CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-683

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

DEC 2 0 1996

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

ALESSE®

Levonorgestrel/Ethinyl Estradiol (100 μg/20μg) tablets

NDA 20-683

Division of Reproductive and Urologic Drug Products

(HFD-580)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

FINDING OF NO SIGNIFICANT IMPACT

ALESSE®

Levonorgestrel/Ethinyl Estradiol (100 µg/20µg) tablets

NDA 20-683

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, ALESSE®, Wyeth-Ayerst Laboratories has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) in the Tier 0 format which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Levonorgestrel and Ethinyl Estradiol are chemically synthesized drugs which are administered as tablets containing 100 µg/20µg, respectively for the prevention of pregnancy in women who elect to use this form of contraception. The drug substance is manufactured by
The drug product is manufactured by Ayerst-Wyeth Pharmaceuticals Inc. in Puerto Rico. The finished drug product will be used in hospitals, clinical settings, and consumer dwellings 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. Returned or out of specification drug substance and rejected or returned drug product will be disposed in the firm's on-site permitted incinerator. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of 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. 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.

2/2/96
Date

Prepared by
Robert H. Seevers, Ph.D.
Chemist
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research

2/4/96
Date

Concurred
Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research

Date

Concurred
Nancy Sager
Acting Supervisor/Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

ENVIRONMENTAL ASSESSMENT REPORT (EA)

This Environmental Assessment is being submitted in accordance with the requirements of 21 CFR 25.31a to accompany Wyeth-Ayerst Laboratories New Drug Application (NDA) for Alesse® Tablets.

1. DATE

March 18, 1996

2. NAME OF APPLICANT

Wyeth-Ayerst Laboratories

3. ADDRESS

P.O. Box 8299
Philadelphia, PA 19101-1245

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Requested Approval

This Environmental Assessment (EA) is part of the New Drug Application (No. 20-683) for levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets. The levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets are marketed in both a 21-day and a 28-day regimen. For the 28-day regimen, 21 active tablets are packaged together with 7 placebo tablets. The 21-day and the 28-day regimes are available in mini-packs and the 21-day regime is also available in blisters.

4.2 Need for Action

Levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets are an oral contraceptive which will provide a new choice for contraceptive therapy. This product will provide contraceptive therapy with the lowest doses of levonorgestrel and ethinyl estradiol available in the United States.

4.3 Production Locations

Drug Substance

Levonorgestrel and ethinyl estradiol are synthesized by

The bulk levonorgestrel and ethinyl estradiol will be manufactured in the

chemical production facility located in The bulk levonorgestrel and ethinyl estradiol are micronized in the production facility located in The foreign drug manufacturer has submitted an environmental compliance statement which is included as Appendix B.

Drug Product

Formulation, compression, coating and packaging of the final drug product will take place at:

Ayerst-Wyeth Pharmaceuticals Inc.
State Road # 3, Km 142.1
Guayama, Puerto Rico 00784

The Ayerst-Wyeth (AWPI) facility is located in the southern region of the island of Puerto Rico, approximately 3 kilometers north of the Caribbean Sea and 2 kilometers southwest of Guayama along the north side of State Road No. 3. This region is characteristically warmer and drier than other parts of the island due to the influence of the easterly tradewinds and the proximity of the Cordillera Central to the north. According to the USDA (1977), there is no dry or wet season; however, the period between December through April is drier than the remainder of the year. Heavier rains often occur in May and October.

The area surrounding the plant is typical of a rural industrial setting consisting of lands occupied by sugar c me fields and other manufacturing operations. The plant is bordered on the south by sugar cane fields, on the west by another pharmaceutical facility and a parking lot, on the east by an electrical substation, and on the north by another pharmaceutical company owned by . There are no private residences located near the facility. The facility is located on a 94 acre site, with one main manufacturing building occupying 700,000 square feet.

All statements made in this report regarding environmental controls, waste management, worker protection, manufacturing processes, use of resources and energy, and training and emergency procedures refer to drug product formulation and packaging at the Ayerst-Wyeth Pharmaceuticals inc. (AWPI) facility. AWPI's Environmental Compliance Statement is included in Appendix C.

4.4 Locations of Use

As a prescription oral contraceptive therapy, the drug product will be distributed throughout the United States for oral administration. Locations of use include hospitals, clinics and the homes of patients.

4.5 Disposal Sites

The amount of drug product that is eliminated or excreted will enter the wastewater stream. Rejected raw material will be shipped back to the supplier.

Returned, recalled, or expired goods will be disposed of in an appropriate manner according to established procedures by Wyeth-Ayerst. The goods may be collected, processed and incinerated at the following location.

Wyeth-Ayerst Laboratories
31 Morehall Road
Frazer, PA 19355

This WAL facility is located in a hilly, light industrial/commercial, suburban area with a temperate climate. The Wyeth-Ayerst facility operates under the following permits:

Permit Name	Permit Number	Issue Date	Expiration Date
Solid Waste incinerator Permit (PADEP)	400516	12/12/1984	7/4/1997
Municipal Waste incinerator Permit (PADEP)	15-301-071	7/10/1991	7/30/1998

Incineration may also take place at the following location:

owns and operates a commercial facility for the storage and treatment (incineration) of hazardous and nonhazardous waste and materials. The facility is located on the site of an abandoned oil refinery, east of , in The surrounding area is relatively flat, fairly rural and has a temperate climate. The nearest residential neighbor is approximately 0.5 mile west of the facility. Various industrial facilities are located north of the facility. Natural forested areas and swampland border the south and east sides of the facility. The main gate of the facility is approximately 5000 feet south of the intersection of a tributary of , runs through the eastern portion of the site. A line runs through the property, approximately bisecting it into a north section and a south section. facility operates under the following permits:

Permit Name	Permit Number	Issue Date	Expiration Date
RCRA Part B Permit: Arkansas Department of Pollution Control and Ecology Hazardous	10-H	5/26/1988	7/2/1998

Waste Management Permit.			
Permit Modification Approval Letter	10-HR-1	2/19/1992	7/2/1998
USEPA HSWA Hazardous Waste Permit	ARD069748192	7/10/1988	7/2/1998
Arkansas Department of Pollution Control and Ecology -- Air Permit	1009-A	8/15/1990	Permit has no exp. Date
Arkansas Department of Pollution Control and Ecology -- Water Permit Renewal submitted 5/2/95, new permit pending	NPDES AR0037800	10/28/1990	10/31/1995

Incineration may also take place at the following location:

is a major full service hazardous waste management company engaged in the treatment and destruction of hazardous and toxic wastes. This incineration facility is located on a 500 acre site in a semi-rural area of approximately one mile north of The facility is located in an area with relatively flat topography and a temperate climate. Lands to the north, east and west are used for farming. There is a 0.5 mile buffer distance from the property lines to the operations areas. is situated along the western border of the facility. discharges to the facility operates under the following permits:

Permit Name	Permit Number	Issue Date	Expiration Date
RCRA Part B NJDEP Hazardous Waste Facility Permit; Renewal application submitted 3/1993, new permit pending.	0809DIHP01	3/31/1989	3/31/1994
US EPA HSWA Permit; Renewal application submitted 3/1993, new permit pending.	NJD 053 288 239	3/31/1989	3/31/1994

Nonhazardous waste may be incinerated at the following location:

operates a waste-to-energy plant in that accepts and incinerates nonhazardous pharmaceutical wastes. The incineration facility is located on a 15 acre site in a densely populated urban area . The surrounding area has a relatively flat topography and a temperate climate. The surrounding land-use is 50% industrial and 50% residential. There are no surface waters located within a one mile radius of the site. facility operates under the following permit:

Permit Name	Permit Number	Issue Date	Expiration Date
NYSDEC Solid Waste Permit	1-2820-01127/0 0010-0	7/24/95	7/23/2000
NYSDEC Air Permit	1-2820-01727/0 0001-0	8/7/95	8/6/96

Rejected, outdated or returned goods may also be collected and processed at:

for subsequent incineration at:

owns and operates an infectious and pharmaceutical waste incineration facility approximately 3 miles outside of
The facility is located in a rural area with a temperate climate. Approximately 95 % of the surrounding land use is agricultural, the remaining is industrial. The nearest residences and a college are located approximately 1-1.5 miles west of the facility. is located approximately 500 feet east-southeast of the site. : feeds the which is used by the as a drinking water source. This facility operates under the following permits.

Permit Name	Permit Number	Issue Date	Expiration Date
NC EMC Solid Waste Permit	01-02-I	12/31/91	Review 12/1996
Landfill Permit	13-04	8/25/1995	8/25/1996
NC EMC Air Quality Permit	5896R4	7/12/91	7/1/1996
NC Water Authority Waste Water Permit	0030	12/20/91	6/30/1996

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THIS PROPOSED ACTION

5.1 Levonorgestrel

Chemical Name (-)-13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one

United States Adopted Name (USAN) levonorgestrel

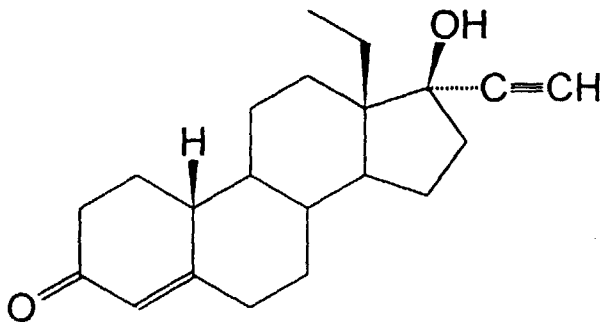
Brand/Proprietary Name Alesse

Chemical Abstracts Service (CAS) Registry No. 797-63-7

Molecular Weight 312.45

Molecular Formula $C_{21}H_{28}O_2$

Structural Formula



Physical Description

White or practically white powder

Additives None

Impurities

Material Safety Data Sheet Provided in Appendix A

5.2 Ethinyl Estradiol

Chemical Name 19, norpregna- 1,3,-5(10)-trien-20-yne-3,17-diol, (17α)
or 19-nor-17α-pregna- 1,3,-5(10)-trien-20-yne-3, 1 7-diol

United States Adopted Name (USAN) ethinyl estradiol

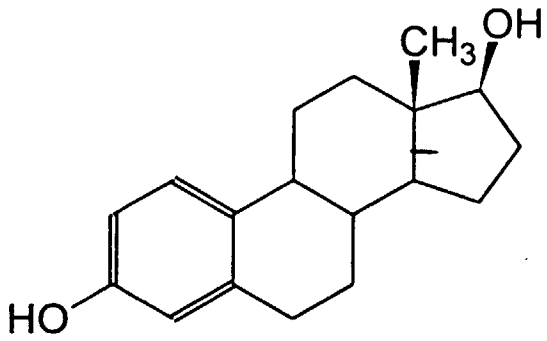
Brand/Proprietary Name Alesse

Chemical Abstract Service (CAS) Registry No. 57-63-6

Molecular Weight 296.41

Molecular Formula $C_{20}H_{24}O_2$

Structural Formula



Physical Description

White to creamy white crystalline powder

Additives None

Impurities

Material Safety Data Sheet Provided in Appendix A

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 Substances Expected To Be Emitted During Drug Substance Production and Controls Exercised

The drug substance manufacturer, identified specifically in paragraph 4.3, is located in The synthesis of levonorgestrel and ethinyl estradiol complies with government environmental laws. Whenever possible, the material, byproducts, and/or emissions from manufacturing are reused/regenerated/recycled back into the process. Where reuse/recycling is not feasible, the materials in question are disposed of or emitted in accordance with appropriate laws and regulations. A Certificate of Environmental Compliance for the foreign manufacturer is included in Appendix B.

6.2 Substances Expected To Be Emitted During Drug Product Production and Controls Exercised

The drug product manufacturer, identified specifically in paragraph 4.3, is located in The process for tablet manufacturing is a batch operation in the following sequence: (l) formulation (2) compression (3) coating, and (4) packaging. Manufacturing controls and permit information for the AWPI facility are described below.

Aqueous Waste

All process related aqueous wastes pass through an on-site complete activated sludge treatment plant with ozonation, treating an average daily flow of 140,000 gpd. The Waste Water Treatment Plant (WWTP) consistently achieves 98 % and greater Biochemical Oxygen Demand (BOD) and Chemical Oxygen Demand (COD) removal.

Addition of this process is not expected to cause an exceedance of the permitted average daily flow of 236,030 gpd for this discharge point.

The AWPI facility discharges treated waste to under NPDES Permit No. PR0024- 24 (expiration 11/30/95, renewal submitted 5/27/95). The EPA inspects the AWPI WWTP annually (at a minimum). This facility is in compliance with its permit which incorporates the effluent guidelines for pharmaceutical mixing/compounding and formulation (40 CFR 439).

Residual levonorgestrel and ethinyl estradiol may enter the on-site wastewater treatment system as a result of equipment wash downs. Calculation of drug substance flow to the wastewater treatment plant and the expected removal efficiency is located in Appendix I. Any levonorgestrel and ethinyl estradiol entering the treatment plant will be subjected to biological, chemical and photochemical degradation processes before being discharged.

Air Emission

Dust generated during formulation and packaging is removed via dust collection systems. A 99.99 % removal of particulate matter is achieved prior to discharge to the atmosphere. The Environmental Quality Board in Santurce, PR has granted Air Permit #PFE-LC-30-0593-0626-I-II-0 (expiration 2/27/2000) to operate this emission source. Periodic inspections are conducted by the local authority to ensure all control devices are operated in accordance with the permit parameters. Personal safety equipment is worn by operators when handling the drug substances.

Solid Wastes

Solid wastes generated during the manufacture and packaging of this product consist of the following: product rejects and damaged product QA/QC samples and related wastes; exhausted HEPA filters used to purify room air and exhaust. These wastes will be collected and incinerated at one of the following locations.

has operated a medical and nonhazardous incineration facility on a six acre site in The surrounding area is occupied by commercial and industrial facilities. There is some unoccupied land in the vicinity of the site that serves as a buffer. The nearest surface water is the

located approximately 350 meters from the site.
operates under the following permits:

Permit Name	Permit Number	Issue Date	Expiration Date
Environmental Quality Board Nonhazardous Facility Operating License			—
a. Incineration Operating License	SI-93-0002	1/18/1993	1/19/1997
b. Recollection Operating License	SR-0057	1/25/1995	1/19/1998
EQB PEE Air Emission Permit (New Title V Operating Permit pending)	PFE-LC-16-0393-0305-III-0	6/25/1993	6/25/1995
ARPE Use Permit	86-20-F-305-OPC	6/1/1987	Permit has no exp. date

operates a nonhazardous and biomedical waste incineration facility in an industrial park in The facility is located in an urban area. Approximately 70% of the surrounding land use is mixed commercial, light industrial and residential. The remaining 30% is undeveloped or unoccupied. Vacant lots are situated to the north and east. A machine maintenance shop is located to the south and an access road to the industrial park is located to the west. The nearest residential area is approximately 0.5 kilometers to the south. The nearest surface water is a river located approximately 0.5 kilometers to the east of the property. The river is not used as a source of drinking or irrigation water.

Permit Name	Permit Number	Issue Date	Expiration Date
Environmental Quality Board Nonhazardous Facility Operating License			
a. Incineration Operating License	SI-93-0007	9/9/1993	9/9/1996
b. Transportation Operating License	SR-0028	1/25/1995	1/19/1998
EQB UIC Permit (Renewal submitted 6/30/95, new permit pending)	UIC-89-0019	8/30/93	8/29/95
EQB PEE Air Emission Permit	PFE-LC-13-0994-1145-II-0	7/18/1994	3/31/1996
ARPE Use Permit	94-46-C-163-KPU	4/29/1994	Permit has no exp. date

Non-contaminated, damaged, empty packaging components will be disposed of as solid wastes at the landfill.

Pollution Prevention

AWPI has in place a pollution prevention program. The participants are actively involved in optimizing production processes, minimizing waste generation and improving waste management practices for new products such as levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets. No solvents are used in the production of levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets.

Addition of this process to the AWPI facility is not reasonably expected to adversely impact the environment.

6.3 Citation of and Statement of Compliance with Applicable Requirements

6.3.1 Drug Substance Manufacturer

The facility located in manufactures levonorgestrel and ethinyl estradiol in accordance with all applicable environmental programs. Letters from the appropriate government authority certifying that the facility is in full compliance with the environmental laws of is provided in Appendix B.

6.3.2 Drug Product Manufacturer

The pollution control devices and waste disposal methods described in paragraph 6.2 serve to minimize environmental emissions from the production of levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets at AWPI. The plant complies with the following federal, state and local regulations.

Clean Air Act, as Amended

The AWPI facility operates under air Permit #PFE-LC-30-0593-0626-I-II-0 (expiration 2/27/2000). Addition of this process is not reasonably expected to affect the compliance status of this facility.

Federal Water Pollution Control Act of 1977, the Clean Water Act and the Water Quality Act of 1987 as amended

The AWPI facility is in compliance with NPDES permit No. PR0024724 (expiration 11/30/95, renewal submitted 5/27/95, new permit pending) and with the effluent guidelines for pharmaceutical mixing/compounding and formulation (40 CFR 439), as described in paragraph 6.2. Addition of this process is not reasonably expected to affect the compliance status of this facility.

The AWPI facility uses the waters generated from cooling tower blowdown and boiler blowdown to irrigate the grounds, under permit No. C-AG-84-0016 (expiration 8/31/96). The permit limit is 47,100 gallons per day with a condition of non-irrigation, when precipitation has saturated the ground, making irrigation ineffective.

Resource Conservation and Recovery Act (RCRA) of 1976 and Amendments of 1984

The facility is in compliance with all federal and state regulations governing hazardous waste generators.

Nonhazardous solid waste generated from manufacturing and packaging this product will be disposed of at fully permitted landfills. All rejected waste is destroyed at a permitted incineration facility. Any hazardous waste generated from this process will be destroyed at a RCRA-permitted disposal facility in accordance with all applicable regulations.

Wastewater treatment sludge is subjected to aerobic digestion and dewatering (via sludge drying beds) prior to landfill disposal. Although the EPA's Standards for the Disposal of Sewage Sludge" (40 CFR 503) do not apply to Industrial Sludges, the AWPI facility sludge has been examined and determined to be in compliance with the "Ceiling limits" for the constituents addressed by this recently promulgated regulation.

Workplace

Chemicals in the workplace are stored, handled, and managed in accordance with Good Manufacturing Practice (GMP) and OSHA standards. Ventilation, air filtration, personal protection equipment, and industrial hygiene monitoring are employed to ensure containment of chemicals and minimal exposure of workers and the workplace to chemicals. GMP regulations are followed for all equipment and operating procedures.

Compliance Statement

A compliance statement for the AWPI facility is included in Appendix C.

6.4 Effect of Approval on Compliance with Current Emission Requirements

The manufacture of levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets will not create any adverse environmental effects. The addition of this process to the AWPI facility will not cause the facility to exceed permit limits for solid waste, wastewater or air. No endangered or threatened species will be affected and natural resources in critically short supply will not be depleted.

6.5 Concentration of Levonorgestrel and Ethinyl Estradiol in the Environment from Product Use and Disposal

Levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets will be distributed to locations throughout the United States for oral administration. The amount that is eliminated or excreted will enter the wastewater stream. For purposes of this Environmental Assessment, the parent molecules are used to evaluate environmental release mechanisms and estimated environmental concentrations.

6.5.1 Expected Introduction Concentration (EIC) From Use

6.5.1.a Levonorgestrel

The EIC for the aquatic compartment, assuming all Levonorgestrel is used, is evenly distributed throughout the United States per day and without metabolism or depletion mechanisms taken into account is stated below. Calculations for the EIC appear in Appendix J.

EIC Aquatic = 2.34×10^{-6} ppm

The EIC for the terrestrial compartment is estimated to be zero because any small fraction of Levonorgestrel that might be adsorbed onto the sludge of the wastewater treatment plant will be disposed of in a landfill.

The EIC for the atmospheric compartment is estimated to be zero since Levonorgestrel is a crystalline solid at room temperature and is expected to have a negligible vapor pressure.

6.5.1.b Ethinyl Estradiol

The EIC for the aquatic compartment, assuming all Ethinyl Estradiol is used, is evenly distributed throughout the United States per day and without metabolism or depletion mechanisms taken into account is stated below. Calculations for the EIC appear in Appendix J.

EIC Aquatic = 4.67×10^{-7} ppm

The EIC for the terrestrial compartment is estimated to be zero because any small fraction of Ethinyl Estradiol that might be adsorbed onto the sludge of the wastewater treatment plant will be disposed of in a landfill.

The EIC for the atmospheric compartment is estimated to be zero since Ethinyl Estradiol is a crystalline solid at room temperature and is expected to have a negligible vapor pressure.

6.5.2 Expected Introduction Concentration (EIC) From Disposal

6.5.2.a Levonorgestrel

The EIC from dispose is zero since all rejected product and pharmaceutical waste containing Levonorgestrel is disposed of via incineration.

6.5.2.b Ethinyl Estradiol

The EIC from disposal is zero since all rejected product and pharmaceutical waste containing ethinyl estradiol is disposed of via incineration.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

7.1 Identification of Substances of interest

7.1.1. Levonorgestrel

The pharmacokinetics of Levonorgestrel has been investigated in mice, rats, rabbits, dogs, monkeys and humans. In all species, absorption was rapid with peak plasma concentrations at one to two hours, except in the monkey which was nine hours. The amount of Levonorgestrel excreted in the urine and feces varies among the test species. These metabolites are similar in structure and are the result of

The only substance that will enter or exit the environment is levonorgestrel. Structurally related substances (SRSs) such as metabolites and degradants exist in minute quantities, substantially below 10% of the dose, and therefore will not be addressed in detail.

7.1.2 Ethinyl Estradiol

The pharmacokinetics of ethinyl estradiol has been investigated in rats, dogs and monkeys. In general, ethinyl estradiol has been found to be rapidly absorbed but highly metabolized in all species investigated. Oxidation at various positions on each ring followed by glucuronidation or sulfation has led to numerous metabolites.

The only substance that will enter or exit the environment is ethinyl estradiol. Structurally related substances (SRSs) such as metabolites and degradants exist in minute quantities, substantially below 10% of the dose, and therefore will not be addressed in detail.

7.2 Physical/Chemical Characterization

7.2.a Levonorgestrel

A data summary table for Levonorgestrel is contained in Appendix E.

7.2.a.1 Water Solubility < 0.1%

7.2.a.2 Dissociation Constant Levonorgestrel does not have a dissociation constant.

7.2.a.3 Octanol/Water Partition Coefficient Approximately 8.

7.2.a.4 Vapor Pressure Levonorgestrel is a crystalline solid at room temperature. A vapor pressure test was not conducted since the results would be negligible.

7.2.b Ethinyl Estradiol

A data summary table for ethinyl estradiol is contained in Appendix E.

7.2.b.1 Water Solubility Ethinyl estradiol is practically insoluble in water.

7.2.b.2 Dissociation Constant 3.98×10^{-11} or pKa = 10.4

7.2.b.3 Octanol/Water Partition Coefficient 6.5

7.2.b.4 Vapor Pressure Ethinyl estradiol is a crystalline solid at room temperature. A vapor pressure test was not conducted since the results would be negligible.

7.3 Environmental Depletion Mechanisms

7.3.1 Biodegradation

7.3.1.a Levonorgestrel

An aerobic biodegradation study of levonorgestrel in water was conducted. The method was coupled with techniques to determine study results. This study was conducted for 28 days with levonorgestrel at 10.1 mg/L and with reference article, sodium benzoate, at mg/L.

The mean cumulative CO_2 evolved (amount of degradation) from aqueous medium fortified with sodium benzoate was 93.6% of the initial sodium benzoate applied, according to the titration measurements. This resulting mineralization of the reference

article confirmed the carbon dioxide evolution method as a valid procedure to evaluate test article biodegradation.

The mean cumulative CO_2 evolved (amount of degradation) from the aqueous medium fortified with levonorgestrel was 423 % of the initial amount, according to the titration measurements. This result is erroneously high and is due to an additional carbon source in the test system that led to variable measurements (i.e. acetone, the test article vehicle, was not fully removed upon application). Therefore, neither the nor the results can be used to reliably evaluate biodegradation in this case. However, based on HPLC-UV results, after 28 days, 95.8% of the Levonorgestrel initially applied remained. Based on the HPLC-UV results and under the test conditions employed, Levonorgestrel is not expected to biodegrade significantly. Results of the study are given below and a report of this study is included in Appendix D and a summary of the results is included in Appendix E.

Results of HPLC-UV analysis for levonorgestrel during the 28-day biodegradation study in water.[a]

Replicate	Nominal Concentration (mg/L)	Retention Time (in minutes)	Analytical Results (mg/L)	Percent of Nominal
Day 0				
1				68.9
2				95.3
3				86.7
Day 7[b]				
1				5.90
2				51.7
3				91.8
Day 14[b]				
1				6.90
1				7.60
2				79.1
2				75.2
3				9.10
3				12.2
Day 15[b]				
1				86.8
1				86.5
2				103
2				72.7
3				71.9
3				84.0
Day 21				
1				95.3
2				76.5
3				148
3[c]				84.2
Day 28				
1				89.2
2				88.3
3				110

[a] Calculations were performed using unrounded analytical data, not the rounded values presented in this table. Minor discrepancies may be attributed to rounding.

[b] Additional analytical chemistry was performed to invstigate the variability in chemistry results. After the Day 15 sampling, the variability in the chemistry results was determined to be due to a mixing problem which caused the test system to be non-homogenous. Mixing was improved for the remainder of the study.

[c] Second Replicate 3 sample taken 3 to 4 hours after the initial Replicate 3 sample.

7.3.1.b Ethinyl Estradiol

An aerobic biodegradation study of ethinyl estradiol in water was conducted. The method was coupled with techniques to determine study results. This study was conducted for 28 days with ethinyl estradiol at 10.0 mg/L and with reference article, sodium benzoate, at mg/L.

The mean cumulative CO_2 evolved (amount of degradation) from aqueous medium fortified with sodium benzoate was 93.6% of the initial sodium benzoate applied, according to the titration measurements. This resulting mineralization of the reference article confirmed the carbon dioxide evolution method as a valid procedure to evaluate test article biodegradation.

The mean cumulative CO_2 evolved (amount of degradation) from the aqueous medium fortified with ethinyl estradiol was 656% of the initial amount, according to the titration measurements. This result is erroneously high and is due to an additional carbon source in the test system that led to variable measurements (i.e. acetone, the test article vehicle, was not fully removed upon application). Therefore, neither the results can be used to reliably evaluate biodegradation in this case. However, based on results, after 28 days, 92.9% of the ethinyl estradiol initially applied remained. Based on the results and under the test conditions employed, ethinyl estradiol is not expected to biodegrade significantly. Results of the study are listed below and a report of this study is included in Appendix D and a summary of the results is included in Appendix E.

Replicate	Nominal Concentration (mg/L)	Retention Time (minutes)	Analytical Result (mg/L)	Percent of Nominal
Day 0				
1				93.1
2				89.5
3				89.6
Day 7				
1				95.4
2				91.0
3				92.5
Day 14				
1				89.5
2				90.7
3				88.7
Day 21				
1				90.7
2				87.6
3				87.6
Day 28				
1				97.8
2				89.0
3				92.0

* Calculations were performed using unrounded anlyatical data, not the rounded values presented in this table. Minor discrepancies may be attributed to rounding.

7.3.2 Wastewater Treatment Plant Simulation of Ethinyl Estradiol

A study was conducted to simulate the treatment of aqueous effluent with ozone at the AWPI waste water treatment facility in Guayama, Puerto Rico. Aqueous solutions of ethinyl estradiol were prepared and treated with % (w/w) ozone for minutes. This ethinyl estradiol concentration and ozone scenario are typical of the operating parameters found at the AWPI facility. The degradation of the test article was monitored by

The test system consisted of duplicate mL glass flasks with stir bars. Test 1 utilized a ng/L solution of ethinyl estradiol with an ozone flow rate of mL/min and test 2 utilized a ng/L solution of ethinyl estradiol with an ozone flow rate of mL/min. Results of the tests are listed below.

Test #1, ozone flow rate = [redacted] mL/min ozone exposure time	sample ID	nominal conc. ng/L	measured conc. (ng/L)	% nominal
pre-treatment	C1295-12			96%
	C1295-13			89%
[redacted] minutes	C1295-14			<15%
	C1295-15			<15%
[redacted] minutes	C1295-16			<15%
	C1295-17			<15%

Test # 1 of this study indicates that at an ozone flow rate of [redacted] mL/min, a [redacted] ng/L solution of ethinyl estradiol will be degraded on an average of 85% in both a [redacted] and [redacted] minutes test, resulting in a concentration of mL/min is the typical ozone flow rate used at the AWPI waste water facility.

Test #2, ozone flow rate = [redacted] mL/min ozone exposure time	sample ID	nominal conc. ng/L	measured conc. (ng/L)	% nominal
pre-treatment	C1295-18			101%
	C1295-19			86%
[redacted] minutes	C1295-20			16%
	C1295-21			16%
[redacted] minutes	C1295-22			16%
	C1295-23			16%

Test # 2 of this study also indicates that at an ozone flow of [redacted] mL/min, a [redacted] ng/L solution of ethinyl estradiol will be degraded on an average of 84% in both a [redacted] and [redacted] minute test, resulting in a concentration of [redacted] ng/L.

7.4 Expected Environmental Concentration (EEC)

7.4.1 Levonorgestrel

The expected environmental concentration (EEC) of Levonorgestrel has been calculated to be mg/L. This concentration was calculated by taking the mg/L), a worst case discharge scenario, and assuming a conservative dilution factor of one order of magnitude. The result, mg/L, is a conservative estimate of the concentration of levonorgestrel in the surface waters of the United States. No further depletion mechanisms have been taken into account in this calculation.

7.4.2 Ethinyl Estradiol

The expected environmental concentration (EEC) of ethinyl estradiol has been calculated to be mg/L. This concentration was calculated by taking the mg/L), a worst case discharge scenario, and assuming a conservative dilution factor of one order of magnitude. The results, mg/L, is a conservative estimate of the concentration of ethinyl estradiol in the waters of the United States. No further depletion mechanisms have been taken into account in this calculation.

7.5 Maximum Expected Emitted Concentration

The maximum expected emitted concentration (MEEC) is equal to the expected environmental concentration (EEC) or the expected introduction concentration (EIC), whichever is greater. In the case of levonorgestrel, the MEEC is 2.46×10^{-6} mg/L, and in the case of ethinyl estradiol the MEEC is 4.92×10^{-7} mg/L.

7.6 Summary

7.6.1 Aquatic Environment

The waste waters from the manufacture and packaging of the drug product at the AWPI facility in Guayama, PR pass through an on-site complete activated sludge treatment plant with ozonation, treating an average daily flow of 140,000 gpd. The WWTP consistently achieves 98 % and greater BOD and COD removal. Ethinyl estradiol will be further degraded by ozone treatment. Therefore, animals, plants and other organisms that may be exposed to minute amounts of levonorgestrel and ethinyl estradiol in the aqueous environment are not expected to be adversely effected. No accumulation in any of these species is expected.

No levonorgestrel or ethinyl estradiol will be present in the air compartment, therefore, transport from the air to the aqueous compartment via rainout is not expected. Additionally, since levonorgestrel and ethinyl estradiol are expected to have a negligible vapor pressures, volatilization from the aqueous compartment to the air compartment is not expected.

7.6.2 Terrestrial Environment

Solid wastes containing levonorgestrel and ethinyl estradiol, generated during the manufacture of levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets will be collected and disposed of as described in paragraph 6.2. No levonorgestrel or ethinyl estradiol will be released to the terrestrial compartment. Therefore, no animals or plants will be exposed to levonorgestrel or ethinyl estradiol in this environmental compartment.

Levonorgestrel and ethinyl estradiol will not be present in the air, therefore, transport from the air to the terrestrial compartment via rainout is not expected.

7.6.3 Atmospheric Environment

During all manufacturing at this plant, particulates are removed via local HEPA filters and dust collection systems, which has an efficiency of 99.99%. As a result of the environmental controls described in paragraph 6.2, a minute number of particulates are expected in this environmental compartment. Approximately 1.5×10^{-1} kg of levonorgestrel and 3×10^{-2} kg of ethinyl estradiol are trapped in HEPA filters on an annual basis and approximately 1.5×10^{-5} kg of levonorgestrel and 3×10^{-6} kg of ethinyl estradiol may be released to the atmosphere on an annual basis. No solvents are used in the production of levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets. Levonorgestrel and ethinyl estradiol are crystalline solids at room temperature and therefore the vapor pressures are expected to be negligible. Thus, levonorgestrel and ethinyl estradiol are not expected to volatilize into the air compartment.

Since no levonorgestrel or ethinyl estradiol is expected in the air compartment, no transportation or dispersion to other compartments by rainout or any other mechanism is expected.

8.0 ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

8.1 Literature Review

In *Estrogenic Effects of Effluent From Sewage Treatment Works*[3], C. E. Purdem et al describe the observation of hermaphroditic fish in many wastewater treatment plants of England. Although it was hypothesized that estrogenic compounds, specifically ethinyl estradiol, in the water caused the noted effect, analysis could not identify the substance(s) which caused the effect. Subsequent laboratory studies conducted on trout and carp demonstrated levels as low as 1 - 10 ng/L of ethinyl estradiol could cause hermaphrodism and 0.1 - 0.5 ng/L could generate an increase in plasma vitellogenin, a protein synthesized by the liver of oviparous fish in response to estrogen stimulation. The protein is then conveyed by the blood to the ovary, where it is sequestered by oocytes to form the yolk. Thus the presence of vitellogenin in the plasma is indicative of estrogen stimulation of the liver. Vitellogenin synthesis, even in male fish, can be induced by exogenous estrogens. Hence, the presence of hermaphroditic fish, with elevated plasma vitellogenin levels, have been studied and this effect is believed to be caused by estrogenic compounds. It is hypothesized that ethinyl estradiol is one such compound although it has not been detected in wastewater treatment facilities.

8.2 Microbial inhibition

8.2.1 Levonorgestrel

The objective of the study was to determine the minimum inhibitory concentration (MIC) of levonorgestrel for a series of microorganisms in vitro. The MIC is defined as the lowest concentration of test material that completely inhibits growth of the test organism. The agar plate dilution method was used to evaluate the toxicity of levonorgestrel to pure cultures of bacteria, fungi and blue-green algae.

The test was conducted using 100-millimeter round Petri dishes. Each Petri dish was labeled with the name of the test organism, replicate and test article concentration. The test concentrations for the study were 1.0, 10, 100 and 1000 mg/L of levonorgestrel.

Bacterial growth was determined visually at the termination of the test. Data for plates containing visible growth, evidenced by opacity, were recorded as having growth. A plate that was completely clear or contained a single colony or barely visible haze was considered to have a concentration at or above the MIC.

Results of this test, shown below, indicate that all 5 test organisms have a MIC for levonorgestrel of greater than 1000 mg/L:

Species	Levonorgestrel MIC (mg/L)
Aspergillus niger	>1000
Trichoderma viride	>1000
Clostridium perfringens	>1000
Bacillus subtilis	>1000
Nostoc sp.	>1000

A report of this study is included in Appendix D. A summary of the results is included in Appendix E.

8.2.2 Ethinyl Estradiol

The objective of the study was to determine the minimum inhibitory concentration (MIC) of ethinyl estradiol for a series of microorganisms in vitro. The MIC is deemed as the lowest concentration of test material that completely inhibits growth of the test organism. The agar plate dilution method was used to evaluate the toxicity of ethinyl estradiol to pure cultures of bacteria, fungi and blue-green algae.

The test was conducted using 100-millimeter round Petri dishes. Each Petri dish was labeled with the name of the test organism, replicate and test article concentration. A preliminary test was conducted with each species using test concentrations of 1.0, 10, 100, and 1000 mg/L of ethinyl estradiol. At the end of the preliminary test, no growth inhibition was observed for Bacillus subtilis, Trichoderma viride or Aspergillus niger. Total growth inhibition was evident for Clostridium perfringens at 100 mg/L, with no

growth inhibition observed at the lower concentrations. For Nostoc sp., no growth occurred at the 100 mg/L concentration, while growth did occur in the 1000 mg/L. Because of these preliminary results, definitive testing was conducted on Clostridium perfringens and Nostoc sp. No definitive tests were required for Bacillus subtilis, Aspergillus niger or Trichoderma viride because no inhibitory effects were observed at concentrations up to and including 1000 mg/L.

A definitive test for Clostridium perfringens was conducted at 10, 20, 40, 60, 80 and 100 mg/L. Since no growth inhibition was observed at less than or equal to 40 mg/L but was observed at concentrations greater than or equal to 60 mg/L, the MIC of ethinyl estradiol for this species was determined to be 60 mg/L.

At the termination of the initial definitive test for Nostoc sp., growth was observed in one replicate of the 800 and 1000 mg/L concentrations, however, since growth was observed at all lower concentrations, the definitive test was repeated at 10, 20, 40, 60, 80 and 100 mg/L. This test resulted in growth inhibition being observed at concentrations greater than or equal to 40 mg/L. Therefore, the MIC of ethinyl estradiol to this species is determined to be 40 mg/L.

Bacterial growth was determined visually at the termination of the tests. Data for plates containing visible growth, evidenced by opacity, were recorded as having growth. A plate that was completely clear or contained a single colony or barely visible haze was considered to have a concentration at or above the MIC.

Therefore, results of these tests, shown below, indicate that MIC of ethinyl estradiol for Aspergillus niger, Trichoderma viride and Bacillus subtilis is greater than 1000 mg/l. Clostridium perfringens has a MIC for ethinyl estradiol of 60 mg/L and Nostoc sp. has a MIC for ethinyl estradiol of 40 mg/L.

Species	Levonorgestrel MIC (mg/L)
Aspergillus niger	>1000
Tichoderma viride	>1000
Clostridium perfringens	60
Bacillus subtilis	>1000
Nostoc sp.	40

A report of this study is included in Appendix D and a summery of the results is included in Appendix E.

8.3 Aquatic Toxicity in Daphnia magna

8.3.1 Levonorgestrel

The acute toxicity (EC50) and No-Observed-Effect Concentration (NOEC) of levonorgestrel to daphnids *(Daphnia magna)* were estimated using static acute renewal test conditions and a 48-hour exposure period. The test was conducted following FDA TAD §4.08.[2] The EC50 is defined as the concentration of the test article in dilution water which causes immobilization of 50% of the exposed test population after a fixed period of time. The NOEC is defined as the highest concentration tested at and below which there were no toxicant-related immobilization or physical and behavioral abnormalities (e.g. lethargy), when compared to control organisms. This information is often used as a relative indicator of potential acute hazards resulting from release of the test article into aquatic environments.

Replicate 1000 mL test vessels were used for each treatment level and the controls. Daphnids, ≤ 24 hours old, were impartially distributed one at a time to each vessel of each concentration and the controls (five daphnids per replicate). The mean measured concentrations tested (0.11, 0.21, 0.34, 0.56, and 0.94 mg/l) and the corresponding immobilization data were used to estimate the 24- and 48-hour median effect concentrations (EC50) and 95 % confidence intervals. Throughout the 48-hour study, no immobilization or sublethal effect (lethargy) were observed among daphnids exposed to the concentration range tested. Due to the limited water solubility of levonorgestrel further testing was not practical.

These results indicate that levonorgestrel is estimated to have a 48-hour EC50 value of > 0.94 mg/L and a No-Observed-Effect Concentration through 48 hours of 0.94 mg/L, the highest mean measured concentration measured.

A report of this study is found in Appendix D. A summary of results is found in Appendix E.

8.3.2 Ethinyl Estradiol

The acute toxicity (EC50) and No-Observed-Effect Concentration (NOEC) of ethinyl estradiol to daphnids *(Daphnia magna)* were estimated using static acute renewal test conditions and a 48-hour exposure period. The test was conducted following FDA TAD §4.08.[2] The EC50 is defined as the concentration of the test article in dilution water which causes immobilization of 50% of the exposed test population after a fixed period of time. The NOEC is defined as the highest concentration tested at and below which there were no toxicant-related immobilization or physical and behavioral abnormalities (e.g. lethargy), when compared to control organisms. This information is often used as a relative indicator of potential acute hazards resulting from release of the test article into aquatic environments.

Replicate 1000 mL test vessels were used for each treatment level and the controls. Daphnids, ≤ 24 hours old, were impartially distributed one at a time to each vessel of

each concentration and the controls (five daphnids per replicate). The mean measured concentrations tested (1.4, 2.3, 4.0, 6.6 and 11 mg/L) and the corresponding immobilization data were used to estimate the 24- and 48-hour median effect concentrations (EC50) and 95% confidence intervals.

These results indicate that ethinyl estradiol has a hour EC50 value of mg/L and a No-Observed-Effect Concentration through hours is mg/L.

		95% Confidence Interval	
	EC50[a] mg/mL	Lower[a] mg/mL	Upper[a] mg/mL
Hour[a]	8.4	7.3	9.6
Hour[b]	5.3	4.0	6.6
	NOEC Through Hours[a] = mg/mL		

a EC50 value and 95 % confidence interval were calculated by probit analysis
b EC50 value estimated by nonlinear interpolation, 95% confidence interval calculated by binomial probability.

A report of this study is found in Appendix D. A summary of results is found in Appendix E.

8.4 Mammalian Toxicological Data

8.4.1 Levonorgestrel

The acute LD50 in the mouse, rat and dog is greater than 5000 mg/kg. Seven year studies with daily doses of 0.5 mg/kg have been conducted in dogs and 10 year studies with daily doses of 1 mg/kg have been conducted in monkeys. Effects were minor except for effects on the reproductive system.

Ovulation was inhibited as it is in humans. Doses of 20 mcg per day cause some inhibition of ovulation and disruption of menstrual bleeding pattern in women. Doses of 80 mcg per day inhibit ovulation in approximately 90 percent of cycles.

8.4.2 Ethinyl Estradiol

Acute toxicity studies using ethinyl estradiol were conducted using mice, rats and dogs. Oral LD50 are reported at 2.5 gm/kg in mice, > 5 gm/kg in rats and > 1 gm/kg in dogs. The subcutaneous LD50 in mice is > 2.6 gm/kg, while the intraperitoneal LD50 in mice is 0.7 gm/kg and 1.0 gm/kg in rats.

8.5 Tiered Testing Assessment

8.5.a.1 Levonorgestrel

8.5.a.1 Tier 0

Although levonorgestrel clearly meets the Tier 0 requirement of having a MEEC value of less than 1 ppb (MEEC of levonorgestrel = 2.46 x 10^{-6} mg/L or 0.00246 ppb), fate and effects testing was conducted. The reason for this testing was two-fold; first, Wyeth-Ayerst Laboratories wants to be confidant that the materials they discharge are environmentally safe at the specified concentrations, and secondly, fate and effects testing was already initiated when the Center For Drug Evaluation and Research (CDER) released its November 1995 guidance document which details the tiered testing protocol.

Following the *Tiered Approach to Fate and Effect Testing* listed in Figure I of the CDER's guidance document the next step requires an investigation of depletion mechanisms.

Aerobic biodegradation as a depletion mechanism was investigated. Test results are listed in paragraph 7.3.1. The data indicates that levonorgestrel does not aerobically biodegrade in less than eight hours and thus does not qualify as a rapid depletion mechanism as per the CDER's November 1995 guidance document.

Figure 1 of the November 1995 guidance document indicates that if a rapid depletion mechanism is not found, a microbial inhibition test should be performed. A microbial growth inhibition test was conducted and complete results of this test are discussed in paragraph 8.2. Data indicates that the minimum inhibitory concentration of levonorgestrel to microbial growth is greater than 1000 mg/L. Although these results indicate that levonorgestrel does not cause inhibition of microbial growth at concentrations as high as 1000 mg/L, a Tier 1, acute toxicity test was conducted.

8.5.a.2 Tier 1

Tier 1 acute toxicity testing of Levonorgestrel was conducted on Daphnia magna. Complete test results are summarized in paragraph 8.3. Data from the test indicated the EC50 to > 0.94 mg/L and the NOEC to be 0.94 mg/L. The *Tiered Approach to Fate and Effects Testing* requires that the EC 50 be divided by the MEEC. If the result is greater than or equal to 1000 and there are no observed effects at the MEEC, (the MEEC is less than the NOEC) the requirements have been fulfilled and fate and effects testing may cease. Calculations for Levonorgestrel are listed below:

EC50 = > 0.94 mg/L
NOEC = 0.94 mg/L
MEEC = 2.46 x 10^{-6} mg/L

EC50/MEEC = 3.8 x 10^{5}

Tier 1 testing has been satisfied because the EC50 divided by the MEEC has resulted in a number greater than 1000 and the MEEC is less than the NOEC, proving that there are no observed effects at the MEEC>

Fate and effects testing requirements for Levonorgestrel have now been fulfilled.

8.5.b Ethinyl Estradiol

8.5.b.1 Tier 0

Although ethinyl estradiol clearly meets the Tier 0 requirement of having a MEEC value of less than 1 ppb, (MEEC of ethinyl estradiol = 4.92×10^{-7} mg/l or 0.000492 ppb) fate and effects testing was conducted. The reason for this testing was two-fold; first, Wyeth-Ayerst Laboratories wants to be confident that the materials they discharge are environmentally safe at the specified concentrations, and secondly, fate and effects testing was already initiated when the Center For Drug Evaluation and Research (CDER) released its November 1995 guidance document which details the tiered testing protocol.

Following the *Tiered Approach to Fate and Effect Testing* listed in Figure 1 of the CDER's guidance document the next step requires an investigation of depletion mechanisms.

Aerobic biodegradation as a depletion mechanism was investigated. Test results are listed in paragraph 7.3.1. The data indicates that ethinyl estradiol does not aerobically biodegrade in less than eight hours and thus does not qualify as a rapid Depletion mechanism as per the CDER's November 1995 guidance document.

Figure 1 of the November 1995 guidance document indicates that if a rapid depletion mechanism is not found, a microbial inhibition test should be performed. A microbial growth inhibition test was conduced and complete results of this test are discussed in paragraph 8.2. Data indicates that the minimum inhibitory concentration of ethinyl estradiol to microbial growth is greater than 1000 mg/L m the case of Aspergillus niger, Trichoderma viride, and Bacillus subtilis. Nostoc sp. and Clostridium perfringens have a minimum inhibitory concentration of 40 mg/l and 60 mg/l respectively. Although these results indicate that ethinyl estradiol does not cause inhibition of microbial growth at fairly high concentrations, a Tier 1, acute toxicity test was conducted.

8.5.b.2 Tier 1

Tier 1 acute toxicity testing of ethinyl estradiol was conducted on Daphnia magna. Complete test results are listed in paragraph 8.3. Data from the test indicated the ECS0 to be 5.3 mg/l and the NOEC to be 2.3 mg/l. The *Tiered Approach to Fate and Effects Testing* requires that the ECS0 be divided by the MEEC. If the result is greater or equal to 1000 and there are no observed effects at the MEEC, (the MEEC is less than the

NOEC) the Tier 1 requirements have been fulfilled and fate and effects testing may cease. Calculations for ethinyl estradiol are listed below.

EC50 = 5.3 mg/L
NOEC = 2.3 mg/L
MEEC = 4.92 x 10^{-7} mg/L
EC50/MEEC = 1.1 x 10^{7}

Tier 1 testing has been satisfied because the EC50 divided by the MEEC has resulted in a number greater than 1000 and the MEEC is less than the NOEC, proving that there are no observed effects at the MEEC.

Fate and effects testing requirements for ethinyl estradiol have now been fulfilled.

8.6 Potential Toxicity Effects

Wyeth-Ayerst believes it is important to determine the concentration of the drug product in the local wastewater treatment plant and local surface water and compare it to acceptable discharge standards. Minute quantities of drug product may be lost during the manufacturing process and be discharged to the manufacturing facility's wastewater treatment plant. Calculations of the wastewater treatment plant loading and removal are found in Appendix I. These calculations are used in conjunction with the definition listed below to draw a conclusion.

As defined in 21 CFR 25. 15(b)(6), a substance is considered toxic in the environment if the maximum concentration of the substance at any point in the environment, i.e., either at any point of entry or any point where higher concentrations are expected as a result of bioaccumulation or other types of concentration processes, exceeds the concentration of the substance that causes any adverse effect in a test organism species (minimum effect level-MEL) or exceeds 1/100) of the concentration that causes 50% mortality in a test organism species (LD50 or LC50), whichever concentration is less. This concentration is defined as the "Criterion Concentration" (CC).

8.6.1 Levonorgestrel

The concentration of Levonorgestrel in AWPI's local surface water, , is calculated to be 7.88 x 10^{-5} mg/L, (see Appendix I for calculations). This discharge may be present due to the loss of minute quantities of the drug product during manufacturing. in this case is mg/L (this value is 1/100 of the EC50). Therefore the possible discharge due to manufacturing loss mg/L) is less than the mg/L) and is considered nontoxic by definition.

8.6.2 Ethinyl Estradiol

The concentration of ethinyl estradiol in AWPI's local surface water, , is calculated to be mg/L (see Appendix I for calculations). This discharge may be present due to the loss of minute quantities of drug product during manufacturing. in this case is mg/L (this value was obtained from paragraph 8. l and is considered more conservative than the NOEC or 1/100 of the EC50). Therefore the possible discharge due to manufacturing loss mg/L) is less than the mg/L) and is considered nontoxic by definition.

9. USE OF RESOURCES AND ENERGY

The raw materials used to manufacture levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets are readily available. The production of the drug product and the energy use involved therein do not deplete any natural resources that are in critically short supply.

The energy consumed in the manufacture of the drug product is less than 0.1% of the total energy consumption of the facility. The addition of this process is not expected to have any significant impact on energy usage.

The manufacturing facility is in compliance with laws governing the protection of threatened and endangered species. There are no known endangered or threatened species and no historic places are found at or near the facility.

10. MITIGATION MEASURES

The AWPI plant has taken measures (described in Section 6) to achieve compliance with the regulations governing the proposed manufacture of levonorgestrel (0.1 mg)/ethinyl estradiol (0.02 mg) tablets.

Emissions of the drug product to the air are controlled by high efficiency control equipment described in Section 6. Emissions of the drug product to wastewater are controlled by onsite treatment which includes activated sludge treatment with ozonation. Emissions to the land do not occur because all solid waste generated during manufacturing is incinerated as described in Section 6.

In addition to air, wastewater and solid waste control measures previously discussed, all responses to hazardous materials emergencies are governed by plant emergency response procedures. All operations are conducted in a manner which minimizes the potential for environmental incidents and are in compliance with emergency preparedness and prevention requirements.

11. ALTERNATIVES TO THE PROPOSED ACTION

Since negative environmental impacts are not expected, alternatives to the proposed action are not being considered.

12. LIST OF PREPARERS

Diane L. Smith, Ph.D.	Environmental Specialist Wyeth-Ayerst Laboratories Environmental Science Masters Degree Professional Experience: 10 years
Craig Seyfried	Associate Director, Environmental Control Wyeth-Ayerst Laboratories Environmental Health Masters Degree Professional Experience: 20 years
Eunice G. Kulesza	Environmental Scientist Wyeth-Ayerst Laboratories Ph.D., Analytical Chemistry Professional Experience: 15 years

The preparers' resumes are provided in Appendix F.

13. CERTIFICATION

The undersigned certifies that the information presented is true, accurate, and complete to the best of the knowledge of Wyeth-Ayerst Laboratories.

Date March 19, 1996

Signature Craig F. Seyfried

C. Seyfried.
Director, Environmental Control
Wyeth-Ayerst Laboratories

14. REFERENCES

1. Pharmaceutical Manufacturers Association, *Interim Guidance to the Pharmaceutical Industry for Environmental Assessment Compliance Requirements for the FDA*. July 1991.

2. U.S. Food and Drug Administration, *Environmental Technical Assistance Handbook*, PB87-175345, U.S. Department of Commerce National Technical Information Service, Springfield, VA. 1987.

3. C. E Purdom et al, *Estrogenic Effects of Effluent From Sewage Treatment Works* Chemistry and Ecology, 1994, Vol 8, pp. 275-285.

15. APPENDICES

Item
Environmental Assessment
Non-Confidential Appendices
Appendix A: Material Safety Data Sheets
Appendix B: Foreign Manufacturer's Environmental Compliance Statement
Appendix C: AWPI's Environmental Compliance Statement
Appendix D: Analytical Studies Conducted By
Appendix E: Data Summary Tables
Appendix F: Preparers' Résumés
Confidential Appendices