CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20747

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

COPY

FREEDOM OF INFORMATION (FOI)
NON-CONFIDENTIAL
ENVIRONMENTAL ASSESSMENT

FOR

NDA 20-747

ACTIQ (Oral Transmucosal Fentanyl Citrate)
200, 400, 600, 800, 1200 and 1600 mcg

For the management of chronic pain in patients already receiving opioid therapy and who are tolerant.

EXECUTIVE SUMMARY

This Environmental Assessment (EA) has been prepared as part of the New Drug Application (NDA) submitted by Anesta Corp. for Oral Transmucosal Fentanyl Citrate lozenge. The purpose of the EA is to supply information that will allow the Food and Drug Administration (FDA) to implement the provisions of the National Environmental Policy Act of 1969 (NEPA). This Act (NEPA) requires the FDA to identify actions that may significantly affect the quality of the human environment (21 CFR 25.1(b)(1)). In this EA, the manufacture, distribution, and use of the aforesaid new product are examined from the perspective of resource utilization, environmental releases, and ultimate disposition of the drug substance and all related materials.

The approach used for preparation of this EA was to identify and then focus on significant issues that will control the environmental impact of the proposed action. In doing so, it was ascertained that resource utilization during manufacture and distribution of this new drug product will require no irreversible or irretrievable commitment. Besides the fentanyl citrate, the other raw materials are commodity chemicals. Solid wastes generated during manufacture and distribution will be recovered, landfilled, or incinerated. Furthermore, releases of the drug substance to the environment will occur principally from product formulation activities in the form of wastewater discharges.

Analysis of the available scientific information on fate and transport of the released substances indicates that the environmental effects will be negligible. The relatively small quantity of drug available to the environmental compartments, and the extremely dilute aqueous concentration expected further reduced any environmental impact. These environmental characteristics will prevent the drug substance from adversely impacting the biota of any ecosystem. Release of all but minute amounts to surface waters is not expected, because fentanyl citrate will be removed from sewage treatment plants by aerobic degradation.

1. DATE

November, 1996

2. NAME OF APPLICANT

Abbott Laboratories
Hospital Products Division

3. ADDRESS

1401 Sheridan Road
North Chicago, Illinois 60064-4000

4. DESCRIPTION OF THE PROPOSED ACTION

4.1 REQUESTED APPROVAL

The proposed action encompasses formulation, packaging, and use of the new product known as Oral Transmucosal Fentanyl Citrate, which is formulated as a lozenge. The drug substance in the lozenge is fentanyl citrate. The per lozenge fentanyl (base) doses will be 200 micrograms, 400 micrograms, 600 micrograms, 800 micrograms, 1200 micrograms and 1600 micrograms.

This Environmental Assessment (EA) is part of the New Drug Application (NDA) for Oral Transmucosal Fentanyl Citrate (OTFC). Its format is arranged as required by 21 CFR 25.31(a).

4.2 NEED FOR ACTION

Fentanyl citrate is a strong narcotic analgesic used pre-operatively, during surgery, and in the immediate post-operative period for its analgesic action. In the lozenge form, fentanyl citrate can be self-administered under medical supervision.

4.3 LOCATIONS OF PRODUCTION

The bulk drug substance will be purchased by Abbott Laboratories. The fentanyl citrate is then processed into dosage forms (oral lozenges) at the Abbott, North Chicago, facility, 1401 Sheridan Road, North Chicago, IL 60064-4000.

4.4 LOCATIONS OF USE AND DISPOSAL

As prescribed medication for its analgesic action, fentanyl citrate, may be eliminated wherever the patients spend their day. The amount that is eliminated (or

excreted) would enter municipal treatment systems throughout the United States. Unsold Oral Transmucosal Fentanyl Citrate lozenges may be returned by pharmaceutical distributors to Abbott Laboratories for disposal. Partially used lozenges or lozenges purchased but unused by patients will be disposed of at the point of use via the sanitary sewer. Because this product is a controlled substance disposal in landfill should not occur. Packaging waste will be disposed of in municipal landfills throughout the United States.

4.5 ENVIRONMENTAL SETTING OF FACILITIES

4.5.1 Lake County, Illinois

The properties of Abbott Laboratories are located within the Wheaton Morainal Country physiographic division of Illinois (Visocky et al., 1985). The North Chicago property lies 600 to 1000 feet west of Lake Michigan at an elevation ten to fifteen feet above the average 580 foot MSL elevation of the lake. The Abbott Park property is located approximately eight miles to the west. The area is topographically flat and slopes very gently to the east, toward Lake Michigan. Drainage is dominantly to the east-southeast, again toward the lake.

The climate of northeastern Illinois is characterized by warm summers (74-80 degrees F) and cold winters (20-32 degrees F). The average annual rainfall for the Chicago area is 32 inches. Wind directions are highly variable.

Most industries and residences near the Abbott facilities are served by the City of North Chicago municipal water supply. The source of the municipal water supply is Lake Michigan. The Abbott Park facility currently uses both municipal water and groundwater from on-site wells. Land use near the Abbott facilities is primarily residential and industrial. The portion of Lake County in which they are located is part of the Chicago metropolitan area.

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

The new drug for which this application is prepared is Oral Transmucosal Fentanyl Citrate. The active drug substance is Fentanyl Citrate, USP.

5.1 NOMENCLATURE

5.1.1 Chemical Name

N-(1-Phenetheyl-4-Piperidyl) Propionanilide, Citrate (1:1)

5.1.2 Trade Name

Actiq™

5.1.3 Pharmacologic Name

Fentanyl Citrate

5.1.4 CAS Registry Number

990-73-8

5.1.5 Molecular Formula

$C_{22}H_{28}N_2O \cdot C_6H_8O_7$

5.1.6 RTECS Number

UE560000

5.2 PHYSICAL DESCRIPTION

As the citrate, fentanyl is a white crystalline substance that is slightly soluble in water. Its chemical and physical properties are listed in Table 5-1. Because it is an emphoteric substance ($pK._1 = 7.26$; $pK._2 = 9.02$), fentanyl citrate is ionic in aqueous solutions.

TABLE 5-1

Chemical and Physical Properties of Fentanyl Citrate

Molecular formula: $C_{22}H_{28}N_2O \cdot C_6H_8O_7$

Molecular weight: 528.61 gm/gm mole

Melting point: 149-151°C (reference 14.6)

Solubility in Water: Approximately 25,000 mg/L (reference 14.6)

Log organic carbon partition coefficient (range)

Log K_{OC} = 1.2 to 2.1 (estimated range)

Dissociation constants

pK_a 1 = 7.26
pK_a 2 = 9.02

Vapor Pressure

V.P. < = 10^{-6} Torr

5.3 FORMULATION COMPONENTS

The formulation components that are present in the Oral Transmucosal Fentanyl Citrate prepared with fentanyl citrate are listed in Table 5-2. Impurities have been detected only at low levels in bulk lots of fentanyl citrate that were maintained under expected conditions of storage. Concentrations of total impurities do not exceed 1 percent in any bulk lot.

TABLE 5-2

Composition of Oral Transmucosal Fentanyl Citrate

Product Components

Fentanyl Citrate, USP
Sucrose, NF
Glucose
Dye, White Dispersion
G.B.
Raspberry Artificial Flavor
Water for Injection

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

6.1 SUBSTANCES EMITTED

6.1.1 Oral Transmucosal Fentanyl Citrate Production

During production of Oral Transmucosal Fentanyl Citrate, the North Chicago facility will ultimately discharge the processing wastestreams to a municipal wastewater treatment facility (the North Shore Sanitary District). The solid waste resulting from the production steps described in Section 4.3.1 would be removed for disposal as indicated by the following:

Stream A:	Packaging Waste
Stream B:	Formulation Components
Stream C:	Equipment Cleaning
Stream D:	Off-specification Product

Non-hazardous solid waste is disposed of at Waste Management of Wisconsin (19414 60th Street, Bristol, Wisconsin 53104). Packaging waste, fiberboard containers, plastic bags, and are placed in 20- or 30-yd^3 rolloff boxes and transported by Abbott Laboratories to Waste Management. Steel drums at North Chicago are washed in a drum washing facility and then shipped to a drum reconditioner. Packaging waste is either recycled or disposed of as a non-hazardous waste. With the exception of fentanyl citrate, other formulation components will be disposed of as non-hazardous solid waste.

Fentanyl citrate or Oral Transmucosal Fentanyl Citrate product is disposed of as a controlled substance using the product destruction facility at Abbott's North Chicago facility (shredded and sewered).

Table 6.1 shows the anticipated losses from the distribution of one kilogram of Oral Transmucosal Fentanyl Citrate.

Table 6-1

Waste Generated from One Kilogram of Oral Transmucosal Fentanyl Citrate to Sales

Component	Losses to Wastewater (gm/kg)	Landfilling (kg/kg) Packaging
Fentanyl Citrate	0.03	
Water for Injection	2.23	
Sucrose	57.3	
Glucose	59.65	
Dye (White Dispersion, G.B.)	0.64	
Raspberry Flavor	1.06	
Packaging	—	< 4.0

6.2 CONTROLS EXERCISED ON RESIDUALS AND EMISSIONS

6.2.1 North Chicago

There are no ambient air emissions of fentanyl citrate associated with this action. When aqueous wastes streams from the North Chicago facility are sewered to the North Shore Sanitary District (NSSD) wastewater treatment plant, their treatability (without disrupting the sludge culture) is ensured by their lack of toxicity to such cultures Fentanyl that is not degraded can be adsorbed to the sludge and, thus, further reducing fentanyl concentrations in the effluent from the treatment plant

6.3 COMPLIANCE OF PROPOSED ACTION WITH APPLICABLE EMISSION REQUIREMENTS

The North Chicago facility is subject to effluent guidelines and standards for pharmaceutical manufacturing, and a local sanitary sewer permit. The standards are contained in the US EPA regulations 40 CFR Part 439. The manufacturing operations for Oral Transmucosal Fentanyl Citrate will be conducted in compliance with these regulations.

6.3.1 North Chicago

Wastewater from the Oral Transmucosal Fentanyl Citrate manufacturing facility at North Chicago is discharged in accordance with the facility process wastewater permit issued by the North Shore Sanitary District.

Air emissions from Abbott's facility at North Chicago are permitted by the Illinois Environmental Protection Agency. However, no air emission of Oral Transmucosal Fentanyl Citrate raw materials are associated with this action.

6.4 EFFECT OF PROPOSED ACTION ON COMPLIANCE WITH CURRENT EMISSION REQUIREMENTS

At North Chicago, the manufacture of Oral Transmucosal Fentanyl Citrate will not increase air emissions over existing emissions. Compliance with current emission limitations will be maintained.

During Oral Transmucosal Fentanyl Citrate production, wastewater discharges from North Chicago would not exceed the current limitations.

6.5 AMOUNT OF FENTANYL CITRATE ENTERING THE ENVIRONMENT

The potential routes by which fentanyl and related substances could enter the environment are (1) the manufacturing effluent, and (2) use and elimination by human patients. The amount of fentanyl citrate annually released to sewage systems via human patients is insignificant. This release is assumed to be evenly distributed throughout the population of the United States.

6.5.1 Human Elimination

The 1990 Census gives the population of the United States as 250,378,000. Typical minimum and maximum flow rates for publicly owned wastewater treatment systems range from 280 to 1,500 L/person/day (Metcalf & Eddy, Inc., 1979). The drug concentration at the treatment plant can be estimated from the following equation:

$$C = \frac{(A)\,(10^6\ mg/kg)}{(V)\,(2.5 \times 10^8\ persons)\ (365)\ days/yr}$$

where:

C = Concentration of drug at the treatment plant (mg/L).

A = Mass of drug used per year (.800) kg/yr)

V = Volume of wastewater entering a typical treatment plant (280 to 1,500 L/person/day).

Based on the fifth-year production forecast of Oral Transmucosal Fentanyl Citrate, the concentration of fentanyl estimated for a wastewater treatment plant would vary from 1.1×10^{-8} to 2.1×10^{-9} mg/L.

The foregoing estimate for potential concentration of fentanyl citrate in surface water was calculated with the assumption that this drug substance is not degraded or adsorbed to the sludge in the treatment facility, and hence, are conservatively high.

6.5.2 Oral Transmucosal Fentanyl Citrate Production

For 1.0 kg of Oral Transmucosal Fentanyl Citrate to sales, an average 0.03 gm of fentanyl will enter the North Shore Sanitary District treatment plant.

At Abbott's North Chicago facility, the mass of drug that would be released in wastewater during the anticipated fifth year of production.

The Abbott Laboratories North Chicago plant average wastewater flow to the North Shore Sanitary District is 1.6 MGD. The average effluent flow from the NSSD treatment facility is 17.0 MGD. Application of these values to the fentanyl loss figures results in the following estimates:

Average concentration of fentanyl citrate in Abbott's discharge is

9×10^{-6} mg/L.

Concentration of fentanyl citrate in Abbott's discharge from a year's

production discharged in one day is 2.3×10^{-2} mg/L.

Average concentration of fentanyl citrate in NSSD discharge is

9×10^{-7} mg/L.

Concentration of fentanyl in the NSSD effluent discharge from one year's production discharged in one day is 2.3×10^{-3} mg/L.

7. FATE OF EMITTED SUBSTANCES IN THE ENVIRONMENT

The predicted concentrations of substances entering the environment as a result of the proposed action are based on these processes and on the emissions discussed under preceding Section 6, Introduction of Substances into the Environment.

7.1 AIR

There are no releases of fentanyl citrate to the atmosphere during lozenge production in North Chicago, or use and disposal by patients. Particulate from the North Chicago facility is collected by filters for disposal. If any fentanyl citrate containing particulate matter escapes the filtration system, it will be eventually deposited and become strongly adsorbed to the surrounding soil where it should undergo slow biodegradation. Because fentanyl is an emphoteric substance (Table 5-1), it will always be ionic in both surface water and soil. Therefore, its volatilization to the atmosphere from these media is not expected.

7.2 WATER

Dilution of the effluent in surface water and adsorption of the remaining fentanyl to suspended particulates and sediment would further diminish the concentration.

Based on these observations, it can be concluded that fentanyl will not be present in detectable quantities in the aqueous phase of surface waters. The amount that becomes adsorbed to the sediment would ultimately undergo degradation catalyzed by extracellular enzymes of the sedimentary microbiota.

7.3 SOIL

If sewage sludge and residual material produced during manufacturing are landfilled, significant leaching of fentanyl would not be expected because of its adsorption to soil constituents. More importantly, the small quantities and

concentrations available to the environment make quantification of impact in soil unnecessary. The ultimate fate of fentanyl in soil would be biodegradation. This biodegradation would probably be catalyzed by the extracellular enzymes of the extant microbiota.

8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

In the surface water that receives the effluent, negligible or no fentanyl is expected, because of the small losses of the drug and the demonstrated biodegradation of the material. Based on the above considerations of concentration and toxicity, it is concluded that the environmental effects of the proposed action are negligible.

9. USE OF RESOURCES AND ENERGY

The estimate for energy usage during production of a typical batch is < 3,000 BTU per kilogram of product. During the fifth year of production, the energy usage would be this estimate multiplied by the production forecast. Incremental facility energy usage, and solid waste disposal requirements are less than 0.001% and 0.01%, respectively.

Because the bioavailability of fentanyl is negligible, no threatened or endangered species can be affected. Also, no significant expansion in manufacturing facilities is expected to result from the proposed action.

The State of Illinois does not regard property in the vicinity of the Abbott Park or North Chicago facilities to have historical or archaeological importance.

10. MITIGATION MEASURES

Compliance of the proposed action with applicable emission requirements is discussed in Section 6.3. Unused drugs are returned to Abbott Laboratories for disposal via the Returned Goods disposal system.

Waste minimization studies are an ongoing activity at Abbott facilities. As their results become available, practical measures to further control waste are incorporated into manufacturing procedures. Minimization of waste increases profitability and, therefore, receives substantial attention.

11. ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental impacts have been identified for the proposed action. Release of fentanyl citrate to the environment will be removed from exposure pathways, and by aqueous aerobic biodegradation. Because no adverse environmental impact is expected, alternatives to the proposed action are not being considered.

12. PREPARER

John H. Robbins, Abbott Laboratories, Manager, HPD Environmental Engineering,

B.S., Chemical Engineering, University of Wisconsin/Madison, 1977

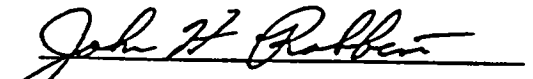
M.S,, Environmental Engineering, Illinois Institue of Technology, 1992

Professional Engineer, Wisconsin (28531)

Certified Hazardous Material Manager (2399)

13. CERTIFICATION

The undersigned certifies that the information presented is true, accurate, and complete to the best of the knowledge of the firm responsible for the preparation of the environmental assessment. This document has been prepared in accordance with 21 CFR 25.31a.

Signature  Date: Februrary 14, 1997

Title Environmental Engineer, Hospital Products Division, Abbott Laboratories

14. REFERENCES

14.1 Howard, P.H., ed., 1990. Handbook of Environmental Fate and Exposure Data for Organic Chemicals. Lewis Publishers, Inc., Chelsea, Michigan.

14.2 U.S. Food and Drug Administration. 1987. Environmental Assessment Technical Assistance Handbook. Washington, D.C.: U.S. FDA Center for Food Safety and Applied Nutrition. FDA/CFSAN-87/30. (NTIS PB87-175345).

14.3 Visocky, A.P., Sherrill, M.G., and Cartwright, K., 1985. Geology, Hydrology, and Water Quality of the Cambrian and Ordovician System in Northern Illinois. State of Illinois, Department of Natural Resources.

14.4 Wollman, H.B., 1971. Summary of the Geology of the Chicago Area. Illinois State Geological Survey, Circular 460.

14.5 Lyman, W.J., Reehl, W.F., Rosenblatt, D.H., 1990. Handbook of Chemical Property Estimation Methods. American Chemical Society.

14.6 Windholz, M., ed., 1983. The Merck Index, 10th Edition, Page 575, Entry Number 3926.

14.7 Zepp, R.G., and Cline, D.M., 1977. Rates of Direct Photolysis in Aquatic Environment. Environmental Science and Technology, 11:359-366.

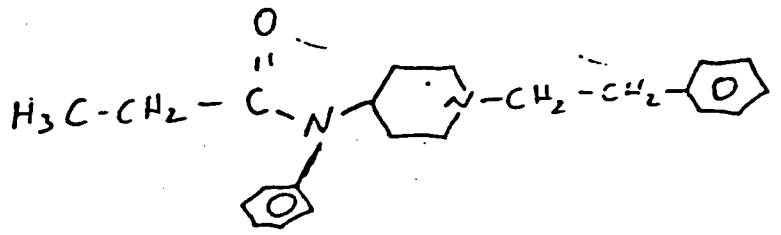
MATERIAL SAFETY DATA SHEET

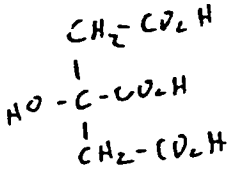
Sigma-Aldrich Corporation
1001 West Saint Paul Ave, Milwaukee, WI 53233 USA

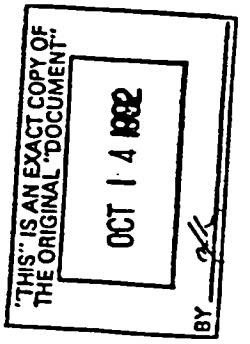
COPY

Valid 5/92- 7/92

	Sigma	Aldrich
For Emergency Contact USA/Canada	800-325-5832	800-231-8327
Outside USA/Canada	314-771-5765	414-273-3850







---------- IDENTIFICATION ----------

PRODUCT #: F7141
CAS #: 118357-30-5
MF: C22H28N2O

NAME: FENTANYL-D5 CITRATE--DEA SCHEDULE II ITEM

SYNONYMS

FENTANEST * FENTANYL CITRATE * LEPTANAL * MCN-JR 4263 * MCN-JR-4263-49 * FENTANYL * N-(1-PHENETHYL-4-PIPERIDINYL)PROPIONANILIDE DIHYDROGEN CITRATE * N-(1-PHENETHYL-4-PIPERIDYL)PROPIONANILIDE CITRATE * N-(1-PHENETHYL-4-PIPERIDYL)PROPIONANILIDE DIHYDROGEN CITRATE * PHENTANYL CITRATE * R 4263 * R 5240 * SUBLIMAZE * SUBLIMAZE CITRATE *

---------- TOXICITY HAZARDS ----------

RTECS DATA AND SYNONYMS SUPPLIED ARE FOR A CLOSELY RELATED COMPOUND.

RTECS NO: UE5600000
PROPIONANILIDE, N-(1-PHENETHYL-4-PIPERIDYL)-, CITRATE (1:1)

TOXICITY DATA

ORL-RAT LD50:18 MG/KG	TXAPA9 18,185,71
IPR-RAT LD50:2070 UG/KG	YAKUDS 21,535,79
SCU-RAT LD50:5460 UG/KG	NIIRDN 6,666,82
IVN-RAT LD50:990 UG/KG	NIIRDN 6,666,82
ORL-MUS LD50:368 MG/KG	YAKUDS 21,535,79
IPR-MUS LD50:68400 UG/KG	YAKUDS 21,535,79

SCU-MUS LD50:62 MG/KG
IVN-MUS LD50:10100 UG/KG

TXAPA9 6,48,64
NIIRDN 6,666,82

REVIEWS, STANDARDS, AND REGULATIONS
NOES 1983; HZD X3543; NIS 2; TNF 349; NOG 5; TNE 3782; TFE 2924
ARGET ORGAN DATA
PERIPHERAL NERVE AND SENSATION (FLACCID PARALYSIS WITHOUT ANESTHESIA)
BEHAVIORAL (SOMNOLENCE)
BEHAVIORAL (CONVULSIONS OR EFFECT ON SEIZURE THRESHOLD)
ONLY SELECTED REGISTRY OF TOXIC EFFECTS OF CHEMICAL SUBSTANCES (RTECS)
DATA IS PRESENTED HERE. SEE ACTUAL ENTRY IN RTECS FOR COMPLETE INFORMATION.

---------- HEALTH HAZARD DATA ----------

ACUTE EFFECTS
MAY BE FATAL IF INHALED, SWALLOWED, OR ABSORBED THROUGH SKIN.
MAY CAUSE ALLERGIC REACTION.
EXPOSURE CAN CAUSE LIGHT-HEADEDNESS, DIZZINESS, SEDATION, NAUSEA, VOMITING, SWEATING, RESPIRATORY DEPRESSION, APNEA, CIRCULATORY DEPRESSION, RESPIRATORY ARREST, SHOCK AND CARDIAC ARREST.
CHRONIC EFFECTS
PROLONGED OR REPEATED EXPOSURE CAN LEAD TO HABITUATION OR ADDICTION.
TARGET ORGAN(S):
CENTRAL NERVOUS SYSTEM
HEART
FIRST AID
IF SWALLOWED, WASH OUT MOUTH WITH WATER PROVIDED PERSON IS CONSCIOUS. CALL A PHYSICIAN.
IN CASE OF SKIN CONTACT, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. REMOVE CONTAMINATED CLOTHING AND SHOES. CALL A PHYSICIAN.
IF INHALED, REMOVE TO FRESH AIR. IF BREATHING BECOMES DIFFICULT, CALL A PHYSICIAN.
IN CASE OF CONTACT WITH EYES, FLUSH WITH COPIOUS AMOUNTS OF WATER FOR AT LEAST 15 MINUTES. ASSURE ADEQUATE FLUSHING BY SEPARATING THE EYELIDS WITH FINGERS. CALL A PHYSICIAN.

---------- PHYSICAL DATA ----------

APPEARANCE AND ODOR
SOLID.

---------- FIRE AND EXPLOSION HAZARD DATA ----------

EXTINGUISHING MEDIA
CARBON DIOXIDE, DRY CHEMICAL POWDER OR APPROP .IATE FOAM.
WATER SPRAY.
SPECIAL FIREFIGHTING PROCEDURES
WEAR SELF-CONTAINED BREATHING APPARATUS AND PROTECTIVE CLOTHING TO PREVENT CONTACT WITH SKIN AND EYES.
UNUSUAL FIRE AND EXPLOSIONS HAZARDS
EMITS TOXIC FUMES UNDER FIRE CONDITIONS.

---------- REACTIVITY DATA ----------

STABILITY
STABLE.
CONDITIONS TO AVOID
PROTECT FROM LIGHT.
HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS
TOXIC FUMES OF:
CARBON MONOXIDE, CARBON DIOXIDE
NITROGEN OXIDES
HAZARDOUS POLYMERIZATION
WILL NOT OCCUR.

---------- SPILL OR LEAK PROCEDURES ----------

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

WEAR RESPIRATOR, CHEMICAL SAFETY GOGGLES, RUBBER BOOTS AND HEAVY RUBBER GLOVES.

SWEEP UP, PLACE IN A BAG AND HOLD FOR WASTE DISPOSAL.

AVOID RAISING DUST.

VENTILATE AREA AND WASH SPILL SITE AFTER MATERIAL PICKUP IS COMPLETE.

WASTE DISPOSAL METHOD

CONTACT THE DRUG ENFORCEMENT ADMINISTRATION CONCERNING THE DISPOSAL OF CONTROLLED SUBSTANCES.

OBSERVE ALL FEDERAL, STATE, AND LOCAL LAWS.

--- PRECAUTIONS TO BE TAKEN IN HANDLING AND STORAGE ---

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

MAY CAUSE SENSITIZATION BY INHALATION AND SKIN CONTACT.

IF YOU FEEL UNWELL, SEEK MEDICAL ADVICE (SHOW THE LABEL WHERE POSSIBLE).

WEAR SUITABLE PROTECTIVE CLOTHING, GLOVES AND EYE/FACE PROTECTION.

TARGET ORGAN(S):

CENTRAL NERVOUS SYSTEM

HEART

LIGHT SENSITIVE

THE ABOVE INFORMATION IS BELIEVED TO BE CORRECT BUT DOES NOT PURPORT TO BE ALL INCLUSIVE AND SHALL BE USED ONLY AS A GUIDE. SIGMA ALDRICH SHALL NOT BE HELD LIABLE FOR ANY DAMAGE RESULTING FROM HANDLING OR FROM CONTACT WITH THE ABOVE PRODUCT. SEE REVERSE SIDE OF INVOICE OR PACKING SLIP FOR ADDITIONAL TERMS AND CONDITIONS OF SALE

RTECS

Topic: PROPIONANILIDE, N-(1-PHENETHYL-4-PIPERIDYL)-, C
ITRATE (1:1)

1.0 SUBSTANCE IDENTIFICATION
RTECS NUMBER: UE3600000
CHEMICAL NAME: PROPIONANILIDE, N-(1-PHENETHYL-4-PIPERIDYL)-,
CITRATE (1:1)
CAS NUMBER: 990-73-8
MOLECULAR FORMULA: C22-H28-N2-O.C6-H8-O7
MOLECULAR WEIGHT: 528.66
WISWESSER NOTATION: T6NTJ A2R& DNR&V2 &OV1XOVO&1VO
SUBSTANCE INVESTIGATED AS: Drug
LAST REVISION DATE: 9112
2.0 SYNONYM(S) / TRADE NAME(S)
1. FENTANEST
2. [redacted]
3. LEPTANAL
4. McN-JR 4263
5. MCN-JR-4263-49
6. PENTANYL
7. N-(1-PHENETHYL-4-PIPERIDINYL)PROPIONANILIDE DIHYDROGEN CITRATE
8. N-(1-PHENETHYL-4-PIPERIDYL)PROPIONANILIDE CITRATE
9. N-(1-PHENETHYL-4-PIPERIDYL)PROPIONANILIDE DIHYDROGEN CITRATE
10. PHENTANYL CITRATE
11. R 4263
12. R 5240
13. SUBLIMAZE
14. SUBLIMAZE CITRATE
3.0 HEALTH HAZARD DATA
3.1 ACUTE TOXICITY
3.1.3 LD50/LC50 - LETHAL DOSE/CONC 50% KILL
A. RAT
1. LD50; ROUTE: Oral; DOSE: 16 mg/kg; REFERENCE: Toxicology and Applied Pharmacology 18:185, 1971. <CODEN TXAPA9>
2. LD50; ROUTE: Intraperitoneal; DOSE: 2070 ug/kg; REFERENCE: Gekkan Yakuji. Pharmaceuticals Monthly 21:535, 1979. <CODEN YAKUD5>
3. LD50; ROUTE: Subcutaneous; DOSE: 3460 ug/kg; REFERENCE: Drugs in Japan 6:656, 1982. <CODEN NIIRDN>
4. LD50; ROUTE: Intravenous; DOSE: 990 ug/kg; REFERENCE: Drugs in Japan 6:606, 1982. <CODEN NIIRDN>
B. MOUSE
1. LD50; ROUTE: Oral; DOSE: 368 mg/kg; REFERENCE: Gekkan Yakuji. Pharmaceuticals Monthly 21:535, 1979. <CODEN YAKUD5>
2. LD50; ROUTE: Intraperitoneal; DOSE: 66400 ug/kg; REFERENCE: Gekkan Yakuji. Pharmaceuticals Monthly 21:535, 1979. <CODEN YAKUD5>
3. LD50; ROUTE: Subcutaneous; DOSE: 62 mg/kg; TOXIC EFFECTS: PERIPHERAL NERVE AND SENSATION - Flaccid paralysis without anesthesia; BEHAVIORAL - Somnolence (general depressed activity); BEHAVIORAL - Convulsions or effect on seizure threshold; REFERENCE: Toxicology and Applied Pharmacology 6:48, 1964. <CODEN TXAPA9>

RTECS

Topic: PROPIONANILIDE, N-(1-PHENETHYL-4-PIPERIDYL)-, C
ITRATE (1:1)

4. LD50: ROUTE: Intravenous; DOSE: 10100 ug/kg; REFERENCE: Drugs in Japan 6:666, 1982. <CODEN NIIRDN>

5.0 NIOSH DOCUMENTS

1. National Occupational Exposure Survey 1983: Hazard Code X9543; Number of Industries 2; Total Number of Facilities 349; Number of Occupations 5; Total Number of Employees 3782; Total Number of Female Employees 2924.