps for the collection and concentration of volatile organic compounds. Gas samples are pulled through the first trap with a small vacuum pump at a rate of 6 ml/min for one minute. During this time the trap is maintained at a temperature of 0°C. Trapped compounds are desorbed by ballistically heating the trap to 200°C. The desorbed compounds are transferred to a second trap, mounted in place of the GC injector. This trap is maintained at a temperature of -140°C. Upon initiation of the GC-MS run, this trap is ballistically heated to 250°C, transferring the sample onto the head of the GC column. Table 1 lists the GC and MS parameters used in the VOA analysis.

4.2 Semi-Volatile Organic Analysis

4.2.1 R-11 samples

10 mls of R-11 sample were transferred to 15 ml glass centrifuge tubes by pouring. Semi-volatile components were concentrated by taking the sample to just dryness with a gentle stream of nitrogen. Samples were then redissolved in 100 μ ls of CH_2Cl_2 , and a 1 μ l aliquot was taken for injection into the GC-MS system. Upon injection, the GC temperature program was initiated. MS data acquisition was started 30 seconds after injection.

In the case of samples which were too contaminated with oil to be taken to dryness, a 5 μ l aliquot of the resulting oil was dissolved in 100 μ ls of CH_2Cl_2 , and a 1 μ l aliquot taken for analysis.

4.2.2 R-12 Samples

Following VOA analysis, the gas sampling bags were removed from the sample concentrator and 2000 μ ls of CH_2Cl_2 were introduced with a 1000 μ ls gas-tight syringe. The bag was sealed and swirled by hand in order to dissolve any remaining material. During the course of this rinsing, the majority of the solvent (CFC) volatilized, concentrating the sample. The bags were swirled until 100-200 μ ls of solvent remained, which were then collected at one corner of the sampling bag. Aliquots were removed by puncturing the bag with a 10 μ l GC syringe and withdrawing a 1 μ l aliquot. This was manually injected into the GC-MS system. Upon injection, the GC temperature program was initiated. MS data acquisition was started 30 seconds after injection.

4.2.3 Control Samples

R-11 controls consisted of a 1 μ l injection of CH_2Cl_2 directly into the GC-MS system.

R-12 controls consisted of flushing 3 liter tedlar gas sampling bags with UHP Helium a total of seven times. 2000 μ ls of CH_2Cl_2 were introduced with a 250 μ l gas-tight syringe. The bag was sealed, and gently swirled until 100-200 μ ls of solvent remained. the bag was punctured with a 10 μ l GC syringe, and a 1 μ l aliquot was removed for analysis.

4.2.4 GC-MS Conditions for Semi-VOA Analysis

The GC-MS system used consisted of a VG Trio-II quadrupole mass spectrometer interfaced to a HP 5890 Gas Chromatograph. Table 2 lists the GC and MS parameters used in the semi-VOA analysis.

5.0 Data Reduction

GC-MS data was searched using an automated peak detection and identification algorithm, followed by manual inspection of the resultant spectra and their library matches. Peak heights (in millivolts) of identified spectra were used to estimate the absolute concentration of the identified contaminants based on instrument specifications.

6.0 Additional Information

Raw data (all computer hardcopy, notes, magnetic tapes, etc.) will be archived at Arthur D. Little until approval is received from the client for their disposal.

Recovered and reclaimed CFCs samples will also be retained by Arthur D. Little, Inc. until such time as we receive authorization for their disposal.

During the course of storing data files on magnetic tape, some data corruption was incurred. At the time of this writing, efforts to retrieve this information were not successful. We expect to be able to retrieve this information in the near future for archiving.

7.0 Results

7.1 Overview of Data Presentation

Table 3 lists the GC-MS datafiles that are referenced throughout this report. Additional samples were analyzed but are not included in the summary of the data. The appendix to the report contains the tables and representative chromatograms (total ion profiles) discussed in this report.

For the purposes of discussing the results, this section is broken into 4 elements:

- R-11 Recovered
- R-11 Reclaimed
- R-12 Recovered
- R-12 Reclaimed

7.2 R-11 Samples

7.2.1 R-11 Recovered Samples

Figure 1 shows the total ion current chromatograms (this is an indication of the organic compounds present in this volatility range) from the semi-volatile analysis of three different samples of R-11 recovered CFC. The horizontal axis (scan number/retention time) gives an indication of the relative volatility of the components found in each sample. Figure 2 shows the same 3 samples, this time inclusive of the solvent peak. The amount of impurity in the three samples varies dramatically. To a close approximation, the sampling technique was identical, and the data presentation is normalized to the same scale. Observation of Figure 2 shows a significantly higher amount of impurities in the Mechanical Maintenance and TK Electric samples (top two chromatograms) compared to the Boland sample (lower chromatogram). In the cases where sample dilution or concentration occurred, these have been accounted for in the appropriate tables. The estimated concentration of selected impurities is listed in the identified component comparison tables. Table 4 has been corrected for dilution of samples and demonstrates the differences between recovered samples in terms of different impurities dominating different samples.

It can be seen that many of the analytes present in one sample are absent or at significantly lower concentration in another. An example would be toluene, present in the Mechanical Maintenance sample, but not detected in the other two recovered R-11 samples. Undecane is found in the Mechanical Maintenance and TK Electric sample at similar concentrations, but was not detected in the Boland sample. This list is not inclusive of all contaminants present, but represents different classes of chemicals that were found in the samples.

7.2.2 R-11 Reclaimed Samples

Figure 3 shows the semi-volatile fraction for two R-11 reclaimed samples, FT-001 and FT-665. Figure 4 shows the same components relative to the solvent peak. As with all the samples, the semi-volatile fraction demonstrates an abundance of contaminants in both samples. For these reclaimed R-11 samples, there are over 100 individual contaminants. In addition, as with the recovered samples, the nature and amount of contaminants is different for each sample. Figures 5 and 6 show the corresponding volatile fraction chromatograms for the R-11 reclaimed samples. The number of contaminants found in the volatile fractions are lower than in the semi-volatile, but they still add additional complexity to the overall nature of a reclaimed CFC. Tables 5 and 6 list analytes representative contaminants found in the volatile and semi-volatile analysis of reclaimed R-11 samples.

Again there are several noticeable differences in the relative amounts of each component from one sample to another, and indeed there are many different analytes compared to

the recovered samples of R-11. Although there is no relationship between the origin of these samples and the recovered, it does further illustrate the diversity and extent of contaminants in both recovered and reclaimed CFC samples. Upon examining Tables 5 and 6, it is seen that the same contaminants are identified in both reclaimed samples for the volatile as well as the semi-volatile analysis. The estimated concentrations of these contaminants are approximately the same in both samples.

7.3 R-12 Samples

7.3.1 R-12 Recovered Samples

The chromatograms highlighting the contaminant profiles for R-12 Recovered samples are given in Figures 7 and 8. These chromatograms highlight the different nature of contaminants (and relative amounts) of contaminants found in these R-12 samples (B/L #74289, GE R-12 Composite and B/L #72483). A good example are the series of peaks observed between scans 3500 to 4000, which were identified as an isomeric series of substituted propanoic acid esters. Samples #742289 is dominated by a peak at scan 3644. This peak is not observed in the other two samples. A second peak in this sample (scan 3960) is observed in the GE composite sample, but not in sample #72483, which exhibits a large peak at scan 3791; this isomer is absent in the samples. Table 7 highlights significant differences between the samples for the volatile fractions.

The sample B/L #72483 appears to have a significant amount of low molecular weight polyaromatics naphthalenes compared to the other samples. Again this emphasizes the significant differences which make total characterization of these recovered CFCs a complicated task.

As we look at the chromatogram for the semi-volatile fraction of a recovered R-12, Figures 9 and 10, the trace is dominated by a large "mound". This is not column bleed, as may be seen by comparing figure 9 with figure 11, the chromatogram obtained from a control sample. Comparison of normalization factors (the number in the upper right hand corner of the chromatogram) shows that the control sample is more than 700 times lower than the recovered R-12 sample. There are predominantly hydrocarbons under this mound, but the intensity of them compared to the solvent front (see Figure 10), demonstrates the overwhelming complexity and contamination of the R-12 recovered CFC. To illustrate the chemistry present, we have expanded the early part of the chromatogram in Figure 12. The following Table 8, lists significant compounds found in this R-12 samples prior to the large hydrocarbon "mound".

The identity of many of the components in this sample were difficult to establish due to the high intensity of the hydrocarbon background. Relative to other samples analyzed, the total ion (and in turn, the relative semi-volatile organic component) is approximately 5-fold higher.

7.3.2 R-12 Reclaimed Samples

The reclaimed R-12 samples again demonstrate differences in the nature and relative intensities of contaminants. Figures 13 and 14 show the volatile fractions. Table 9 lists representative compounds found in the three samples (FT 1325, FT 689 and FT 445).

From the semi-volatile fraction of these three samples, it appears that FT-445 has far more contaminants than FT-689 or FT-1325. Figures 15 and 16 illustrate the difference between these samples. Figure 15 is normalized on the contaminants, 16 on the CFC (R-12).

A partial listing of the significant contaminants is given in Table 10.

The origin of these three samples is not known, but it is interesting that some of the same contaminants are found in all three. Particularly of interest are the phosphorous chemistry.

7.4 Conclusions from this Study

These studies have shown that both recovered and reclaimed CFCs are complex mixtures. While the predominant contaminant in recovered CFCs are straight-chain, aromatic and polycyclic hydrocarbons, hundreds of other compounds are present in smaller amounts. An exhaustive identification of every component of every sample is, however, outside the scope of this study. Even when concentrating on the more abundant components of these mixtures, it is evident that no two samples are alike in either composition or concentration. This is true for both the reclaimed and the recovered CFCs. It is interesting to note that several contaminants appear to be exclusive to the reclaimed samples, such as the phosphorus compounds. While these may indeed originate from the original recovered material, the reclamation process as well as storage and handling conditions should also be investigated as sources of contamination.

Appendix

Table 1 VOA GC-MS Parameters

GC Conditions

Instrument:	HP5890
Column:	30 M x 0.32 mm i.d. SPB-1, 4.0 μ film
Carrier:	UHP Helium @ 14 psi
Injector:	250°C
Temperature Program	
Initial Temp.:	30°C
Initial Time:	10 mins.
Program Rate 1:	5°C/min
Final Temp 1:	250°C
Final time 1:	15 mins.

Sample Concentrator Conditions

Instrument:	CDS Model 330
Trap A Temp:	0°C
Trap A Time:	1 min.
Trap A desorption Temp:	200°C
Trap A Desorption time:	5 mins
Trap B Temp:	-140°C
Trap B Desorption Temp:	250°C
Trap B Desorption Time:	15 mins

MS Conditions

Instrument:	VG Trio-II
Source Temp:	220°C
Transfer Line Temp:	250°C
Mass Range:	35-400 amu
Scan Rate:	0.6 sec/scan
Ionization:	70 ev electron-impact (regulated at 200 μ A)

Table 2 Semi-VOA GC-MS Parameters

GC Conditions

Instrument:	HP 5890
Column:	30 M x0.32 mm i.d. DB-1, 1.0 μ film
Carrier:	UHP Helium @ 5 psi
Injector:	250°C
Temperature Program	
Initial Temp.:	40°C
Initial Time:	5 mins.
Program Rate 1:	8°C/min
Final Temp 1:	180°C
Final time 1:	0 mins.
Program Rate 2:	10°C/min
Final Temp 2:	275°C
Final Time 2:	30 mins

MS Conditions

Instrument:	VG Trio-II
Source Temp:	255°C
Transfer Line Temp:	250°C
Mass Range:	35-400 amu
Scan Rate:	0.6 sec/scan
Ionization:	70 ev electron-impact (regulated at 200 μ A)

Table 3 List of Datafiles and Their Respective Sample Designation

	<u>Volatiles</u>	<u>Semi-Volatile</u>
R-11		
RECOVERED		
Mechanical main. 81442	10272B02	10152A05
TK Electric	10272B03	10152A04
Boland	10232B05	10162A01
RECLAIMED		
FT-001	10232B04	10212A01
FT-665	10232B02	10212A03
R-12		
RECOVERED		
Mars Mrk. 74289	BJ16D	10192A02
GE	BJ16E	10202A01
Sup. Srvs 72483	10222B01	10202A03
RECLAIMED		
FT-1325	10222B02	10232A04
FT-689	10222B03	10232A03
FT-445	10222B04	10232A02

**Table 4 Estimated Concentrations of Components in
R-11 Recovered Samples (semi-volatiles)**

Analyte	Scan	Sample Identification		
		Mechanical	TK Electric	Boland
		Estimated Concentration (ppb)*		
Trichlorotrifluoroethane	347	<1	0	0
Trichloroethane	380	3	2	0
Carbon tetrachloride	419	19	8	0
Tetrachlorodifluoroethane	552	2	<1	0
Tetrachloroethylene	928	4	<1	1600
Toluene	779	75	0	0
Nonane	1208	75	0	0
Trimethylheptane	1340	0	30	0
Methylheptanone	1353	75	0	0
Dimethyloctene	1399	0	5	0
Methylethenylbenzene	1429	0	4	0
Limonene	1551	0	20	0
Undecane	1705	175	25	0
Nonylcyclopropane	1901	25	140	0
Dimethylbutylcyclohexane	1966	0	5	0
Ethyldecanol	2049	0	20	0
Tetradecene	2124	0	10	0
Diethyldimethylcyclohexane	2230	8	30	0
Octylcyclohexane	2395	0	125	0
bis-dimethylcyclohexadiene-1,4-dione	2437	25	0	0
bis-dimethylethylmethylphenol	2502	75	65	0
octahydrohexamethylindene	2583	25	0	0
Butylhexyloctahydroindene	2730	50	0	0
Trimethyldodecane	2760	175	0	24000
Butylbenzenesulfonamide	2879	175	0	0
Tetracontane	3582	0	0	16000

* (ppb) = parts per billion

**Table 5 Estimated Concentrations of Components in
R-11 Reclaimed Samples (volatiles)**

Analyte	Scan	Sample Identification	
		FT-001	FT-665
		Estimated Concentration (ppb)*	
Trichlorotrifluoroethane	666	7100	7000
Bromodichlorofluoromethane	743	1650	9
Bromochloromethane	811	19	1
Carbon tetrachloride	1002	875	780
Tetrachlorodifluoroethane	1174	200	188
Dichlorofluoromethane	1551	15	<1
Phenol	2125	7500	12500
Dichlorobenzene	2232	1250	2250
Methylnaphthalene	3071	1250	2500
Dimethylnaphthalene	3389	1250	2000
bis-dimethylethylmethylphenol	3586	750	2000
C ₁₆ H ₃₀ O ₄ (aromatic subst. propanoic acid)	3789	100000	225000

* (ppb) = parts per billion

**Table 6 Estimated Concentrations of Components in
R-11 Reclaimed Samples (semi-volatiles)**

Analyte	Scan	Sample Identification	
		FT-001	FT-665
		Estimated Concentration (ppb)*	
Trichlorofluoroethene	347	0	2
Trichloroethane	380	0	35
Carbon tetrachloride	419	6	85
Tetrachlorodifluoroethane	552	<1	26
Tetrachloroethylene	928	<1	3
Tetradecene	2273	45	50
bis-dimethylethylmethylphenol	2493	45	60
Hexadecene	2594	140	225
Pentadecanone	2707	20	20
Tetradecanol	2975	20	15
Undecylcyclohexane	3183	20	20
bis-ethylhexylphthalate	3786	100	400

*(ppb) = parts per billion

**Table 7 Estimated Concentrations of Components in
R-12 Recovered Samples (volatile)**

Analyte	Scan	Sample Identification		
		#74289	GE Comp.	#72483
		Estimated Concentration (ppt)*		
Trichlorofluoromethane	638	1855	6500	6000
Trichlorotrifluoroethane	718	0	130	110
Fluorotrimethylsilane	1305	0	0	1500
Toluene	1547	410	170	0
Dimethyl benzene	1938	170	0	0
Methyl hexanone	2007	170	0	0
Dimethyl acetamide	2044	1330	340	0
Butoxy-ethanol	2096	170	340	0
Methyl heptanone	2229	330	0	0
Dichlorobenzene	2232	0	0	250
Heptanol	2293	80	0	0
Dimethylpyridine	2376	0	170	0
Octamethylcyclotetrasiloxane	2410	0	80	0
Methylthio-butanamine	2471	0	250	0
Ethylhexanol	2480	80	0	0
Methylnaphthalene	3071	0	0	250
Dimethylnaphthalene	3354	0	0	170
C ₁₅ H ₃₂ hydrocarbon	3571	0	0	340
C ₁₆ H ₃₀ O ₄ (aromatic subst. propanoic acid ester)	3644	3420	0	0
C ₁₆ H ₃₀ O ₄ (aromatic subst. propanoic acid isomer)	3791	0	0	8330
C ₁₆ H ₃₀ O ₄ (aromatic subst. propanoic acid isomer)	3960	1670	4165	0

* (ppt) = part per trillion

**Table 8 Estimated Concentration of Components In
R-12 Recovered Sample (semi-volatiles)**

Analyte	Scan	Sample Identification
		#74289 Estimated Concentration (ppt)*
Trichlorofluoromethane	189	15
Carbon tetrachloride	417	<1
Tetrachloroethylene	928	<1
Toluene	775	30
Dimethylacetamide	1097	120
Tetrahydrodimethylnaphthalene	2317	10
Octahydrohexamethylindene	2387	50
Dihydrotrimethylnaphthalenone	2534	20
C ₁₆ H ₃₄ hydrocarbon	2745	50

*(ppt) = parts per trillion

**Table 9 Estimated Concentrations of Components in
R-12 Reclaimed Samples (volatiles)**

Analyte	Scan	Sample Identification		
		FT-1325	FT-689	FT-445
		Estimated Concentration (ppt)*		
Trichlorofluoromethane	607	195	325	1880
Trichlorotrifluoroethane	646	0	0	245
Butanol	814	0	670	0
Methylheptane	1439	0	0	170
Ethylhexyloxy-methyloxirane	2305	0	0	60
Methoxypropylphenol	2520	0	0	170
Methoxypropylphenol (isomer)	2547	0	0	83
Decahydrodimethylnaphthalene	2719	0	0	17
Unsaturated hydrocarbon	2835	0	1500	170
Methylnaphthalene	3070	0	25	60
Octadecyne	3290	0	0	34
Dimethylnaphthalene	3352	0	0	50
C ₁₆ H ₃₀ O ₄ (aromatic subst. propanoic acid)	3788	5000	2920	4420

*(ppt) = parts per trillion

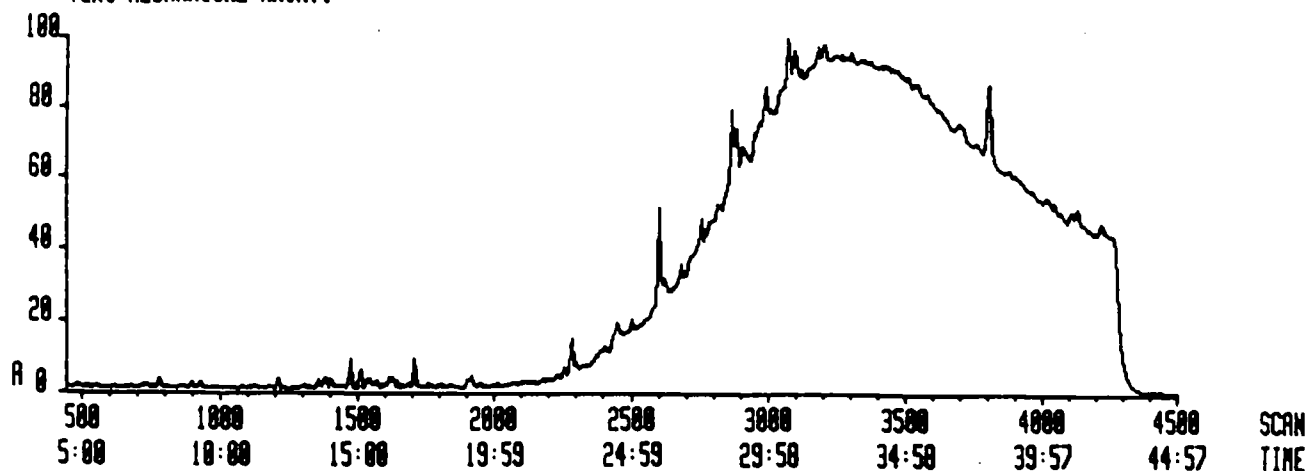
**Table 10 Estimated Concentrations of Components in
R-12 Reclaimed Samples (semi-volatiles)**

Analyte	Scan	Sample Identification		
		FT-1325	FT-689	FT-445
		Estimated Concentration (ppt)*		
Trichlorofluoromethane	189	62	21	57
Trichloroethane	367	5	0	0
Tetrachloroethylene	928	<1	<1	<1
Hydroxybenzenesulfonicacid	1399	10	2	2
Benzenedicarboxylic acid-butyl methylpropyl ester	3060	120	430	217
Phosphorous acid, triphenyl-ester	3402	150	50	100
Octacosane	3519			
Phosphoric acid, triphenyl-ester	3582	50	17	33
bis(2-ethylhexyl) phthalate	3779	100	50	50

*(ppt) = parts per trillion

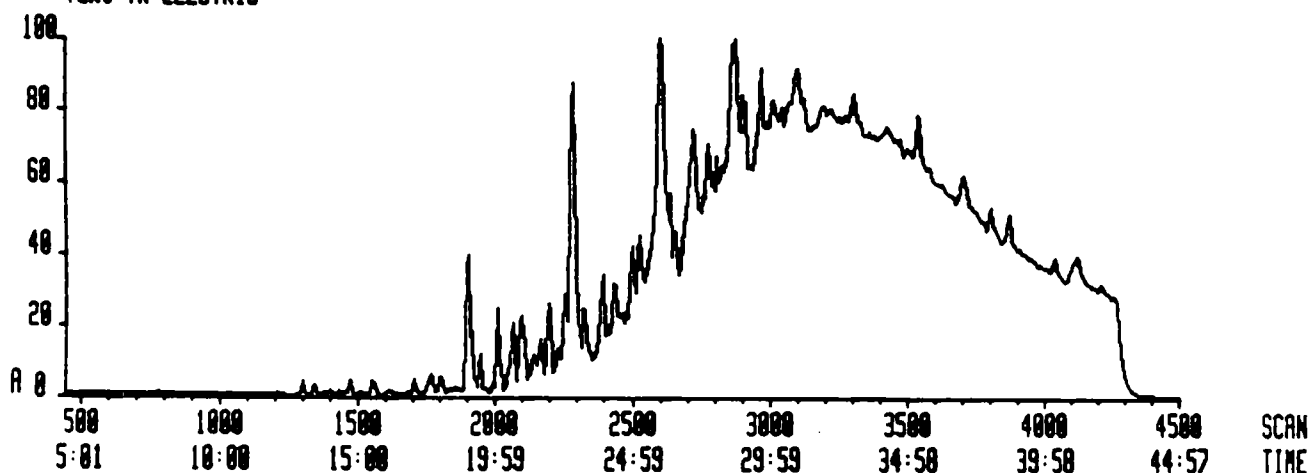
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IHP
 A: 14100



10152A04 #450-4500 15-OCT-92 14:54 TR10-2 (EI+)
 Chromatogram Identifiers : A :ATIC
 Text:TK ELECTRIC:

IHP
 A: 19600



10162A01 #450-4500 16-OCT-92 09:46 TR10-2 (EI+)
 Chromatogram Identifiers : A :ATIC
 Text:RECOVERED BOLAND R11

IHP
 A: 3362

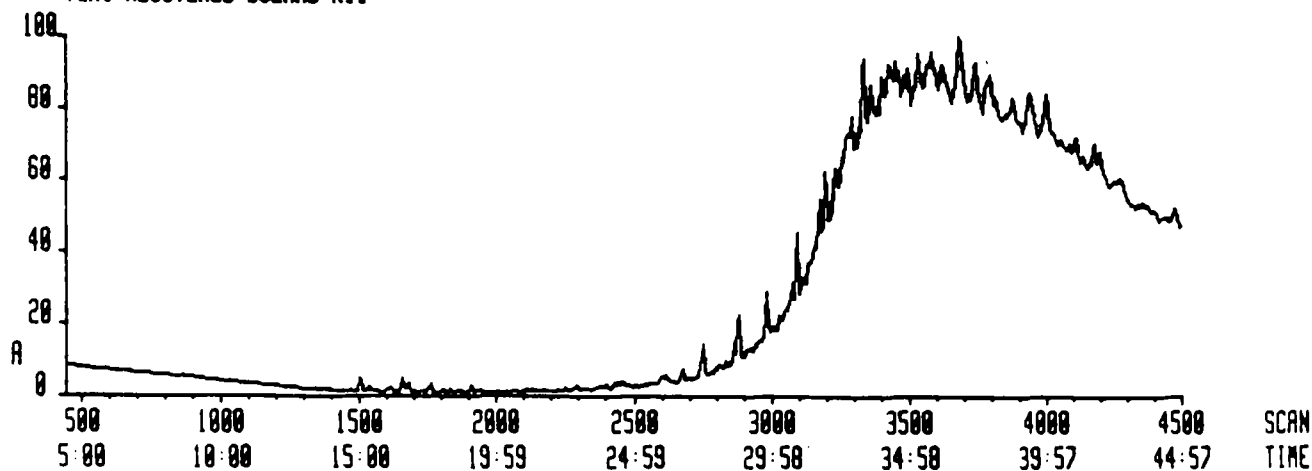
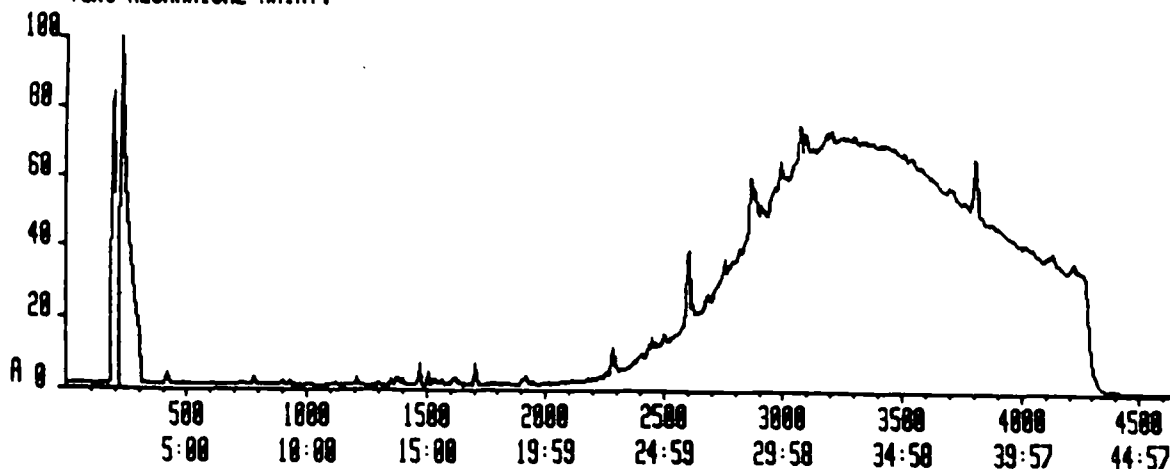


Figure 1 Total Ion Chromatograms for R-11 Recovered Samples (semi-volatile)
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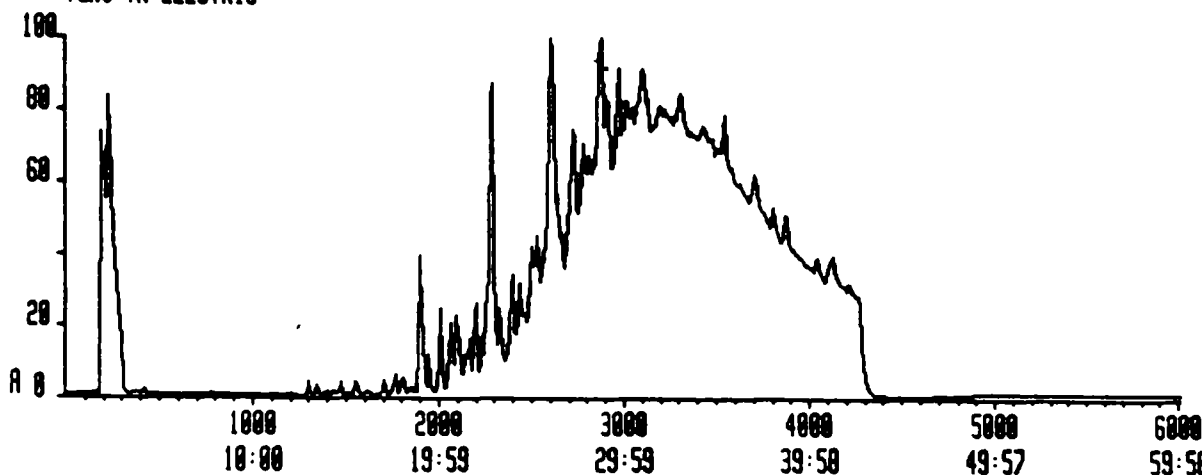
10152005 #1-4663 15-OCT-92 16:23 TR10-2 (EI+)
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 Text:MECHANICAL MAINT.

IHP
 A: 18659



10152004 #1-6007 15-OCT-92 14:54 TR10-2 (EI+)
 Chromatogram Identifiers : A :ATIC
 Text:TK ELECTRIC:

IHP
 A: 19600



10162001 #1-5070 16-OCT-92 09:46 TR10-2 (EI+)
 Chromatogram Identifiers : A :ATIC
 Text:RECOVERED BOLAND R11

IHP
 A: 24171

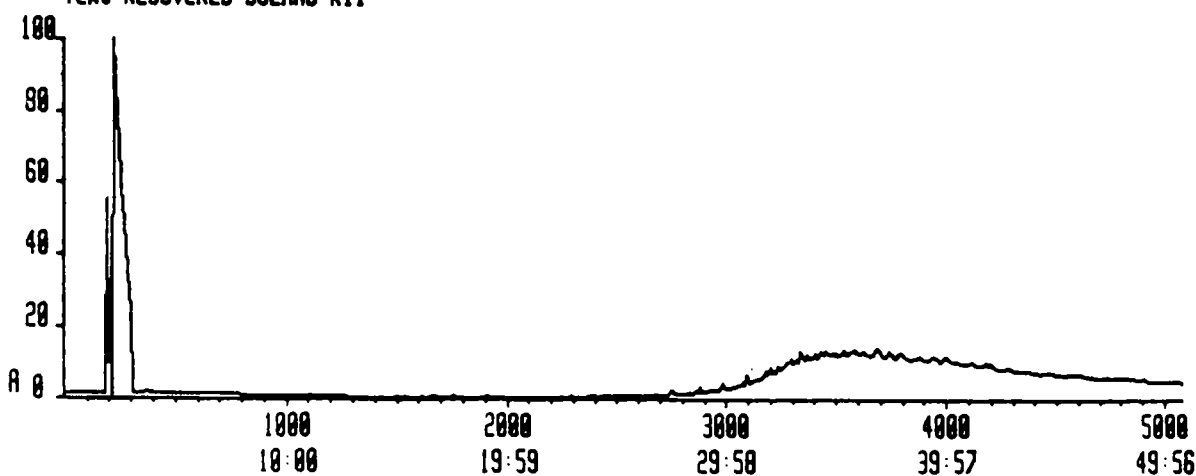


Figure 2 Total Ion Chromatograms for R-11 Recovered Samples;
 Inclusive of Solvent Peak (semi-volatile)

Arthur D Little

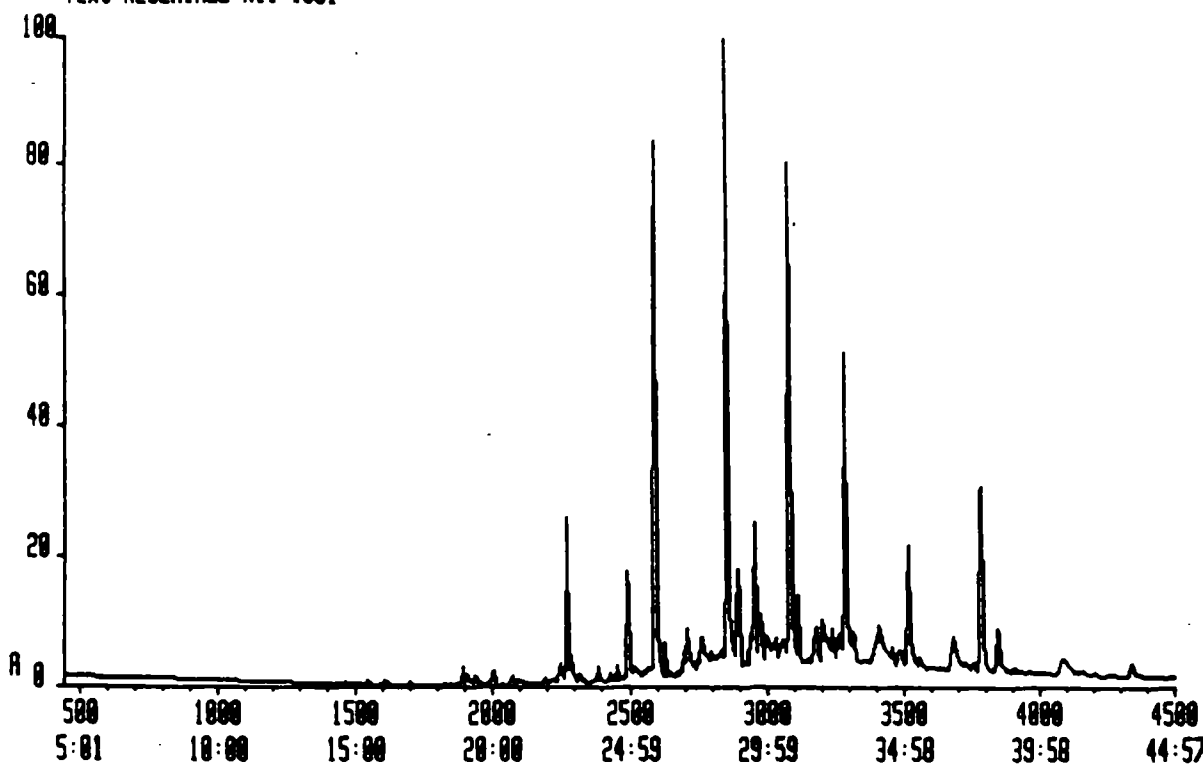
10212A01 1450-4500 21-OCT-92 10:44 TR10-2 (EI+)

Chromatogram Identifiers : A : ATIC

Text: RECLAIMED R11 1001

IHP

A: 11903



10212A03 1450-4500 21-OCT-92 14:07 TR10-2 (EI+)

Chromatogram Identifiers : A : ATIC

Text: RECLAIMED R-11: FT-665

IHP

A: 17755

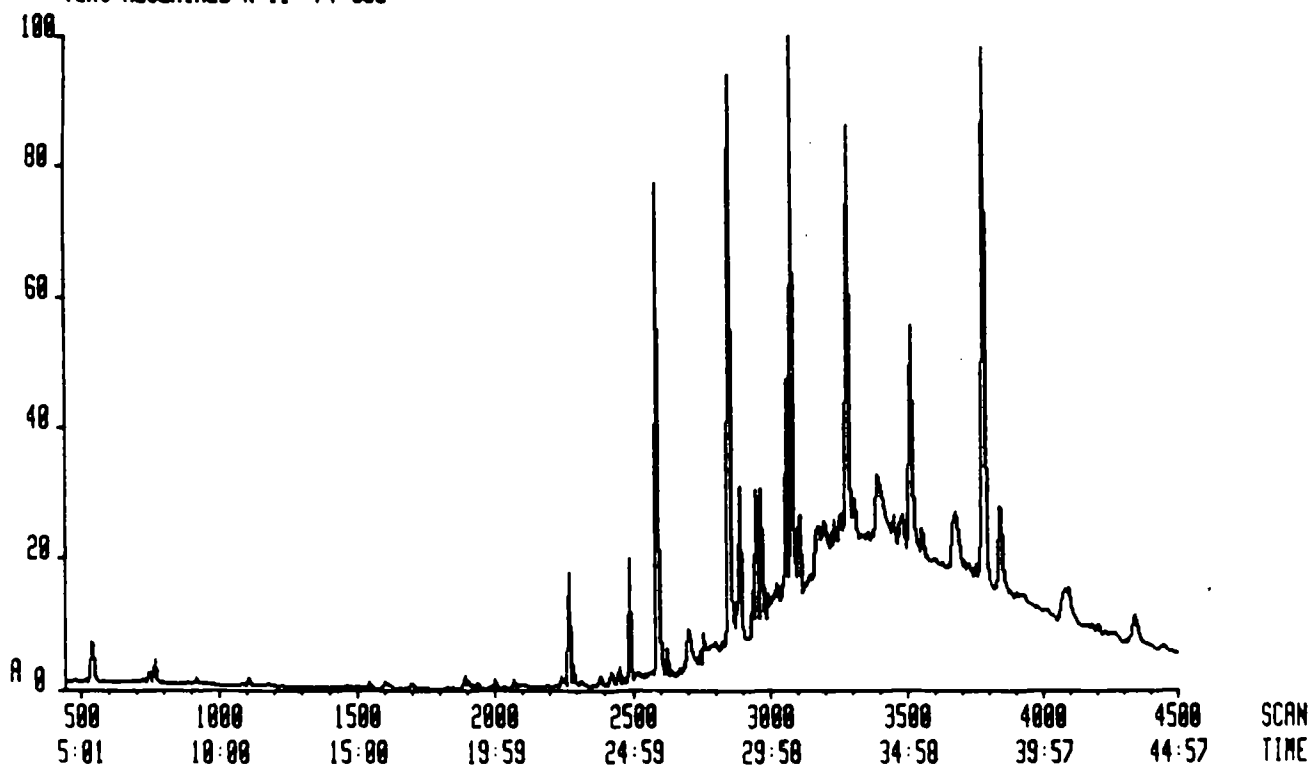
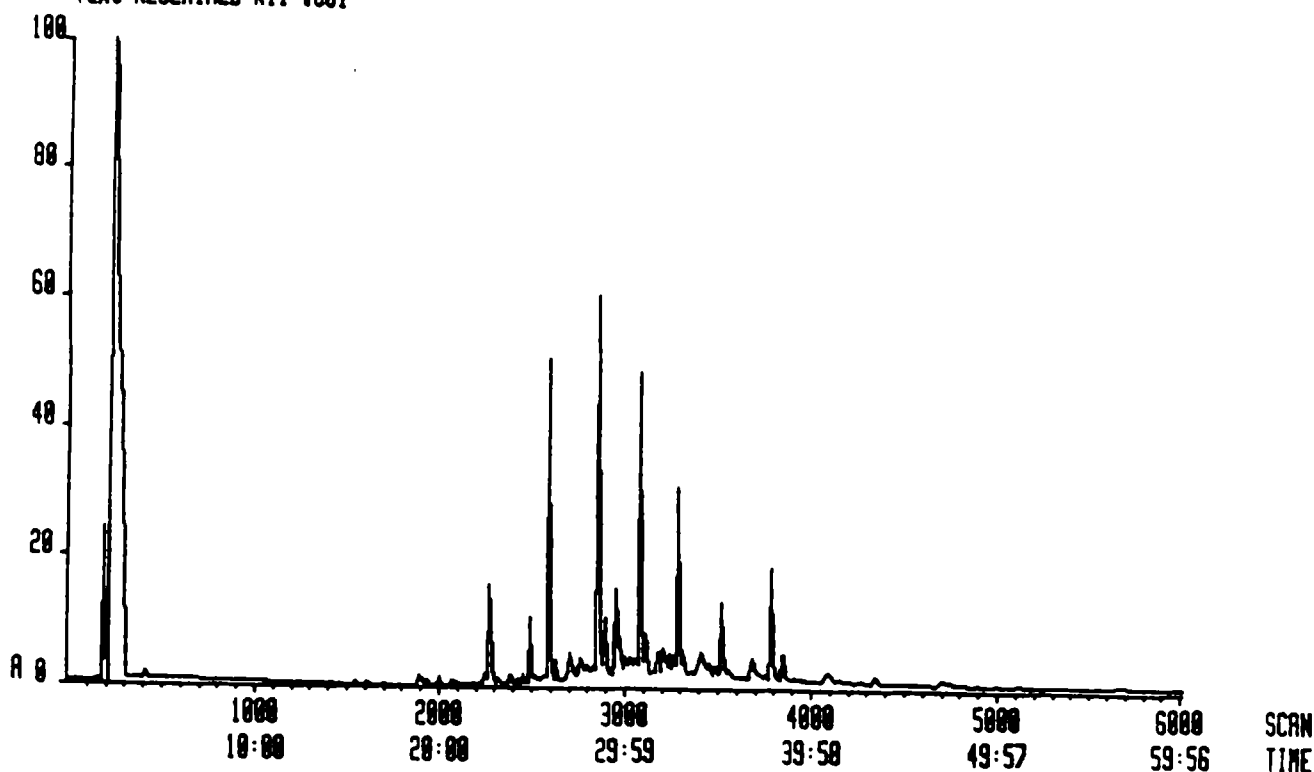


Figure 3 Total Ion Chromatograms for R-11 Reclaimed Samples (semi-volatile)

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10212001 #1-6000 21-OCT-92 10:44 TR10-2 (EI+)
 Chromatogram Identifiers : A : ATIC
 Text: RECLAIMED R11 #001

IHP
 A: 19650



10212003 #1-6000 21-OCT-92 14:07 TR10-2 (EI+)
 Chromatogram Identifiers : A : ATIC
 Text: RECLAIMED R-11: FT-665

IHP
 A: 21106

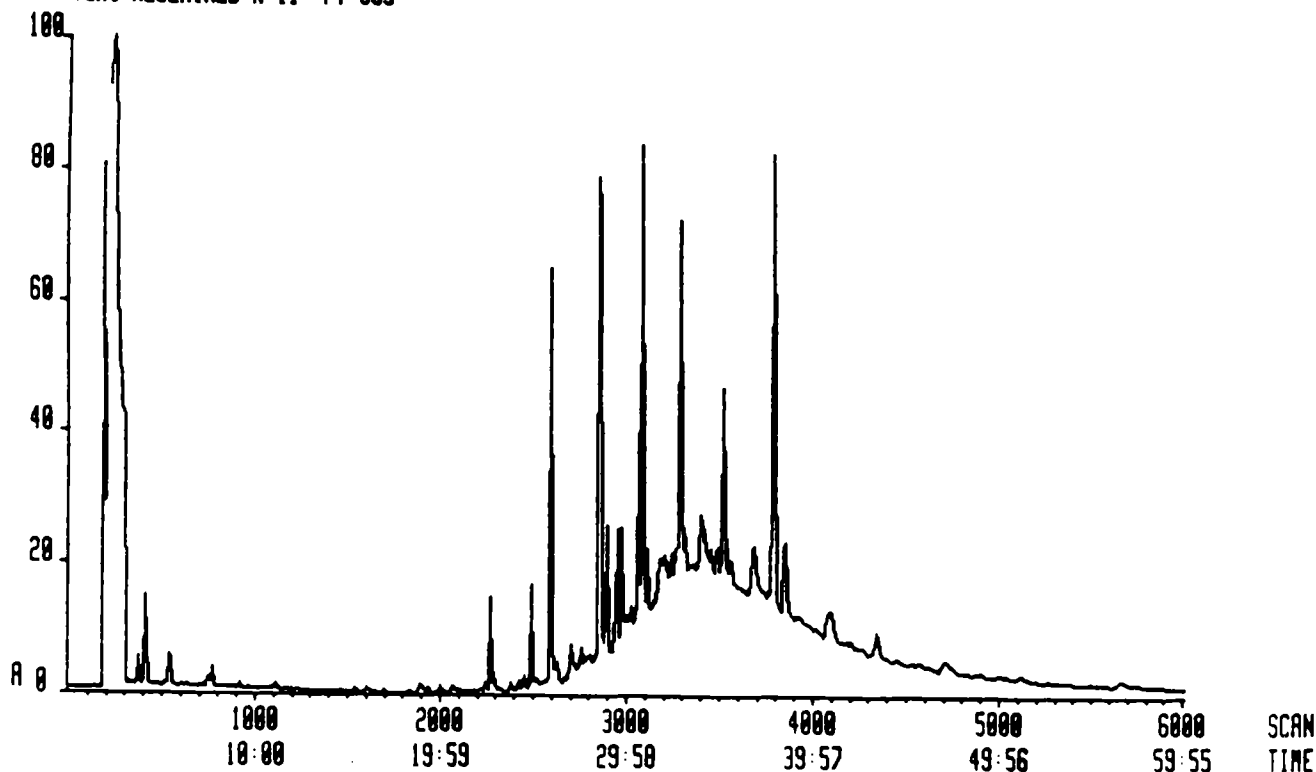
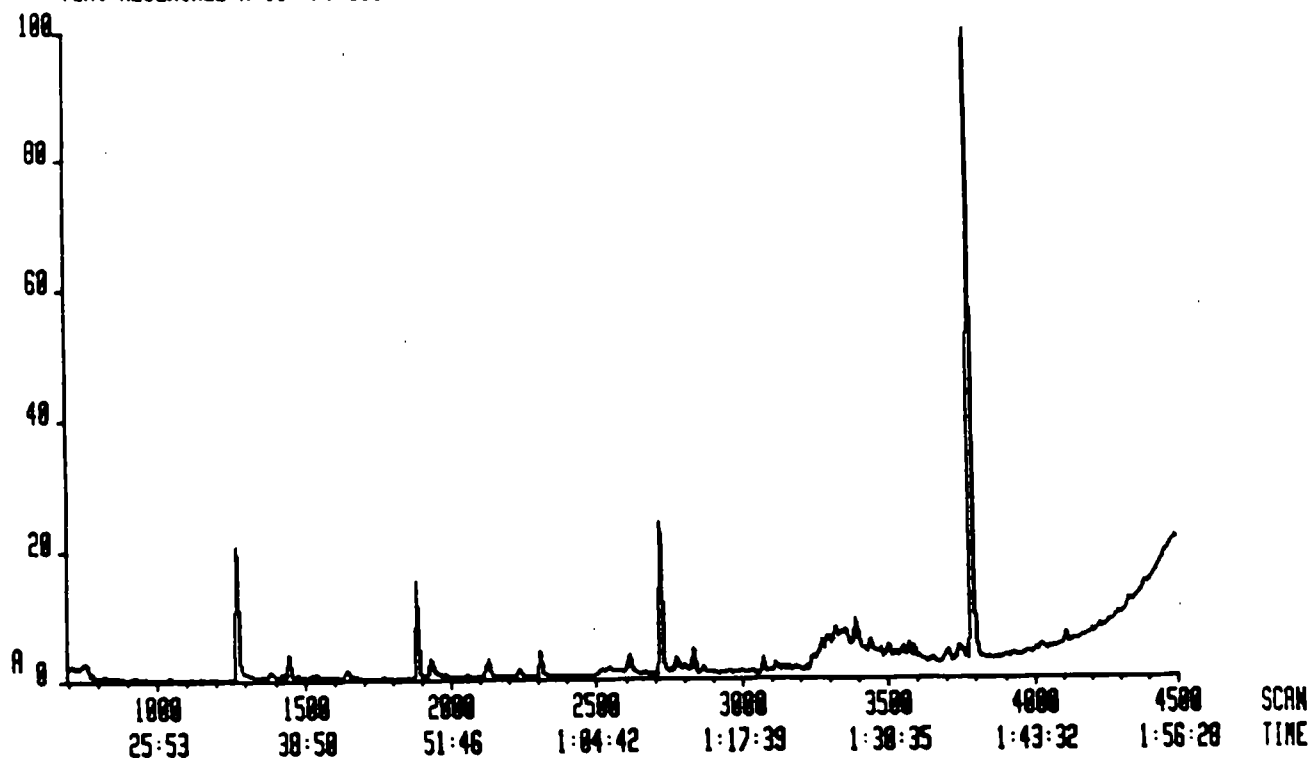


Figure 4 Total Ion Chromatograms for R-11 Reclaimed Samples;
 Inclusive of Solvent Peak (semi-volatile)

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10232004 1700-4500 23-OCT-92 03:33 TR10-2 (EI+)
Chromatogram Identifiers : A :ATIC
Text:RECLAIMED R-11: FT-001

IHP
A: 3079



10232002 1700-4500 24-OCT-92 01:31 TR10-2 (EI+)
Chromatogram Identifiers : A :ATIC
Text:RECLAIMED R-11: FT-665

IHP
A: 0903

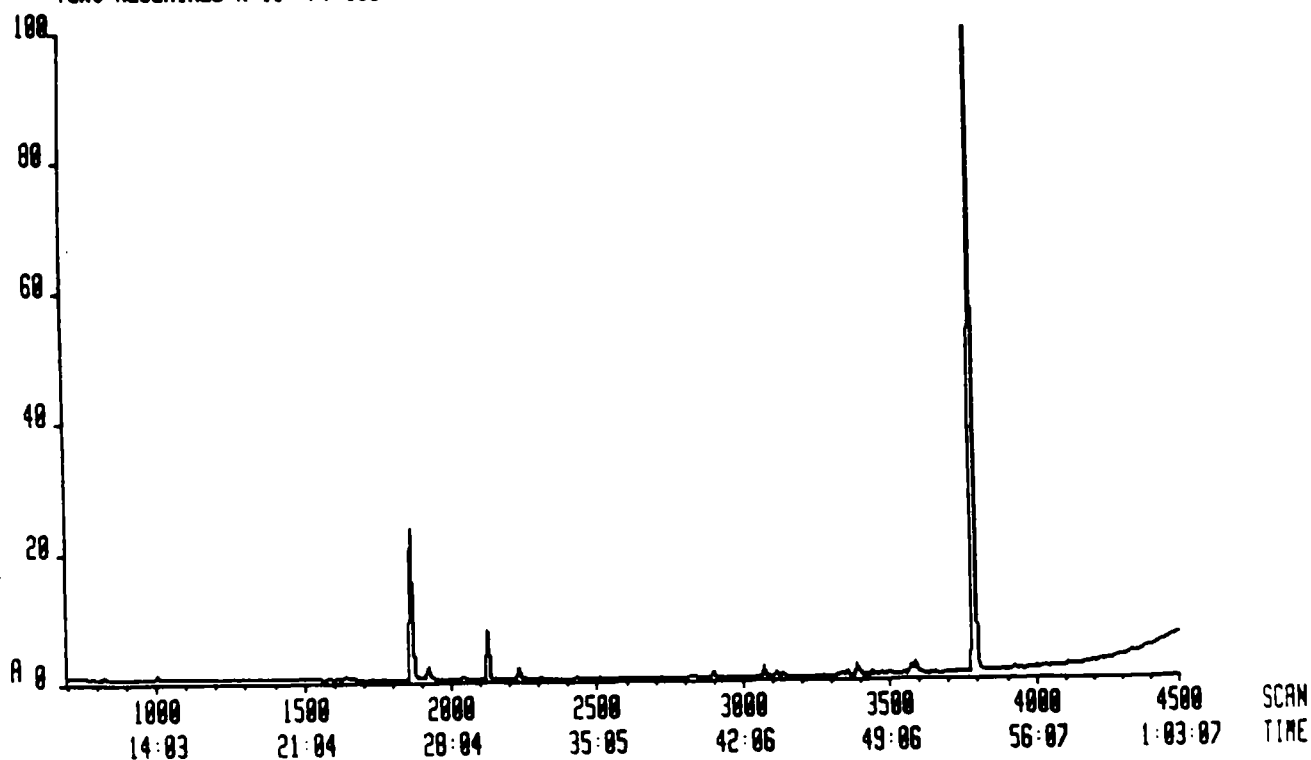


Figure 5 Total Ion Chromatograms for R-11 Reclaimed Samples (volatile)

Arthur D Little

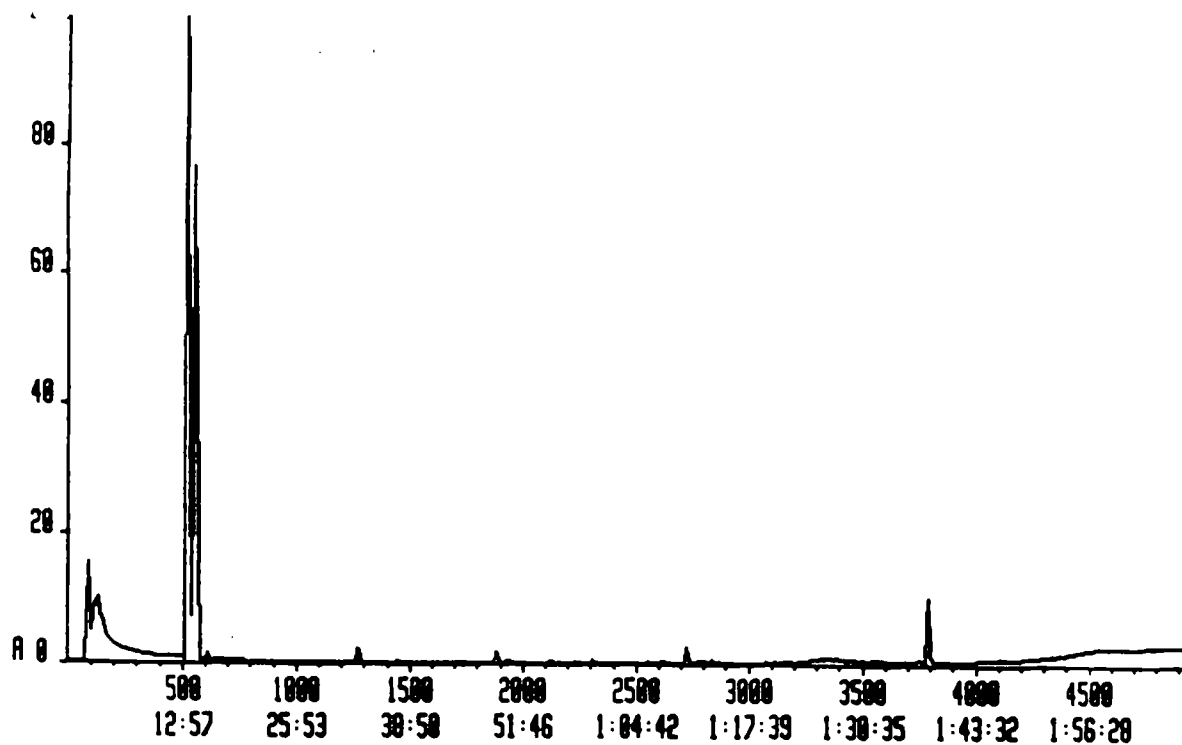
10232004 01-4920 23-OCT-92 03:33 TR10-2 (EI+)

Chromatogram Identifiers : A :ATIC

Text:RECLAIMED R-11: FT-001

IHP

A: 30302



SCAN
TIME

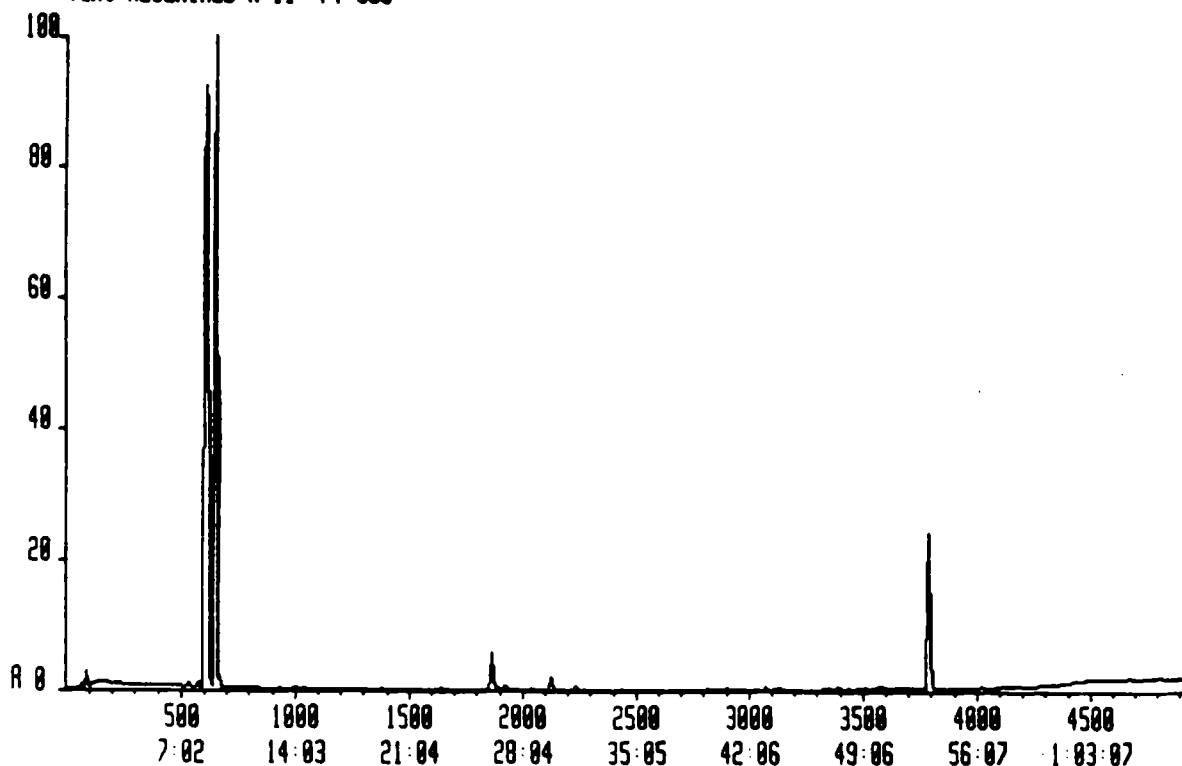
10232002 01-4919 24-OCT-92 01:31 TR10-2 (EI+)

Chromatogram Identifiers : A :ATIC

Text:RECLAIMED R-11: FT-665

IHP

A: 36814



SCAN
TIME

Figure 6 Total Ion Chromatograms for R-11 Reclaimed Samples;
CFC R-11 on Scale (volatile)

Arthur D Little

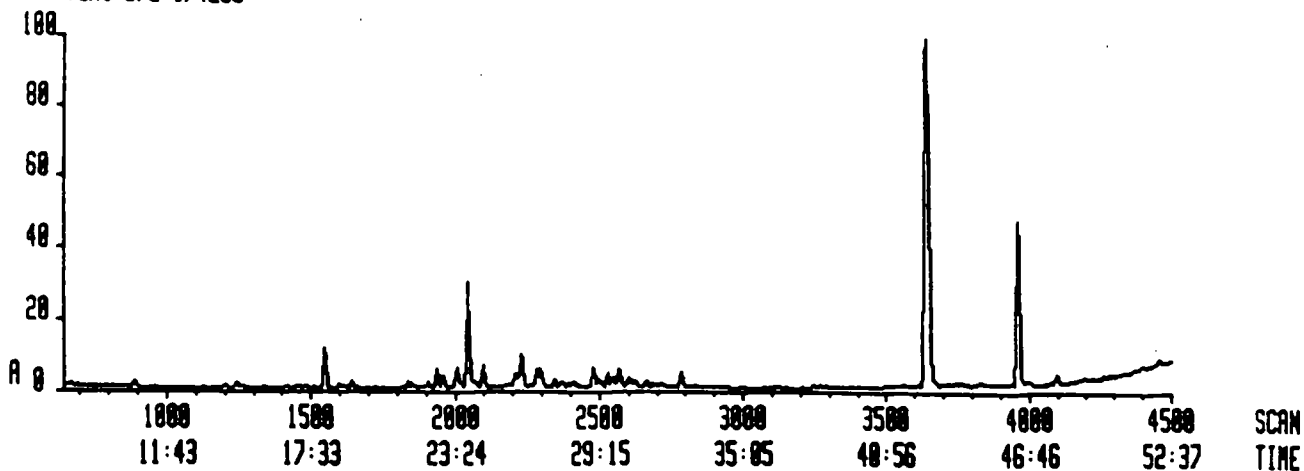
BJ160 #650-4500 16-OCT-92 11:53 TR10-2 (EI+)

Chromatogram Identifiers : A :ATIC

Text: B/L #74209

IHP

A: 4606



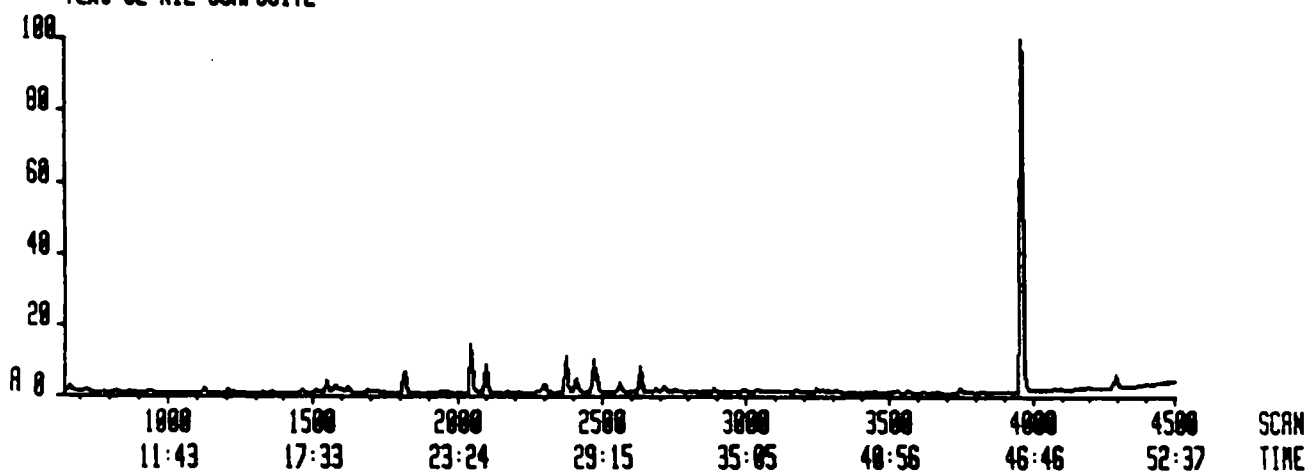
BJ16E #650-4500 16-OCT-92 13:35 TR10-2 (EI+)

Chromatogram Identifiers : A :ATIC

Text: GE R12 COMPOSITE

IHP

A: 5666



10222001 #650-4500 22-OCT-92 20:00 TR10-2 (EI+)

Chromatogram Identifiers : A :ATIC

Text: TXT B/L #72483

IHP

A: 30609

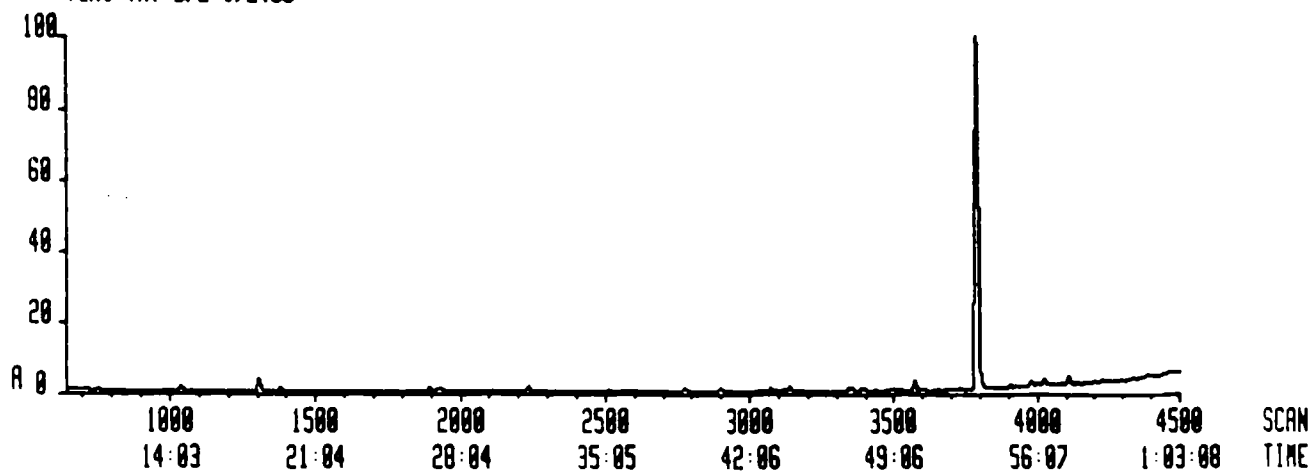
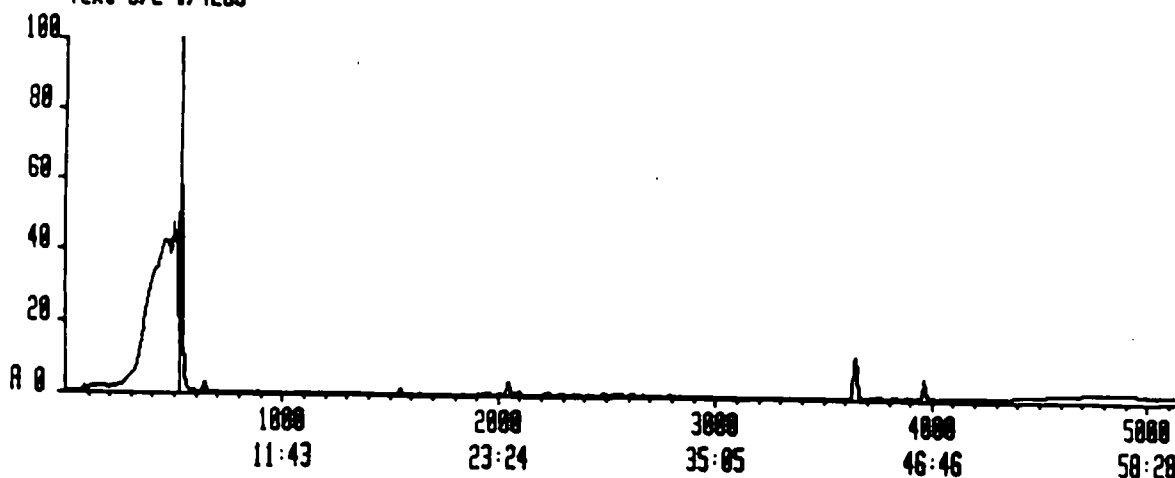


Figure 7 Total Ion Chromatograms for R-12 Recovered Samples (volatile)

Art: D Little

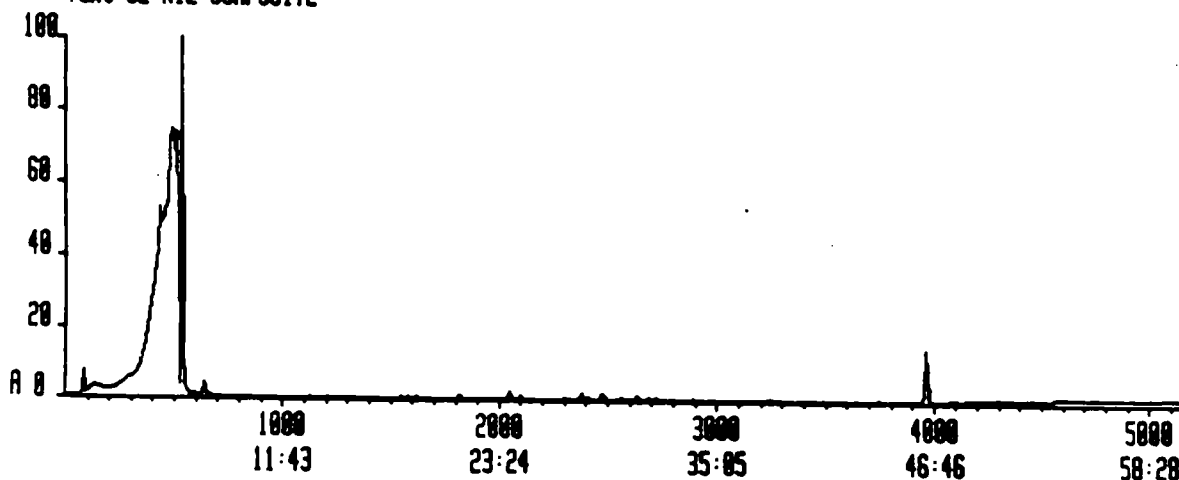
BJ160 #1-5132 16-OCT-92 11:53 TR10-2 (EI+)
 Chromatogram Identifiers : A :ATIC
 Text: B/L #74289

IHP
 A: 39785



BJ16E #1-5132 16-OCT-92 13:35 TR10-2 (EI+)
 Chromatogram Identifiers : A :ATIC
 Text: GE R12 COMPOSITE

IHP
 A: 38974



10222001 #1-4919 22-OCT-92 20:00 TR10-2 (EI+)
 Chromatogram Identifiers : A :ATIC
 Text: TXT B/L #72483

IHP
 A: 31992

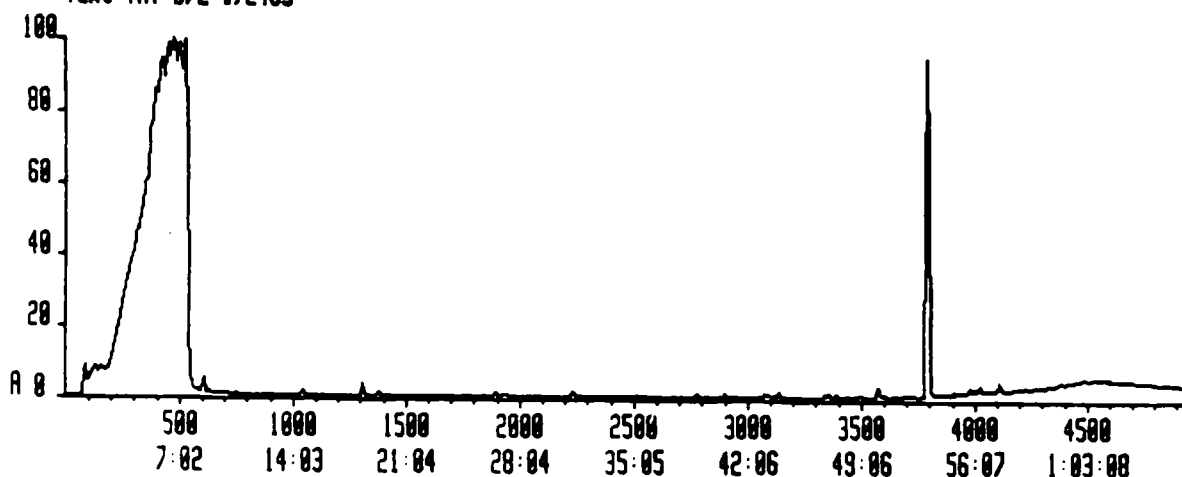
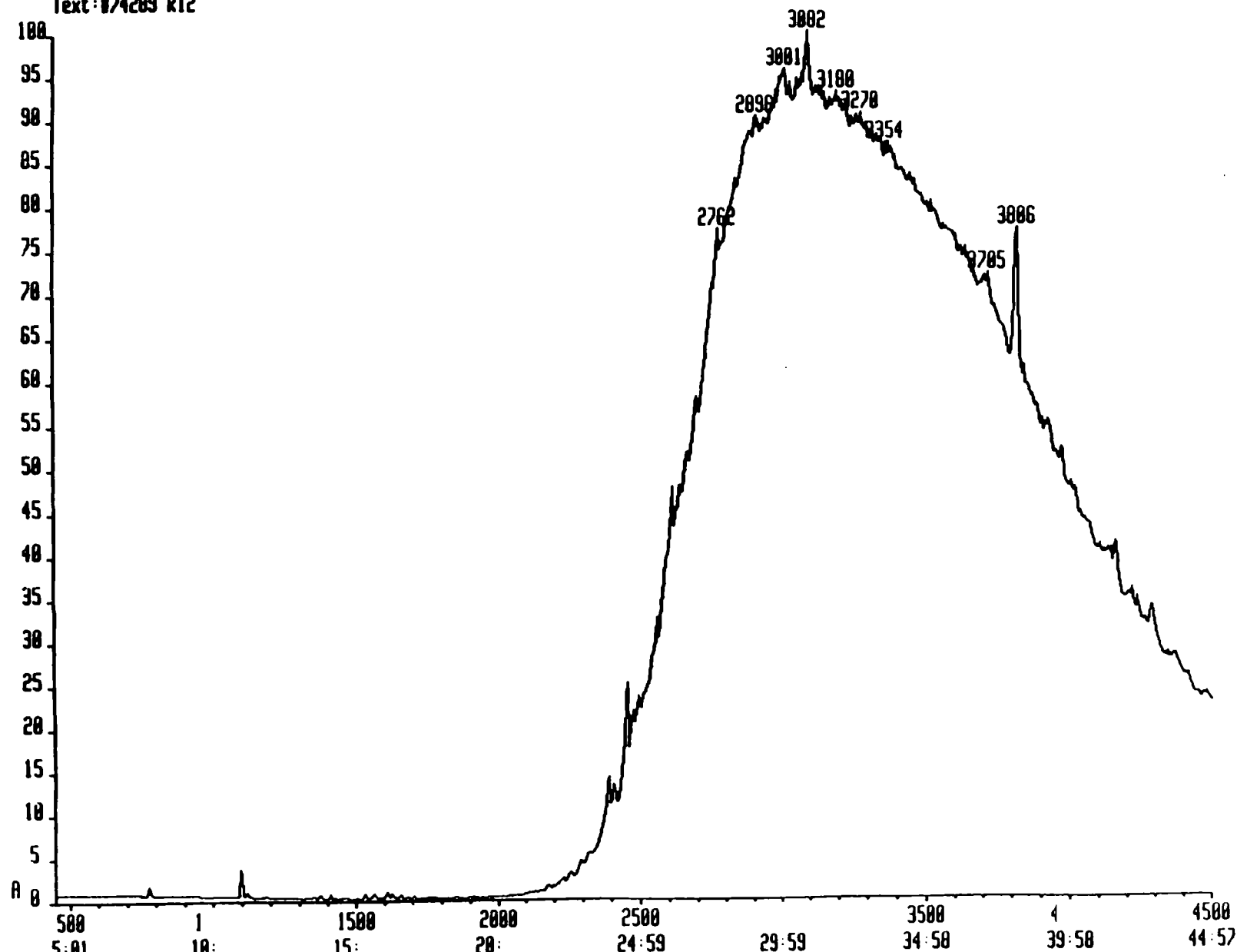


Figure 8 Total Ion Chromatograms for R-12 Recovered Samples;
 CFC R-112 on Scale (volatile)

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10192A02 1450-4500 19-OCT-92 14:25 TR10-2 (EI+)
Chromatogram Identifiers : A : ATIC
Text: 074289 R12

IHP
A: 21432



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10192002 0450-4500 19-OCT-92 14:25 TR10-2 (EI+)
Chromatogram Identifiers : A : ATIC
Text: 074209 R12

IHP
R: 21432

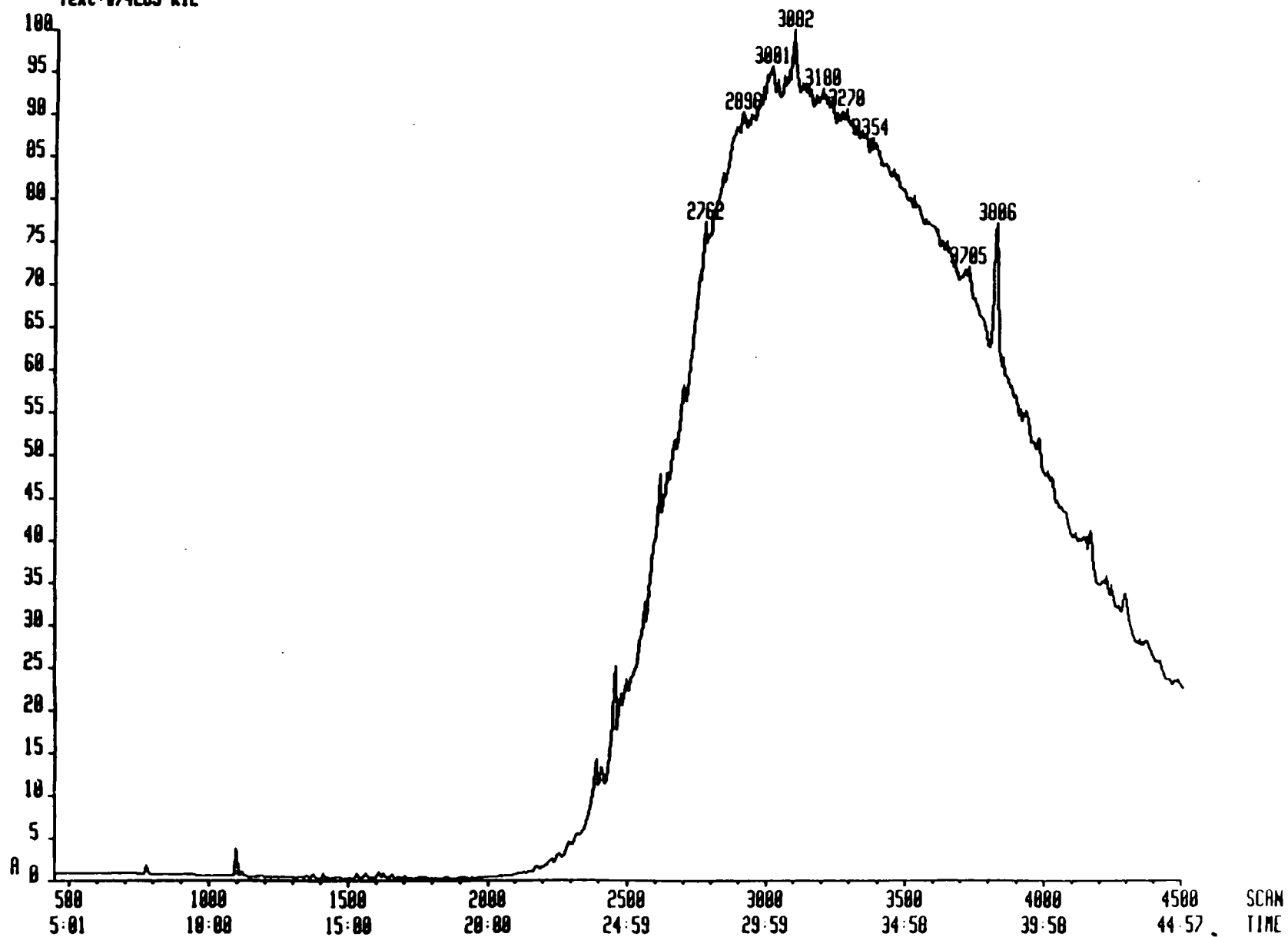


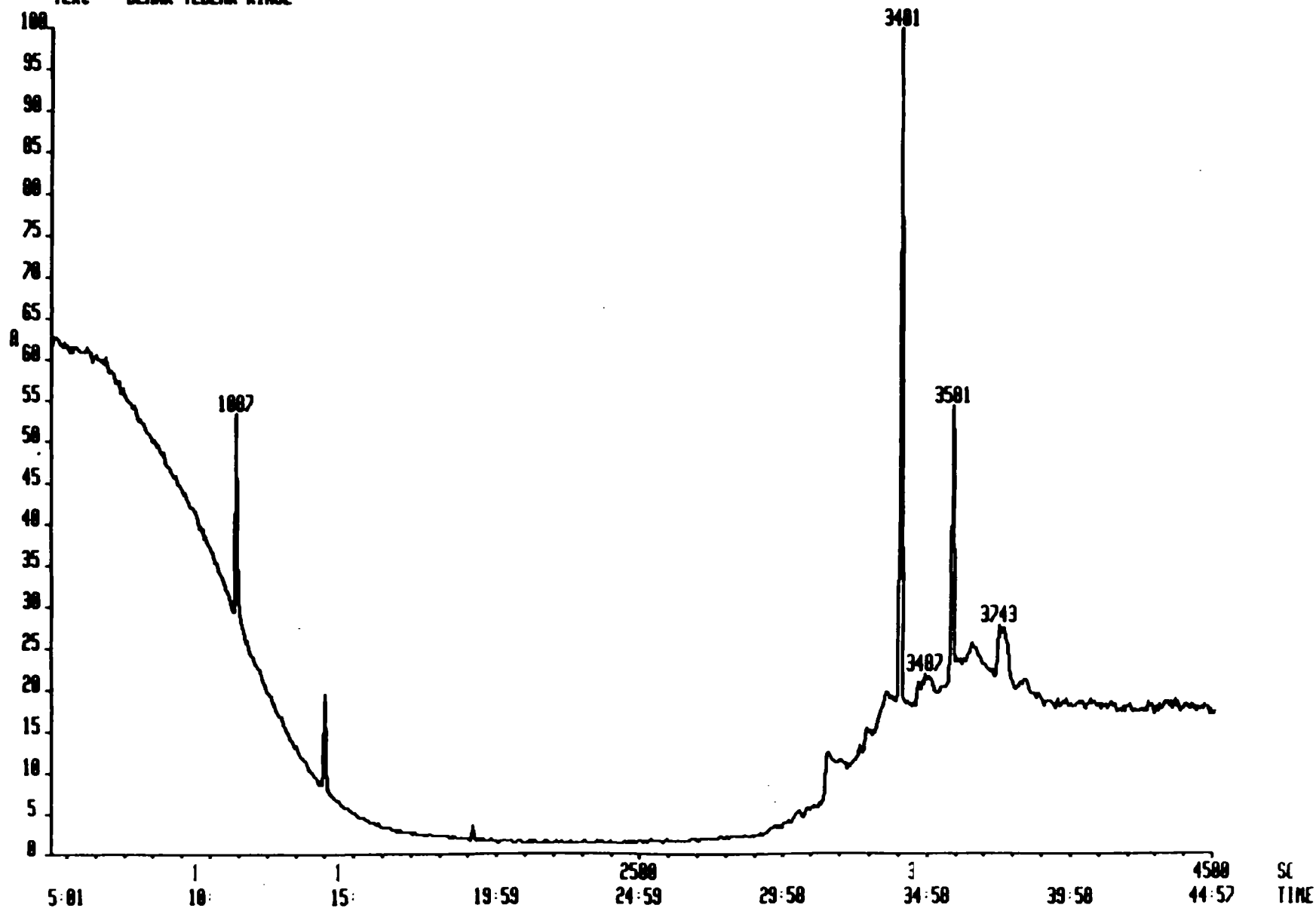
Figure 9 Total Ion Chromatogram for R-12 Recovered Sample, 74209 (semi-volatile)

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1823:001 0450-4500 23-OCT-92 09:23 TR10-2 (E1+)
Chromatogram Identifiers : A :ATIC
Text: BLANK TEDLAR RINSE

Sys:SYSTEMDEF

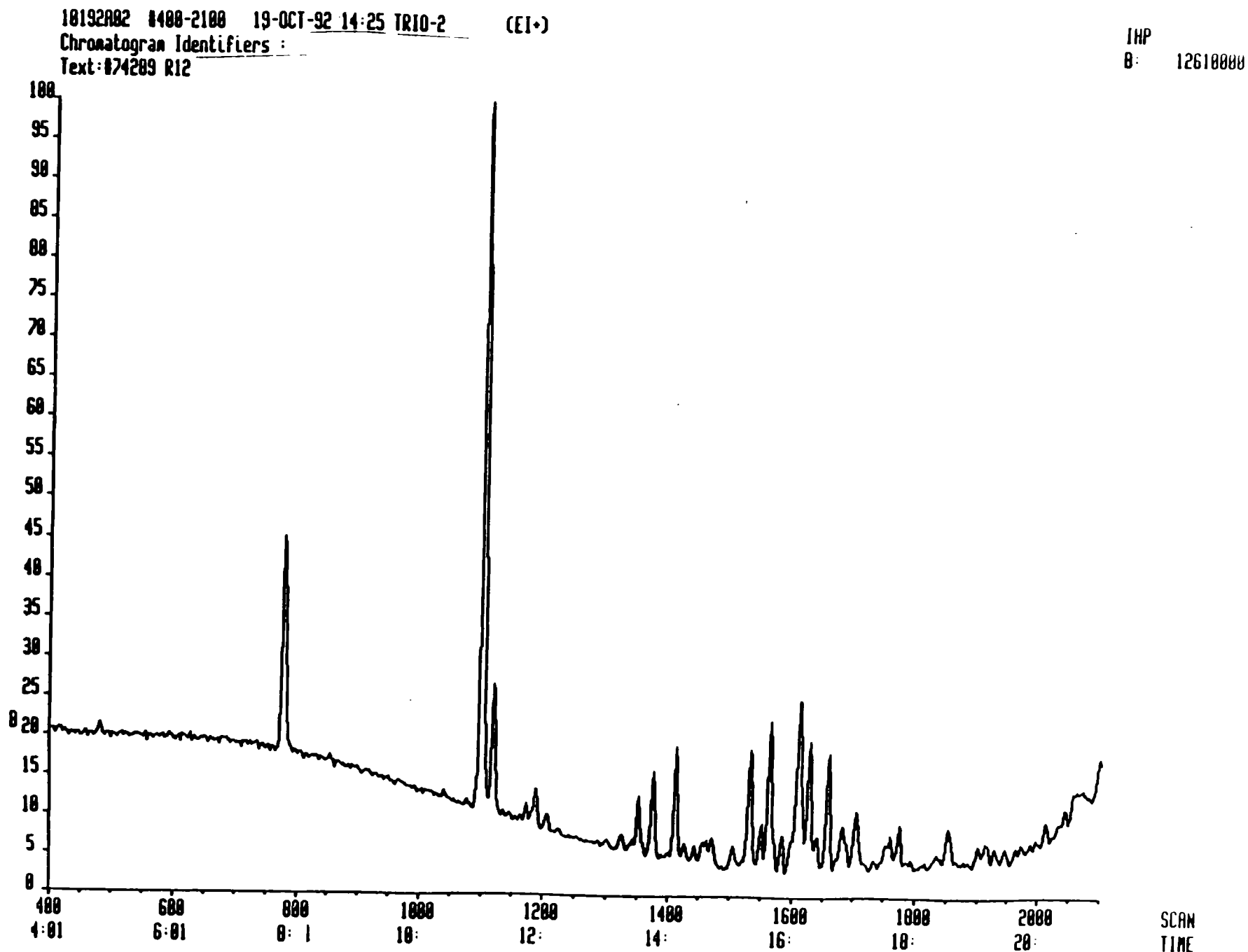
IHP
A: 342



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Figure 12 Total Ion Chromatogram for R-12 Recovered Sample, 74289, Expanded View



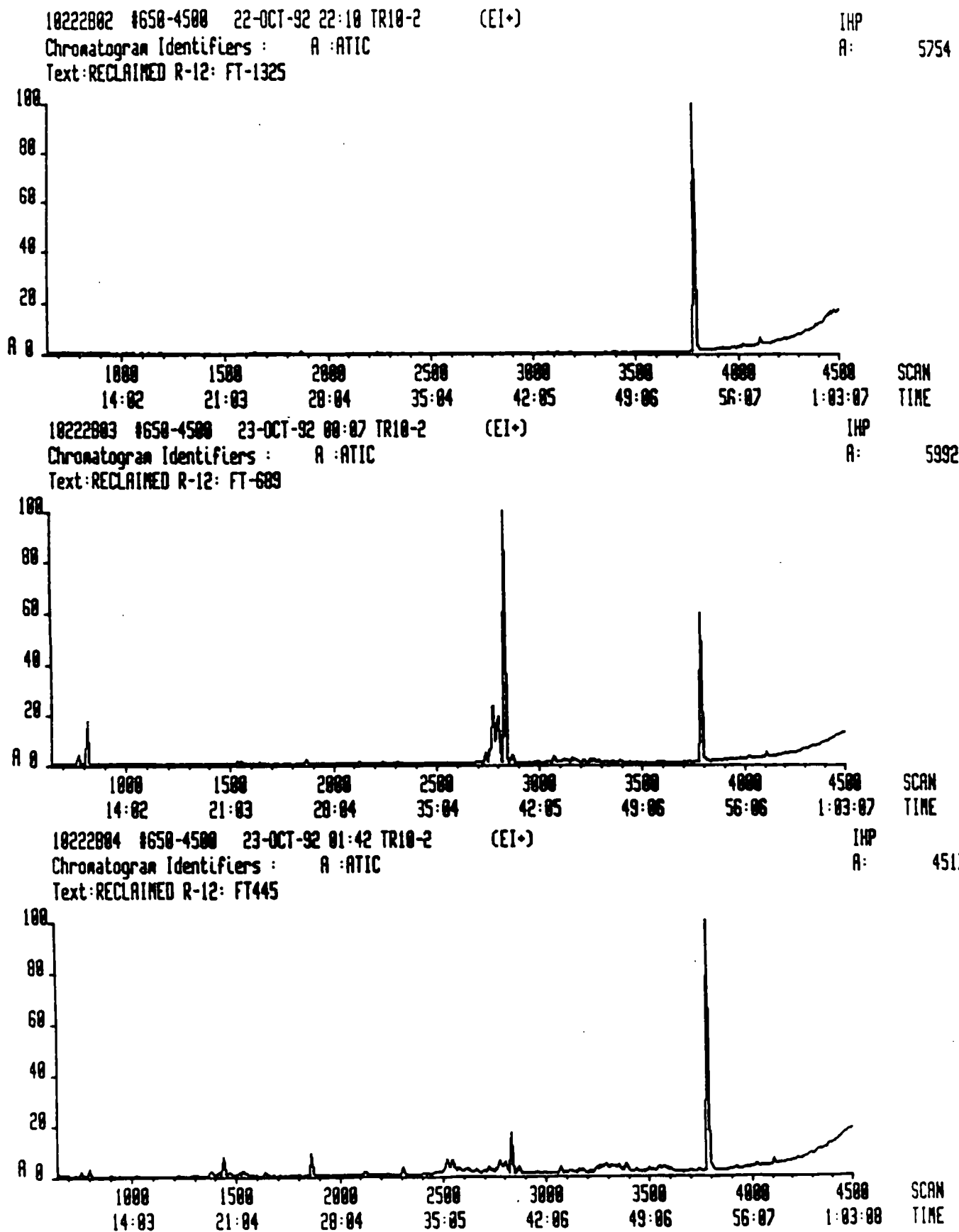
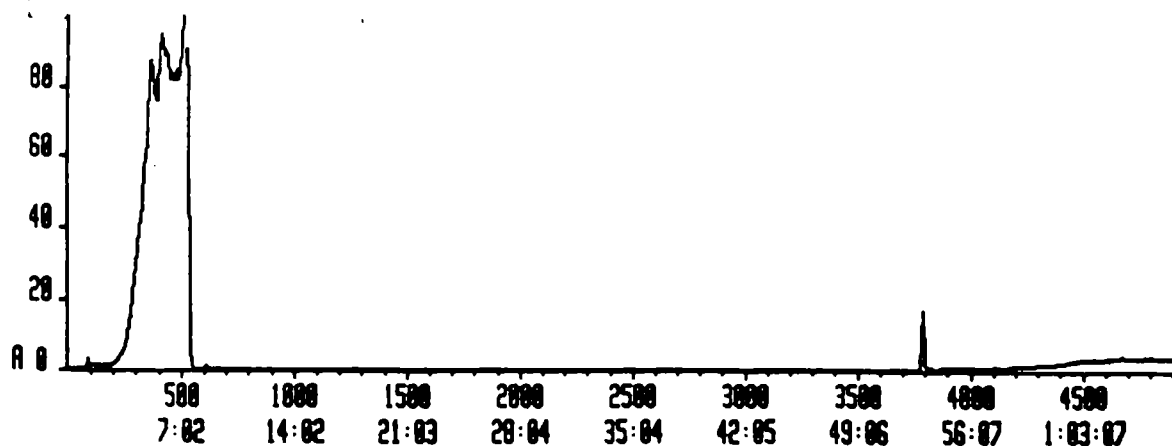


Figure 13 Total Ion Chromatograms for R-12 Reclaimed Samples (volatile)

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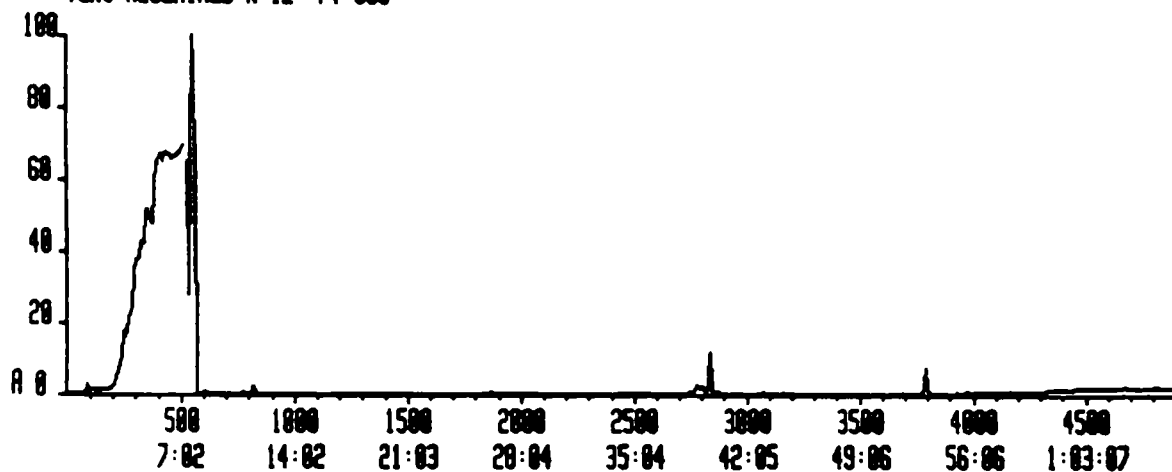
18222802 81-4928 22-OCT-92 22:18 TR10-2 (EI+)
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 Text: RECLAIMED R-12: FT-1325

IHP
 A: 33866



18222803 81-4928 23-OCT-92 00:07 TR10-2 (EI+)
 Chromatogram Identifiers : A : ATIC
 Text: RECLAIMED R-12: FT-689

IHP
 A: 51166



18222804 81-4919 23-OCT-92 01:42 TR10-2 (EI+)
 Chromatogram Identifiers : A : ATIC
 Text: RECLAIMED R-12: FT445

IHP
 A: 50074

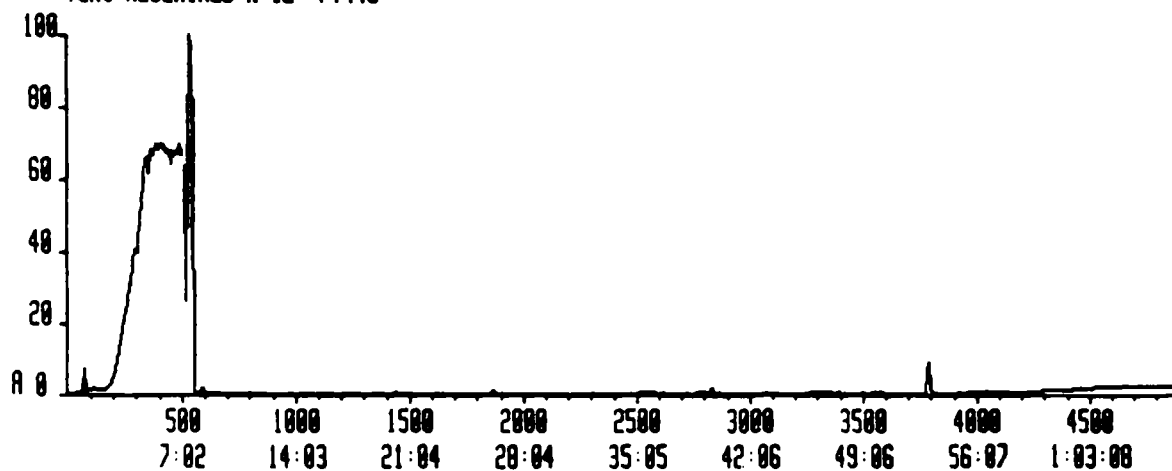
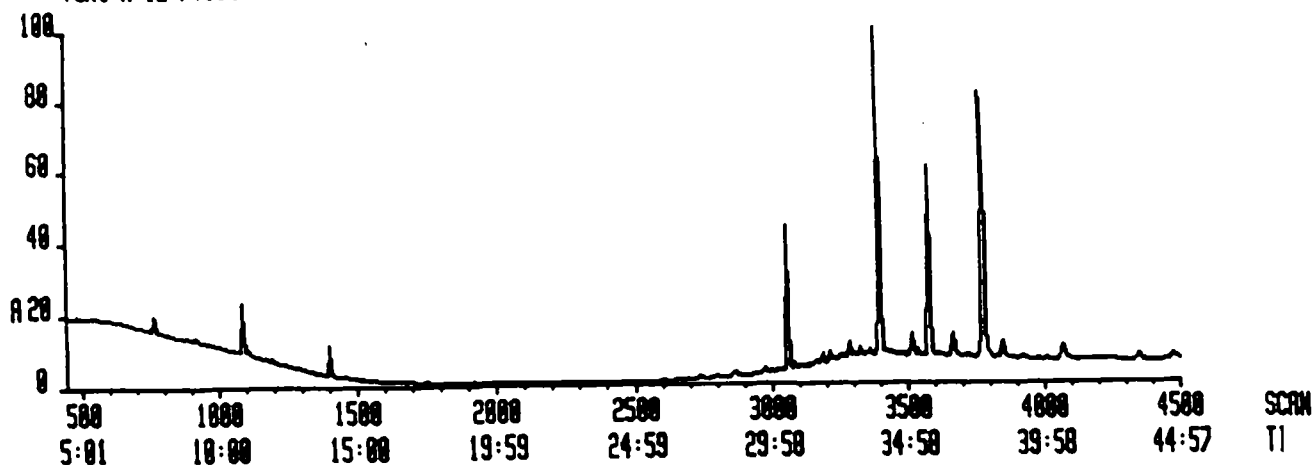


Figure 14 Total Ion Chromatograms for R-12 Reclaimed Samples;
 CFC R-12 on Scale (volatile)

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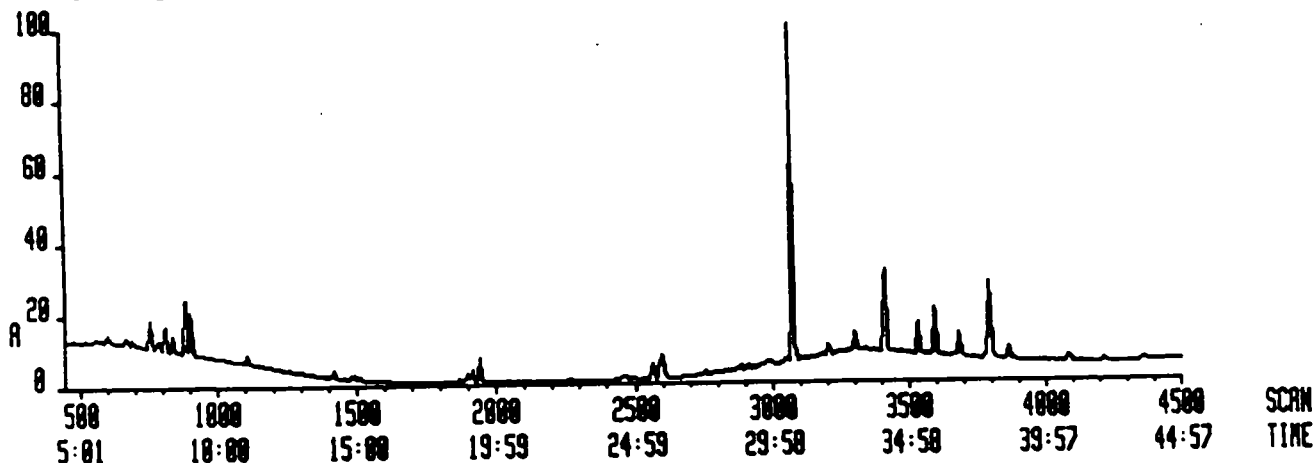
10232004 1450-4500 23-OCT-92 12:56 TR10-2 (EI+)
 Chromatogram Identifiers : A : ATIC
 Text: R-12 FT1325

IHP
 A: 1387



10232003 1450-4500 23-OCT-92 11:47 TR10-2 (EI+)
 Chromatogram Identifiers : A : ATIC
 Text: R-12 FT-689

IHP
 A: 2060



10232002 1450-4500 23-OCT-92 10:37 TR10-2 (EI+)
 Chromatogram Identifiers : A : ATIC
 Text: R-12 FT-445

IHP
 A: 2633

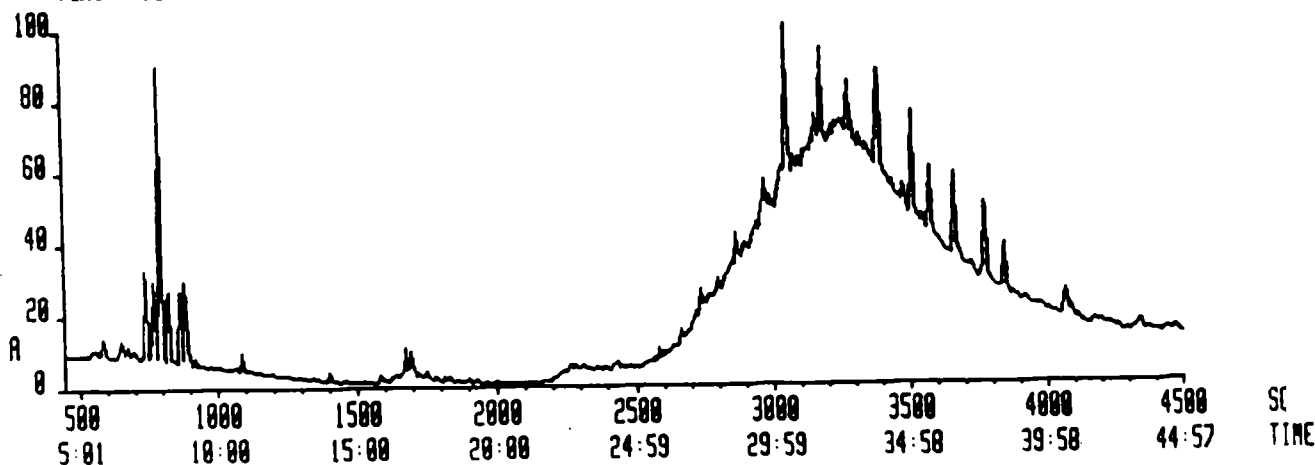
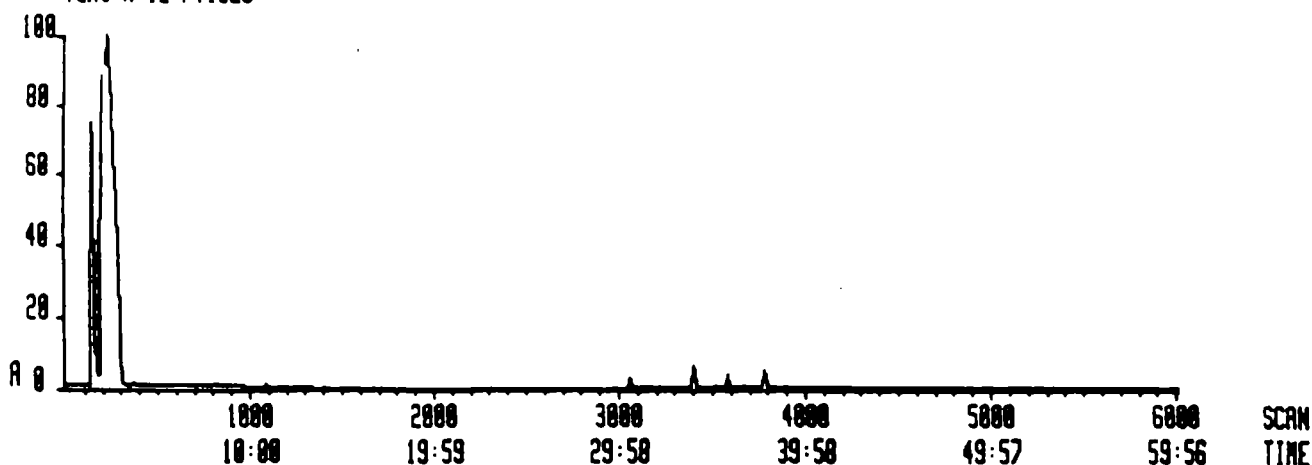


Figure 15 Total Ion Chromatograms for R-12 Reclaimed Samples (semi-volatile)

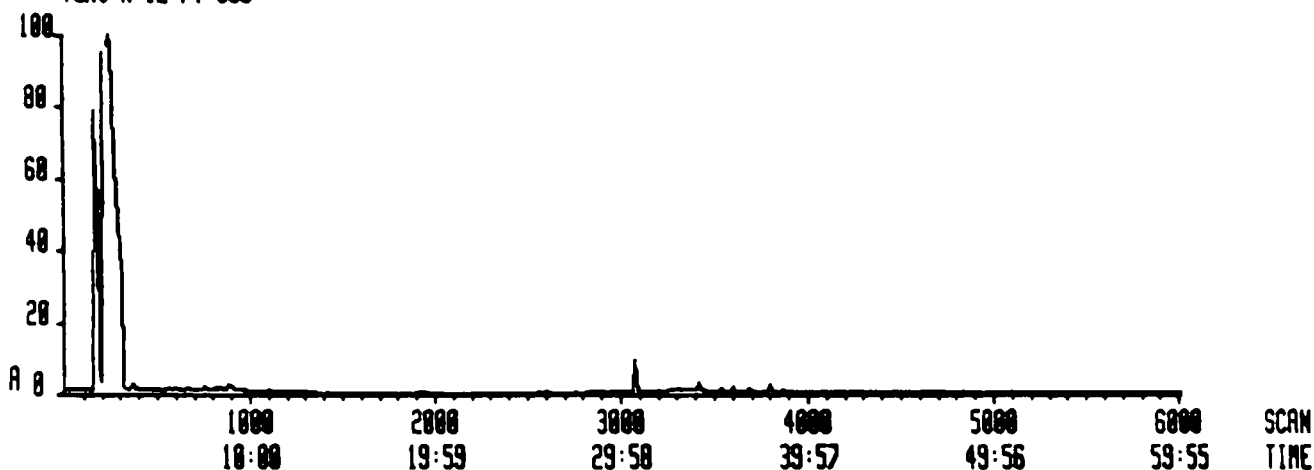
10232004 #1-6000 23-OCT-92 12:56 TR10-2 (EI+)
Chromatogram Identifiers : A : ATIC
Text: R-12 FT1325

IHP
A: 21579



10232003 #1-6000 23-OCT-92 11:47 TR10-2 (EI+)
Chromatogram Identifiers : A : ATIC
Text: R-12 FT-689

IHP
A: 21638



10232002 #1-6007 23-OCT-92 10:37 TR10-2 (EI+)
Chromatogram Identifiers : A : ATIC
Text: R-12 FT-445

IHP
A: 20001

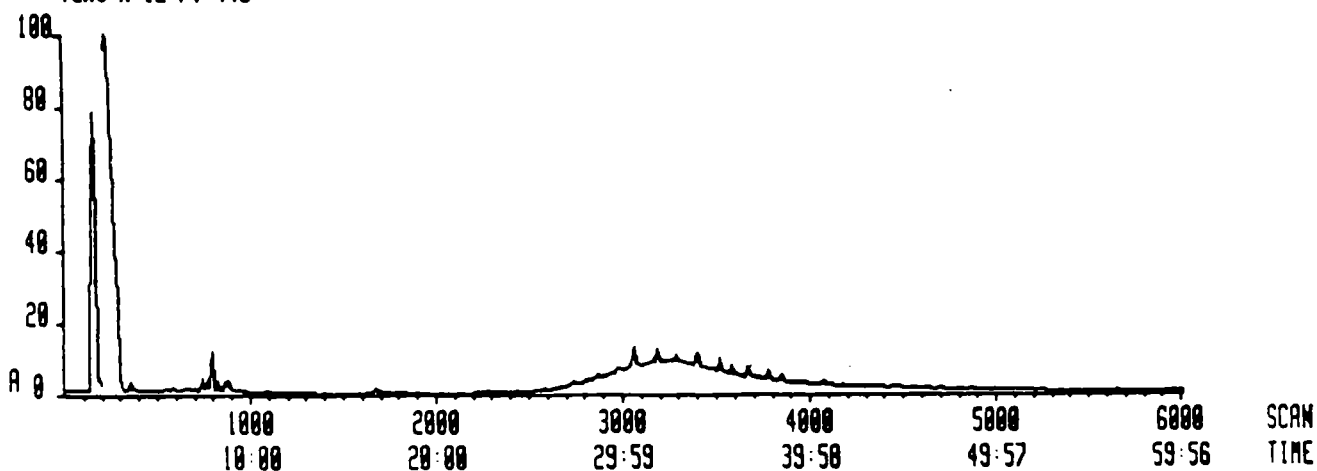


Figure 16 Total Ion Chromatograms for R-12 Reclaimed Samples;
Inclusive of Solvent Peak (semi-volatile)

Arthur D Little