CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20812

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

PEDIATRIC ADVIL® SUSPENSION

IBUPROFEN

NDA 20-812

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION of ANTI-INFLAMMATORY

(HFD-550)

FINDING OF NO SIGNIFICANT IMPACT

[NDA 20-812]

[PEIDATRIC ADVIL®)

[IBUPROFEN]

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Pediatric Advil®(Ibuprofen), Suspension, 100 mg/2.5mL, Whitehall-Robins Healthcare has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR ~~25.31a~~ part 25 (a)(attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

* * *

Pediatric Advil®(Ibuprofen), Suspension, 100 mg/2.5mL, is a non-steroidal anti-inflammatory drug administered orally. This product is recommended for children 2 to 3 years old, and 24 to 35 pounds for the reductions of fever and the temporary relief of minor aches and pains. It is not recommended for children under 24 pounds and/or under 2 years old. Drug substance will be manufactured and supplied to Whitehall-Robins Healthcare by a contract drug substance manufacturer. The drug product will be manufactured and packaged at Whitehall-Robins Healthcare/A.H. Robins Inc./Wyeth-Ayerst Laboratories, 2248 Darbytown Road, Plant B, Richmond, Virginia 23231 (AH Robins Co., Inc. is a subsidiary of American Home Products, Richmond, Virginia). The final drug product will be used at home and in hospitals throughout the United States.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging.

Rejected and returned product will be disposed of in approved incinerators.

Waste generated from the manufacture of the drug product at the manufacture site will be disposed of in accordance with the appropriate Environmental Protection Agency

regulations.

The disposal of waste materials from the packaging process will be identical as that for the drug product.

Pediatric Advil®(Ibuprofen), Suspension, 100 mg/2.5mL, can be discharged into septic tanks or municipal sewage treatment facilities. Ibuprofen is rapidly metabolized and eliminated in the urine. There are no known active metabolites of ibuprofen. One hundred percent of a dose of ibuprofen is excreted in the urine in the first 24 hours. 1 to 14% of a dose of ibuprofen is found in the urine as unchanged ibuprofen. Ibuprofen is not expected to persist in the aquatic environment since it is inherently biodegradable.

Ibuprofen and the other components in the formulation of the tablets are known not to be volatile and, therefore, release into the air would not be expected from therapeutic use or disposal.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured and used without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Whitehall-Robins Healthcare has received authorization from the appropriate authorities to operate the plant and has provided certification that operation is in accordance with applicable environmental regulations.

Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

APPEARS THIS WAY
ON ORIGINAL

ENVIRONMENTAL ASSESSMENT FOR THE USE OF

PEDIATRIC ADVIL® DROPS

FOR THE REDUCTION OF FEVER AND THE TEMPORARY RELIEF OF MINOR ACHES AND PAINS

REDACTIONS MADE BY APPLICANT

THROUGHOUT EA

WHITEHALL-ROBINS HEALTHCARE
DIVISION OF AMERICAN HOME PRODUCTS
5 GIRALDA FARMS
MADISON, NEW JERSEY 07940

ENVIRONMENTAL ASSESSMENT FOR THE USE OF PEDIATRIC ADVIL® DROPS

1. Date October 1996

2. Applicant Whitehall-Robins Healthcare
Division of American Home Products

3. Address 5 Giralda Farms
Madison, New Jersey 07940-0871

4. Description of the Proposed Action

The proposed action is to manufacture fruit and grape flavored Pediatric Advil® Drops. The active ingredient in this product is manufactured and supplied to Whitehall-Robins Healthcare by . The subject drug product will be manufactured and packaged by Whitehall-Robins Healthcare / A.H. Robins Inc. / Wyeth-Ayerst Laboratories, 2248 Darbytown Road, Plant B, Richmond, Virginia 23231. The product was developed by Whitehall-Robins Healthcare. The building is operated under the A.H. Robins Inc. name. Manufacturing operations will be conducted by Wyeth-Ayerst Laboratories. Whitehall-Robins Healthcare, A.H. Robins Inc. and Wyeth-Ayerst Laboratories are sister divisions within American Home Products Corporation.

Pediatric Advil® Drops is indicated for the reduction of fever and the temporary relief of minor aches and pains. The dosing directions for this product are recommended for children ages

two to three. The maximum recommended dosage in a 24 hour period is 8 dropperfuls, or 4 doses, for children 24-35 pounds and age 2 to 3 years old. A dose, or 2 dropperfuls (2 x 1.25ml), equals 2.5 ml and 100 mg of ibuprofen. This product is not recommended for children under 24 pounds and/or under 2 years.

The final drug product will be used by the general child population of 2 to 3 year olds at home and in hospitals throughout the United States and could potentially be introduced into the following environments:

a. The environments adjacent to the manufacturing facility are as follows: The manufacturing plant in Richmond, Virginia is located in a temperate climate in a light industrial area. The area surrounding the facility is currently occupied to the east by the Wyeth-Ayerst distribution center, to the west by vegetation, trees, then the Virginia Electric & Power Company, to the north by acres of undeveloped woods, and to the south by Darbytown Road.

b. The facility in destroys Wyeth-Ayerst waste from the dust collection at the manufacturing site in Richmond, Virginia. is located in a temperate climate in a rural area.

c. Traces of product, <2%, may be detected in the waste water from the cleaning of equipment at the manufacturing facility in Richmond, Virginia.

d. Either of two facilities are used for the destruction of rejected and returned product. These facilities are all located in temperate climates.

One is located in a rural area:

And the other is in a commercial area:

The following is a brief description of the environment around the two facilities that will be employed for the destruction of rejected and returned product.

Residences:	1 mile	1/2 mile
Waterways:	1 mile	3/4 mile
Public Facilities:	1/2 mile	3/4 mile
Schools:	None	>1 mile south, 1.5 miles north
Wetlands:	1/2 mile	3/4 mile
Flood Plain:	None	Outside 500 yd. flood plain
Topography:	Flat (Moderate)	Flat (Moderate)
Site Surroundings:	Landfill, prison, farm	Commercial businesses and industrial area
Site Limitations:	3000 tons/day	975 tons/day

The facilities method of destruction for Whitehall-Robins Healthcare's drug product is incineration. The following describes the operating permits associated with the operation of the two facilities:

The facility located in is a waste-to-energy facility, which operates in compliance with the Federal Clean Air Act and the Commonwealth of Regulations for the Control and Abatement of Air Pollution. The facility accepts municipal solid waste and light commercial waste, including EPA non-hazardous waste. The facility permits are as follows:

The facility located in is a mass burning incineration facility, which operates in compliance with the Federal Clean Air Act and the Commonwealth of Regulations for the Control and Abatement of Air Pollution. The facility accepts municipal solid waste and light commercial waste, including EPA non-hazardous waste. The facility permits are as follows:

(See Appendix 1, for a copy of the Air Quality Permits)

e. Sewage treatment facilities throughout the United States receiving waste from hospitals and homes where Pediatric Advil® Drops are used.

f. Septic tanks receiving wastes from homes where Pediatric Advil® Drops are used.

g. Some larger accounts contract their own return and credit facilities which are not within the control of Whitehall-Robins Healthcare.

5. Identification of Chemical Substance

DRUG SUBSTANCE

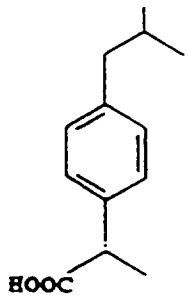
a. Description Including Physical and Chemical Characteristics and Stability

(1) Names

Established name:	Ibuprofen
Chemical name:	(±)-2-(p-isobutylphenyl) propionic acid
Chemical Abstracts Service (CAS) registry number:	15687-27-1

(2) Physical and chemical characteristics

General Chemical Structure:



Molecular Formula:	$C_{13}H_{18}O_2$
Molecular Weight:	206.28

Description:	White or almost white powder or crystals with a characteristic odor.
Solubility:	Low solubility in water; soluble 1 in 1.5 of alcohol, 1 in 1 of chloroform, 1 in 2 of ether and 1 in 1.5 of acetone. Ibuprofen is also soluble in an aqueous solution of alkali hydroxides and carbonates.
Melting Point:	75-78□C

Ibuprofen, Process Impurities, and Degradation Products

Compound Name	Process Impurity or Degradation Product

QUALITATIVE COMPOSITION

PEDIATRIC ADVIL® DROPS
IBUPROFEN ORAL SUSPENSION

The manufacturing of the drug product consists of the following procedure:

Fruit Drops:

Raw Material*
Ibuprofen, USP

Grape Drops:

Raw Material*
Ibuprofen, USP

* The above list should not be interpreted as a restriction from using an equivalent grade of a particular inactive ingredient provided that it has been qualified for use in this product.

1 Listed on OSHA's Table Z-1-A.

Note: Appendix 4, 5 and 6 contain copies of all MSDS sheets for the ingredients as well as the drug product.

(3) **Stability**

Information regarding stability studies conducted on bulk ibuprofen can be located in

b. **Manufacturer**

c. **Method of Manufacture**

For information regarding the manufacture of the ibuprofen drug substance (i.e. reagents, synthesis, etc.), please refer to

d. **Specifications and Analytical Methods**

The drug substance will be tested pursuant to the raw material test monograph for ibuprofen included in this application. For information relative to
- test specifications and analytical methods for ibuprofen, please refer to their drug master file

6. Introduction of Substance into the Environment

supplies ibuprofen in bulk to Whitehall-Robins Healthcare facility in Richmond, Virginia. All manufacturing, formulating, packaging, and distribution of Pediatric Advil® Drops will take place in Richmond, Virginia.

, has provided bulk ibuprofen, the drug substance, to the pharmaceutical industry since manufacturers the bulk ibuprofen in a process of

produces ibuprofen in a facility in compliance with all applicable Federal, State, and local emissions requirements. Supplying bulk ibuprofen to Whitehall-Robins Healthcare will not affect qualitative composition of the emissions from the facility, nor affect the ability of the facility to comply with all Federal, State, and local emissions requirements.

All substances with the potential to be emitted as a result of the production of the new drug product at Whitehall-Robins Healthcare, 2248 Darbytown Road, Richmond, Virginia 23231, the drug product manufacturing facility, and at the two waste disposal facilities of . would be at very low levels and would not be likely to have a significant environmental impact.

The statue(s) or law(s) that are applicable to the Whitehall-Robins, Richmond, Darbytown Road plant are as follows:

Resource Conservation and Recovery Act of 1976
Hazardous and Solid Waste Amendment of 1984
Clean Air Act of 1990
Emergency Planning and Community Right to Know Act of 1986
Hazardous Materials Transportation Act

The environmental permits associated with the operation of the Whitehall-Robins, Richmond, Darbytown Road Plant and the manufacture of Pediatric Advil® Drops are listed below.

Permit Number	Expiration
VPDES Permit for Stormwater VAR 240017	June 29, 1999
EPA Generator Number - VAD188141626	none
Air Permit Registration # 50898	none

This facility will manufacture the finished product under current FDA Good Manufacturing Practices.

Releases into the environment of wastewater pollutants or liquid, solid, or gaseous pollutants resulting from the manufacturing of Pediatric Advil® Drops are controlled. Diluted wash water resulting from the equipment is treated by the . The discharge of effluent by the treatment facility is monitored. Discharges could potentially contain traces of ibuprofen. After treatment, effluent is discharged in the . The maximum amount of the active ingredient, associated with the manufacture of Pediatric Advil® Drops at the Whitehall-Robins Healthcare facility from routine cleaning of equipment, that could potentially be in the wastewater discharged to the treatment facility is estimated at 26 ppm.

Whitehall-Robins Healthcare will comply with all applicable Federal, State, and local regulations at the production facility in Richmond, Virginia.

Attached is a table describing the effluent limitations and the monitoring requirements. (See Appendix 2)

Less than 0.002 % of the daily discharge of wastewater is associated with the manufacture of Pediatric Advil® Drops at the Whitehall-Robins Healthcare facility. The total facility discharge is approximately 30,000 gallons/day.

The manufacture of Pediatric Advil® Drops involves four chemicals on the OSHA Air Contaminants List (See section 5). The Whitehall-Robins facility in Richmond, Virginia is designed and operated for the manufacture of human drug products. Emission control equipment and treatment systems are in place for this facility.

All waste generated from the manufacture of the drug product at the Whitehall-Robins Healthcare facility in Richmond, Virginia will be disposed of in accordance with the Virginia Environmental Control Board and the US Environmental Protection Agency regulations. The disposal of the four OSHA air contaminants added during the manufacture of the drug product are as follows:

Small amounts of *Glycerin* and dissolved *Sucrose* can be expected to be discharged to the County's POTW during cleaning of the tanks between campaigns. In addition, any dust created during the addition of sugar will be collected in the dust collectors. This is expected to be minimal.

Microcrystalline Cellulose and Carboxymethylcellulose Sodium collected in the dust collector will be placed into a non-hazardous waste drum and sent to the , as non-hazardous waste for destruction by incineration.

Pediatric Advil® Drops will be packaged in amber glass and natural plastic bottles. The plastic bottles will consist of high-density polyethylene and polypropylene with the chasing arrow recycle symbol. The closures for both bottles will be polypropylene screw caps.

The disposal of waste materials from the packaging process will be identical as that for the drug product. The site of disposal is a mass burning facility located in a rural area. The method of distruction is incineration. The facility permits are as follows:

The site of disposal is a waste-to-energy facility located in a commercial area. The method of distruction is incineration. The facility permits are as follows:

The following are the permit limitations at each facility.

Non-criteria pollutant emissions from the operation of each furnace/boiler shall not exceed the limitations specified below:

Sulfur Acid Mist (H_2SO_4)	28.30 tons\yr.
Hydrogen Chloride (HCl)	113.60 tons/yr.
Hydrogen Bromide (HBr)	7.57 tons/yr.
Cadmium (Cd)	0.19 tons/yr.
Antimony (Sb)	0.55 tons/yr.
Arsenic (As)	0.03 tons/yr.
Mercury (Hg)	1.32 tons/yr.
Beryllium (Be)	7.94×10^{-4} tons/yr.
Fluoride (as HF)	1.78 tons/yr.
Dioxins (USEPA Toxic Equivalents)	2.42×10^{-6} tons/yr.
Particulate Matter	30.0 tons/yr.
Sulfur Dioxide	176.6 tons/yr.
Volatile Organic Compound	6.8 tons/yr.
Nitrogen Oxides	716.2 tons/yr.
Carbon Monoxide	60.3 tons/yr.
Lead	6.7 tons/yr.

Emissions from the operation of each municipal waste combuster unit shall not exceed the limitations specified below:

Particulate Matter	36.0 tons/yr.
Sulfur Dioxide	69.0 tons/yr.
Volatile Organic Compounds	3.0 tons/yr.
Nitrogen Oxides	277.0 tons/yr.
Carbon Monoxide	23.1 tons/yr.
Hydrogen Chloride	173.0 tons/yr.
Lead	2.32 tons/yr.
Arsenic	0.04 tons/yr.
Antimony	0.175 tons/yr.
Beryllium	2.63×10^{-4} tons/yr.
Cadmium	0.142 tons/yr.
Hydrogen Bromide	31.97 tons/yr.
Hydrogen Floride	7.45 tons/yr.
Mercury	0.96 tons/yr.
Total Dioxins and Furans	6.7×10^{-5} tons/yr.

Whitehall-Robins Healthcare will comply with all applicable Federal, State, and local regulations concerning emission control and waste treatment at the production facility in Richmond, Virginia. In accordance with Virginia's Environmental Quality Board Regulations, A.H. Robins Inc. Richmond manufacturing facility's current air permit will be amended to incorporate all sources of emissions associated with the manufacture of the drug product. No significant impact on the waste streams is foreseen by the proposed manufacturing process.

•The introduction of Pediatric Advil® Drops into the environment will be the general geographical distribution pattern of the United States pediatric human population of 2 to 3 year olds.

•The recommended maximum daily dosage is 8 dropperfuls which is equivalent to 4 doses (2 dropperfuls/dose four times per day). Each dose contains 100mg of ibuprofen, therefore the maximum daily intake of ibuprofen per day would equal 400mg.

4 doses/day x 100mg ibuprofen/dose = 400mg ibuprofen/day

•The five year projected total production of pediatric drops is estimated as follows, with the fifth year estimated at 6,414,000 ounces.

Estimated Annual Volumes in Ounces (x 1000)

1yr.	2yr.	3yr.	4yr.	5yr.
411	3,618	4,934	6,085	6,414

•Based on the fifth years production, which is the highest production volume, the total estimated ibuprofen that could be consumed from the production of this product if all liquid produced was consumed would be 7,546 kg/yr.

5th year production = 6,414,000 oz. of Pediatric Advil® Drops
1 dose = 2 dropperfuls = 2 drops x 1.25ml. /drop = 2.5 ml.
Given, 1 oz. = 29.573 ml.
Then, 1 oz. x 2.5 ml./dose ÷ 29.573 ml. = 0.085 oz./dose of Pediatric Advil® Drops
6,414,000 oz./yr. ÷ 0.085 oz./dose = $7{,}545.88 \times 10^4$ doses /yr.
$7{,}545.88 \times 10^4$ doses/yr. x 100 mg. of ibuprofen/dose =
$7{,}545.88 \times 10^6$ mg/yr. of ibuprofen
Given, 1 mg. = 10^{-6} kg.
Then, $7{,}545.88 \times 10^6$ mg/yr. x 10^{-6} kg./1mg. = 7,545.88 ≈ 7,546 kg./yr. of ibuprofen

•Given there will be 6,414,000 oz. of Pediatric Advil® Drops produced in the fifth year, and assuming all is consumed, 75.5 million doses /yr. at 2 dropperfuls (2.5 ml.) per dose could potentially be consumed in a year.

1 dose = 2 dropperfuls = 2 drops x 1.25ml./drop = 2.5 ml.
If, 1 oz. = 29.573 ml.
Then, 1 oz. x 2.5 ml./dose ÷ 29.573 ml. = 0.085 oz./dose of Pediatric Advil® Drops
6,414,000 oz./yr. ÷ 0.085 oz./dose = 7,545.88 x 10^4 doses /yr.
= 75.5 million doses/ year

•Based on the data contained in reference 1, the total US Population, during the fifth year of production 2001, is anticipated to be 279 million people. The projected population of children ages 2 to 3 years is 8.5 million. Of that population of 2 to 3 year olds, 74% or 6.3 million children recieving the maximum dose of 8 dropperfuls per day for three days would consume the entire production volume. This represents 2% of the entire US Population. This is a minimal percentage of the US Population that could potentially be taking Pediatric Advil® Drops.

(75.5 million doses/ yr.) / (3 days/ child x 4 doses/ day) = 6.3 million children/ year to consume the entire production volume.
8.5 million children = 100% of the US Child Population ages 2-3 years
6.3 million children = x% of the US Child Population ages 2-3 years
needed to consume the entire production volume.
(100% x 6.3 million children) / 8.5 million children = x% =
74 % of the US polulation of children 2 to 3 years of age could be using Pediatric Advil® Drops based on production.

279 million people = 100% of the US Population during the fifth year of production
8.5 million children= x% of the US Child Population ages 2-3 years
(100 x 8.5)/279 = x% = 3.0% of the US Child Population are ages 2-3 years

If, 3.0% of the US Child Population are ages 2-3 years = 8.5 million children.
And, 74% of the 3% of the US Population of children ages 2-3 yrs.= x % of the Total US Population that could potentially be dosing Pediatric Advil® Drops based on production volume
= 2%

Each dropperful contains 50mg ibuprofen, the active ingredient, or 4% of the weight per volume of the finished product ((50mg./1.25ml.) (g./1000mg.) = 0.04 g/ml. = 4% wt./vol.).

7. Fate of Emitted Substance in the Environment

Pediatric Advil® Drops can be discharged into septic tanks or municipal sewage treatment facilities. Studies have shown that following ingestion of ibuprofen, approximately 45% to 79% of a dose is recovered in the urine within 24 hours as metabolite A (25%), (+)- 2- (p-(2hydroxymethylpropyl)-phenyl) propionic acid and metabolite B (27%), (+)- 2-(p-(2carboxypropyl)-phenyl) propionic acid; the percentages of free and conjugated ibuprofen are approximately 1% to 14%, respectively. Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose is administered. The serum half-life is 1.8 to 2.0 hours. There are no known active metabolites of ibuprofen (refer to reference 3).

One hundred percent of a dose of ibuprofen is excreted in the urine in the first 24 hours. On the average, 1 to 14% of a dose of ibuprofen is found in the urine as unchanged ibuprofen. Ibuprofen is not expected to be found in the aquatic environment.

When the highest recommended dosage of Pediatric Advil® Drops is administered, the maximum concentration of ibuprofen that could potentially be found in a sewage treatment facility would be 0.05 µg/L. Since ibuprofen is absorbed rapidly when orally administered, and water is treated prior to being introduced into the surface water, the level of ibuprofen would be diluted well below 0.05 µg/L.

a. Potential Concentrations in Septic Systems.

- Assuming the average septic tank associated with a private home with four occupants holds approximately 1000 gallons, and the average person contributes 50 gallons of water each day to the septic, a septic tank could potentially be filled in about 5 days. 4 occupants x 50 gals. = 200gal/day x 5 days = 1000 gals.

- If one child in the household excretes the equivalent of the maximum recommended dosage, or 400 mg, of ibuprofen or four doses of two dropperfuls each day, the concentration of ibuprofen in the septic tank would reach about 0.53 mg/L. ((400 mg/day)/(200 gal/day x 3.785 L/gal)) = 0.53 mg/L

b. Potential Concentration in Sewage Treatment Facility.

- If Pediatric Advil® Drops were administered for 3 days at the highest recommended dosage (400mg ibuprofen), approximately 2 % of the US population would administer product.

  2 % the US population could potentially administer product (reference calculation in section 6 of this report)

- In any community of 100,000 people, assuming 25 % of that population are children, up to 500 children ages 2-3 yrs. could be using finished product containing 400 mg per day of ibuprofen.

  100,000 people x 0.25 of population are children = 25,000 children
  2 % of 25,000 children = 500 children
  (reference calculation in Section 6)

- On average, it is estimated up to 7 children could ingest the ibuprofen product on any given day during the year.

  (500 children x 5 days/365days) = approximately 7 children

- With a maximum dose of 400 mg/child/day, about 2.8 g. of ibuprofen could be used in this community in any day.

  (7 children x 400 mg/child/day)/1000 mg/g = 2.8 g.

- Assuming 15 million gallons of waste is generated per day by the community (This includes cleaning, personal hygiene, and drinking), the highest concentration of ibuprofen in the wastewater going into the sewage treatment facility theoretically would be 0.05 µg/L.

$2.8\ g \times (10^6\ \mu g/g) = 2.8 \times 10^6\ \mu g$
$15{,}000{,}000\ gal. \times 3.787\ L/gal = 56.8 \times 10^6\ L$
$(2.8 \times 10^6\ \mu g / 56.8 \times 10^6\ L) = 0.05\ \mu g/L$

c. MAXIMUM EXPECTED EMITTED CONCENTRATION (MEEC)

The following calculation is the maximum expected emitted concentration (MEEC) for the entire Advil® product-line production for all indications, strengths and population groups. The calculation includes the entire production at all facilities.

The total annual Advil production for all currently marketed products equals 5714 in millions of tablets, and 150,000 gallons of suspension.

1.) The total ibuprofen used in the production of solid dosage forms equals 1.1428×10^6 kg./yr., rounded to 1.14×10^6 kg./yr..

Calculation:

- 5717×10^6 total production in tablets/year x 200 mg/tablet
  $= 1{,}142{,}800 \times 10^6$ mg./yr.
- $1{,}142{,}800 \times 10^6$ mg./yr. x 0.000001 kg./mg.
  $= 1.1428 \times 10^6$ kg./yr.
  rounded to 1.14×10^6 kg./yr.

The maximum expected emitted concentration (MEEC) baseline for the current usage of ibuprofen in the production of all solid dosage forms of Advil in a mature market equals 0.022 ppm.

Calculation:

- $(1.14 \times 10^6$ kg./yr.) (2.21 lbs./kg)
  $= 2.5194 \times 10^6$ lbs./yr.
  MEEC = ppm (in environment) = lbs./yr. production x $8.9\ E^{-9}$
  $=(2.5194 \times 10^6$ lbs./yr.) $(8.9\ E^{-9})$
  $= 0.02242266$ ppm
  rounded to 0.022 ppm

The current baseline of ibuprofen used in the production of all solid dosage forms of Advil is 0.022 ppm, or 22 ppb. According to reference 1, a maximum of 14% of free and conjugated ibuprofen would be recovered in the urine after ingestion within the first 24 hours. Therefore, reducing **the maximum emitted expected concentration (MEEC) to 3 ppb.**

Calculation:

(22 ppb) (14%)
= 3.08 ppb
rounded to 3 ppb

2) The MEEC calculated for the production of all Advil® suspensions is 0.03 ppb.

The MEEC value was calculated using the following equation:

MEEC = (lbs./yr production) x ($8.9\ E^{-9}$) ppm (in environment)
(150,000 gallons/yr.) (100 mg/tsp.)(1 tsp./5 ml)(1000 ml/L)(3.787 L/gal.)
11,361,000,000 mg/yr. rounded to 11.4×10^{9} mg/yr.
(11.4×10^{9} mg/yr) (1.0×10^{-6} kg/mg) = 11,400 kg/yr.
11,400 kg/yr x 2.21 lbs/kg = 25,194 lbs/yr.
= 25,194 lbs/yr. production
= (25,194 lbs/yr production) x ($8.9\ E^{-9}$)
= 0.0002242266 ppm
rounded to 2.2×10^{-4} ppm , or 0.22 ppb

After calculating the maximum of 14% of free and conjugated ibuprofen in the urine after ingestion within the first 24 hours. **The MEEC equals 0.03 ppb.**

(0.22 ppb) (14%)
= 0.03 ppb

3) The MEEC calculated for the introduction of Pediatric Advil® Drops has been calculated based on the estimated fifth year production equaling 6,414,000 ounces.

The total ibuprofen used in the production equals 7,546 kg./yr

Calculation:

5th year production = 6,414,000 oz. of Pediatric Advil® Drops
1 dose = 2 dropperfuls = 2 drops x 1.25ml. /drop = 2.5 ml.
If, 1 oz. = 29.573 ml.
Then, 1 oz. x 2.5 ml./dose ÷ 29.573 ml. = 0.085 oz./dose of Pediatric Advil® Drops
6,414,000 oz./yr. ÷ 0.085 oz./dose = $7,545.88 \times 10^{4}$ doses /yr.

$7{,}545.88 \times 10^4$ doses/yr. x 100 mg. of ibuprofen/dose =
$7{,}545.88 \times 10^6$ mg/yr. of ibuprofen
Given, 1 mg. = 10^{-6} kg.
Then, $7{,}545.88 \times 10^6$ mg/yr. x 10^{-6} kg./1mg. = 7,545.88 ≈ 7,546 kg./yr. of ibuprofen

The maximum expected emitted concentration (MEEC) for the expected usage of ibuprofen in the production of Pediatric Advil® Drops in a mature market equals 0.00015 ppm.
The MEEC[1] value was calculated using the following equation:

(7,546 kg./yr.) (2.21 lbs./kg)
= 1.667666×10^4 lbs./yr. production or 1.67×10^4 lbs./yr.
MEEC = ppm (in environment) = (lbs./yr. production) x ($8.9\ E^{-9}$)
($8.9\ E^{-9}$ is a given constant)
=(1.67×10^4 lbs./yr.) ($8.9\ E^{-9}$)
= 0.00014863 ppm
rounded to 0.00015 ppm or 0.15 ppb

After calculating the maximum of 14% of free and conjugated ibuprofen in the urine after ingestion within the first 24 hours. **The MEEC equals 0.02 ppb.**

(0.15 ppb) (14%)
= 0.021 ppb
rounded to 0.02 ppb

4) The total estimated maximum expected emitted concentration (MEEC) of ibuprofen calculated on total current mature market of Advil® plus the anticipated markets from Pediatric Advil® Drops is **3.05 ppb**.

3 ppb (solid dosage forms) + 0.03 ppb (suspension) + 0.02 ppb (Pediatric Drops)

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. The serum half life is 1.8 to 2.0 hours. The MEEC calculation assumes that all that is consumed is excreted within 24 hours, which is the worst case scenario. The calculation does not take into consideration that the sewage treatment facility treats the water prior to introduction into the surface water, as a result the MEEC level of ibuprofen would be considerably lower than 3.05 ppb.

The production of Pediatric Advil® Drops represents less than a 1% increase over the current MEEC value previously calculated for the mature market of the entire Advil® product-line production.

The MEEC calculation result is expected to be significantly less than the calculated 3.05 ppb, likely less than 1 ppb level established by CDER to have no significant effect on relevant standard test organisms, and therefore, unlikely to have a significant effect on the environment for the following reasons: **1)** the calculation does not consider the treatment process in the sewage treatment facility prior to entering the environment, which would decrease the MEEC substantially, **2)** the calculation is based on the maximum amount of unchanged ibuprofen recovered in the urine after ingestion within the first 24 hours, representing the worst case scenario, and **3)** ibuprofen has been reported as inherently biodegradable (see reference 2, pages 3 and 10).

Advil® products have been marketed since May 18, 1994. The addition of Pediatric Advil® Drops is not expected to substantially increase the maximum expected emitted concentration (MEEC) of ibuprofen into the environment.

The MEEC has been calculated based on all ibuprofen used in the production of the Advil® product line. Since ibuprofen is supplied to Whitehall-Robins Healthcare by two manufacturers, the following DMF's (see reference 3) may be referenced for additional information:

The DMF contains acute toxicity, aquatic toxicity and biodegradation screening.

8. Effects on the Environment of Released Substances

Toxicity

In Appendix 4, page 3 of Material Safety Data Sheet, the acute oral LD_{50} in rats was reported to be 1.8 g/kg for ibuprofen. At the recommended dosage levels ibuprofen has not been linked to mutagenic, carcinogenic, teratogenic, or reproductive toxicant effects.

Biodegradability

The biodegradability of ibuprofen is reported as inherently biodegradable (see the attached copy of reference 4, pages 3 and 10).

Conclusion

The maximum concentration of ibuprofen in Pediatric Advil® Drops that could potentially be found in a sewage treatment facility prior to water treatment, and prior to introduction into the surface water, is calculated to be 0.05 µg/L. When human metabolism and biodegradation are considered, the level of ibuprofen in surface water would be minimal and would not be expected to be detected in the environment. (See reference 3, page 4, Table 2, titled Pharmaceutical chemicals found in sewage, sewage effluent, river and potable waters. Samples by analysis.)

9. Utilization of Natural Resources and Energy

The Whitehall-Robins Healthcare facility in Richmond, Virginia is designed for the production of pharmaceuticals. This facility operates according to current Good Manufacturing Practices.

To the best of our knowledge, endangered and threatened species are not affected by the manufacturing of Pediatric Advil® Drops. Also, the properties listed in the National Register of Historic Places will not be affected by the manufacturing of Pediatric Advil® Drops.

Environmental concerns are not anticipated with the production of Pediatric Advil® Drops at the Richmond, Virginia facility. The production associated with the manufacturing of this product would have minimal impact on the utilization of the natural resources related to energy consumption at the entire facility.

10. Mitigation Measures

The proposed action is not expected to have any adverse effects on human health or the environment. Pediatric Advil® Drops is produced under current Good Manufacturing Practices. All controls and waste treatment practices are in place to minimize release of raw materials and finished product. In the plant, all necessary protective equipment is worn where required. The Material Safety Data Sheets for all raw materials are attached. The manufacturing of the finished product requires the use of 4 chemicals that appear on the OSHA Z-1-A List.

11. Alternatives to the Proposed Action

As previously described in Section 8 of this document, the proposed action is not expected to have adverse effects on human health or the environment. There are no known benefits to the environment from the production and use described in the proposed action, there are, also, no known risks to the environment. Therefore, alternatives to the proposed action do not need to be addressed.

12. List of Preparers

The following personnel of Whitehall-Robins Healthcare are responsible for the preparation of the Environmental Assessment.

Debra A. Iorio
Regulatory Affairs Associate

10-24-96
Date

B.A. Chemistry
15 yrs. experience in the Environmental, Safety and Health field
American Industrial Hygiene Association member since 1986

13. Certification

The undersigned official certifies that the information presented in this Environmental Assessment is true, accurate, and complete to the best of his knowledge.

Dave H. Fore — 10-24-96

Dave H. Fore — Date

Director, Environmental Health and Safety

John Jacobs — 10/31/96

John Jacobs — Date

Vice President, Regulatory Affairs

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3.) Physicians Desk Reference 49th Edition 1995, p.2565.

4.) Journal of Pharmacy and Pharmacology, 1985, 37:1-12, "The fate of pharmaceutical chemicals in the aquatic environment," M.L. Richardson and J.M. Bowron (attached pages 32-43).

15. Appendices

Reference 4

Reference 4

J. Pharm. Pharmacol. 1985, 37: 1–12

REVIEW

The fate of pharmaceutical chemicals in the aquatic environment

MERVYN L. RICHARDSON AND JUDITH M. BOWRON

Thames Water Authority, New River Head, Rosebery Avenue, London EC1R 4TP, UK

Increased demands for potable water, especially where supplies are drawn from lowland rivers has necessitated a greater degree of water re-use. As water undertakings have a duty to maintain the wholesome quality of potable water supplies, increasing concern is being expressed over the presence of organic micro-contaminants (contaminants found at $\mu g\ litre^{-1}$ concentrations). This study outlines some of the problems encountered in assessing the risk from pharmaceutical chemicals which might enter the water cycle from domestic and industrial sources. Analytical chemistry was of value for only a few of the 200 compounds studied. However, much useful information was derived from the human metabolic routes of the drugs and is collated in Appendix I. Biodegradation studies and other ecotoxicity/environmental toxicology data may be required to a greater extent in the future. Particular consideration is given to vulnerable sections of the population.

During the Catchment Quality Control (CQC) studies undertaken by Thames Water Authority (TWA) (Fish & Torrance 1977, 1978; Wood & Richardson 1978, 1980; Nicolson et al 1981; Richardson & Bowron 1983; Bowron & Richardson 1984) it became apparent that pharmaceutical chemicals would enter the water cycle via two main routes.

(1) The industrial route: i.e. a point discharge to a sewage treatment works where the manufacturer or packer of a pharmaceutical product might incur 1–5% wastage of their product. This could find its way to drain and hence to the sewage treatment works, as a normal consented discharge. This percentage wastage of chemicals is low compared with many other industries because of the care necessary in handling very high cost chemicals often in controlled environments such as sterile packaging areas. Furthermore, the pharmaceutical industry works to stringent guidelines such as Good Manufacturing Practice and the Medicines Act.

(2) The 'domestic route': most pharmaceutical chemicals, both proprietary and ethical preparations, having left the factory, will be dispensed or sold to the public. These preparations will be administered either in the home, or in hospitals or clinics.

Excreta containing such drugs or their metabolites, or excess drugs if sluiced away, will reach sewage treatment works (STWs).

At STWs there are three principal possible fates for any individual pharmaceutical chemical:

(a) It might be ultimately biodegradable, i.e. to carbon dioxide, water, e.g. aspirin.

(b) It might undergo some form of metabolism or rather partial degradation e.g. penicillins.

(c) It might be persistent e.g. clofibrate.

Hence STWs effluent could contain either intact or partially degraded pharmaceutical chemicals.

STWs effluents discharge into rivers, many of which are subsequently abstracted for potable water supply purposes. As it was assumed that drug residues would survive the various water treatment processes, there seemed to be a distinct possibility that pharmaceutical chemicals at low concentrations ($\mu g\ litre^{-1}$) would be present in potable water supplies. Therefore, the question arises 'What is the long term public health risk of ingesting such drugs and/or their metabolites for up to about 70 years at a fraction (~1%) of their therapeutic dose?'

Treatment at STWs and waterworks could be improved by costly and advanced procedures such as activated carbon plants. These can be effective for the removal of a wide range of noxious organic chemicals, thereby improving the position relating to otherwise recalcitrant organic chemicals.

It was appreciated that drug prescriptions fall into two major categories:

(a) Short term—in this situation drugs are usually taken for a period of up to, say, two weeks and any excess usually retained in the household, returned to

the pharmacy, disposed of to refuse or flushed into the drain as earlier indicated.

(b) Long term—in this situation there is unlikely to be any excess drug to waste unless the formulation/prescription has to be changed.

It was also appreciated that whilst it is an acceptable risk to administer chemicals having high biological activity like cytotoxic drugs for instance, to the chronically ill, such a risk may not be acceptable for neonates and in pregnancy, despite the very low levels.

Furthermore, although many of the drugs studied in this investigation have been known and prescribed for many years, half a century in a few cases, this is insufficient reason for complacency.

In view of the foregoing the investigation was undertaken.

DETAILS OF THE INVESTIGATION

In the case of drug manufacturers and compounders within the TWA freshwater catchment, it was a reasonably easy matter to obtain, in strict confidence, an estimate of the quantities of each pharmaceutical chemical wasted to drain on a per annum basis (Fish & Torrance 1977, 1978; Wood & Richardson 1980). It was then simple to calculate the predicted concentration at the various downstream potable water abstraction points. On the assumption that the average person drank two litres of water per day an estimate of the likely ingested dose was made.

However, during our preliminary studies (Wood & Richardson 1980), it became apparent that wastage from manufacturing units was likely to contribute only marginally to the overall load of pharmaceutical chemicals that could be found in potable water supplies, at least as far as TWA catchments were concerned. The major source would be the home and hospitals, and for this reason a water authority would be unable to seek control, as would be the case with an industrial discharge.

Chemical analysis was then considered but it was rapidly concluded that this would not be practical except for a few pharmaceutical chemicals.

Firstly, the analysis of such chemicals in water, a surprisingly difficult matrix, at $\mu g\ litre^{-1}$ concentrations would be likely to involve considerable resources for a comparatively small number of chemical compounds. That is, a small number compared with 10 000+ industrial and related chemicals used in the EEC in quantities >1 tonne per annum, all of which are likely to enter water resources. Secondly, it was appreciated that human metabolism and sewage works treatment would be likely to modify the structure of the pharmaceutical chemical, in many cases removing the analytical determining group. Thirdly, all the pharmaceutical chemicals would be present in admixture with industrial, domestic and allied chemicals.

Whilst analysis was found to be practical for a few pharmaceutical chemicals, the separation techniques at the predicted concentrations were a major problem. This was so notwithstanding the unlimited size of the samples available, a very different situation from clinical analysis. In the latter, sample volumes are small, whereas volumes of samples for water analysis can be 20 litres before preconcentration.

Because of these analytical chemical problems it was decided to predict the quantities/concentrations of pharmaceutical chemicals that were likely to be present in the River Lee as a worst case situation.

A 'rule of thumb' calculation indicated that if one tonne of a pharmaceutical (or other chemical) was evenly discharged to the rivers in England and Wales over one year then a concentration of very approximately $0{\cdot}1\ \mu g\ litre^{-1}$ was likely to be achieved in the River Lee, assuming that no degradation or metabolism occurred.

The River Lee is a source of potable water for North London and during summer months and dry weather conditions it can be composed of some 60% of STWs effluent.

The concentration criterion of $0{\cdot}1\ \mu g\ litre^{-1}$ was selected for this study as in 1975 this concentration was one order of magnitude more stringent than any quoted in water quality criteria (Fish & Torrance 1977, 1978; Wood & Richardson 1978, 1980).

A computer print-out of drugs prescribed by general practitioners (200 or more prescriptions) for the year 1976 was obtained from the Department of Health and Social Security. This excluded drugs administered in hospitals and private practice. Similar details were obtained from the Proprietary Association of Great Britain for proprietaries.

The document gave the number of tablets, capsules, injectables etc. prescribed. These were then translated into tonnes of active pharmaceutical chemical ingredients. A total of 716 prescribable preparations were considered; this gave a list of 1600 chemicals. Some active ingredients were contained in over 30 formulations. Approximately 170 pharmaceutical chemicals were found to be used in excess of one tonne per annum or, using the factor referred to above, gave a predicted concentration of $0{\cdot}1\ \mu g\ litre^{-1}$ or above in the River Lee. Additional pharmaceutical chemicals were added to this list, see

Appendix I. e.g. drugs used in cancer chemotherapy because they are noxious.

The pharmaceutical chemicals were then individually considered with particular relevance to the information collated in Appendix I, e.g. metabolism, presence in maternal milk, ability to cross the placenta, plasma half life. This information was obtained from standard textbooks such as Martindale—The Extra Pharmacopoeia, British Pharmaceutical Codex, Association of the British Pharmaceutical Industry Data Sheet Compendium. The information was enhanced by on-line searching.

This exercise led to the following deductions:

(a) That a significant number of pharmaceutical chemicals undergo Phase I and II mammalian metabolism usually yielding conjugates. The toxicity and pharmacological activity of these is much lower than that of the parent compound. Microbial metabolism can also lead to similar transformations. Furthermore, such conjugates can be hydrolysed in STWs by enzymic processes, e.g. β-D-glucuronidase, to yield innocuous but stable products. Many of these will not have the analytical determining groups possessed by the parent compound.

(b) Whilst pharmaceutical chemicals are studied in depth for their pharmacological and clinical action, they are little studied for their environmental effects and ecotoxicity.

In view of this, the pharmaceutical chemicals listed in Table 1 were selected for biodegradation studies on the basis of the high quantity in use, potential for being noxious or because on reviewing the literature the drug seemed to survive sewage treatment. (Cytotoxic drugs were considered later.)

The methods for testing were those recommended by the Department of Environment, Standing Committee of Analysts (1981) and by King (1981).

Degradation or metabolism in the pharmacological sense is ultimately aimed at the removal of a biological effect; but biodegradation from the ecotoxicological stand point requires a different approach. It must be considered whether the compound is likely to be ultimately degraded, partially degraded (in which case metabolites may be of importance), or persistent. In the last instance further studies may be needed.

As earlier indicated, there was the need to consider chemical analysis.

This was undertaken in two ways:

(i) Gas chromatography–mass spectrometry (GC–MS). This technique is now used for indicating the presence of organic micro contaminants in various water samples. Suitable preconcentration (liquid–liquid extraction or by use of XAD resins) of samples is needed and in fact concentration factors of up to 10 000 can be achieved. From this type of analysis, lists of chemicals are identified in such samples. GC–MS has the disadvantage that, in general, it will only detect those chemicals which are volatile or easily derivatized to volatile chemicals, a maximum of some 20–25% of chemicals considered to be present in many water samples.

Table 1. Summary of biodegradability test results.

Compound	Result
Amitriptyline	Non-biodegradable
Ampicillin	45% biodegradable
Aspirin	Readily biodegradable
Caffeine	Readily biodegradable
Chlorhexidine	Non-biodegradable
Clofibrate	Non-biodegradable
Codeine phosphate	Non-biodegradable
Dextropropoxyphene	Non-biodegradable
Ephedrine	Readily biodegradable after acclimatisation
Erythromycin	Non-biodegradable
Ibuprofen	Inherently biodegradable
Menthol	Readily degradable
Meprobamate	Non-biodegradable
Methyldopa	Non-biodegradable
Metronidazole	Non-biodegradable
Naproxen	Non-biodegradable
Nicotinamide	Readily biodegradable
Paracetamol	Readily biodegradable after acclimatisation
Phenylpropanolamine	Readily biodegradable after acclimatisation
Sulphamethoxazole	Non-biodegradable
Sulphasalazine	Non-biodegradable
Tetracycline	Non-biodegradable
Theobromine	Readily biodegradable after acclimatisation
Theophylline	Readily biodegradable
Tolbutamide	Non-biodegradable

In fact very few pharmaceutical chemicals were identified by this technique (see Table 2).

In addition to samples of river and potable supply water, a sample of hospital effluent was examined and apart from methaqualone (see page 5) few pharmaceutical chemicals were identified. Disinfectants and detergents were most in evidence.

The EEC, within its COST 64b project, has made a computer-based compilation (CICLOPS) of those organic micro-pollutants reported worldwide. Few pharmaceutical chemicals are included. However, one of the more extensive studies is that by Watts et al (1983) of the Water Research Centre, Medmenham who report the presence of several antimicrobials (erythromycin, sulphamethoxazole, tetracycline) and theophylline, in river water samples. They used field desorption mass spectrometry and high performance liquid chromatography.

(ii) *Analysis of individual and groups of chemicals.* Whilst gas chromatography and high performance liquid chromatography have been used to identify specific pharmaceutical chemicals (Table 2), further compounds have been studied using immunoassay techniques. These have been in use for many years in clinical analytical chemistry but their application to water chemistry is new and shows considerable promise for the larger molecules. Aherne (1984) and Aherne & English (1984) have successfully used such techniques for the assay of methotrexate, progesterone, norethisterone and ethinyloestradiol in various river and potable water samples. After sample concentration by lyophilization, detection limits of between 5 and 10 ng litre^{-1} were achieved.

Table 2. Pharmaceutical chemicals found in sewage (S), sewage effluent (E), River (R) and potable waters (P). Samples by analysis.

Compound	Sample type	Concn (litre^{-1})	Remarks
Aspirin	(E)	$-1\,\mu g$	See text*
Caffeine	(E)	$-1\,\mu g$	See text*
	(P)	$>1\,\mu g$	See text*
Clofibrate†	(R)	-40 ng	
Diazepam	(E)	$<1\,\mu g$	See Appendix 1* and
	(R)	-10 ng	Waggott (1981)
	(P)	-10 ng	
Dextro-propoxyphene	(R)	$-1\,\mu g$	See text*
Erythromycin	(R)	$-1\,\mu g$	See Watts et al. (1983)
Methaqualone	(S)	$-1\,\mu g$	See text*
Methotrexate	(S)	$-1\,\mu g$	See text and Aherne
	(R)	$<6{\cdot}25$ ng	& English (1985)
	(P)	$<6{\cdot}25$ ng	
Morphinan substructure	(R)	$<1\,\mu g$	See text*
Oral contraceptives	(R)	$<0{\cdot}2\,\mu g$	See text and Aherne
	(S)	$<0{\cdot}1\,\mu g$	& English (1985)
Penicilloyl groups	(R)	>25 ng	See text
	(P)	>10 ng	
Sulphamethoxazole	(R)	$-1\,\mu g$	See Watts et al. (1983)†
Tetracycline	(R)	$-1\,\mu g$	See Watts et al. (1983)†
Theophylline	(R)	$-1\,\mu g$	See Watts et al. (1983)†

* GC analysis. † HPLC analysis.

MATTERS HIGHLIGHTED

The experimental findings from the biodegradation and analytical chemical studies, coupled with the information retrieved from the literature, suggested a significant conclusion. This was that very few pharmaceutical chemicals were likely to survive STWs treatment, river retention, reservoir detention and waterworks treatment in the form of the intact molecule. The conclusion enhances the view that advanced treatment, such as the use of activated carbon is unlikely to be required at least for pharmaceutical chemicals.

Of those pharmaceutical chemicals that were not ultimately degraded, most were likely to be metabolized to pharmacologically inactive sub-structures or conjugates. Even if these were likely to persist through various water treatment processes and be present in water supplies, the concentrations in the majority of instances would be unlikely to pose a public health risk. The same deduction would also apply to a large extent to the parent molecules. The predicted ingested quantities, as can be seen from Appendix I, are so small that a life-time ingestion of a pharmaceutical chemical from potable water would only give of the order of one day's recommended therapeutic dose. For example, 70 years' exposure to paracetamol would give four times the adult daily dose, to diazepam one day's dose, and to clofibrate one-sixth of a daily dose.

Antineoplastic agents and immunosupressants

Notwithstanding the above predictions, particular attention was given to drugs used in cancer chemotherapy, and immunosuppressive agents. This was because many of these are mutagens, mitotic inhibitors, antimetabolites or alkylating agents. Methotrexate was chosen by Aherne & English (1985) as a model compound because it may be used in substantial doses (up to 22 g day^{-1}), its use is widespread, and a sensitive immunoassay was available for its measurement.

Apart from a sewer immediately downstream of a large oncology clinic, no methotrexate concentration in excess of 6·25 ng litre^{-1} (the limit of detection) was found in any sample of river or tap water examined by Aherne & English (1985). Therefore, it was considered reasonable to deduce that there should be no risk from such potentially noxious chemicals.

Morphinan substructure

Results from the chemical analysis (GC–MS) indicated the presence of a morphinan sub-structure in a sample of river water downstream from a STW receiving much hospital effluent. The matter was pursued with the Pharmaceutical Society of Great Britain and the Regional and Area Health Authority Pharmaceutical Officers. It was considered that the presence of this structure could be due to excess drugs such as codeine, morphine or related compounds being sluiced away instead of being incinerated which is the procedure preferred by the

Pharmaceutical Society Inspectorate for disposal of such unwanted drugs. Adoption of this procedure resulted in this substructure not being found in subsequent river water samples.

Methaqualone

In this respect it was interesting that methaqualone was found in a sample of hospital effluent. This was at the time when use of this drug was being discontinued and hence it was deduced that surplus drug was being sluiced away.

Oral contraceptives

In the past decade, concern has been expressed over the possible presence of oral contraceptives in water samples. Aherne & English (1985) reviewing this noted their apparent absence (norethisterone <10 ng litre^{-1} and ethinyloestradiol <5 ng litre^{-1}) in the samples of potable water they examined. They also indicate that had they been present at the quoted limit of detection 10 and 5 ng litre^{-1} respectively this would have equated to an individual ingesting 1/17 500 and 1/2000 of the prescribed daily dose.

Penicillin allergy

Potential concern has also been expressed over the possible allergenic effects from penicillins. These had been found to be partially biodegradable (to ~50%) in a conventional biodegradation study (Water Research Centre). It was postulated that a penicillenic acid may be formed which in turn might form the penicillolyl determinant. Attempts were therefore made to assay the latter by an immunoassay technique (Wal et al 1975). The results indicated that, if present, such determinants would be unlikely to exceed 25 ng litre^{-1} in river water and 10 ng litre^{-1} in potable water.

Considerable doubt has been expressed by Dewdney & Edwards (1983) over Siegel's (1959) extrapolated figure of 0·24 µg as a single dose. Even if this literature figure were accepted as being capable of causing a reaction in a sensitive person, Dewdney & Edwards' study of the literature failed to identify any reference that indicated an amount lower than 0·24 µg would cause a reaction. The immunoassay findings were at concentrations some 100 fold less than this and hence there should be no risk of a sensitization reaction from potable water supplies.

Aspirin and salicylates

As aspirin is ultimately biodegradable, it was surprising that it was found in a number of river water samples (Water Research Centre—see Table 1 and CICLOPS). Moreover it was considered that its presence was due to it being a microbial metabolite of naphthalene oils, resulting from oil spillages.

Caffeine

The caffeine present was considered to be more attributable to beverages than from its use as a drug.

Dextroproxyphene

1,1-Diphenyl-butene (1,1-Db) was found to be present by GC–MS in a sample of river water. 1,1-Db by structure activity relationships was considered to be ultimately degradable. A literature search indicated that 1,1-Db was a pyrolysis product of dextropropoxyphene, Millard et al (1980) suggesting that 1,1-Db was being formed in the injection port of the GC. Hence, the presence of dextropropoxyphene was indicated in the sample considered. This was supported by spiking a sample from another river.

VULNERABLE SECTORS OF THE POPULATION

Young infants/foetus

Many drugs can be secreted into mothers milk and/or cross the placenta, see Appendix 1. The risk to the very young or to the foetus is hence much greater from a mother being prescribed pharmaceutical preparations than the risk to a young infant of drinking water which may contain a few µg litre^{-1} of a drug. See Appendix 1.

Renal dialysis patients

These patients are likely to be in contact with up to 100 times the volume of water consumed per head by the population at large. Also the route of exposure by-passes the normal gastrointestinal processes. Thus it is important to consider the effects of micro-contaminants as obviously the patient's life span should not be reduced by the presence of such impurities in the water used. However, as the impurities would have to pass through a dialysis membrane to reach the patient, small molecules, such as the halomethanes are likely to pose a greater risk than pharmaceutical chemicals whose molecules are often large, especially if they are conjugated. It is stressed that naturally occurring residues of aluminium salts or aluminium salts used for flocculation in water treatment are likely to be of much greater concern than drug residues.

In making a risk assessment it must not be overlooked that a patient receiving a transplant kidney is likely to receive immunosuppressive drugs for a considerable period. In view of their mutagenic

properties, any additional risk from mutagens that might be present in water will be minimal.

Population groups with enzyme deficiencies

The predicted presence of most drugs as biologically inactive metabolites rather than the pharmacologically active parent compounds in re-used water is of significance when enzyme deficiencies are considered. Glucose-6-phosphate dehydrogenase deficiency, for example, occurs among the population, the percentage being higher in certain Mediterranean countries. This deficiency can lead to haemolytic anaemia following the ingestion of certain drugs, including primaquine, phenacetin and aspirin. There might be cause for concern over residues of such drugs in potable water if it were not for the low predicted concentrations and the lack of pharmacological activity of the residues.

The situation is similar for mono-oxygenases. Küpfer et al (1982) report on several examples of genetic polymorphism of drug oxidation in man (and rat). They indicated that between 1–9% of the population they studied were deficient in their relative ability to effect the oxidative metabolism of debrisoquine, sparteine and phenformin. In 1976, the predicted concentration of phenformin in the River Lee was 0·15 μg litre^{-1} with the other two drugs at less than 0·1 μg litre^{-1}. However, even if this deficiency occurred in a significant proportion the same mitigating factors apply as before. Normal persons will excrete the drugs as hydroxylated conjugates or microsomal metabolism will occur during STWs' processes and the concentrations are low.

Drug–drug and drug–food interaction

Such interactions, whilst theoretically possible, are unlikely to be caused by drug residues in water. This is again mainly due to the lack of pharmacological activity of most relevant residues.

Inhibition of both microsomal and non-microsomal enzymes has been shown in man. The latter effect is exemplified by the monoamine oxidase inhibitors which increase sensitivity to some sympathomimetic amines found in certain foods and other drugs. The inhibition of tolbutamide metabolism by dicoumarol, phenylbutazone, phenyramidol and sulphaphenazole is a microsomal effect which can lead to the plasma elimination half-life of tolbutamide being increased fivefold.

The drugs causing enzyme inhibition are not thought likely to be present in re-used water at either sufficient concentration or retain sufficient properties of active form to cause any problems.

OTHER USES OF DRUGS

Whilst this review outlines the probable effects of pharmaceutical chemicals used for human therapy, no detailed consideration has been given to veterinary drugs.

There is little or no evidence to suggest that a different pattern should emerge for drugs used for treating farm animals, but the situation is not necessarily the same for substances used for treating fish. Such chemicals, in many cases, will be added either directly to water, or to fish food. Fish in many cases have different metabolic mechanisms. Furthermore, waste waters from fish farms will not be subject to STW processes.

Hence, further investigation is considered necessary for drugs such as nitrofurans and nitrothiazoles which can be used for disease control in fish farming.

In fact, the use of this type of antimicrobial in fish farms upstream of potable water abstraction points cannot be condoned. Care is also required where previously accepted veterinary products are used as industrial biocides.

CONCLUSIONS

Catchment Quality Control studies have indicated that pharmaceutical chemicals may enter potable water supplies from both domestic sources, including hospitals, and from manufacturing units. The latter is likely to be the lesser source of organic micropollutants and such discharges can be controlled.

Some 200 pharmaceutical chemicals were considered in the study described. It was appreciated that many would metabolise to innocuous substances e.g. conjugates. Such conjugates may then be hydrolysed to pharmacologically inactive compounds by STW processes.

Biodegradation studies made on 25 of the major use drugs indicated which drugs would survive STW processes and which were ultimately or partially degraded during such treatment. In considering the effects of new pharmaceutical chemicals, it is advocated that ecotoxicological/environmental toxicity tests such as biodegradation testing should be included in the portfolio of tests undertaken.

Attempts to analyse for individual pharmaceutical chemicals were not fruitful. However, such analyses as were possible indicated that the concentrations were <1 μg litre^{-1} in most cases. Some analyses of the more refractory compounds are recommended to be undertaken on an infrequent basis.

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APPENDIX—*see over*

Appendix 1. Pharmaceutical data summary. This indicates paediatric dose data where available and the maximum adult dose for each of the drugs considered. In addition, the *predicted* concentration in the River Lee of most of the drugs is given in μg litre^{-1}; these concentrations were obtained by taking the usage data from general practitioners' prescription information obtained from the National Health Service for 1976–7. From the predicted concentration data the I_m figures (mg) were calculated by assuming a person would consume 2 litre of water day^{-1} for 70 years. Other information used in making risk assessments for the pharmaceutical chemicals considered in depth in this study included metabolism, the possibility of the drug crossing the human placenta, secretion into maternal milk, plasma half lives (P$\frac{1}{2}$) (see footnotes).

Acebutolol	AD 400 mg. RL 0·29. I_m 15. M1Ac.
Acintirazole	Now only used in veterinary medicine, e.g. fish farming, see text.
Allopurinol	PD 20 mg kg^{-1}. AD 600 mg. RL 0·59. I_m 30. M1OH. P$\frac{1}{2}$ 2 h; P$\frac{1}{2}$ 25 h—for alloxanthine.
Alocs	AD 200 mg (proprietary use—no total tonnage data available). DAP. S. not recommended for nursing mothers.
Aminophylline	PD 25 mg up to 1 yr. AD 500 mg. RL 1·02. I_m 52·5. M1NdM; Ox. DAP. P$\frac{1}{2}$ 3–9 h.
Amitriptyline	PD not recommended. AD 150 mg. RL 0·85. I_m 45. M1OH; NdM, M11 gluc. P$\frac{1}{2}$ 9–76 h (N-oxide formation). non-biodegradable.
Amoxycillin	PD 125 mg up to 10 yrs. AD 1·0 g. RL 1·9. I_m 97. DAP. S (allergen?—see text).
Ampicillin	PD 62·5–125 mg up to 1 yr. AD 6·0 g. RL 7·9. I_m 405. M1OH. DAP. S. (allergen see text). 48% biodegradable in SCAS test, see text.
Amyl-*m*-cresol	Proprietary use—no tonnage data, low toxicity.
Amylobarbitone	AD 200 mg. RL 1·75. I_m 90. M1OH; NOH; Ox. DAP. S. P$\frac{1}{2}$ 20 h.
Aspirin	PD 75–150 mg 1–2 yrs. AD 5·0 g. RL 14·6 (161 if 1000 tonnes proprietary inc.). M1OH. M11 gluc; gly. readily degradable (see text).
5-Azacytidine	Antineoplastic agent, soln unstable.
Azathioprine	M11glut. P$\frac{1}{2}$ 24 h (mutagen and antimetabolite).
Benorylate	PD 25 mg kg^{-1} up to 1 yr. AD 8·0 g. RL 9·2. I_m 470 (readily hydrolysed to paracetamol and acetylsalicylic acid).
Benzathine penicillin	PD <300 mg for 6–12 yrs. AD 1·8 g. RL 0·29. I_m 15 (converts to benzylpenicillin and benzathine).
Benzocaine	PD not recommended. AD 200 mg. RL 0·15. I_m 7·5. M1Hyd (mainly external application).
Benzyl benzoate	RL 1·32. I_m 67·5. M1Hyd. M11gly (forms benzoic acid—external application).
Benzylpenicillin	PD 0·5–1·0 g. AD 6·0 g (max 24·0 g). RL 0·15. I_m 7·5. DAP. P$\frac{1}{2}$ 30–160 min.
Bismuth subgallate	RL 0·15. I_m 7·5 (external application).
Butaphyllamine	PD not recommended for <5 yr old. AD equiv. 600 mg theophylline. RL 0·15. I_m 7·5. M1NdM, see also theophylline.
Butobarbitone	AD 200 mg. RL 1·17. I_m 60. M1Ox. DAP. S. P$\frac{1}{2}$ 55 h.
Caffeine	AD 300 mg. RL 0·29. I_m 15. M1NdM; Ox. S. P$\frac{1}{2}$ ~10 h. readily biodegradable, found in sewage, rivers and present in beverages, see text.
Carbamazepine	PD 600 mg up to 12 yrs. AD 2·2 g. RL 0·44. I_m 22·5. M1OH; Ox. M11gluc. DAP. S. P$\frac{1}{2}$ 21–53 h (epoxide formed?).
Carbocisteine	PD 500 mg for 2–5 yrs. AD 2·2 g. RL 0·44. I_m 22·5. M1S-OX.
Carbromal	PD not recommended. AD 1·0 g. RL 0·29. I_m 15. M1OH.
Carmustine	Alkylating agent, small usage. P$\frac{1}{2}$ 15 min.
Cephalexin	PD 50 mg kg^{-1}. AD 4·0 g. RL 0·59. I_m 30. DAP. S. P$\frac{1}{2}$ 0·5–2 h.
Chlordiazepoxide	PD 20 mg. AD 60 mg. RL 0·29. I_m 15. M1OH; NdM, M11gluc. DAP. S. P$\frac{1}{2}$ 6–28 h.

continued

Key

PD = Paediatric dose
AD = Adult dose
RL = River Lee μg litre^{-1}
I_m = Ingestion for 70 yrs (mg)
MI = Phase I metabolism
MII = Phase II metabolism (conjugation)
DAP = Drug crosses placenta
S = Secreted into mother's milk
P$\frac{1}{2}$ = Plasma half life

Ac = Acetylation
dAc = Deacetylation
deC = Decarboxylation
Hyd = Hydrolysis
NdM = *N*-demethylation
NOH = *N*-hydroxylation
NM = *N*-methylation
Nox = *N*-oxidation
OdM = *O*-demethylation
OH = Hydroxlation
OM = *O*-methylation
Ox = Oxidation
OxD = Oxidative deamination
S-OX = *S*-oxidation

cyst = conjugation with cysteine
gluc = conjugation with glucuronide
glut = conjugation with glutathione
gly = conjugation with glycine
SO_4 = conjugation with sulphate

Chlorhexidine	AD 2·0 g (human metabolic experiment), can hydrolyse to form 4-chloroaniline, proprietary preparation—no usage data available, non-biodegradable.
Chlormethiazole (edisylate)	PD not recommended, AD max 8·0 g, RL 0·44, I_{70} 22·5, MIOH; Ox, DAP, P½ 4 h, dechlorinates.
Chlormezanone	AD 800 mg, RL 0·29, I_m 15, MIOx; Hyd.
Chloroform	Use restricted see Statutory Instrument 1979 No 352, WHO Drinking Water Guidelines 30 μg litre^{-1}.
Chlorothiazide	PD 25 mg kg^{-1}, AD 2·0 g, RL 0·15, I_{70} 7·5, DAP (very little metabolism).
Chlor-promazine	PD <60 mg for 6–12 yrs, AD 200 mg, RL 0·29, I_m 15, MIOH; NdM; S-OX; Nox, M11gluc, DAP, P½ 4 h (induces liver enzymes).
Chlor-propamide	AD 500 mg, RL 0·73, I_m 37·5, MIOH, hyd, P½ 25–42 h.
Chlor-tetracycline	PD 20 mg kg^{-1} (only if essential), AD 3·0 g, RL 0·15, I_{70} 7·5, DAP, S, P½ 5–6 h.
Chlorthalidone	AD 200 mg, RL 0·15, I_{70} 7·5, P½ 50–90 h (very little metabolism).
Choline salicylate	See Aspirin.
Choline theophyllinate	PD <375 mg for 3–6 yrs, AD 1·6 g, RL 1·02, I_{70} 52·5 (see theophylline).
Cisplatin	Antineoplastic agent—used in small quantities, not recommended in pregnancy, P½ 25–49 min to 58–73 h.
Clindamycin	PD 24 mg kg^{-1}, AD 1·8 g, RL 0·15, I_{70} 7·5, MINdM; S-OX, DAP, S, P½ 2–3 h.
Clofibrate	PD 1·0 g for 10 yr old, AD 2·0 g, RL 6·3, I_{70} 321, M11gluc, non-biodegradable see text.
Clomipramine	PD <30 mg for >5 yrs, AD 150 mg (oral); 50 mg (i.v.), RL 0·15, I_{70} 7·5, MIMdM; OH.
Codeine (phosphate)	PD not recommended up to 6 yrs, AD 60 mg, RL 0·88, I_m 45, MIOdM; NdM, M11gluc; SO_4, DAP (codeine, norcodeine or morphine conjugates found—see text).
Crotamiton	RL 0·15, I_{70} 7·5 (external application only).
Cyclandelate	AD 1·6 g, RL 1·02, I_{70} 52·5.
Cyclizine	PD 25 mg for 3–5 yrs, AD 150 mg, RL 0·15, I_{70} 7·5, MINdM.
Cyclo-phosphamide	Antineoplastic agent used in small quantities, MIOH, DAP, S, P½ 3–11 h (hydrolyses in water).
Danthron	PD 25 mg, AD 50 mg, RL 0·29, I_{70} 15, M11gluc, S.
Debrisoquine	PD not recommended, AD 300 mg, see text.
Demeclocycline	PD 6 mg kg^{-1} (only if essential), AD 1·5 g, RL 0·15, I_{70} 7·5, P½ 10–15 h.
Dextro-methorphan	PD 15 mg for 2–4 yrs, AD 30 mg, proprietary usage—hence no tonnage available, MINdM; OdM, M11SO_4, degrades to morphinan struct, see text.
Dextro-propoxyphene	PD not recommended, AD 520 mg, RL 3·2, I_{70} 164, MINdM, non-biodegradable.
Diazepam	PD 5 mg kg^{-1}, AD 30 mg, RL 0·44, I_{70} 22·5, MINdM; OH; M11gluc, DAP, S, P½ <5 days.
Dichloral-phenazone	PD 270 mg up to 1 yr, AD 1·3 g, RL 0·88, I_{70} 45, MIOH; NdM, M11gluc, P½ <15 h as trichloroethanol.
Dicoumarol	AD 300 mg, small usage (largely replaced by warfarin), DAP, S, can cause microsomal inhibition.
Diethylpropion	PD 50 mg for 6–12 yrs, AD 75 mg, RL 0·59, I_{70} 30, MINOH, M11gluc, P½ 1·5–3 h.
Dihydrocodeine (tartrate)	PD 0·5 mg kg^{-1}, AD 60, RL 0·29, I_m 15, DAP.
Dimethicone	PD 100 mg day^{-1}, AD 400 mg, RL 4·4, I_{70} 224, low toxicity, non-biodegradable.
Dioctyl sodium sulphosuccinate	PD 125 mg, AD 500 mg, RL 0·15, I_m 7·5, little metabolism.
Diphen-hydramine	PD 200 mg for 6–12 yrs, AD 200 mg, RL 1·02, I_{70} 52·5, P½ 15–21 h (extensive first pass in liver).
Dithiepin	AD 150 mg, RL 0·29, I_{70} 15, see also diazepam.
Emepronium (bromide)	AD 600 mg, RL 0·29, I_{70} 15, P½ 2 h (excreted mainly unchanged).
Enheptine	Used in fish farming.
Ephedrine	PD 750 μg kg^{-1}, AD 60, RL 0·44 (also proprietary use), I_m 22·5, MINdM; OxD, M11gluc, P½ 3–11 h.
Erythromycin	PD 2·0 g day^{-1} for 20 kg child, AD 4·0 g, RL 2·2, I_{70} 112, M11OdM, non-biodegradable.
Ethynyl oestradiol	AD 50 μg, RL 0·003, I_{70} 0·14, see text.
Ethoheptazine	PD not recommended, AD 60, RL 0·73, I_{70} 37·5, extensive metabolism.
Ethylene oxide-propylene oxide	(inert binder)
Fenfluramine	PD 20 mg for 6–10 yrs, AD 120 mg, RL 0·15, I_{70} 7·5, M11glyc, DAP, P½ 11–30 h (forms hippuric acid).
Fenoprofen	PD not recommended, AD 2·4 g, RL 1·61, I_m 82, MIOH, M11gluc, S (little), P½ 2–3 h (phenobarbitone induces metabolism).
Ferrous fumarate	PD 140 mg for up to 6–12 yrs, AD 600 mg, RL 0·59, I_{70} 30.
Flucloxacillin	PD 500 mg up to 2 yrs, AD 2·0 g, RL 0·29, I_m 15, P½ ~50 min (very little metabolism).
Fludro-cortisone	AD 0·3 g, very small usage, P½ ~30 min, not recommended during pregnancy.
5-Fluorouracil	PD not recommended, cytotoxic agent used in small quantities, AD 15 mg kg^{-1} i.v., P½ < 3 h.
Flurazepam	PD not recommended, AD 30 mg (100 mg for anaesthesia), RL 0·15, I_{70} 7·5, MIOH (little, M11gluc; SO_4; N-Ac, P½ ~75 h.
Frangula (chrysophanic acid; emodin; frangutin)	RL 1·17, I_m 60 (contains <6% glucofrangulins ~0·5 tonne).
Frusemide	PD 3 mg kg^{-1}, AD 400 mg, RL 1·32, I_{70} 67, M11gluc, P½ 60 min (little metabolism).

Gentian (gentiopicrin, gentisic acid, gentisin)	RL 0·15, I_{70} 7·5 (each <1 tonne).
Glutethimide	PD 125 mg for 1–5 yrs, AD 500 mg, RL 0·59, I_{70} 30, MIOH, S (little), Pl 5–22 h.
Glyceryl guaicolate (guaiphenesin)	PD 75 mg for 3–12 months, AD 1·6 g, RL 1·02, I_{70} 52·5, MIOx, Pl 1 h.
Glycol salicylate	RL 0·29, I_{70} 15, MIIgluc, DAP, S (applied externally).
Hexetidine	RL 0·15, I_{70} 7·5 (external application only).
Hydrochlorothiazide	PD 2·5 mg kg^{-1}, AD 100 mg, RL 1·02, I_{70} 52·5, Pl 3 h (very little metabolism).
Hydrocortisone	PD 6–10 mg kg^{-1}, AD 50 mg, RL 0·15, I_{70} 7·5, MIOH, MIIgluc; SO_4, Pl 100 min (reduction of A-ring, 20-keto reduction).
Hydrotalcite	Inert.
Hyoscyamus (hyoscyamine, hyoscine)	PD 0·6 mg up to 10 yrs, AD 3·0 mg, RL 0·15, I_{70} 7·5, MIIgluc.
Ibuprofen	PD max of 500 mg day^{-1} if body weigh: <30 kg, AD 1·2 g, RL 9·5, I_{70} ~86, MIOH; deC; Nox, inherently biodegradable.
Imipramine	PD 30 mg for 6–10 yrs, AD 150 mg, RL 0·29, I_{70} 15, MIOH; NdM; Nox, MIIgluc, DAP (rats), Pl 3–4 h.
Indomethacin	AD 200 mg, RL 1·32, I_{70} 67, MIOdM, MIIgluc (also N-deacylation).
Inositol nicotinamide	PD not recommended, AD 1·5 g, RL 3·8, I_{70} 194 (see nicotinamide).
Ipecacuanha	PD not recommended, RL 1·17, I_{70} 60 (contains <2% alkaloids).
Isophosphamide	PD very limited use only, AD max 10 g, cytotoxic drug used in very small quantities, MIOH (hydrolyses slowly in water).
Karaya gum	PD up to 3·0 g day^{-1}, AD 24·0 g, RL 9·2, I_{70} ~70 (hydrolyses to form carbohydrates).
Ketoprofen	PD not determined, AD 200 mg, RL 0·44, I_{70} 22·5, MIOH, MIIgluc, Pl 1·5–2 h.
Levodopa	PD not recommended, AD 8·0 g, RL 0·59, I_{70} 30, MIOH; OM; OxD; deC, S, Pl of 3-O-methyldopa ~13 h.
Levonorgestrel	AD 0·03 g, very limited usage, see text.
Lymecycline	PD 36 mg kg^{-1}, AD 1·6 g, RL 0·15, I_{70} 7·5, DAP, little metabolism.
Lynoestrenol	AD 2·5 g, RL 0·09, very limited usage, see text.
Mebeverine	PD 7 yrs & over—adult dose, AD 400 mg, RL 0·29, I_{70} 15.
Mebhydrolin	PD up to 200 mg for 10 yrs, AD 300 mg, RL 0·15, I_{70} 7·5.
Mefenamic acid	PD 25 mg kg^{-1} day up to 6 months, AD 1·5 g, RL 1·17, I_{70} 60, MIOx, S (little), some conjugation.
Menthol	PD not for use up to 6 yrs, proprietary use, MIIgluc (fatal dose man 2·0 g), readily biodegradable.
Meprobamate	PD not recommended, AD 1·2 g, RL 2·6, I_{70} 134, MIIgluc; SO_4, DAP?, S? (to be avoided with nursing mothers), non-biodegradable.
Metformin HCl	AD 3·0 g, RL 0·44, I_{70} 22·5, Pl 3 h.
Methaqualone	AD 300 mg, RL 0·59, I_{70} 30, MIOH, MIIgluc, S (little) Pl 2–3 h, see text.
Methocarbamol	PD 15 mg kg^{-1} 6 h^{-1}, AD 8·0 g, RL 0·59, I_{70} 30, MIOdM; OH (rat), ~MIIgluc; SO_4, Pl 1–2 h.
Methotrexate	AD up to 22 g day^{-1}, cytotoxic agent, used in small amounts, see text.
Methyldopa	PD max 65 mg kg^{-1} day^{-1}, AD 3·0 g, RL 17·5, I_{70} 597, MIOM; deC, MIISO$_4$, non-biodegradable.
Methyl salicylate	See aspirin.
Metronidazole	PD 15 mg kg^{-1}, AD 2·4 g, RL 0·29, I_{70} 15, MIOx, MIIgluc, DAP, S, Pl 6 h, non-biodegradable under aerobic conditions, see text.
Misonidazole	Neoplastic agent used in very small quantities.
Morphine (morphinan)	See text.
Nalidixic acid	PD 60 mg kg^{-1}, AD 4·0 g, RL 1·02, I_{70} 52·5, MIOH, MIIgluc, Pl 90 min.
Naproxen	PD not recommended, AD 500 mg, RL 2·3, I_{70} 119, MIOdM, MIIgluc, DAP, S, non-biodegradable.
Neomycin	PD 50 mg kg^{-1} for 6–12 yrs, AD 3·0 g, RL 0·29, I_{70} 15, Pl 2 h (only 1–6% absorbed).
Nicotinamide	PD 20 mg kg^{-1}, AD 500 mg, RL 2·0, I_{70} 105, readily biodegradable, hydrolyses to nicotinic acid.
Nicotinic esters	AD 500 mg, RL 0·29, I_{70} 15, MIHyd, MIIgluc; cyst; gly, hydrolyses to nicotinate; 15–20 mg day^{-1} required by humans.
Nitrazepam	PD 5 mg kg^{-1}, AD 10 mg, RL 0·29, I_{70} 15, MIOH; Ac, MIIgluc, S, Pl 17–28 h.
Nitrofurantoin	PD 6 mg kg^{-1} day^{-1}, AD 360 mg, used in small quantities in human therapy—also used in fish farming DAP, S, Pl ~20 min, mutagen?
Nitrofurazone	AD 2·0 g, used in small quantities—also in fish farming, mutagen?
Nitrothiazole	Used in fish farming—mutagen?
Norethisterone	AD 400 mg, RL 0·04, I_{70} 2·2, see text.
Nystatin	PD 90 mg, AD 900 mg, RL 0·29, I_{70} 15, poorly absorbed.
Orciprenaline	PD 2·6 mg (inhaled), AD 60 mg, RL 0·15, I_{70} 7·5, MIOM, MIISO$_4$, Pl up to several h.
Orphenadrine	PD not recommended, AD 400 mg, RL 0·29, I_{70} 15, MIOxD, NdM; Nox, MIIgluc; SO_4, Pl 14–25 h.
Oxazepam	PD not recommended, AD 150 mg, RL 0·15, I_{70} 7·5, MIIgluc, Pl 4 h.
Oxprenolol	PD <1 mg kg^{-1}, AD 2·0 g, RL 1·46, I_{70} 75, MINdM, MIIgluc, Pl 80–120 min, extensive first-pass metabolism.
Oxyphenbutazone	PD 10 mg kg^{-1}, AD 400 mg, RL 0·29, I_{70} 15, MIOH, Pl 27–64 h.

Oxytetracycline	PD up to 30 mg for 2 yrs. RL 6·7. I_{70} 344. see tetracycline.
Paracetamol	PD up to 120 mg for 1 yr. AD 4·0 g. RL 84·1 (but 3·0 if proprietary use included). I_m 4295 (13374). MIOH: OM. M11gluc; SO_4: cys. readily biodegradable after acclimatization.
Penicillin(s) inc. penicillin V	See ampicillin and text.
Pentazocine	PD 50 mg for 6–12 yrs. AD 800 mg. RL 0·29. I_m 15. MIOx. M11gluc DAP. Pl 2–3 h.
Pentobarbitone	PD not recommended. AD 200 mg. RL 0·59. I_m 30. MIOH: Ox. Pl <50 h. some ring fission and further oxidation.
Phenacetin	PD not recommended. AD 3·0 g.. RL 0·44. I_m 22·5. M11gluc: SO_4: glut. Pl 1–2 h.
Phenbutrazate	PD not recommended. AD 60 mg. RL 1·02. I_{70} 52·5.
Phenethicillin (potassium)	PD 500 mg up to 10 yrs. AD 1·5 g. RL 0·15. I_{70} 7·5. DAP. Pl 30–50 min.
Phenformin	AD 200 mg. RL 0·15. I_{70} 7·5. MIOH. Pl <13 h. nearly half excreted unchanged. can cause microsomal inhibition.
Phenobarbitone	PD 60 mg for 12 yrs. AD 350 mg. RL 1·17 I_{70} 60. MIOH. M11SO_4. Pl 100 h. a major inducer of mixed function oxidase. Pl less in newborn.
Phenol-phthalein	AD 300 mg. RL 0·15. I_{70} 7·5. mainly excreted in faeces.
Phenylbutazone	PD 5–10 mg kg^{-1}. AD 400 mg. RL 1·61. I_{70} 82. MIOH. Pl 1–7 days. no conjugates.
Phenylephrine	PD up to 6 yr not recommended. AD 50 mg. proprietary composition.
Phenylpro-panolamine	PD 15 mg for 3–5 yrs. AD 150 mg. RL 0·29. I_{70} 15. 10% degrades to hippuric acid in humans. readily biodegradable after acclimatisation. in STW processes: also proprietary use.
Phenyramidol	Little used. can cause microsomal inhibition.
Phenytoin	PD 150 mg up to 3 yrs. AD 400 mg. RL 1·46. I_{70} 75. MIOH: Hyd. M11gluc. S. Pl 7–40 h (dose-dependent). subject to enterohepatic circulation.
Piperazine	PD 750–2000 mg up to 2–4 yrs depending on infection. AD 4·0 g. RL 0·15. I_{70} 7·5. excreted unchanged.
Poloxamers	Inert binder.
Prenylamine	PD not recommended. AD 300 mg. RL 0·15. I_{70} 7·5. Pl 7 h.
Primodone	PD 750 mg up to 3–5 yrs AD 2·0 g. RL 1·32. I_m 67. MIOH: Ox: deC. S. Pl 3–25 h.
Prochlor-perazine	PD 5 mg up to 1–5 yrs. AD 100 mg. RL 0·15. I_m 7·5 Pl 10–30 h. rats: ring fission. N-dealkylation.
Progesterone	AD 60 mg (intramuscular injection). small use. M11gluc. Pl few min. see text.
Promethazine	PD 10 mg up to 1 yr. AD 50 mg. RL 0·15. I_m 7·5. MIOx. M11gluc. S. Pl 4 h. high first-pass metabolism.
Propranolol	PD 1 mg kg^{-1}. AD 2·0 g. RL 1·61. I_{70} 82. MIOH: OxD: NdM. M11gluc: SO_4. DAP. 2. 2–4 h. high first-pass metabolism.
Pseudophedrine	PD 45 mg up to 1 yr. AD 180 mg. RL 1·17. I_{70} 60. MINdM. Pl 5–8 h. 98% excreted unchanged.
Pyridoxine HCl	AD 300 mg. RL 0·15. I_m 7·5. pyridoxic acid mainly excreted.
Quinal-barbitone	AD 250 mg (pre-med): 100 mg (hypnosis). RL 0·73. I_m 37·5. MIOH. Ox. DAP. S. Pl 29 h.
Quinidine	AD 3·0 g. RL 1·61. I_{70} 82. Pl 6–7 h. ~50% excreted unchanged.
Riboflavine	AD 10·0 mg. RL 0·15. I_m 7·5. DAP. S. rapidly metabolised.
Rutoside	AD 300 mg. RL 0·29. I_m 15.
Salbutamol	PD 0·8 mg (inhaled). AD 16 mg. RL 0·15. I_{70} 7·5. Pl 2–7 h. high first-pass metabolism.
Salicylamide	See aspirin.
Salicylic acid	See aspirin—external application. RL 0·29. I_{70} 15.
Sodium acetal	Inorganic hexitol complex—biodegradable.
Sodium chomoglycate	AD 120 mg (inhalation). RL 0·29. I_m 15. Pl 80 min. excreted unchanged—more in faeces than urine.
Sodium poly-hydroxl-aluminium monocarbonate-hexitol complex	RL 1·32. I_m 67.
Sodium valproate	PD 20 mg kg^{-1} up to 20 kg. AD 2·0 g. RL 0·29. I_m 15. MIOx. M11gluc. S. Pl 6–16 h.
Sparteine	AD 600 mg. small use. can cause microsomal inhibition.
Spironolactone	PD 3 mg kg^{-1}. AD 400 mg. RL 0·29. I_{70} 15. M11gluc. S (competitive inhibitor of aldosterone-thioacetyl group is readily removed forming canrenone. which is found in milk)
Sulpha-guanidine	AD 10·0 g. RL 0·29. I_m 15. M1Ac. Pl 2 h.
Sulpha-methizole	AD 1·2 g. RL 0·29. I_m 15. M1Ac (converted to sulphonamide).
Sulpha-methoxazole	PD 200 mg day^{-1} in 5 + 1 ratio with trimethoprim. AD 2·4 g. RL 7·2. I_m 366. M1Ac. non-biodegradable.
Sulpha-phenazole	AD 2·0 g. can cause microsomal inhibition.
Sulphasalazine	PD <150 mg kg^{-1}. <3.0 g for 20 kg child. AD 12·0 g. RL 1·8. I_m 90. MIOH. M11gluc. non-biodegradable (undergoes azo reduction in the human intestine).
Synthetic steroids	See text.
Tetracycline	PD 10–50 mg kg^{-1} day^{-1}. for 20 kg = 1·0 g/day (stains teeth). AD 3·0 g. RL 2·9. I_m 149. DAP. S. non-biodegradable.
Tetrahydro-furfuryl (salicylate)	RL 0·29. I_{70} 15. applied externally.
Theobromine	PD not given. AD 900 mg. RL 0·29. I_m 15. MINdM. readily biodegradable.

Theophylline	AD 700 mg, redily biodegradable.	Thyroxine	AD 0·3 mg, RL 0·15, I_m 7·5, DAP, PI 6–7 days (enterohepatic circulation—normally produced by thyroid gland).
Thiamine	AD 100 mg, RL 0·44, I_m 22·5, S.		
Thioridazine	PD 1 mg kg^{-1}, AD 600 mg, RL 0·15, I_m 7·5, MIOH, MIIgluc, DAP, PI 9–10 h (similar to chlorpromazine metabolism, may persist up to 1 yr).	Tolbutamide	PD not recommended, AD 2·0 g, RL 2·2, I_m 112, MIdeC, S, non-degradable (not recommended in pregnancy), also see text.
Thuryl salicylate	External application only, see aspirin.	Trimethoprim	AD 1·5 g, RL 1·46, I_m 75, MIOH; OdM; Ox, MIIgluc; SO_4, DAP, PI 11–17 h.
Thymoxamine	PD not recommended, AD 480 mg, RL 0·15, I_m 7·5, MIdAc.	Trimipramine	PD not normally given, AD 150 mg, RL 0·15, I_m 7·5 (extensive metabolism).

Appendix 1

Appendix 2

Appendix 3

Appendix 4

MATERIAL SAFETY DATA SHEET
Children's Advil® Infant Drops and Suspension

Whitehall-Robins
1407 Cummings Drive
Richmond, Virginia 23220
General Telephone No.: 804-257-3685
Emergency Telephone No.: 804-257-2000

Preparation Date: 08/29/1996
Revision Date: 08/29/1996

1. PRODUCT and COMPANY IDENTIFICATION

1.1 PRODUCT NAME:	Children's Advil® Infant Drops (WH-0694-0001), Infant Grape Drops (WH-0694-0002) and Grape Suspension (WH-0438-0126)
1.2 USE/SIZE:	A flavored liquid containing 4.00% ibuprofen, an analgesic, as the active ingredient.
1.3 PRODUCT NO.:	WH-0694-0001, WH-0694-0002, WH-0438-0126
1.4 CAS NO.:	Mixture (see CAS numbers below)
1.5 SYNONYMS:	—
1.6 TRADE NAMES:	Advil®

2. COMPOSITION/INFORMATION ON INGREDIENTS

NO.	INGREDIENT NAME	SYNONYMS	CAS NO.	% WEIGHT
1	Ibuprofen	p-Isobutylhydratropic Acid	15687-27-1	1-5
2	Sucrose	Sugar	57-50-1	50-60
3	Glycerin	Glycerol	56-81-5	5-10
4	Sorbitol Solution	Glucitol	50-70-4	5-10

3. HAZARD IDENTIFICATION

EMERGENCY OVERVIEW

A red or purple liquid with a fruity odor. The health hazards of this product have not yet been determined experimentally. However, this product is not expected to present any immediate health, physical or environmental concerns for emergency personnel.

3.1 POTENTIAL HEALTH EFFECTS

This product is a mixture for which no health effects data exist. The information provided below is a comprehensive overview of the effects of the product's hazardous ingredients. The health effects described primarily represent the hazards associated with ibuprofen, the product's active ingredient, which is present in the mixture at 1-5%.

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3.1.1 ACUTE EFFECTS:

INHALATION: Inhalation is not expected to be a significant route of occupational exposure to this product.

INGESTION: Accidental ingestion of small amounts is not expected to be toxic. Therapeutic doses of ibuprofen have been reported to cause the following symptoms in some patients: nausea, vomiting, stomach pain, and nervousness. Less common side effects include headache, dizziness, vision problems, ringing in the ears, bloating, loss of appetite, skin rashes, blood disorders, bronchospasms, and abnormal heart rhythms. In rare cases, oral treatment has caused severe anemia, acute hepatitis, and acute renal failure.

SKIN: May cause mild skin irritation. Repeated or prolonged exposure to ibuprofen may cause allergic skin reactions.

EYE: Direct eye contact with the liquid may cause irritation with redness and tearing.

3.1.2 TARGET ORGAN EFFECTS (SUBCHRONIC/CHRONIC):

Chronic ingestion may affect the kidney, liver, and gastrointestinal system. In some cases, prolonged oral treatment with ibuprofen has caused gastrointestinal bleeding and ulceration, hepatitis, jaundice, and kidney damage.

3.1.3 CARCINOGENIC EFFECTS:

No human or animal carcinogenicity data are available for the product or its hazardous ingredients.

3.1.4 REPRODUCTIVE/TERATOGENIC EFFECTS:

Ingestion of ibuprofen by women has been associated with menstrual changes and disorders. In addition, in animal studies this compound has been found to cause fetotoxicity, decreased litter size, and male and female reproductive effects. Glycerin has been found to affect fertility in male test animals.

3.2 CARCINOGENICITY STATUS:

The product and its ingredients are not listed as carcinogenic by NTP, IARC, or OSHA.

3.3 MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE:

Persons with active ulcers, chronic bleeding of the stomach or intestine, impaired kidney function, high blood pressure, or heart problems are at increased risk to the toxic effects of ibuprofen. This compound also presents a greater risk to pregnant women.

4. FIRST AID MEASURES

INHALATION: No specific treatment is necessary since this material is not likely to be hazardous by inhalation. However, if cough or other symptoms develop, remove to fresh air and get medical attention.

INGESTION: If subject is conscious, give 1-2 glasses of water to dilute the product. Call a physician immediately. Induce vomiting only under the instructions of medical personnel.

Never give anything by mouth to an unconscious person. If the victim is unconscious, keep airway open and lay the victim on his or her side with the head lower than the body. Get immediate medical attention.

SKIN: Wash skin with soap and flush thoroughly with plenty of water. Obtain medical attention if

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irritation develops, or other symptoms occur. Wash clothing before reuse.

EYE: First check the victim for contact lenses and remove if present. Immediately flush eyes with plenty of water or normal saline for at least 15 minutes while holding eyelids open. If symptoms such as redness or irritation develop or persist, get immediate medical attention. Do not put any medication in the victim's eyes unless instructed by a physician.

5. FIRE FIGHTING MEASURES

5.1 FLASH POINT: No data available. METHOD: —

5.2 AUTOIGNITION TEMPERATURE: No data available.

5.3 FLAMMABILITY LIMITS:
LOWER LIMIT: No data available.
UPPER LIMIT: No data available.

5.4 UNUSUAL FIRE AND EXPLOSION HAZARDS:
Non-flammable, non-combustible liquid. May burn and add fuel to surrounding fire at elevated temperatures.

5.5 COMMON EXTINGUISHING METHODS:
This product is not flammable. For fires involving its packaging materials, use an agent which is appropriate for combustibles and surrounding class(es) of fire.

5.6 FIRE FIGHTING PROCEDURES:
Keep unnecessary people away; isolate hazard area and deny entry. Remove containers exposed to fire if possible, otherwise cool them from the side with water spray. Emergency equipment including self-contained breathing apparatus (SCBA) and full fire fighting turnout gear should be worn by fire fighters.

6. ACCIDENTAL RELEASE MEASURES

Follow facility-specific procedures for spill response. Isolate the spill area. When cleaning spills, wear appropriate personal protective equipment including splash-proof safety goggles and chemical resistant gloves (See Section 8).

Confine and contain small spills using inert material (e.g., paper towels, spill control pillows, absorbent particulate). In the event of a large spill, contain by diking with dry sand, sorbent booms or other absorbent material. Prevent runoff into sewers, storm drains, surface waters, and soil.

Dispose of all material in accordance with local, state and federal regulations.

7. HANDLING AND STORAGE

Keep containers closed when not in use. Store in a cool, dry, well-ventilated area, away from incompatible materials (see Section 10.)

Continued on Page 4

8.0 EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1 EXPOSURE GUIDELINES:
Neither the Occupational Safety and Health Administration (OSHA) nor the American Conference of Governmental Industrial Hygienists (ACGIH) have developed exposure limits for this product. Exposure limits exist for the following ingredients:

INGREDIENT NAME	OSHA PEL/STEL	ACGIH TLV/STEL
Sucrose	5 mg/m^3 (PEL, respirable fraction) 15 mg/m^3 (PEL, total dust)	10 mg/m^3 (TLV, total dust)
Glycerin	15 mg/m^3 (TWA, total dust); 5 mg/m^3 (TWA, respirable fraction).	10 mg/m^3 (TWA, total dust).

8.2 VENTILATION:
No special ventilation requirements. Good room ventilation should be sufficient to control airborne levels. If operations generate vapor or mist, use adequate general or local ventilation to keep airborne concentrations below exposure limits.

8.3 RESPIRATORY PROTECTION:
A respirator is not required under normal conditions of use if exposure limits are kept below those listed in Section 8.1.

8.4 PROTECTIVE GLOVES:
Wear impervious gloves to prevent skin contact. Selection of appropriate protective gloves for a particular use depends on the properties of the compound and the specific conditions of use, including the level of dexterity and durability needed, and the severity and duration of chemical contact.

8.5 EYE PROTECTION:
Safety glasses are not necessary under normal conditions of use. Care should be taken, however, to avoid accidental exposure since some of the hazardous ingredients in this product can cause mild irritation.

8.6 OTHER:
Depending on the operation, labcoat, apron or other impermeable clothing may be appropriate.

9. PHYSICAL AND CHEMICAL PROPERTIES

9.1 APPEARANCE AND ODOR: A red or purple liquid with a fruity odor.

9.2 MELTING POINT: Not applicable.

9.3 BOILING POINT: No data available.

9.4 SPECIFIC GRAVITY/DENSITY: 1.23-1.24 @ 25°C

9.5 VAPOR DENSITY: No data available.

9.6 VAPOR PRESSURE: No data available.

9.7 SOLUBILITY:
- WATER: Soluble.
- OTHER SOLVENTS: No data available.

9.8 DECOMPOSITION TEMPERATURE: No data available.

9.9 VISCOSITY: 1687-2400 centipoise @ 25°C

9.10 pH: 4.13-4.23 @ 25°C

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10. STABILITY AND REACTIVITY

10.1 STABILITY:

Product is stable under normal conditions of use. Hazardous polymerization has not been reported to occur under normal temperatures and pressures. Product will not react with water.

10.2 HAZARDOUS DECOMPOSITION PRODUCTS:

Not determined for product. Hazardous decomposition products of components include toxic fumes of carbon dioxide and carbon monoxide.

10.3 CONDITIONS TO AVOID:

Avoid heat, high temperatures, pressure, or other conditions that might result in a hazardous situation.

10.4 MATERIALS AND SUBSTANCES TO AVOID (INCOMPATIBILITY):

There are no known materials which are incompatible with this product. However, the product's hazardous ingredients are incompatible with strong oxidizing agents and strong bases.

11. TOXICOLOGICAL INFORMATION

This product is a mixture for which no toxicological data exists. When available, toxicological data for the product's components are provided below. Refer to Section 3.2 for health effects information.

11.1 ACUTE DATA:

INHALATION:

Glycerin — LC_{50} > 570 mg/m^3/1 hour (rat); > 4 mg/L/6 hour (rat)

INGESTION:

Ibuprofen — TDLo = 8 mg/kg (woman: headaches, increased body temperature); 132 mg/kg (woman: blood effects); 120 mg/kg (man: eye effects, increased body temperature); 429 mg/kg (man: kidney effects, respiratory obstruction).
LDLo = 171 mg/kg (man: anesthesia).
LD_{50} = 636 mg/kg (rat); 740 mg/kg (mouse); 495 mg/kg (guinea pig).

Sucrose — LD_{50} = 29,700 mg/kg (rat).

Glycerin — TDLo = 1428 mg/kg (human: headaches, nausea, vomiting).
LD_{50} = 12600 mg/kg (rat); 4090 mg/kg (mouse); 2700 mg/kg (rabbit); 7750 mg/kg (guinea pig).

Sorbitol Solution — TDLo = 1700 mg/kg (woman: hypermotility, diarrhea)
LD_{50} = 15900 mg/kg (rat); 17800 mg/kg (mouse)

EYES:

Glycerin — A 126 mg/kg dose applied to the rabbit eye caused mild irritation. When injected into the rabbit eye, caused inflammation and edema of the cornea.

SKIN:

Glycerin — LD_{50} > 10 gm/kg (rabbit). A 500 mg dose applied to the skin of rabbits for 24 hours caused mild irritation.

11.2 TARGET ORGAN EFFECTS DATA (SUBCHRONIC/CHRONIC)

Ibuprofen — In multidose studies with rats, oral doses of 1200-1300 mg/kg caused changes in liver/thymus weight and hemorrhage; 32760 mg/kg over 26 weeks caused ulceration/bleeding of the intestine, kidney changes and anemia; 2160 mg/kg given orally over 4 days caused peritonitis and kidney changes. In dogs, 480 mg/kg (oral) caused ulceration of the stomach.

Sorbitol Solution — When fed to rats in the diet (20%) for 4 weeks, caused abnormalities in urinary function (reduced pH, increased levels of organic acids).

11.3 CARCINOGENIC EFFECTS DATA:

Continued on Page 6

No data available.

11.4 MUTAGENIC EFFECTS DATA:

Ibuprofen	Cytogenetic analysis (mouse, oral).
Sucrose	Microsomal assay (Salmonella typhimurium); DNA repair (Saccharomyces cerevisiae); cytogenetic analysis (hamster, lung and ovary).
Glycerin	DNA inhibition (human, lymphocyte); cytogenetic analysis (rats, in vivo).
Sorbitol Solution	Cytogenetic analysis (hamster, ovary).

11.5 REPRODUCTIVE/TERATOGENIC EFFECTS DATA:

Ibuprofen	In women, an oral dose of 8 mg/kg caused menstrual cycle changes. In rats, 600-840 mg/kg administered orally during pregnancy caused fetotoxicity, pre-implantation mortality, and effects on newborn growth and litter size. Similar effects were seen in mice following oral exposure to 420-1260 mg/kg.
Glycerin	Oral administration to male rats (100 mg/kg) prior to mating caused post-implantation mortality. Intratesticular injection (119-1600 mg/kg) caused paternal effects (spermatogenesis) and effects on fertility.

12. ECOLOGICAL INFORMATION

12.1 ECOTOXICOLOGICAL INFORMATION:
No data available for the product or its hazardous ingredients.

12.2 CHEMICAL FATE INFORMATION:
No data available for the product of the product's ingredients.

13. DISPOSAL CONSIDERATIONS

Dispose of in accordance will all applicable Federal, state, and local regulations (see Section 15). Under 40 CFR 261, it is the responsibility of the product user to determine at the time of disposal whether a material containing the product or derived from the product should be classified as a hazardous waste.

14. TRANSPORT INFORMATION

14.1 U.S. DEPARTMENT OF TRANSPORTATION (DOT):
This product is not regulated by DOT.

14.2 INTERNATIONAL TRANSPORTATION REGULATIONS:
This product is not regulated under international transportation regulations.

15. REGULATORY INFORMATION

15.1 FEDERAL REGULATIONS:
All of the hazardous ingredients of this product are listed, or are exempt from listing, on the EPA TSCA Inventory. In addition, glycerin is listed in Section 111 of the Clean Air Act (Volatile Organic Compounds).

15.2 STATE REGULATIONS:
This product is not regulated by any state government; however, specific state regulations exist for the following ingredients:

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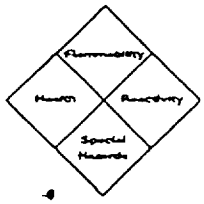
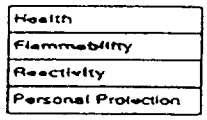
Sucrose	Massachusetts Substance List
Glycerin	Pennsylvania Hazardous Substance List; Massachusetts Substance List (glycerin mist).

16. OTHER INFORMATION

16.1 HAZARD RATINGS*



NFPA:
Health- 1
Flammability- 0
Reactivity- 0
Special Hazards- None



HMIS:
Health- 1*
Flammability- 0
Reactivity- 0
Personal Protection- See Section 8

*A hazard rating has not been developed by NFPA or HMIS for this product. The hazard ratings provided in this MSDS are based on NFPA and HMIS hazard evaluation criteria, as well as professional judgement. This information is intended solely for the use of individuals trained in these hazard rating systems.

16.2 PREPARATION AND REVISION INFORMATION

None.

The information provided in this MSDS is based on sources believed to be accurate. However, Whitehall-Robins assumes no responsibility for the accuracy, completeness or suitability of this information. The product user is responsible to determine the suitability of this information for their particular purposes.