TRENBOLONE ACETATE/ESTRADIOL, Implant tablets

or

REVALOR Implant tablets

NADA Submission

ENVIRONMENTAL ASSESSMENT REPORT

(According to 21 CFR 25.31)

TRENBOLONE ACETATE/ESTRADIOL, Implant tablets

Environmental Assessment Report

(According to 21 CFR 25.31)

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Introduction

This Environmental Assessment Report deals with the production of Trenbolone acetate/Estradiol, Implant tablets.

Three formulae of Trenbolone acetate/Estradiol, implant tablets are either approved by the FDA (i.e. Revalor S 120 mg/24 mg, implant tablets) or in the process of examination by the FDA (i.e. Revalor H 140 mg/14 mg, implant tablets and Revalor G 40 mg/8 mg, implant tablets).

For each type of product, the principle of the manufacturing process is the same, the excipients used are identical, only their proportions vary with that of the active principles.

The present Environmental Assessment is thus valid for all the Revalor implant tablets formulae.

TRENBOLONE ACETATE/ESTRADIOL, Implant tablets

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1. DATE

March 1994

2. NAME OF APPLICANT

Hoechst - Roussel Agri-Vet Company on behalf of Roussel Uclaf.

3. ADDRESS

Route 202-206 North
Somerville, NJ 08876
UNITED STATES

4. DESCRIPTION OF THE PROPOSED ACTION

4.1. Requested approval

The present Environmental Assessment is aimed at showing that production of trenbolone acetate/estradiol, implant tablets as well as manufacture of the concerned active ingredients trenbolone acetate and estradiol are very controlled and will have no adverse effects on the environment.

Approval for manufacturing these products is requested.

4.2. Manufacturing sites

- Manufacturing site of trenbolone acetate : ROUSSEL UCLAF Plant 2
  63480 Vertolaye
  FRANCE

- Manufacturing site of estradiol : ROUSSEL UCLAF Plant 2
  63480 Vertolaye
  FRANCE

  or

  DIOSYNTH BV
  Kloosterstraat 6
  Oss
  HOLLAND

- Manufacturing site of implant tablets : ROUSSEL UCLAF / USIPHAR Plant
  Route de Choisy-au-Bac
  60205 Compiègne
  FRANCE

4.3. Environmental protection

Considering its industrial installations, DIOSYNTH was granted an agreement from the Dutch Ministry of Public Health and Environmental Hygiene for the production of pharmaceutical chemicals.

See attached sheet.

Environmental impact analysis report

Translation of the report

MINISTRY OF
PUBLIC HEALTH
AND ENVIRONMENTAL
HYGIENE

No. 122408
Department DC Vgz/GMI

Register no. 2217 A

THE MINISTER OF PUBLIC HEALTH AND ENVIRONMENTAL HYGIENE
Regarding the request of Diosynth B.V., Kloosterstraat 6 in Oss, dated September 19th 1979;

Taking into account article 2, first paragraph, under d, of the act on medicine supplies (Stb. 1958, 408) in combination with article 2 of the Decree on production and delivery of bulk pharmaceutical chemicals. (Stb. 1977, 538);

Having heard the medicine commission,

DECREES:

As from October 1st 1981 a license has been granted to Diosynth B.V., Kloosterstraat 6 in Oss to manufacture drug substances described in the above mentioned application and to deliver those.

A copy of this decree will be sent to the party concerned, the chief inspector of public health for medicines, the regional inspector of public health for medicines and the central department of financial-economical affairs of the Ministry of public health and environmental hygiene.

Leidschendam, October 1st 1981
The minister above-mentioned
on behalf of the minister:
head of the principal section
on medicines, medical appliances
and infective diseases.

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The Roussel Uclaf Plants which are involved in the production of trenbolone acetate, estradiol and Implant tablets operate with all technical means required to protect, preserve and enhance the quality of the environment as specified by the French Law in the fields of environmental protection and occupational hygiene.

The effluents are submitted to a specific treatment prior to be discharged.

Depending upon their quality, the solvents are either recycled or destroyed in facilities agreed by the French Government Authorities.

The solid wastes are transferred to agreed waste disposal sites.

In addition, the personnel in charge of the manufacture is required to operate at any stage of the chemical and pharmaceutical process in strict conformity with the protective rules prescribed by the French Ministry of Labor and governing occupational hygiene and safety.

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4.3.1. Environmental protection at the site of Vertolaye

The ROUSSEL UCLAF Plant 2 is located in the center of FRANCE, far from any major city, in the vicinicity of a small river (the DORE).

All the effluents emitted at this site are controlled and treated if required, prior to be discharged into the natural environment (atmosphere or river).

For safety's sake the rain water is collected through a specific sewer system connected to the storage tanks which are parts of the water treatment station. It is discharged directly into the river only if no pollution is detected. Otherwise, in the case of accidental pollution for instance, the rain water is submitted to the same biological treatment as that applied to the aqueous effluents emitted by the production plant.

(See the attached flow-sheet of the effluents at the site of Vertolaye).

- Treatment of the liquid effluents

  - Incineration

    The incineration unit is designed to burn yearly about 4500 m^3 of solvents, thus used as combustible for the destruction of about 12000 m^3 of highly polluted aqueous effluents.

    The combustion is performed in a furnace at a temperature of about 1000°C and after cooling to about 600°C the resulting gases are passed through an exchanger for the production of steam.

    The cooled gases are then submitted to a counter-current washing and passed through a dry filter prior to be released into the atmosphere.

    The resulting washings are transferred to the biological treatment station.

    (See the attached diagram of the incineration facilities).

  - Physico-chemical pre-treatment

    The physico-chemical pre-treatment facilities receive all the aqueous effluents emitted during the manufacturing operations.

    After measuring and physical treatment (de-oiling, de-sanding) these effluents usually of acidic nature are neutralized with calcium hydroxide and homogenized in 2 storage tanks.

    In order to develop the proliferation and the action of the micro-organisms the effluents are submitted to a flocculation and to a primary decantation allowing the elimination of some sludges.

- Biological treatment

The pre-treated aqueous effluents are received in two 4000 m^3 activation tanks where the biological epuration is performed by means of micro-organisms fed on a continuous basis with materials essential for their development (oxygen and phosphorus).

The effluents are then transferred to a secondary decanter where sludges are removed and partly recycled. All the sludges coming from every step of the treatment are dehydrated by filtration and transferred to an authorized waste disposal site.

The effluents collected at the outlet of the secondary decanter enter a tertiary treatment stage where a neutralization and a flocculation are applied to complete the separation of the sludge from the treated water which is finally discharged into the river (the Dore).

- Treatment of the gaseous effluents

The gaseous effluents emitted by the boiler plant are discharged without specific treatment into the atmosphere.

The gaseous effluents emitted by the production plant are made dust-free by treatment through a multi-stage filtration system, the last filter operating at an efficiency of 99.9 p.cent.

- Treatment of solid wastes

Specific bins are systematically used to collect all solid wastes or residues produced at the site. The loaded bins are then carried to an approved firm (FRANCE-DECHETS) specializing in waste disposal and destruction.

Wastes are treated in accordance with French and European Community laws, regulations and recommendations.

The waste disposal sites used are agreed by the concerned French Authorities.

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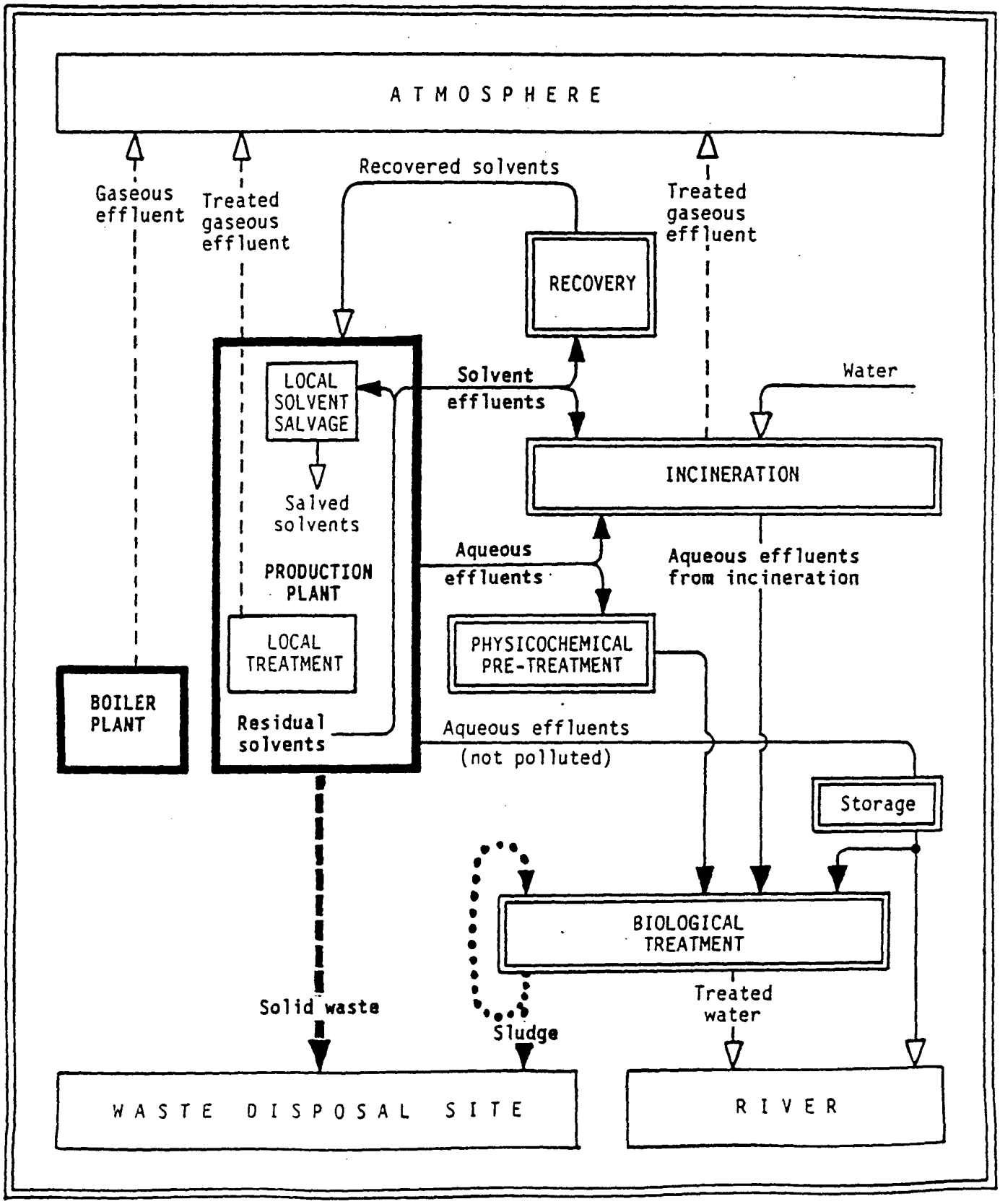
FLOW-SHEET OF EFFLUENTS AT THE SITE OF VERTOLAYE



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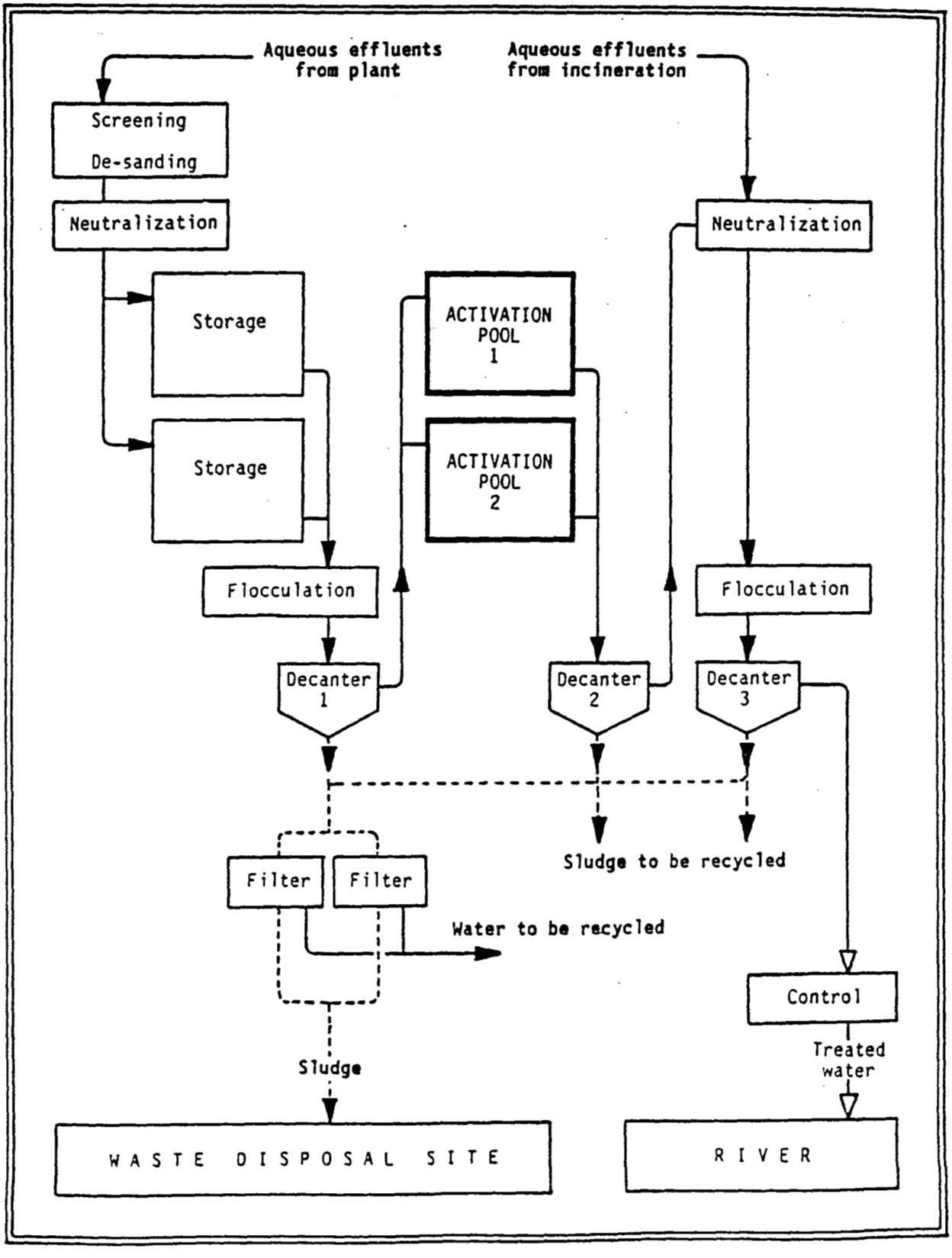
BIOLOGICAL TREATMENT FACILITIES AT VERTOLAYE



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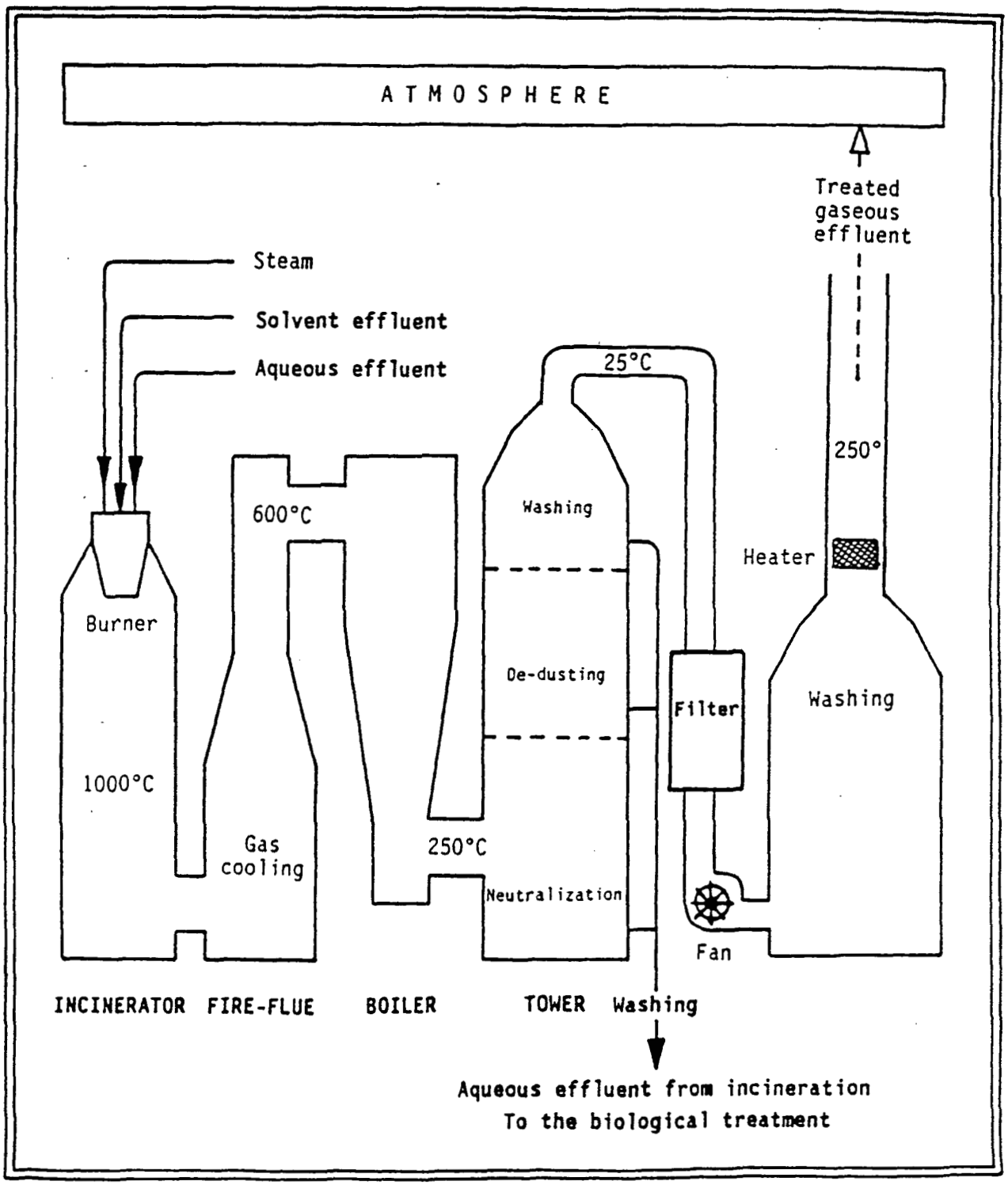
INCINERATION FACILITIES AT VERTOLAYE



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4.3.2. Environmental protection at the site of Compiègne

The ROUSSEL UCLAF/USIPHAR Pharmaceutical plant is located on the southern side of a big river (the Aisne) near the town of Compiègne.

The effluents emitted at this site are submitted to a specific treatment prior to be discharged :

(See the flow-sheet of the effluents at the site of Compiègne).

- Treatment of solid wastes

The solid wastes emitted during the pharmaceutical production (tablets, granule, raw materials, etc) are collected in specific closed bins bearing a specific label "Pharmaceutical wastes for destruction".

Every day these bins are collected, closed and sealed. The wastes are then compacted under the responsibility of the Logistics Dept. and transferred to an authorized incineration station.

The destruction of these wastes is reported in a formal record (ref. CERFA No 070320) referred to as "Follow-up of industrial wastes".

The powder wastes retained in the exhaust filters or collected during the cleaning operations are destroyed according to the same procedure.

Recyclable solid wastes such as paper or cardboard packaging articles are collected in specific bins and sold to a specialized firm authorized to run appropriate recovery treatments.

NB. : The empty containers polluted with raw materials (cartons, cardboard drums, etc) are incinerated as described above.

- Treatment of liquid effluents

. Solvents

The residual solvents emitted by the manufacturing section (wetting solvents, cleaning solvents) or by the laboratories are collected in a dedicated underground tank, 10 000 liters in capacity. They are then transferred under the responsibility of the Logistics Dept. to an authorized incineration station.

The destruction of these solvents is reported on a formal record referred to as "Follow up of industrial wastes".

Every 3 months a status report on the waste elimination is sent to the French Authorities (Direction Générale de l'Industrie et de la Recherche Picardes, 80026 Amiens).

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(Compiègne)

Aqueous effluents

All the aqueous effluents emitted from various sections of the plant undergo a preliminary physico-chemical treatment adapted to their composition prior to transfer to the biological treatment for reprocessing.

The resulting treated water is discharged directly into the neighboring river (Aisne) after a weekly control including the following determinations :

- BOD5 (Biological Oxygen Demand in 5 days)
- Chlorides
- Ammonium salts
- pH.

The aqueous effluents emitted by the plant at Compiègne exhibit the following characteristics :

- a pollution essentially due to the presence of soluble biodegradable organic substances
- a high variability of the amounts of polluting agents as observed within the day, the week or the year
- a variability in the flow-rate resulting from the putting into operation of a various number of pumps
- a high variability in the pH (from pH 2 to pH 9).

These factors have been taken into consideration in designing the depollution facilities which perform the following operations :

A. Screening - De-sanding

The industrial effluents are first passed through a grid made of stainless steel bars, 2 cm spaced from each other and then they are driven to a desanding channel.

The treatment station is thus protected against the big-sized foreign matter and against sand.

B. Homogenization

The effluents received at variable flow-rates are stored in an intermediate pool where they are homogenized prior to be transferred at constant rate on a 24-hour basis to the biological treatment facilities.

The role of this intermediate storage is three-fold :

- homogenization of the pollution degree so as to improve the yield of the biological treatment unit
- absorption of the variations in the flow-rates so as to permit the biological treatment unit to be fed at constant rate
- cross-neutralization of the acidic and alkaline effluents allowing to reduce the expenses related to neutralizing chemicals.

The working capacity of this tank is 144 m^3 and the homogenization is produced by air bubbling.

C. Neutralization

The adequate operation of the biological treatment unit requires the use of practically neutral effluents.

At the outlet of the homogenization pool the effluents are driven to a neutralization box fitted with an air bubbling device and with a pH regulation system. As the effluents are usually acidic, the pH adjustment is performed only by addition of sodium hydroxide.

The effluents homogenized and neutralized are transferred by pumping at constant rate (6 m^3/h) to a distribution vessel.

D. Biological treatment

The biological treatment is based on a long-lasting aeration process run in a pool fed at constant rate. A system of air spargers provides the oxygen supply required for the development of the aerobic bacteria.

Then, the effluents are received in a decanter where the suspended matter (activated sludge) is collected and recycled to the aeration tank whereas the treated water is discharged into the river (Aisne) via a measuring channel.

A part of the sluged produced is passed through a thickener and then transferred to an authorized waste disposal site.

(See attached diagram : Biological treatment facilities at Compiègne).

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(Compiègne)

- **Treatment of gaseous effluents**

The operations dealing with the implant tablets (manufacture and packaging) are run in the Workshop 2600 housed in the Solid Forms Building.

The ventilation in this building is achieved by a 100-p.cent fresh air supply system (i.e., operating with no recirculation).

. Inlet air

The inlet air is passed through a 2-stage filtration system consisting of fiberglass prefilters (85 p.cent in gravimetric efficiency) and filters (95 p.cent in opacimetric efficiency).

. Outlet air

Prior to be discharged into the atmosphere the outlet air is previously passed through an appropriate filtration system.

Three different filtration systems are used in the various premises as described in the table below.

FILTRATION SYSTEM					CONCERNED PREMISES OF WORKSHOP 2600
	Components	Efficiency (p.cent)			
		Gravimetric	Opacimetric	DOP (*)	
1	Prefilters	85			Compression boxes
	Filters		95		
2	Filters		95		Packaging premises
3	Prefilters		85		Raw materials manual weighing premises
	Filters			99.99	

(*) DOP (Dioctylphthalate test).

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Note : For the process vacuum and the cleaning vacuum, the air is passed through filters, 50 p.cent in gravimetric efficiency.

The filtering systems are monitored by a subcontracting firm (Compagnie Générale de Chauffe) which is in charge of cleaning and maintenance at a determined frequency.

The values of the depression are recorded on a follow-up sheet.

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(Compiègne)

Gaseous effluents from boiler plant

The smoke produced by the boiler plant is submitted to the following tests :

- Carbon monoxide content
- Carbon dioxide content.

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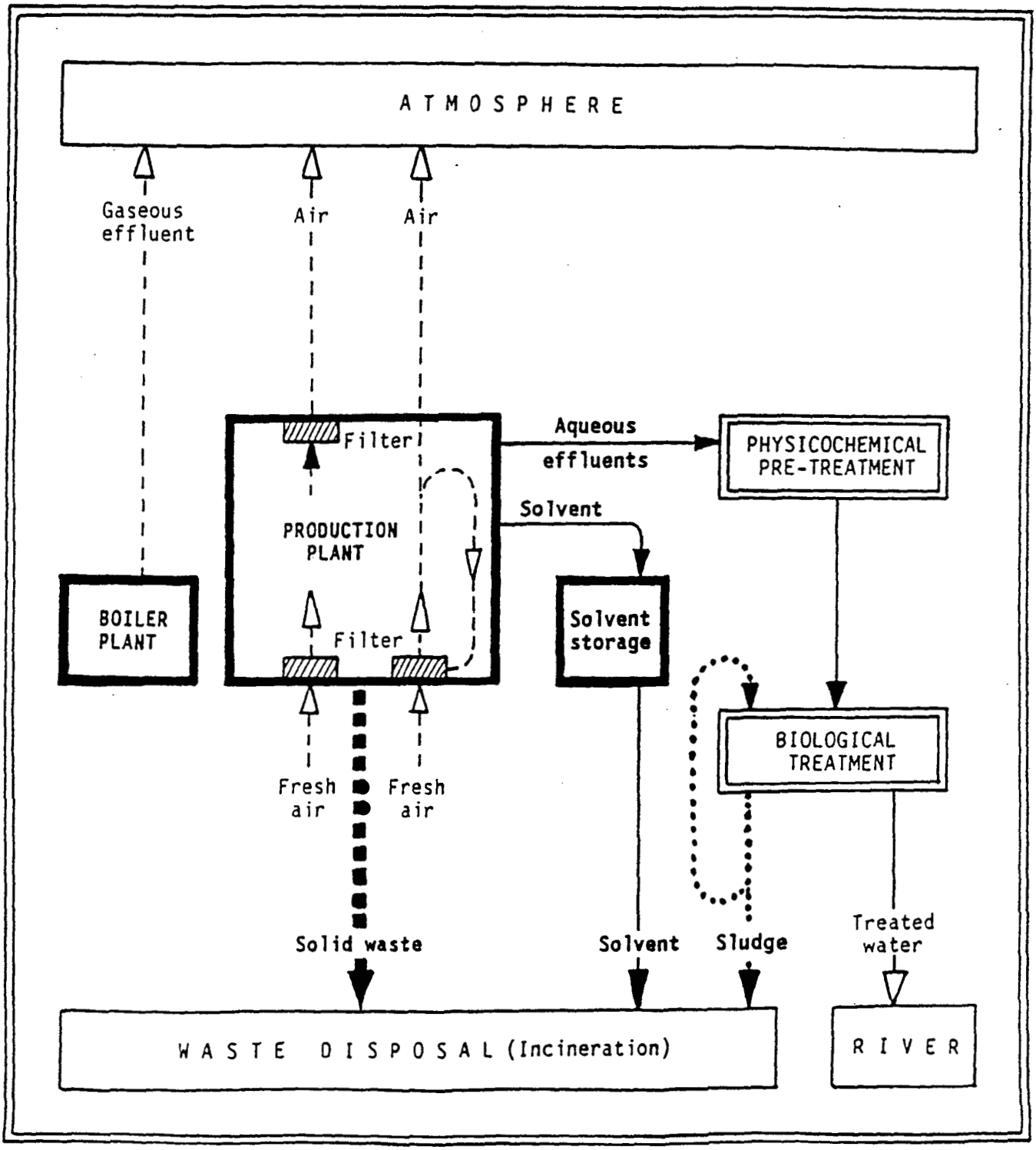
FLOW-SHEET OF EFFLUENTS AT THE SITE OF COMPIEGNE



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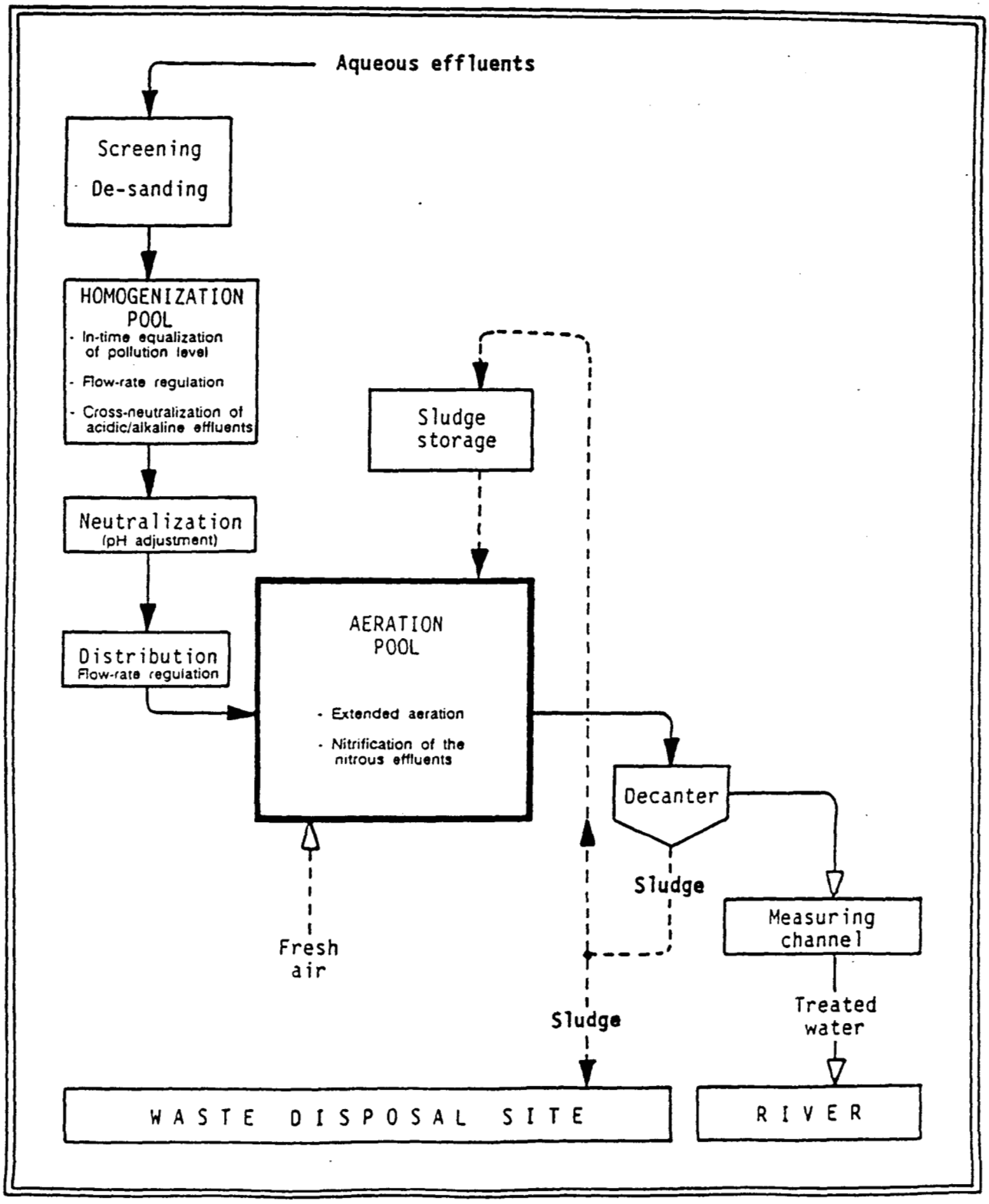
BIOLOGICAL TREATMENT FACILITIES AT COMPIEGNE



5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE SUBJECT OF THE PROPOSED ACTION

Two chemical substances are subject of the proposed action, i.e. both active ingredients trenbolone acetate and estradiol.

5.1. Identification of trenbolone acetate (Drug substance)

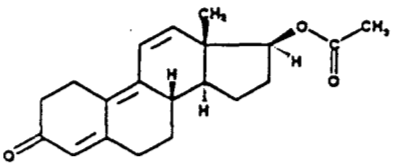
The required technical information on trenbolone acetate is given below :

- Names
  - Chemical Abstracts Nomenclature

    (17β)-Acetoxyestra-4,9,11-trien-3-one

    Registry number : CAS = 10161-34-9
  - IUPAC Nomenclature

    (17β)-Hydroxyestra-4,9,11-trien-3-one, acetate
- Molecular structure



- Molecular formula

  $C_{20}H_{24}O_3$

- Molecular weight

  Mr 312.41

- Physical form

  Crystalline powder.

5.2. Identification of estradiol (Drug substance)

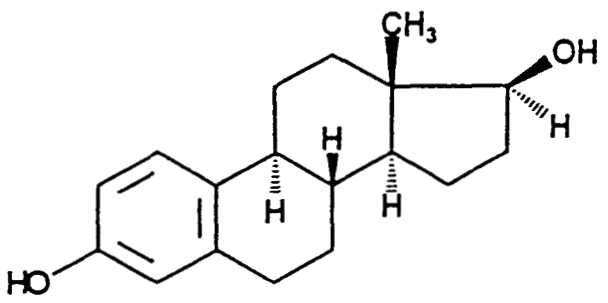
The required technical information on estradiol is given below :

- Names
  - IUPAC Nomenclature

    Estra-1,3,5(10)-triene-3,17β-diol
  - Chemical Abstracts nomenclature

    (17β)-Estra-1,3,5(10)-triene-3,17-diol

    Registry number : CAS = 50-28-2
- Structural formula



- Molecular formula

  $C_{18}H_{24}O_2$
- Relative molecular mass

  272.39
- Physical form

  Microcrystalline powder.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

As concerns production of estradiol by DIOSYNTH, a statement specifically related to the manufacturing of estradiol was obtained from the Dutch authorities. It indicates that the manufacturing of estradiol is in complete compliance with the Netherlands Law.

See attached sheet.

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248693

No. 16...

Ministry of WELFARE, PUBLIC HEALTH and CULTURAL AFFAIRS
Staatstoezicht op de Volksgezondheid
Hoofdinspektie voor de geneesmiddelen
P.O. Box 5406
2280 HK RIJSWIJK
THE NETHERLANDS

S T A T E M E N T

The undersigned, A.J. Smallenbroek, Pharmacist, Director of Public Health for Drugs in the Netherlands herewith declares that the pharmaceutical raw material

ESTRADIOL

in accordance with the Netherlands Law is allowed to be manufactured, sold and exported by Diosynth B.V., Kloosterstraat 6, 5349 AB Oss, The Netherlands.

The present statement is drawn up at the request of the interested party in order to be submitted to the Food and Drug Administration, U.S.A.

Rijswijk, 201293

THE DIRECTOR OF PUBLIC
HEALTH FOR DRUGS IN THE
NETHERLANDS

A.J. Smallenbroek
Pharmacist

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The information which follows specifically relates to the manufacture of trenbolone acetate, estradiol and implant tablets by ROUSSEL UCLAF.

6.1. Substances expected to be emitted

6.1.1. At the ROUSSEL UCLAF Plant 2 at Vertolaye,

Substances likely to be emitted during production of trenbolone acetate and estradiol are the following :

- liquid effluents :
  . mother liquors from crystallization
  . washings of crystallized product
  . solvents from evaporation
  . cleaning solvents or water

- solid effluents
  . charcoal filter-cakes

- gaseous effluents
  . hydrogen

Except aqueous washings or cleaning water which are submitted to a biological treatment, all the other liquid effluents containing organic solvents are incinerated (Refer to treatment of the liquid effluents in subsection 4.3.1. Environmental protection at the site of Vertolaye).

Hydrogen is released into the atmosphere.

Solid effluent is transferred to a waste disposal site (Refer to treatment of solid wastes in subsection 4.3.1. Environmental protection at the site of Vertolaye).

6.1.2. At the ROUSSEL UCLAF/USIPHAR Plant at Compiègne

The substances likely to be emitted in small quantities are the active ingredients, the excipients and the wetting solvent (Ethyl alcohol denatured with ethyl acetate and isopropanol).

This can occur in form of dust emitted during the weighing and at the various steps of the processing : mixing, wetting, calibration, lubrication, tabletting and packaging. This dust is trapped in appropriate filters as detailed in section . Environmental protection at the site of Compiègne, Sub-section : Treatment of gaseous effluents.

The aqueous washings produced during the cleaning of the equipment and of the containers are collected through the specific pipework and transferred to the biological treatment facilities.

6.2. Controls exercised

6.2.1. At the ROUSSEL UCLAF Plant at Vertolaye

- Controls exercised on the liquid effluents

The liquid effluents are controlled by the plant laboratory specializing in de-pollution testing according to methods described in the AFNOR recommendations (French specifications) and adapted to the various types of concerned materials.

In addition, an outside laboratory agreed by the French Ministry of Environmental Protection is in charge of performing every three months a full analysis of homogeneous samples of liquid effluents.

Three types of liquid effluents are emitted at the site of Vertolaye :

. the liquid effluents resulting from the biological treatment and discharged into the Dore river

. the water used for cooling and discharged directly into the Dore river through a specific sewer system

. the rain water which is collected and discharged without treatment into the Dore river, via the storage tanks.

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Environmental Assessment Report

(Vertolaye)

Several parameters are controlled on these effluents according to the following schedule :

PARAMETERS	LIQUID EFFLUENTS		
	Effluent after biological treatment	Water used for cooling	Rain water
Flow-rate	every day	continuously	at each emission
Conductivity	continuously	-	-
Temperature	continuously	continuously	-
pH	continuously	continuously	-
COD	every day	every day	at each emission
BOD 5	every week	-	-
Suspended matter	every week	-	-
Total nitrogen	every week	-	-
Ammoniacal nitrogen	every week	-	-
Salts			
- Chlorides	every week		
- Bromides	every week		
- Fluorides	every week		
- Sulfates	every week	-	-
- Iodides	every week		
- Nitrates	every week		
- Phosphates	every week		
Heavy metals			
- Copper	every week		
- Iron	every week	-	-
- Chromium	every week		
- Zinc	every week		

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(Vertolaye)

- Controls exercised on the gaseous effluents

The smoke produced by the boiler plant and by the incineration plant is submitted to the following tests :

PARAMETERS	SMOKE FROM THE BOILER PLANT		SMOKE FROM THE INCINERATION PLANT	
Carbon dioxide	T	continuously	T	occasionally
Oxygen	T	continuously	R	continuously
Temperature	T	continuously		
Blacking index	R	continuously		
Temperature (outlet)	R	continuously		
Dust	R	continuously	R	continuously
Chlorine			R	continuously
Carbon monoxide			T	occasionally
Unburnt matter			R	twice a year
Heavy metals			R	every 3 months
Ascension velocity			R	if required

R : Control required by the legislation

T : Control applied for operation monitoring.

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6.2.2. At the ROUSSEL UCLAF/USIPHAR Plant at Compiègne

- Controls exercised on the liquid effluents

These controls deal with the aqueous effluents prior to treatment and with the treated water obtained.

. Tests performed by the Quality Control

- Determination of the BOD 5
- Assay for chlorides
- Assay for ammonium salts
- pH

These tests are run once a week.

. Tests performed by the personnel of the treatment unit

- Control of the turbidity of the treated water
- Determination of the sludge content

. Tests performed by the Government Agency

Two or three times a year, the local Government Agency (SATESE at Beauvais) inspects the water treatment and takes samples of the effluent to be treated and of the final treated water. A report on these inspection visits is issued by the agency and communicated to the plant manager along with comments and recommendations.

These controls include :

- Suspended matter
- BOD 5
- COD
- Oxidizable matter
- Total nitrogen (Kjeldahl)

A copy of a recent report is given in Appendix.

- Controls exercised on the gaseous effluents

The smoke produced by the boiler plant is submitted to the following tests :

. Carbon monoxide content
. Carbon dioxide content.

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6.3. Citation of, and statement of compliance with applicable emission requirements at the State level

6.3.1. At VERTOLAYE

The attached documentation deals with the regulatory aspects of the environmental protection concerning the site of Vertolaye (ROUSSEL UCLAF Plant 2).

It includes :

- an English translation of a letter of compliance with the emission requirements *(Page 35)
- an English translation of the applicable emission requirements issued by the Government Office of the concerned department (Puy de Dôme) (Page 36 and* following)
- an English translation of a letter of the Government Office responsible for environmental laws and regulations, certifying that the Roussel Uclaf Plant 2 operates in compliance with the environmental and occupational requirements in France *(Page 60 and following)

(See attached sheets).

*Internal page numbers (top center of page).

STATUS OF THE PLANT AT VERTOLAYE TOWARDS THE REGULATIONS CONCERNING THE ENVIRONMENT

Owing to its industrial activities the Plant at Vertolaye is within the scope of the Law No 76-663 dated July 16, 1976 (and of the corresponding application decree No 77-1134 dated September 21, 1977) which deals with the environmental protection concerning the "Listed Plants" (Etablissements classés).

As such the Prefectoral Administration issued an order referred to as "Listing Order" (Arrêté de classement) dated February 6, 1986 and intended to regulate the activities of the plant.

A. CONTROL OF THE LIQUID EFFLUENTS

The control of the liquid effluents is performed by the Analytical Department of the plant. The methods used are derived from those described in the standards published by the French Association for Standardization (AFNOR) and they are adapted to the nature of the effluents emitted by the plant. The recapitulative table given in appendix (ANNEX 1) summarizes the parameters investigated and the frequency of the analyses. It is to be noted that a control check is performed every third month by a laboratory authorized by the Ministry of Environment.

B. CONTROL OF THE EFFLUENTS RELEASED IN THE ATMOSPHERE

At the present time, the gaseous effluents emitted by the boiler room and by the incineration facilities are checked under consideration of the following parameters :

- Oxygen content
- Carbon monoxide content
- Nitrogen oxide content
- Dust content
- Chlorine content (effluent from the incinerator)
- Non-burnt matter content (effluent from the incinerator)

C. DIFFUSION

Every third month, all the results of the analyses performed on the liquid effluents as well as all information concerning the elimination of the chemical wastes are communicated to the Prefectoral Administration.

CLASSIFICATION ORDER
issued by

THE PREFECT, COMMISSIONER OF THE REPUBLIC
FOR THE DEPARTMENT OF PUY-DE-DÔME
dated 6 February 1986

ARTICLE 1. - As a complement to the orders of the prefect and acknowledgements of declaration already issued, authorizing, in particular, the company ROUSSEL-UCLAF to operate on the territory of the commune of MARAT, at the location known as "La Pâterie", on the land register lots AX Nos 219, 221, 240, 241, 246, 250, 300, 302 and 204, a liquid effluent treatment plant (E.T.P.) comprising:

1. A combustion installation capable of consuming per hour an amount of fuel representing 3,500 therms of Lower Calorific Power. The installation is a furnace serving for the incineration of liquid industrial waste (residual solvents - highly polluted water). Classification 153-bis-1 and 167-c with benefit of the priority.

2. A 210 m^3 atmospheric storage facility for flammable liquids of the 2nd category (residual solvents - methanol). Classification 253-C.

3. A biological station.

The Company ROUSSEL-UCLAF will have to comply with the additional regulations detailed in Articles 2 to 5 below.

ARTICLE 2. - A tertiary physicochemical treatment (flocculation/settling tank) will be added to the current biological station. The E.T.P. supplemented in this way must be operational by 31 December 1986 at the latest.

ARTICLE 3. - The provisions of Articles 3-1, 3-2, 3-6 and 4 of the Order of 19 January 1979 are replaced by the following:

Article 4

◇ WATER POLLUTION: (PROVISIONS APPLICABLE TO THE ESTABLISHMENT AS A WHOLE)

4.1. Drawing of water

4.1.1. The use of surface and underground water for industrial use, and especially that of a quality permitting domestic use, must be restricted, for example by using closed cooling circuits or air cooling.

4.1.2. The operator shall inform the Inspector of Classified Installations annually of his water consumption and of projects relating to the reduction thereof.

4.2. Different types of liquid effluents

The liquid effluents of the establishment comprise

* solvents and residual water which can be incinerated by the operator or a specialist organization, collected in the establishment by specific systems,

* effluents treated in the specialized E.T.P for polluted industrial water,

* other effluents and cooling water discharged directly into the VERTOLAYE.

4.3. Collection of liquid effluents

4.3.1. • All arrangements will be made in order to isolate in the most concentrated possible state the various effluents issuing from each installation with a view to facilitating their treatment.

4.3.2. • It rests with the operator, following examination of the technical and economic study, to propose treatment or destruction of a given effluent when its concentration and the nature of its pollutants justify and permit this.

4.3.3. • The system for collection of effluents which have to undergo treatment or be destroyed shall not, during normal operation, comprise any links allowing direct discharge into the recipient natural environment.

4.3.4 * The piping will be leakproof and its layout will permit cleaning out. Its dimensions and the materials employed to produce it will permit good preservation of this structure with time. When this condition cannot be met because of the characteristics of the products conveyed, it will be capable of inspection or exploration by any other means.

4.3.5. * The piping conveying water polluted by liquids which are or are liable to be flammable must comprise effective protection against the danger of flame propagation (flame trap openings).

4.3.6. * The discharge equipment must be easily accessible and installed in such a way as to permit sampling of the effluent and the measurement of its flow under conditions ensuring the best possible accuracy.

In particular, the effluents issuing from the biological station and those originating from the incinerator will be combined before they are discharged into the Dore through a single emission point.

The technical characteristics of the structures located in the public domain will be defined by the authority responsible for water policing.

4.3.7. * A plan of the piping system, showing the collection sectors, the openings and connection points will be drawn up, regularly updated and made available to the Inspector of Classified Installations.

4.4. Collection of discharged water

To take account of the air cooling installation, the average daily flow, calculated per week, of cooling water into the natural environment is restricted to 20,000 m^3 from June to September and 27,000 m^3 from October to May. The average daily flow of the

effluent originating from the E.T.P. is restricted to 6,500 m^3. These values may be revised by means of a supplementary order in the light of the results obtained by applying the provisions provided above (drawing of water - collection of liquid effluents)

4.5. Quality of the effluents discharged

4.5.1. The effluents must be free from:

* floating matter,

* products capable of releasing toxic or flammable gases or vapors into the drain or into the natural environment directly or indirectly, after mixing with other effluents.

* any products capable of adversely affecting the conservation of structures, as well as materials which may be deposited or precipitated and which, indirectly or directly, after mixing with other effluents, could be liable to impair the correct functioning of the structures.

* substances capable of causing the destruction of fish downstream from the discharge point. The dilution of the effluents from the E.T.P. must be complete approximately 1.3 km downstream of the discharge point. In order to verify compliance with this provision, this reference point will be marked by a surveyor at the cost of the company ROUSSEL-UCLAF and shall be accessible to road vehicles.

Moreover, the effluents must not give rise to significant discoloration of the recipient environment.

Their pH must be between 6.5 and 8.5 and their temperature must be below 30°C.

4.5.2. * The characteristics of the discharge, in particular the daily concentration and the daily flow, of each of the main pollutants shall be less than or

equal to the values given in the tables appended to the present decision.

4.6. Discharge monitoring

4.6.1. * The following shall be measured and recorded continuously for each pre-homogenized effluent:

E.T.P. DISCHARGE	COOLING WATER
- pH	- pH
- temperature	- temperature
- flow	- flow
- cyanide	

The C.O.D. shall be monitored daily on an average 24 hour sample (cooling water).

To achieve greater safety, the determination of the cyanide concentration shall be carried out at the outlet of wash water from the incinerator.

The edited and time-stamped tapes shall be kept available to the Inspector of Classified Installations for a period of one year.

The current discharge points for cooling water shall be joined into a single emission point before discharge into the VERTOLAYE or the Dore (term 1 January 1987).

4.6.2. * Proportional sampling of the discharge flow from the E.T.P. shall be carried out continuously:

- a sample of at least 2 liters per 24-hour period shall be taken which is representative of the average characteristics of the effluent discharged during this period. This sample shall be stored at 4°C for seven days, at the disposal of the Inspector of Classified Installations, in a closed vessel marked with the sampling references.

The following shall be determined on a 24-hour average sample, representative of the characteristics of the effluent discharged from the E.T.P.:

- pH - conductivity - suspended matter - C.O.D. - B.O.D. - NTK - NH_4^+ - Zinc - Cyanides -

The following shall be determined on a weekly (7-day) average sample representative of the characteristics of the effluent discharged form the E.T.P.:

- Nitrates - Phosphates - Total phosphorus - Fluorine - Chlorides - Bromine - Sulfate - Total chromium - Hexavalent chromium - Aluminum - Copper - Iron - Magnesium - Manganese - Hydrocarbons - Phenols

4.6.3. * For implementation of paragraphs 4.6.1 and 4.6.2 and on condition that agreement is given by the Inspector of Classified Installations, the continuous monitoring of the Chemical Oxygen Demand of the effluent may be replaced by continuous monitoring of another parameter representative of the oxidizable pollution (Total Oxygen Demand, for example). In this case, the Inspector of Classified Installations shall set the corresponding values authorized for this parameter.

4.6.4. * Every three-month period of operation of the plant, the operator shall arrange for an analysis of samples representative of the average characteristics of the effluent discharged. The analysis will usually cover all of the parameters mentioned in the appendix to the present order and will be carried out by a body, the choice of which will be submitted to the Inspector of Classified Installations if an agreement has not been made in this respect.

4.6.5. * In the event of significant pollution of the recipient environment, the Inspector of Classified Installations may demand that special analyses of the waste are

carried out within the shortest possible time, if appropriate under the control of an independent body.

4.6.6. Balance

• a report summarizing the analyses and measurements carried out in implementation of the present paragraph 4.6 shall be submitted to the Inspector of Classified Installations each month. A copy shall be submitted to the authority responsible for water policing.

• at the beginning of each year the operator shall submit to the Inspector of Classified Installations the balance sheet of the actions undertaken, the projects and studies under way in order to reduce, in particular, the discharge of total nitrogen and ammonium nitrogen (pilot studies, replacement of reagents etc).

4.7. Prevention of accidental pollution

All measures shall be taken to ensure that in the event of an operating incident occurring within the precincts of the establishment (rupture of a vessel, exchanger leakage) there shall be no direct discharge into the natural environment of dangerous or unhealthy materials of a nature and quantity such that they would be liable to have consequences for this location. In particular, any cyanide concentration in the discharge originating from the E.T.P. in excess of 0.1 mg/l will trigger a sound alarm and immediate action on the part of a qualified official enabling this state of affairs to be remedied within a period which shall not exceed 10 minutes. In particular, the following structural and operating measures shall be complied with.

The pH of the cooling water discharged into the VERTOLAYE must be between

6 and 8. Any departure from this range must entail, without delay:

- storage of the cooling water in buffer tanks,

- shut-down of the plant involved if there is no return to normal conditions.

The cooling water stored in this way may be discharged only after the operator is satisfied of its harmlessness.

The equipment adopted to implement this regulation shall be subject to the approval of the Inspector of Classified Installations.

Term for implementation: 1 JANUARY 1987.

4.7.1. Retention capacities

Those units, parts of units or storage facilities liable to contain, even occasionally, a product which by reason of its characteristics and the amounts used is liable to have an effect on the environment when it is discharged directly therein shall be provided with retention capacity or equipped to permit the products accidentally spilled to be collected in an installation able to ensure their retention and their treatment (pretreatment station for example).

Where the respective properties of the dangerous products and those of the extinguishing or cooling agents allow, measures shall be taken to ensure that the use of protective equipment is not able to give rise to significant run-off of these dangerous substances into the natural environment.

The retention capacities and the collection and storage system for accidental drippings and effluents shall not comprise any means for emptying thereof by simple gravity.

The loading, intermediate storage or discharging of mobile tanks for dangerous or unhealthy materials, such as drums, containers, road and rail tankers, shall comply with the above provisions (term 1 January 1987).

4.7.2. Movement of dangerous or unhealthy products within the establishment

The piping for conveying dangerous or unhealthy fluids within the establishment shall be kept perfectly leakproof. The materials used for their manufacture and their dimensions must permit these structures to be kept in a good state of repair. If this condition cannot be met because of the characteristics of the products to be conveyed, it must be possible to inspect the structures from the outside. Periodic checks shall be made and the reports drawn up will be kept available to the Inspector of Classified Installations for a period of one year.

In no case shall the piping for dangerous or unhealthy products be located in the drains or in pipes directly connected to the drains.

One or more cut-off tanks or disconnection tanks or any other equipment offering equivalent guarantees shall be installed in order to isolate the industrial water systems and to prevent products incompatible with the potability of water from returning into the potable water systems.

The equipment used for this purpose must have given favorable results in technological tests.

The operator shall inform the Inspectorate of Classified Installations of

the location at which the chosen equipment is sited and of its characteristics.

The equipment shall be suited to the characteristics of the systems to be equipped. It shall be installed in an accessible location in such a way that it is protected from any possibility of immersion. It shall be maintained in good operating condition and checked periodically. The check reports shall be held at the disposal of the Inspectorate of Classified Information.

Equipment liable to overflow shall be sited in such a way that the effluents are not diluted in the event of malfunction.

4.7.3. Condition of stocks

Fixed or mobile stocks of dangerous or unhealthy products and the equipment for these which is located in the establishment or temporarily introduced into its precincts must be monitored with particular care by the operator to ensure that they are kept in a good state of repair.

4.7.4. Collection of process water liable to be accidentally polluted

- Process water liable to be accidentally polluted and to cause the fixed thresholds to be exceeded is passed through a buffer tank enabling it to be checked before discharge.

- Appropriate means for monitoring the quality of liquid effluents shall be installed in those sectors particularly exposed to the risk of accidental pollution.

- The causes of any abnormal variation in the characteristics of the effluents shall be the subject of a systematic analysis with the aim of verifying that they do not constitute an anomaly liable to lead to accidental pollution.

4.7.5. Cooling water

The discharge of cooling water in open circuit or of deconcentration purges from closed circuits and originating from cooling circuits feeding exchangers and equipment in which dangerous or unhealthy products are circulated, even occasionally, under pressures higher than those of the water circuits may be carried out only after a check has been made that there has been no accidental pollution.

4.8. Consequences of accidental pollution

4.8.1. Pollution of surface water

In the event of accidental pollution caused by the establishment, the operator must be in a position to supply, within the shortest possible time, the known information available to him enabling determination of the safety measures to be taken with regard to persons, fauna, flora and structures exposed to this pollution, in particular:

1 - the toxicity and the effects of the products discharged;
2 - their evolution and conditions of dispersion into the natural environment;
3 - the definition of areas at risk of being affected by pollutant concentrations liable to have repercussions on the natural environment or the various uses to which the water is put;
4 - the methods to be used for destroying the pollutants;
5 - the curative means which can be used to treat people, fauna or flora exposed to this pollution;
6 - methods for analysis or identification and bodies competent to carry out these analyses.

All of the measures taken and the

bibliographical data collated by the operator in order to comply with the above provisions shall be the subject of a surface-water pollution control file held at the disposal of the Inspector of Classified Installations and regularly updated in order to take account of advances in know-how and technology.

This file shall comprise, in particular:

- The information listed under points 1, 2, 4, 5 and 6 above for the products (used or manufactured in the establishment, even as an intermediate product) which by reason of their characteristics and the amounts used may be able to affect the environment in the event of a direct discharge.

4.8.2. Pollution of underground water

The quality of underground water liable to be polluted by the establishment shall be subject to monitoring, in particular with a view to detecting accidental pollution. Sampling and analysis of this water shall be carried out at least twice a year.

The practical ways and means employed for this monitoring shall be defined in instructions subject to the approval of the Inspector of Classified Installations (creation of a piezometer network, parameters to be determined, following consultation with a hydrogeologist).

In the event of pollution of underground water by the operator, all measures must be taken to remedy the disturbance found.

4.9. Operating instructions

The operating instructions for the various plants, stores or equipment liable to be the source of accidental pollution of

water shall explicitly include checks to be carried out, in normal operation and following a shut-down after modification or maintenance work, in order to confirm that these installations continue to comply with the provisions of the present order.

With regard to the checks to be carried out following maintenance work or a prolonged shut-down, each of these shall be carried out only when authorized by the stamping of a specifically designed form to ensure that operations for bringing installations back into service proceed correctly (work sheet for example).

ARTICLE 5 - ATMOSPHERIC POLLUTION (PROVISIONS APPLICABLE SOLELY TO THE E.T.P.)

5.1 General

5.1.1. The emission into the atmosphere of fumes, vapors, soots, dusts or gases liable to inconvenience the neighborhood and to damage public health or safety is prohibited.

5.1.2. The shape of pipes for release into the atmosphere in particular in the part closest to the outlet, must be designed so as to promote to the maximum the rise and the dispersion of the effluents discharged under normal operation of the installations.

5.2. Accidental pollution

The necessary measures shall be taken to reduce the probability of accidental emissions and to ensure that the corresponding discharges do not present a risk to the health and the safety of people. The design and the siting of safety devices intending to protect equipment against internal overpressure must be such that this aim is achieved, without thereby reducing the efficacy or the reliability of said

equipment.

5.3. Incineration

Treatment capacity

5.3.1. The installation is authorized for a maximum thermal power of 4,200 kW and for a maximum daily treatment capacity of 75 tonnes of waste including chlorinated waste.

5.3.2. Storage

All stores must be provided with leakproof catchment devices for retaining run-off, the capacity of which devices must be greater than or equal to the larger of the following 2 values:

- 100% of the capacity of the largest container,
- 50% of the total volume stored.

The retaining bunds must be correctly maintained and run-off and rainwater must be removed as required. Term for implementation 1 January 1987.

5.3.2.1. Storage in reservoirs (pits or tanks) having a capacity of 1,500 m^3.

The reservoirs for storing liquid or pasty waste shall be covered. If this waste has an unpleasant odor, is volatile (vapor pressure of the waste greater than 100 mb at 25°C or at the storage temperature if this higher) or emits vapors of a certain toxicity, the reservoirs shall be closed.

Any other method preventing the dispersion of vapors may be utilized provided it has an equivalent efficacy.

Liquid waste tanks shall be provided with devices for measuring the level.

These provisions (storage - storage in reservoirs) apply to mobile tanks remaining on site.

5.3.2.2. Storage in drums having a capacity of 100 m^3.

The amount of waste stored in drums and

awaiting treatment may not exceed the daily treatment capacity. All measures shall be taken to ensure that a drum does not remain in store for more than 10 days.

Stacking of drums shall be restricted to 3 high if the drums are on pallets and in good condition and to 2 high in all other cases. The mechanical stability of these stocks must be ensured.

Stores shall be designed so as to permit easy access to the various containers and free movement between the stacks of drums (in this regard, groups of four pallets of drums or racks two pallets wide appear to be acceptable).

The other mobile containers shall not be stacked with the drums.

The manufacturer shall remove any pierced container from the storage area as soon as it is detected.

Filling and discharging shall be carried out in a leakproof area and with containment.

5.3.3. Incineration conditions

Waste to be incinerated shall be subjected to a combination of physicochemical factors guaranteeing the effectiveness of the destruction.

The reaction conditions in terms of temperature, combustion time and oxygen content shall be designed so as to guarantee correct incineration of the waste.

The excess air shall be regulated so as to ensure good combustion of the waste without too great a dilution of the effluent which would compromise the effectiveness of the purification treatment.

The destruction effectiveness shall be monitored on the one hand by continuous measurement of the incineration temperature

and on the other hand by determination of the concentration of unburnt matter in the combustion gases. The waste shall be brought to a temperature of at least 900°C for a period of at least two seconds.

These provisions also apply to any residues introduced in post-combustion.

5.3.4. Characteristics of the gases discharged into the atmosphere under normal operation

The volume of gases emitted shall be measured under standard temperature and pressure conditions: 0°C, 1 bar, and related to 7 % of carbon dioxide, the water being assumed to have remained in the form of vapor.

The gases discharged into the atmosphere must not contain more than:

- 50 mg/Nm^3 of dusts;
- 15 mg/Nm^3 of unburnt matter;
- 5 mg/Nm^3 of heavy metals;
- 20 mg/Nm^3 of elemental chlorine.

The flow shall be restricted to:

- 10 kg/day of dusts,
- 3 kg/day of unburnt matter,
- 1 kg/day of heavy metals,
- 4 kg/day of elemental chlorine.

The dust and elemental chlorine contents of the waste may in no case exceed the values of 600 mg/Nm^3 and 300 mg/Nm^3 respectively.

The uninterrupted periods for which the dust or elemental chlorine contents exceed the values laid down in Article 4 must be shorter than 16 h and the cumulative duration of these periods over one year must be less than 100 h. In the event of these values being exceeded, the operator shall instigate the emergency shut-down procedure defined in the final paragraph of this article.

The current discharges from the incinerator (flow rate, temperature, rate, dusts, unburnt matter, heavy metals, chlorine, HCN, CO, CO_2, O_2 and NO_x) shall be the subject of a measurement campaign, the measurements being carried out by an approved body before 31 March 1986.

The results shall be communicated to the authority responsible for the inspection of Classified Installations. In the light of these results, the discharge norms provided above may be modified or supplemented.

5.3.5. The stack shall have a height of 40 meters.

The vertical ascendant speed of the combustion gases must be greater than 8 m/s.

Equipment which is visible day and night and indicates the local wind direction shall be installed in the vicinity of the installations liable to emit dangerous substances in the event of malfunction.

5.3.6. The dust, oxygen and elemental chlorine content of emissions shall be permanently recorded by monitoring equipment (in respect of elemental chlorine, from the time when approved devices in accordance with the specifications etc are marketed).

The temperature of the combustion gases shall be permanently recorded at a point representative of the combustion conditions.

The analysis of these recordings shall be held at the disposal of the Inspector of Classified Installations and filed for 5 years.

5.3.7. Weight monitoring of the emissions shall be carried out at least once a quarter. This monitoring must determine the flows and concentrations of dusts, elemental chlorine

(total gaseous chlorine) and other pollutants (heavy metals in particular). The level of unburnt matter shall be determined every six months.

Measurements of concentrations or of the flow of pollutants in the emission shall be carried out, if appropriate by a specialist organization, during normal operation of the installations and at the request of the Inspector of Classified Installations.

To enable these checks to be carried out, closable and readily accessible equipment shall be provided in accordance with the standard NFX 44052. Openings which do not comply may be tolerated if the operator demonstrates that he is nevertheless able to comply with the sampling conditions.

At the request of the Inspector of Classified Installations and in accordance with the ways and means which he shall define, measurement campaigns shall be carried out in the environment with the aim of monitoring the effects of pollutants liable to be emitted by the installations.

5.3.8. Quarterly monitoring of the characteristics of the ashes and dusts from the purification treatment shall be carried out on a representative batch made up of samples. The stock present before disposal shall be protected from rain and from blowing away and limited to 2,000 kg. The ash and dust from the treatment shall be disposed of in an installation duly authorized for this purpose pursuant to the Law of 19 July 1976.

5.3.9. The conditions under which the incinerator is used shall be such that the content of unburnt matter in the purification treatment ash and dust as defined in the above paragraph does not exceed 3% of the dry

weight of said ash and dust.

5.3.10. The electrical installations shall comply with the provisions of the Ministerial Order of 31 March 1980 applying to electrical installations in establishments governed by legislation relating to Classified Installations and which are liable to present explosion hazards.

5.3.11. The establishment shall be provided with fire-fighting means appropriate to the nature and the amounts of products and waste stored.

The operator shall take all measures (in particular emergency electrical back-up) in order to ensure that the unavailability of a source of energy supply does not give rise to additional pollutant emissions. A detailed study of the installations requiring back-up in the event of an incident of this type shall be carried out.

The installation shall be designed in such a way that it is possible to carry out an emergency shut-down, in particular in the event of breakdown of the fume-cleaning equipment, without there being any additional emissions into the environment. The installation shall be provided with a flame detector or any other safety device allowing detection of any anomaly in operation the signal from which shall give rise to the appropriate action.

ARTICLE 6.- : NOISE AND VIBRATION - (PROVISIONS APPLICABLE TO THE ESTABLISHMENT AS A WHOLE)

6.1. The establishment shall be constructed, equipped and operated in such a way that its operation is not able to be the cause of noise or vibration liable to disturb the peace of the neighborhood.

6.2. Any disturbance shall be evaluated in accordance with French Standard NF/S/31 010.

A disturbance is presumed to have taken place if the evaluated level of ambient noise, determined in accordance with paragraph 7 of the standard, exceeds the limiting noise level value for the period in question.

6.2.1. Noise within locations inhabited or occupied by third parties liable to be inconvenienced shall be measured in accordance with paragraph 6.2 of the standard if the noise from the installation in question is transmitted mainly by a solid route.

6.2.2. Noise transmitted through the air towards the locations inhabited and occupied by third parties shall be measured outside the buildings containing these locations in accordance with the procedures of paragraph 6.1 of the standard.

6.3. Limiting noise levels (in dB (A))

The evaluated level shall not de facto exceed the establishment of the thresholds laid down in the table below:

	DAY 07.00 to 20.00	INTERMEDIATE PERIOD 06.00 to 07.00 - 20.00 to 22.00 Sundays and public holidays	NIGHT 22.00 to 06.00
Inside buildings occupied or inhabited by third parties (measurements carried out in accordance with para. 4.2.1)	35	30	30
Within the boundaries of the property of the establishment	65	60	55

6.4. The period of reference used to calculate the average in accordance with paragraph 7 of the standard shall be from 08.00 hours in daytime and the noisiest half hour for intermediate periods and at night.

6.5. Vehicles and site machinery used inside the establishment shall comply with the regulations in force. In particular, site machinery shall be of a type approved under the Order of 18 April 1969.

6.6. The use of all acoustic communication equipment (sirens, alarms, loudspeakers, etc) which might disturb the neighborhood is prohibited except where their use is exceptional and reserved for the prevention and signaling of serious incidents or accidents.

6.7. Fixed machinery liable to inconvenience the neighborhood as a result of vibration shall be insulated by means of effective anti-vibration devices.

ARTICLE 7. - The remainder of the petition from the T.O.S. Association is rejected.

ARTICLE 8. - The Association Nationale de Défense des Salmonidés T.O.S. (National Association for the Defence of Salmonidae T.O.S.), the MINISTER OF THE ENVIRONMENT, the Company ROUSSEL-UCLAF and the Commissioner of the Republic for PUY-DE-DOME shall be notified of the dispatch of this order.

6 FEBRUARY 1986.

(illegible signature)

(illegible stamp)

APPENDIX

E.T.P. DISCHARGE

(cf. Article 3 of the provisions)

The following norms, expressed in terms of flow and concentration, shall be simultaneously complied with by 31 December 1986 at the latest (they imply the impossibility of combining maximum flow rate and maximum concentration at the same time, emphasis being laid on the flows discharged).

Limiting values for the flows discharged in kilograms per day

POLLUTANT	AVERAGE DAILY FLOW CALCULATED OVER ONE WEEK
COD	1,800
BOD	325
SUSPENDED MATTER	455
NITROGEN, KJELDHAL	780 subsequently 150 •
NITROGEN, AMMONIACAL	520 subsequently 100 •

The average flows over a two-hour period must not exceed twenty per cent of their average daily value as laid down above.

Limiting values for the concentrations in mg/l

POLLUTANT	AVERAGE CONCENTRATION CALCULATED OVER ONE WEEK
COD	450
BOD5	50
SUSPENDED MATTER	70
NITROGEN, KJELDHAL	120 subsequently 20 *
NITROGEN, AMMONIACAL	80 subsequently 13 *
PHENOLIC COMPOUNDS	0.1
CYANIDES	0.1
TOTAL CHROMIUM	0.1
HEXAVALENT CHROMIUM	0.05
COPPER	0.2
ZINC	0.4
NICKEL	0.1
HYDROCARBONS, NFT 90203	5

The average concentrations over a 2-hour period shall not be higher than at most 50% of the above values.

(*) These norms permit compliance with the aims in respect of the quality of the DORE (2 at the level of the works discharge). They must be achieved as soon as compliance therewith proves technically possible.

COOLING WATER DISCHARGE

The water taken from the natural environment for cooling purposes shall not undergo any change during its use in the works; its characteristics determined at the point of discharge into the natural environment (VERTOLAYE or DORE) shall be identical to those recorded where the water is taken, except for a slight rise in temperature which, however, must at all times be less than or equal to 25°C.

MINISTRY OF INDUSTRY AND NATIONAL AND REGIONAL DEVELOPMENT

Regional Direction of Industry and Research
AUVERGNE

Christian DESMOULINS
Director

The Regional Director
of Industry and Research

to

The Director of ROUSSEL UCLAF
63480 VERTOLAYE

Dear Sir,

This is to answer your letter dated April 11, 1990 about the conformity of your VERTOLAYE Plant with the regulations governing its activity in the field of environment.

The operations you run in manufacturing chemicals correspond to the headings of the "Nomenclature des Etablissements Classés" (Nomenclature of Listed Plants) annexed to the Law No 76-663 dated July 19, 1976 and attached hereto.

Thus, by following the recommendations of the various relevant prefectoral orders, you are in conformity with the prescriptions intended to ensure the public health and safety and consequently, the protection of the environment.

In addition, the setting into operation of the de-pollution and incineration facilities between 1974 and 1981 (this corresponding to a cost of 30 MF at that time) allowed to establish a contractural policy of self-surveillance including several points :

- to monitor the good operation of the facilities
- to prevent the accidental pollutions
- to check the conformity with the legal prescriptions and to follow up the application of the various local plans.

In this line, a determination of the concentration of the various effluents is performed periodically under your responsibility, at the inlet and at the outlet of the de-pollution station. Some parameters are checked continously (pH, temperature, flow-rate, cyanide content), some others, daily (pH, conductivity, suspended matter, chemical oxygen demand, biological oxygen demand, total nitrogen according to the Kjeldahl method, zinc, cyanide content), and some others every week (nitrates, phosphates, total phosphorus, fluorine, chlorides, bromine, sulfate, total chromium, hexavalent chromium, aluminium, copper, iron, magnesium, manganese, hydrocarbons, phenols).

Every third month, in order to validate the results obtained during the self-surveillance operations, an analysis is performed on all the above stated parameters by the authorized laboratory of the city of CLERMONT-FERRAND.

All these results are communicated to us for review.

Finally the numerous contacts we may have with your technical services reveal each time the carefulness you show in dealing with environmental problems.

In these conditions, I have no objection to state that your plant is operated in conformity with the regulations for respect of the public health and safety and of the environment.

Sincerely yours,

TRENBOLONE ACETATE/ESTRADIOL, Implant tablets

Environmental Assessment Report

6.3.2. At COMPIEGNE

The attached documentation includes :

- an English translation of
  the report on the plant inspection visit conducted by a Government Agency (SATESE) on March 6, 1990.

See attached sheets.

DÉPARTEMENT DE L'OISE

Direction Générale — DIRECTION DES INFRASTRUCTURES

Réf : DI/ES/1700

Affair followed up by J.T. — Beauvais, July 9, 1990

LISTING

of the documents forwarded by the PRESIDENT OF THE GENERAL COUNCIL OF THE OISE DEPARTMENT

to Monsieur le Directeur
ROUSSEL UCLAF
60200 COMPIEGNE

Reference : WATER TREATMENT FACILITIES

Number of documents	Designation	Remarks
1	Report on the inspection visit conducted by the SATESE on March 6, 1990	For delivery

On behalf of the General Council,
the Director of the Infrastructures

C. BOISRENOULT

58, Avenue Victor Hugo. B.P. N° 941. 60009 Beauvais Cedex. Téléphone : 44.84.02.72

DÉPARTEMENT DE L'OISE

DIRECTION DES INFRASTRUCTURES
S.A.T.E.S.E

REPORT ON INSPECTION VISIT
WATER TREATMENT FACILITIES OF
ROUSSEL UCLAF at COMPIEGNE

Affair followed up by J.T.
Visit N° 1

in the presence of : M. DANIC

User	: ROUSSEL UCLAF
Capacity	:
Connected	:
Network	: S
Meteorology	: dry
Average flow-rate	: 6 m^3/h
By-pass	:

Analysis results	pH	MES mg/l	BOD5 ad2 mg/l	COD ad2 mg/l	MO mg/l	NKT (N) mg/l	NH4 mg/l	NO2 mg/l	NO3 mg/l	mg/l
Crude water		83	54	260	127	14				
Treated water		17	5	55	22	25				

YIELDS		
	MES (Suspended matter) : 0.79	MO (Oxidizable matter) : 0.89
	NKT (Total nitrogen, Kjeldahl : 0	Global (MES + MO + NKT) : 0.71

COMMENTS

The flow-rate of the feeding pump is 7 m^3/hr instead of 6 m^3/hr.

The volume treated every day ranges between 120 and 140 m^3.

The actual biological treatment was run adequately. It is to be noted that the crude effluent seems to be less concentrated as compared to that observed during our last visits. This facilitates the treatment and especially the elimination of the COD.

It is recommended to maintain the present settings.

Setting of the equipment
Oximeter (1-4 mg/)

Sludge analysis	pH	MES g/l	% MVS	% 30 min dec. crude		O2 mg/l
Activation		8	79	73		2-3

Power Coeff. X	N	P	J
Today			
Previous count			
Difference			
Daily average	kWh		

SLUDGE PRODUCTION	m^3	
From Jan. 1 to Mar. 31 Disposal COMPIEGNE	145 m^3	

Counters	Count	Count	surp.1	surp.2						
Today	1618	16785	8326	12597						
On Dec. 4			8253	12052						
Daily average			3	5.9						

COMMENTS (Cont'd)

6.4. Discussion of the effect that approval will have upon compliance with current emissions requirements at the production site

Approval of the proposed action will have no adverse effect upon compliance with current emissions requirements of the production site.

12. LIST OF PREPARERS

This document was prepared in July 1992 and revised in March 1994. Persons involved in the preparation of this document in 1992 were :

- Mr Paul COSTE (Process Safety and Enviromental Protection at Vertolaye)

  Chemical Engineer, Graduate of the Ecole Nationale Supérieure de Chimie de Clermont-Ferrand, Licencié ès Sciences, Docteur-Ingénieur, who had 27 years of industrial experience as of January 1, 1992.

- Dr Martine DANAN-DURIEUX (Central Department of Toxicoviligance and Industrial Hygiene)

  Medical Doctor, Graduate of the Faculté de Médecine de Paris, post-grade studies in Clinical and Toxicological Pharmacology, who had 18 years of experience in the field of medicine and post-marketing surveillance as of January 1, 1992.

- Mr Jean-Claude GRANEL (Central Department of Environment and Safety)

  Chemical Engineer, Graduate of the Ecole Nationale Supérieure de Chimie de Montpellier, who had 22 years of industrial experience as of January 1, 1992.

- Mr Jean-Pierre TORCQ (Industrial Development at Compiègne)

  Electronics Engineer, who had 22 years of professional experience as of January 1, 1992.

  At this time Mr TORCQ is also in charge of the environmental protection.

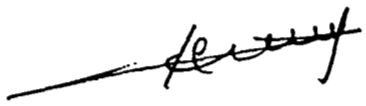
TRENBOLONE ACETATE/ESTRADIOL, Implant tablets

Environmental Assessment Report

13. CERTIFICATION

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

SIGNATURE : DATE : March 17, 1994



J.C. GRANEL

Manager,
Central Department of
Environment and Safety
and Industrial Hygiene

14. REFERENCES

- Material safety data sheets of the chemical substances that are subject of the proposed action

  . Trenbolone acetate

  . Estradiol

  (See attached sheets).

MATERIAL SAFETY DATA SHEET
NN : 1713
NFI :

70

ROUSSEL UCLAF

Date of issue : 12/10/89
Date of revision : 14/02/92
VERSION : (C)

NOTA : THE LATEST PERTINENT MODIFICATION INTRODUCED IN THE SAFETY DATA SHEET ARE SIGNALIZED BY A LETTER PLACED IN FRONT OF THE CONCERNED HEADING
INDUSTRIAL HYGIENE DELEGATION TEL : 48-91-44-31 FAX : 48-91-48-80

1. IDENTIFICATION of the SUBSTANCE/PREPARATION and the COMPANY

1.1. Identification of the substance or preparation

TRADE NAME ..... : TRENBOLONE ACETATE
SYNONYMS ..... : trienolone acetate
RU 1697
finaplix
CHEMICAL NAME ..... : 17 beta-hydroxy-estra-4,9,11-trien-3-one,acétate.
CAS NUMBER ..... : 10161-34-9
EINECS NUMBER ..... : 233-432-5
CHEMICAL FAMILY ..... : Hormone
FORMULA ..... : C20 H24 03
MOLECULAR MASS ..... : 312.41
KIND OF USE ..... : Veterinary use

1.2. Company / Undertaking identification

SUPPLIER ..... : ROUSSEL UCLAF
ADRESS ..... : 35, Bd des Invalides; 75007 PARIS - FRANCE; Tel : 40-62-40-62

1.3. EMERGENCY PHONE NUMBER ..16 (1) 48 91 44 31

2. COMPOSITION/INFORMATION on INGREDIENTS

HAZARDOUS CONSTITUENTS ..... :,
IMPURITIES ..... :

3. HAZARDS IDENTIFICATION

TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

4. FIRST-AID MEASURES

CONTACT WITH SKIN: Rinse with plenty of water .
CONTACT WITH EYES : Rinse immediately with plenty of water for at least 15 minutes.
IN CASE OF INHALATION : Make the victim blow his nose.
IN CASE OF INGESTION : Do not make the victim vomit. Alert a physician.

5. FIRE-FIGHTING MEASURES

SUITABLE EXTINGUISHING MEDIA ..... :Usual means .
UNSUITABLE EXTINGUISHING MEDIA ....:Jet of water from a fire hose
FIRE AND EXPLOSION HAZARDS ..... :None.
SPECIAL PROTECTIVE EQUIPMENT ..... :None.
OTHER RECOMMANDATIONS ..... :None.

6. ACCIDENTAL RELEASE MEASURES

Collect thouroughly into plastic bag. Rinse the polluted area with plenty of water.

7. HANDLING AND STORAGE

7.1 HANDLING

TECHNICAL MEASURES ..... :Mechanical sucking ventilation at source of formation of dust. Handle in closed circuit.

SPECIAL PROTECTION MEASURES ..... :Handle in dust-tight glove-box, whenever possible.

7.2 STORAGE

SENSIBILY TO DAMP ..... :Not observed.
SENSIBILY TO LIGHT ..... :Not observed.
SENSIBILY TO OXIDATION ..... :Sensitive to air
(C) SPECIAL STORAGE REQUIREMENTS ..... :Keep at ambient temperature
LOW TEMPERATURE TO BE AVOIDED .... :
(C) STORAGE CONDITIONS ..... :Keep at ambient temperature Keep under inert gas
SHELF LIFE ..... :3 years
STORAGE FACILITIES ..... :Specific place toxic products
RECOMMENDED PACKAGING MATERIAL ... :Glass, clarylene.
SUPPLIER PACKAGING ..... :Clarylene bag.
PACKAGING MATERIAL TO BE AVOID ... :Unknown.
INCOMPATIBLE SUBSTANCES ..... :Unknown.
OTHER RECOMMENDATIONS ..... :

8. EXPLOSURE CONTROLS/PERSONAL PROTECTION

PERSONAL PROTECTION/WORKSHOP ..... :Wear overalls, skullcap, gloves, goggles and dust respirator Have a shower after handling
PERSONAL PROTECT/LABORATORY ..... :Wear suitable gloves, safety goggles, and dust respirator

STEL .....:ND
TWA .....:ND
OLFACTORY THRESHOLD .....:ND
IDLH .....:

DETECTION ..... :

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE ..... :Yellowish powder.
pH ..... :Not applicable.
CHARACTERISTIC TEMPERATURES ..... :Melting point : 94-97°C
FLASH POINT ..... :Not applicable.
AUTOFLAMMABILITY ..... :Not determined.
INFLAMMABILITY LIMITS ..... :NA
EXPLOSIVE PROPERTIES/KST ..... :
MINIMUM INFLAMMATION ENERGY ..... :
COMMENTS ON FLAMMABILITY ..... :
VAPOUR PRESSURE ..... :Not determined.
RELATIVE DENSITY ..... :Not determined.
SOLUBILITY ..... :Not determined.
PARTITION COEFF. OCTANOL/WATER ... :
VAPOUR/AIR DENSITY ..... :
OTHER DATA ..... :alpha 20D : +39 to +43° (0,5%, methanol)

10. STABILITY AND REACTIVITY

HAZARDOUS REACTIONS ..... :None to our knowledge
HAZARDOUS DECOMPOSIT. PRODUCTS ... :Unknown.
SENSITIVITY TO JOLTING ..... :
PRODUCTS OF DECOMPOSITION
HEAT STABILITY ..... :

11. TOXICOLOGICAL INFORMATION

ACUTE TOXICITY	:LD 50 oral route/rat : > 5000 mg/kg LD 50 oral route /mouse : 2700 mg/kg.
IRRITANT POTENTIAL	:
PHYSIOLOGICAL ACTIVITY	:Substance physiologically very active. androgene anabolisant.
TERATO/MUTA/CARCINOGENICITY	:Cancerogenesis : carcinogenic to experimental animals probably carcinogenic to humans (group 2A/IARC)
COMMENTS/SYMPTOMS	:First signs of exposure: acne, genital troubles, virlization in women... TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED. Avoid any direct contact with product and mucosa.
OTHER RECOMMANDATIONS	:Handling inadvisable for pregnant women Possibly, seek medical advice

12. ECOLOGICAL INFORMATION

Biodegradable in natural media .

13. DISPOSAL CONSIDERATIONS

NEUTRALIZATION OF THE PRODUCT	:Set in specialized and approved recuperator service
DESTRUCTION SOILED PACKAGING	:Set in specialized and approved recuperator service

14. TRANSPORT INFORMATION

TRANSPORT ASSIMILATION	:
SPECIAL PRECAUTIONS	:
ONU	:2811
RTMD (FRANCE)	:6.1,61270a,6.1
RID/ADR	:6.1,90°b,6.1
OMCI/IMDG	:6.1,grII,p6236,6 poison
IATA	:6.1,GR II,,6 poison
CARGO	:615 (100 kg)
PASSENGERS	:613 (25kg)

15. REGULATORY INFORMATION

LABELLING (EEC NUMBER)	:Volontary labelling according to EEC regulations
SYMBOLS	:T
PHRASES	:R23/24/25 S36/37/39
SPECIAL RISKS	:TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
(C) SAFETY ADVICES	:Wear suitable protective clothing, gloves and eye/ face protection. Keep under nitrogen.
(C) ADDITIONNAL LABELLING	:Room temperature (<86 F)
	:
	:
	:
	:
	:
	:
	:
	:
	:
CANCER LIST	:SUBSTANCE BELONGING TO LIST IIA OF I.A.R.C, androgenic (anabolic) steroids

16. OTHER INFORMATION

SUBSTANCE BELONGING TO LIST IIA OF I.A.R.C, androgenic (anabolic) steroids

The information given in this sheet has been introduced in accordance with the guidelines established by article 10 of EEC directive 88/379, dated March 5,1991. This data sheet complement the user's instructions, but does not replace them. The information it contains is based on the knowledge available about the product concerned at the time it was compiled. Users are further reminded of the possible risks of using a product for purposes other then those for which it was intended. The required information complies with current EEC legislation; Adresses are requested to apply any additional national requirements.

MATERIAL SAFETY DATA SHEET
NN : 1674
NFI :

74

ROUSSEL UCLAF

Date of issue : 12/10/89
Date of revision : 25/10/90
VERSION :

NOTA : THE LATEST PERTINENT MODIFICATION INTRODUCED IN THE SAFETY DATA SHEET ARE SIGNALIZED BY A LETTER PLACED IN FRONT OF THE CONCERNED HEADING
INDUSTRIAL HYGIENE DELEGATION TEL : 48-91-44-31 FAX : 48-91-48-80

1. IDENTIFICATION of the SUBSTANCE/PREPARATION and the COMPANY

1.1. Identification of the substance or preparation

TRADE NAME ..... : ESTRADIOL
SYNONYMS ..... : Beta estradiol
cis-estradiol
17 beta OH estradiol
oestradiol
RU 3499
CHEMICAL NAME ..... : 17 beta-oestra-1,3,5(10)-triene-3,17-diol
CAS NUMBER ..... : 50-28-2
EINECS NUMBER ..... : 200-023-8
CHEMICAL FAMILY ..... : Hormone.
FORMULA ..... : C18 H24 O2
MOLECULAR MASS ..... : 272.4
KIND OF USE ..... : Medical use

1.2. Company / Undertaking identification

SUPPLIER ..... : ROUSSEL UCLAF
ADRESS ..... : 35, Bd des Invalides; 75007 PARIS - FRANCE; Tel : 40-62-40-62

1.3. EMERGENCY PHONE NUMBER ..16 (1) 48 91 44 31

2. COMPOSITION/INFORMATION on INGREDIENTS

HAZARDOUS CONSTITUENTS ..... :
IMPURITIES ..... :

3. HAZARDS IDENTIFICATION

TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.

4. FIRST-AID MEASURES

In all cases, alert a physician. CONTACT WITH SKIN: Rinse with plenty of water .
CONTACT WITH EYES : Rinse immediately with plenty of water for at least 15 minutes.
IN CASE OF INHALATION : Make the victim blow his nose.
IN CASE OF INGESTION : Do not make the victim vomit. Alert a physician.

5. FIRE-FIGHTING MEASURES

SUITABLE EXTINGUISHING MEDIA ..... :Usual means .
UNSUITABLE EXTINGUISHING MEDIA ....:Jet of water from a fire hose
FIRE AND EXPLOSION HAZARDS ..... :In case of fire, the product emits toxic fumes. (carbon oxides,.)
SPECIAL PROTECTIVE EQUIPMENT ..... :Wear a self-contained respiratory apparatus.
OTHER RECOMMANDATIONS ..... :None.

6. ACCIDENTAL RELEASE MEASURES

Before intervention see item Collect thouroughly into plastic bag. Rinse the polluted area with plenty of water.

7. HANDLING AND STORAGE

7.1 HANDLING

TECHNICAL MEASURES ..... :Mechanical sucking ventilation at source of formation of dust.

SPECIAL PROTECTION MEASURES ..... :Have a shower after handling.

7.2 STORAGE

SENSIBILY TO DAMP ..... :Hygroscopic.
SENSIBILY TO LIGHT ..... :Sensitive to light.
SENSIBILY TO OXIDATION ..... :Sensitive to air.
SPECIAL STORAGE REQUIREMENTS ..... :Room temperature (<86 F).
LOW TEMPERATURE TO BE AVOIDED .... :
STORAGE CONDITIONS ..... :Keep container tightly closed, away from air, moisture and light.
SHELF LIFE ..... :5 years
STORAGE FACILITIES ..... :Toxic products.
RECOMMENDED PACKAGING MATERIAL ... :glass, polythene.
SUPPLIER PACKAGING ..... :polythene bag in drums packaging.
PACKAGING MATERIAL TO BE AVOID ... :Unknown.
INCOMPATIBLE SUBSTANCES ..... :Unknown.
OTHER RECOMMENDATIONS ..... :

8. EXPLOSURE CONTROLS/PERSONAL PROTECTION

PERSONAL PROTECTION/WORKSHOP ..... :Wear dust-tight overalls pressurized, gloves, boots.
PERSONAL PROTECT/LABORATORY ..... :Wear overalls, skullcap, gloves, goggles and dust respirator.

STEL .....:ND
TWA .....:ND
OLFACTORY THRESHOLD .....:ND
IDLH .....:

DETECTION ..... :

9. PHYSICAL AND CHEMICAL PROPERTIES

APPEARANCE ..... :white powder
pH ..... :Not applicable.
CHARACTERISTIC TEMPERATURES ..... :Melting point : 178°C
FLASH POINT ..... :Not applicable.
AUTOFLAMMABILITY ..... :Not determined.
INFLAMMABILITY LIMITS ..... :ND
EXPLOSIVE PROPERTIES/KST ..... :
MINIMUM INFLAMMATION ENERGY ..... :
COMMENTS ON FLAMMABILITY ..... :
VAPOUR PRESSURE ..... :Not determined.
RELATIVE DENSITY ..... :Bulk : 0.3
SOLUBILITY ..... :Insoluble in water. Soluble in : ethanol,acetone, chloroform,dioxane.
PARTITION COEFF. OCTANOL/WATER ... :
VAPOUR/AIR DENSITY ..... :
OTHER DATA ..... :Alpha D25 : +76 to +83° (dioxane)

10. STABILITY AND REACTIVITY

HAZARDOUS REACTIONS ..... :None to our knowledge .
HAZARDOUS DECOMPOSIT. PRODUCTS ... :Unknown.
SENSITIVITY TO JOLTING ..... :
PRODUCTS OF DECOMPOSITION
HEAT STABILITY ..... :

11. TOXICOLOGICAL INFORMATION

ACUTE TOXICITY ..... :
IRRITANT POTENTIAL ..... :
PHYSIOLOGICAL ACTIVITY ..... :Substance physiologically active at the lowest dose. : estrogenic hormone. Possible adverses effects in case of treatment: central nervous system troubles hypertension, gain of weight ...

TERATO/MUTA/CARCINOGENICITY ..... :Mutagenesis: increase in the number of chromosomal aberrations in cultures of human fibroblasts. Increase in the number of aneuploid cells in cultures. Teratogenesis : effects on genital tract (feminization of male fetuses). Cancerogenesis: sufficient evidence in experimental animals (increase in the numbers of tumors, in several species, by several routes). Probably cancerogenic in humans.
COMMENTS/SYMPTOMS ..... :TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
OTHER RECOMMANDATIONS ..... :Do not expose pregnant women to the product.

12. ECOLOGICAL INFORMATION

Biodegradable in natural media .

13. DISPOSAL CONSIDERATIONS

NEUTRALIZATION OF THE PRODUCT .... :Incineration in accordance with laws.
DESTRUCTION SOILED PACKAGING ..... :Empty and rinse well.

14. TRANSPORT INFORMATION

TRANSPORT ASSIMILATION ..... :
SPECIAL PRECAUTIONS ..... :
ONU ..... :2811
RTMD (FRANCE) ..... :6.1,61270a,6.1
RID/ADR ..... :6.1,90°b,6.1
OMCI/IMDG ..... :6.1,Gr II,p 6236, 6 poison
IATA ..... :6.1,Gr II,,6 poison
CARGO ..... :615 (100 kg)
PASSENGERS ..... :613 (25 kg)

15. REGULATORY INFORMATION

LABELLING (EEC NUMBER) ..... :volontary labelling
SYMBOLS ..... :T
PHRASES ..... :R23/24/25 S7-15-36/37/39
SPECIAL RISKS ..... :TOXIC BY INHALATION, IN CONTACT WITH SKIN AND IF SWALLOWED.
SAFETY ADVICES ..... :Keep container tightly closed . Keep away from heat. Wear suitable protective clothing, gloves and eye/ face protection.
ADDITIONNAL LABELLING ..... :Room temperature (<86 F).
:
:
:
:
:
:
:
:
:
CANCER LIST :SUBSTANCE BELONGING TO LIST I OF I.A.R.C, (steroidal estrogens)

16. OTHER INFORMATION

SUBSTANCE BELONGING TO LIST I OF I.A.R.C, (steroidal estrogens)

The information given in this sheet has
been introduced in accordance with the
guidelines established by article 10 of
EEC directive 88/379, dated March 5,1991.
This data sheet complement the user's
instructions, but does not replace them.
The information it contains is based on the
knowledge available about the product
concerned at the time it was compiled.
Users are further reminded of the possible
risks of using a product for purposes other
then those for which it was intended.
The required information complies with current
EEC legislation; Adresses are requested to apply
any additional national requirements.