

MATERIAL SAFETY DATA SHEET

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Atrovent® Inhalation Aerosol

(203) 798-4081 9AM - 4PM EST

DATE ISSUED: 1/7/03

EMERGENCY TELEPHONE NUMBER
CHEMTREC - 24 hours
1-800-424-9300

1. SUBSTANCE IDENTIFICATION

CHEMICAL NAME: 8-Azoniabicyclo (3.2.1)-octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-,bromide, monohydrate (endo,syn)-,(±).

CAS TYPE: 1

GENERIC NAME: Ipratropium Bromide

MOLECULAR FORMULA: C₂₀H₃₀BrNO₃•H₂O

TRADEMARK: **Atrovent® Inhalation Aerosol**

MOLECULAR WEIGHT: 430.4

PRODUCT USE: Bronchodilator

CAS NUMBER: 22254-24-6

SYNONYMS: Sch 1000, Itrop, Ipratropiumbromide (German)

2. COMPONENTS PER UNIT DOSE

MATERIAL

Active Ingredient:

Ipratropium Bromide

Excipients:

Trichlorofluoromethane (Freon 11)
Dichlorodifluoromethane (Freon 12)
Dichlorotetrafluoroethane (Freon 114)
Soya Lecithin

EXPOSURE LIMITS

15 ug/m³ BIEL**

1000 ppm ceiling*

1000 ppm*

1000 ppm*

No TLV established*

* As per 2002 ACGIH

**BIEL is the BI Exposure Control Level. When lower governmentally imposed occupational exposure limits exist, such limits should take precedence.

3. HAZARD IDENTIFICATION

EMERGENCY OVERVIEW

Milky white liquid.

**Warning: May cause sensitization
May cause eye, skin or respiratory irritation**

Will not burn. If involved in a fire, material emits toxic fumes. Use extinguishing media suitable for the material that is burning.

Pressurized containers may explode when heated.

ROUTES OF ENTRY: Inhalation, Ingestion, Skin and Eye contact.

TARGET ORGANS: Liver, GI tract, adrenals, male reproductive organs and eyes.

CONTRAINDICATIONS: Although rare, this product can cause immediate hypersensitivity in patients. Therefore, **Atrovent® Inhalation Aerosol** should not be used by patients who have had a previous allergic reaction to soya lecithin or related food products such as soybean and peanuts. This product should also not be taken by individuals who have a history of sensitivity to atropine, its derivatives, or any of the product's components.

ADVERSE REACTIONS/SIGNS AND SYMPTOMS OF EXPOSURE TO PRODUCT: Palpitations, nervousness, dizziness, headache, coughing, nausea, dry mouth and nose, nose bleed, dyspnea (difficult or rapid breathing), nasal discharge/irritation, sore throat, back and chest pain, acute eye pain, urinary tract infections, urine retention, rash and alopecia (hair loss), blurred vision and increased sensitivity to light.

WARNING:

Do not spray in eyes. Direct eye contact with product may cause temporary blurring of vision, precipitation or worsening of narrow-angle glaucoma or eye pain. If these symptoms occur, contact your physician.

Immediate hypersensitivity (allergic) reactions may occur after use such as urticaria (hives), angioedema (giant hives), bronchospasm (spasms of the lung's bronchial tubes), oropharyngeal edema (swelling of the lips, tongue and throat) and rash.

CHRONIC EXPOSURE: Possible hypersensitization (development of abnormal sensitivity).

MEDICAL CONDITIONS POTENTIALLY AGGRAVATED BY EXPOSURE: Dust allergies, pre-existing hypersensitivity (allergic reaction) to any of the product's components, narrow angle glaucoma, prostatic hypertrophy, bladder neck obstruction, hepatic (liver) or renal (kidney) dysfunction.

CARCINOGENICITY: Not listed as carcinogen/potential carcinogen by NTP, IARC Monographs or OSHA.

4. EMERGENCY FIRST AID PROCEDURES

Persons developing anaphylactic (life-threatening) reactions, such as difficulty in breathing or unconsciousness, must receive immediate medical attention.

INGESTION: Rinse mouth out with large amounts of water. Do not induce vomiting or give anything by mouth to an unconscious or convulsing person. Seek medical attention.

INHALATION: Remove affected person to a well ventilated area and get immediate medical attention. If breathing becomes difficult, give oxygen. If breathing stops, start artificial respiration.

SKIN CONTACT: Remove contaminated clothing. Flush affected area with copious amounts of water. If irritation or rash develops, get medical attention.

EYE CONTACT: Remove contact lenses if necessary. Flush eyes with large amounts of running water for several minutes. Get immediate medical attention.

NOTE TO PHYSICIAN: Treat symptomatically.

5. FIRE AND EXPLOSION HAZARD DATA

Flash Point 451-455°F (233-235°C)	Flammable Limits	
	Upper N/A	Lower N/A

FIRE EXTINGUISHING MEDIA: Water spray, dry chemical, carbon dioxide or foam as appropriate for surrounding fire and materials.

SPECIAL FIRE FIGHTING PROCEDURES: As with all fires, evacuate personnel to safe area. Firefighters should use self-contained breathing equipment and protective clothing. Use water spray to keep fire-exposed containers cool and protect against all exposures.

UNUSUAL FIRE AND EXPLOSION HAZARDS

Pressurized containers may explode when heated. When heated to decomposition, material emits toxic fumes of bromide, acid gases and phosgene.

6. SPILL AND ACCIDENTAL RELEASE MEASURES

STEPS TO BE TAKEN IN THE EVENT OF A SPILL: Wear approved respirator and chemically compatible gloves if containers have been compromised. Use absorbent material to clean-up spills. Place material in appropriate container for waste disposal. Wash contaminated clothing before reuse. Ventilate area, wash down spill site and control wash water.

7. PRECAUTIONS FOR SAFE HANDLING AND USE

HANDLING AND STORAGE PRECAUTIONS:

WARNING - CONTENTS UNDER PRESSURE

Do not puncture or incinerate container except at a facility capable of handling pressurized canisters. Store between 59°F (15°C) and 86°F (30°C) KEEP OUT OF THE REACH OF CHILDREN.

Avoid contact with eyes, skin or clothing. Avoid breathing aerosol. Store in airtight container and protect from light.

OTHER PRECAUTIONS: Wash thoroughly after handling material. Wear fresh clothing daily. Wash contaminated clothing before reuse.

8. CONTROL MEASURES

ENGINEERING CONTROLS: Not generally required when handling containers. (See section 2 for exposure limits.) Use appropriate respiratory protection based on an industrial hygiene survey.)

RESPIRATORY PROTECTION: The need for respiratory protection should be determined by an industrial hygiene survey. (See Section 2 for exposure limits.) NIOSH/MSHA approved respirators for protection should be used if respirators are found to be necessary.

VENTILATION: General ventilation should be adequate to maintain exposure levels below recommended established exposure limits. If general ventilation is not sufficient, local exhaust is recommended.

PERSONAL PROTECTIVE EQUIPMENT: Not generally required when handling final product. If containers are compromised or exposure to the active ingredient or mixture is likely wear:

Eye Protection: Safety glasses w/ sideshields or goggles

Hand Protection: Neoprene gloves

Protective Clothing: Laboratory coats

Other: Eye wash

WORK/HYGIENIC PRACTICES: Do not permit eating, drinking or smoking near this material.

9. PHYSICAL/CHEMICAL CHARACTERISTICS

APPEARANCE AND ODOR: Milky white liquid

Boiling Point: N/A

Specific Gravity: N/A

Vapor Pressure (mmHg): N/A

Melting Point: N/A

Vapor Density: N/A

Evaporation Rate: F-11 63

Water Solubility: Soluble

pH: N/A

10. REACTIVITY DATA

STABILITY: Stable.

CONDITIONS TO AVOID: None known.

INCOMPATIBLE MATERIALS: Alkalis, iodine, mercury salts and tannic acid.

HAZARDOUS DECOMPOSITION OR BY-PRODUCTS: When heated to decomposition, material emits toxic fumes of bromide, acid gases and phosgene.

HAZARDOUS POLYMERIZATION: Will not occur.

11. TOXICOLOGICAL INFORMATION

ACUTE TOXICITY for Active Ingredient:

Rat LD50 - Oral; **DOSE:** 1663 mg/kg **TOXIC EFFECTS:** *Behavioral* - Convulsions or effect on seizure threshold. *Behavioral* – Ataxia. *Lung, Thorax, or Respiration* - Dyspnea

Mouse LD50 - Oral; **DOSE:** 1001 mg/kg **TOXIC EFFECTS:** *Behavioral* - Convulsions or effect on seizure threshold. *Behavioral* – Ataxia. *Lung, Thorax, or Respiration* – Dyspnea

Dog LD50 -Oral; **DOSE:** 1300 mg/kg **TOXIC EFFECTS:** *Behavioral* - Convulsions or effect on seizure threshold. *Behavioral* – Ataxia. *Lung, Thorax, or Respiration* – Dyspnea

Human TDLO: Inhalation; **Dose:** 1 ug/kg **TOXIC EFFECTS:** Gastrointestinal –other changes

ACUTE TOXICITY for Excipients:

1/7/03

Atrovent® Inhalation Aerosol

Page 4 of 7

Freon F-11 Animal Toxicity Data:

1. LD50 Guinea pig inhalation 250,000 ppm/30 min
2. LD50 Rat inhalation 100,000 ppm/30 min
3. LD50 Rat oral 3725 mg/kg
4. LC50 Mouse inhalant 10,000 ppm/ 30 minutes
5. LC50 Hamster inhalation 571 g/cu m/4 hr

Freon F-11 Human Toxicity Data

1. By inhalation, large, acute doses have resulted in cardiac sensitization (arrhythmia) or bronchial constriction leading to death.
2. Human exposure to 1000 ppm, 8 hr/day, 5 days/wk for a total of 18 exposures had no untoward subjective effects, & there were no changes in the electrocardiogram or pulmonary function tests. The venous blood levels of F11 after 8 hr were as high as 4.69 ug/ml. The gradual attainment of this level represents a low uptake of the gas.
3. Bradycardia is the usual response in human subjects inhaling 10% of CFC 11. ... It is reasonable to suggest that bradycardia in man originates from irritation of the upper respiratory tract, & that cardiac effects can be initiated prior to absorption of CFC 11 in the lungs.
4. Gas of low toxicity but not entirely inert.
5. May be central nervous system depressant in high concentration.

Freon F-12 Non-Human Toxicity Values:

1. LD50 Mouse inhalation 760,000 ppm/30 min
2. LD50 Guinea pig inhalation >800,000 ppm/30 min
3. LD50 Rabbit inhalation >800,000 ppm/30 min
4. LD50 Rat single oral >1 g/kg
5. LD50 Rat inhalation >800,000 ppm/30 min

Freon F-12 Human Toxicity Data

1. Fatal case of bronchopneumonia /reported/ in man who punctured freezing coil of refrigerator containing F-12. It is probable that he aspirated cold concentrated vapor or liq, or was exposed to degradation products of refrigerant compound.
2. If inhaled at 5% by vol concentration induces dizziness in man. If inhaled at 15% concentration, loss of consciousness results.
3. Studies on ... Volunteers showed that inhalation of 10,000 ppm of fF12 for 2.5 hr causes 7% reduction in standardized psychomotor scores.
4. At concentration of 1000 ppm for 8 hr/day, 5 days/wk for total of 17 repetitive exposures, there were no untoward subjective responses & no abnormal physiological responses of lungs or heart.
5. Concentration as high as 27,000 ppm of F12 for 15 to 60 sec caused increase in airway resistance & electrocardiographic changes

Freon F-114 Non-Human Toxicity Values:

1. CFC-114 caused no effects in mice, rats, guinea-pigs, cats, or dogs after intermittent exposure to concentrations as high as 711 g/cu m (100 000 ppm). At higher dose levels (995-1422 g/cu m; 140,000-200,000 ppm) signs of intoxication were noted in guinea-pigs, dogs, rats, and mice.
2. Exposure at 20% by volume caused tremors and convulsions in dogs. after single 8-hour exposures the animals recovered, but repeated exposures for 8 hours daily were fatal after 3 or 4 days. single 16-hour exposures were also lethal to dogs.
3. Dogs survived 21 eight-hr exposures at 142,000 - 150,000 ppm CFC-114; the animals showed slight blood changes & symptoms ranging from in coordination to occasional convulsions.
4. Dogs survived eight-hr exposures at 200,000 ppm CFC-114; however a single 16-hr exposure or three to four 8-hr exposures were lethal. High concentration produced clinical signs of tremors, convulsions, & incoordination.
5. Concentrations around 1% caused slight irritation in guinea pigs; concentrations of 2 to 4.7% caused distinct irritation and increased respiration, but no pathological changes after 2 hours.
6. An increase in red blood cells, hemoglobin, & /immature/ forms of polymorphonuclear leucocytes were reported in dogs following exposure to vapors

F 114 Human Toxicity Data

1. In one study, ten subjects were exposed to CFC-11, CFC-12, and CFC-114; two mixtures of CFC-11 and CFC-12; & a mixture of CFC-12 and CFC-114 (breathing concentration between 16 & 150 g/cu m [2300 & 21,400 ppm]) for 15, 45, or 60 sec. Significant acute reduction of ventilatory lung capacity was reported in each case, as well as bradycardia & increased variability in heart rate & atrioventricular block. It was concluded that the mixtures exerted stronger respiratory effects than individual chlorofluorocarbons at the same level of exposure.

TERATOGENICITY: PREGNANCY CATEGORY B: No evidence of teratogenic effects have been reported following oral administration or inhalation of Ipratropium bromide in animals (Pakes et al, 1980; Massey & Gotz, 1985). A slight reduction in weight of rat fetuses fed 500 mg/kg of Ipratropium bromide during organogenesis was reported by Nishimura et al (1978). Consult physician if you suspect you are pregnant, pregnant or nursing.

CARCINOGENESIS/MUTAGENESIS: Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic potential at doses of Ipratropium Bromide up to 1,250 times the maximum recommended human daily dose for Atrovent. Results of various mutagenicity studies were negative.

IMPAIRMENT OF FERTILITY: Fertility of male or female rats at oral doses up to approximately 10,000 times the maximum recommended human daily dose was unaffected by Atrovent administration. At doses above 18,000 times the maximum recommended human daily dose, increased resorption and decreased conception rates were observed.

12. ECOLOGICAL INFORMATION

The active ingredient was shown to exhibit moderate break down in biological degradation testing. After 47 days of testing, 37 % of the material had been broken down to CO₂. Octanol-water partition studies indicate the K_{ow} is less than one at the three pH levels studied. The active ingredient did not inhibit the growth of 5 commonly studied microorganisms at concentrations of 1000 mg/L.

WARNING: Contains trichloromonofluoromethane (CFC-11), dichlorodifluoromethane (CFC-12) and dichlorotetrafluoroethane (CFC-114), substances which harm public health and the environment by destroying ozone in the upper atmosphere.

13. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL CONSIDERATIONS: Dispose of in accordance with local, state and federal regulations. Recommended method is incineration at a facility capable of handling pressurized canisters.

14. TRANSPORT INFORMATION

D.O.T. Proper Shipping Name: Consumer commodity, ORM-D
Hazard Class: N/A
Identification Number: N/A
Packing Group: N/A
Label: N/A
Emergency Response Guidebook - N/D

15. REGULATORY INFORMATION

This product contains trichloromonofluoromethane (CFC-11), dichlorodifluoromethane (CFC-12) and dichlorotetrafluoroethane (CFC-114), which have been designated as Class I, Ozone Depleting Substances, in 40 CFR 82, Subpart A, Appendix A.

Medical aerosols are excluded from the definition of a "controlled product" under 40 CFR Part 82 - Protection of Stratospheric Ozone.

16. OTHER INFORMATION

ABBREVIATIONS:

BIPI - Boehringer Ingelheim Pharmaceuticals, Inc.

N/A - Not applicable.

PREPARATION INFORMATION

Prepared by: Environmental Affairs & Safety.

Date Revised: 1/7/03

Replaces: 7/17/02

REVISION INFORMATION:

1. Revised Section 7 – Precautions For Safe Handling And Use
2. Revised Section 2 – Components Per Unit Dose
3. Revised Section 3 – Emergency Overview
4. Revised Section 13 – Disposal Considerations

The opinions expressed herein are those of qualified experts within Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). We believe that the information contained within this MSDS is current as of the date issued. Since the use of this information and these opinions and the conditions of use of this material are not within the control of BIPI, it is the user's obligation to determine the conditions of safe use of this material. BIPI urges the users of this product to study this MSDS and become aware of any hazards associated with this material. In the interests of safety, the information contained in this MSDS should be made available to your employees, agents and contractors who handle this material.

SEE CURRENT PACKAGE INSERT FOR FURTHER INFORMATION

REFERENCES

1. Investigator's Brochure for Atrovent®.
2. Physician's Desk Reference, 55th Edition, 2001.
3. MICROMEDEX Systems Integrated Index Copyright® 1974 - 2002