

TRILOSTANE

MATERIAL SAFETY DATA SHEET

In accordance with Regulation (CE) 1907/2006, (CE) 1272/2008 and (EU) 453/2010 (Annex I)
Revision no. 4 - Revision date: April 5, 2012

SECTION 1. IDENTIFICATION OF THE SUBSTANCE AND OF THE COMPANY

1.1. Substance identifier

| | |
|---|--|
| Substance name: | Trilostane |
| Other names (if available): Name in Annex VI-CLP: Name reported in the inventory of harmonized classification and labelling: | 4 α ,5 α -epoxy-3,17 β -dihydroxy-3-oxo-androstane-2 α -carbonitrile unlisted not available |
| CAS number | 13647-35-3 |
| REACH registration number | Exempt of registration |

1.2. Relevant identified uses of the substance and uses advised against

| | |
|----------------------|--|
| Relevant use(s) | Synthetic hormone - API (Active Pharmaceutical Ingredient) |
| Uses advised against | none |

1.3. Details of the supplier of the safety data sheet

Manufacturer/Distributor:

Company name: **STERLING S.r.l**

Address : **Via della Carboneria, 30 Solomeo
06073 Corciano (PG) – Italy**

Phone number : 075/5294001

Fax number: 075/5294000

Competent person responsible for the safety data sheet:

Aragona Anna Alessandra
e-mail: aragona@sterling.it

1.4. Emergency telephone number

02 66101029 (Centro Antiveleni Niguarda Ca' Granda – Milano)

SECTION 2 HAZARDS IDENTIFICATION

2.1 Classification of the substance

Classification of the substance in accordance with Regulation (CE) n. 1272/2008:

| Hazard class | Class code and hazard category | Hazard statement | Hazard warning |
|-----------------------|--------------------------------|------------------|---------------------------------|
| Reproductive toxicity | Repr. Cat. 2 | H361f | Suspected of damaging fertility |

Classification in accordance with Directive 67/548/CEE :

| Classification | Risk phrases | |
|------------------|--------------|--------------------------------------|
| Repr. Cat 3, R62 | R62 | Possible risk of impaired fertility. |


Main adverse effects
Physico-chemical effects
Health effects

No adverse effects known.
Suspected of damaging fertility.
No acute adverse effects known. The incidence of adverse effects increases with dose and duration of exposure. Possible allergic reaction to material if inhaled, ingested or in contact with skin.
No adverse effects known.

Environmental effects
See also sections from 9 to 12

2.2 Label elements

Labelling in accordance with regulation n. 1272/2008/EC

| | |
|---------------------------------------|--|
| Warning |  |
| Signal Word | Warning |
| Hazard indication (H)) ^[1] | H361f - Suspected of damaging fertility. |
| Safety statements (P) ^[1] | P201, P202, P281 P308+313 P405 P501 |
| - Prevention | |
| - Reaction | |
| - Storage | |
| - Disposal | |

^[1] For the explanation of H and P statements: see Section 16

2.3 Other hazards (which do not results in the classification)

The substance satisfies the PBT criteria

- PBT
- vPvB

| YES | NO |
|-----|----|
| | X |
| | X |

- Health hazards
- Environmental hazards
- Physico-chemical hazards

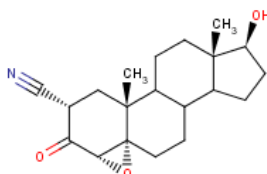
May be harmful if ingested, inhaled or in contact with skin. May be irritant or sensitizer.
not known
not known

- Specific effects

unknown

SECTION 3 COMPOSITION/INFORMATION ON INGREDIENTS

Description: Active Pharmaceutical Principle; Synthetic hormone.

| | |
|-------------------------------------|--|
| <i>Name of the component</i> | Trilostane |
| <i>Concentration</i> | Pure substance |
| <i>Structural formula</i> |  |
| <i>Chemical formula</i> | C ₂₀ H ₂₇ NO ₃ |
| <i>Molecular weight</i> | 329,4 g/mol |
| <i>Substance with Community OEL</i> | No |
| <i>CAS name</i> | Androst-2-ene-2-carbonitrile, 4,5-epoxy-3,17-dihydroxy-, (4.alpha.,5.alpha.,17.beta.)- |
| <i>CAS number</i> | 13647-35-3 |
| <i>IUPAC name</i> | (4alpha,5alpha,17beta)-3,17-dihydroxy-4,5-epoxyandrost-2-ene-2-carbonitrile |
| <i>EC number</i> | 237-133-0 |
| <i>Index number</i> | not assigned |
| <i>Impurity/ies (if classified)</i> | - |
| <i>Additive/ies (if classified)</i> | - |

SECTION 4 FIRST AID MEASURES

4.1 Description of the first aid measures

- | | |
|----------------|---|
| - Eye contact | Wash immediately with large amounts of water or normal saline. Keep eyelid open during the washing. Get medical advice if adverse symptoms will appear. |
| - Skin contact | Remove contaminated clothes (eventually shoes). Wash affected area with soap or mild detergent and large amount of water until no evidence of substance remains. Get medical advice if adverse symptoms will appear. |
| - Ingestion | If swallowed wash mouth with large amounts of water provided person is conscious. If victim is conscious and alert, give milk or water. Get medical advice if adverse symptoms will appear. |
| - Inhalation | Remove the person from the exposed area to fresh air immediately. If breathing has stopped perform artificial respiration, keep person warm and at rest. Get medical advice if the exposure was significant in terms of quantity or time. |

4.2 Most important symptoms and effects (acute and delayed)

- | | |
|---------------------------|---|
| - <i>Acute effects</i> | Possible eye, skin, gastrointestinal, and/or respiratory tract irritation. |
| - <i>Delayed effects:</i> | Suspected of damaging fertility. Possible allergic reaction to material if inhaled, ingested or in contact with skin. |

4.3 Indication of any immediate medical attention and special treatment needed

- | | |
|---|-------------------------------|
| - <i>Medical monitoring:</i> | In case of prolonged exposure |
| - <i>Antidotes, if known</i> | unknown |
| - <i>Contraindications</i> | unknown |
| - <i>Immediate treatment at workplace</i> | not known |

SECTION 5 FIREFIGHTING MEASURES

5.1 Extinguishing media

- | | |
|---|---|
| - <i>Suitable extinguishing media</i> | Water spray or chemical foam, dry foam, CO ₂ . |
| - <i>Unsuitable extinguishing media</i> | not known |

5.2 Special hazards arising from the substance

- | | |
|--|---|
| - <i>Hazardous combustion products</i> | May generate toxic fumes of CO _x and NO _x . |
| - <i>Other special hazards</i> | not known |

5.3 Advice to firefighters

- | | |
|--|---|
| - <i>Technical actions for protection</i> | Keep containers cool with water. |
| - <i>Special protective equipment for firefighters</i> | Wear boots, overalls, gloves, eye and face protection and breathing apparatus. Equipment must be conformed with EN criteria and used in highest condition of protection on the basis of the information reported in the previous sub-sections |

SECTION 6 ACCIDENTAL RELEASE MEASURES

6.1 Personal precautions, protective equipment and emergency procedures

- For non-emergency personnel

Wear appropriate protective equipment (see Section 8) to prevent contamination of the skin, eyes and personal clothing. In case of fire and/or explosions avoid breathing fumes and vapors. Use a self-contained breathing apparatus (SCBA) and appropriate protective clothing. The fumes can be eliminated by spraying with water. See also section 8

- For emergency responders

See section 8.

6.2 Environmental precautions

In case of accidental release in the environment avoid that the substance can reach drains, surface water and ground water. Contact local authorities in case of environmental release.

6.3 Methods and material for containment and clearing up

- *Containment procedures:* Coverage of the discharges
- *Cleaning up procedures:* Recover the substance for suction or other mechanical means and wash the area with plenty of water and detergents. Store the material into a company that specializes pending disposal. Containers must be cleaned up and disposed of as waste remediation above.

6.4 Reference to other sections

See also section 8 and 13.

SECTION 7 HANDLING AND STORAGE

7.1. Precautions for safe handling

- *Recommendation for handling:* Handle away from sparkles and flames - sources of ignition
Handle in a well ventilated place
Avoid contact with incompatible materials
Wear suitable Personal Protection Equipment (see section 8)
Keep the substance away from drains, surface or ground waters
- *Recommendation for personal hygiene:* Do not absolutely eat, drink and smoke in the working areas
Wash hands after handling the substance
Remove contaminated clothing and protective equipment before entering eating areas

7.2. Condition for safe storage including any incompatibilities

The substance is not classified for any physical and chemical properties and no risk management is foreseen.

Other advice

Store at 20°C to 25°C (68°F to 77°F), excursion permitted between 15°C and 30°C (between 59°F and 86°F)
Brief exposure to temperature up to 40°C (104°F) may be tolerated provided the mean kinetic temperature does not exceed 25°C (77°F); however, such exposure should be minimized

- *Ventilation requirements* Use in a well ventilated place at room temperature
- *Containers* Keep containers tightly closed and correctly labeled
- *Specific design of storage rooms* Not requested on the base of the classification
- *Quantity limits for storage* Not requested on the base of the classification
- *Packaging compatibilities* See also section 10.5

7.3. Specific end use(s)

- Recommendation for specific final use(s): Active Pharmaceutical Principle

| | | |
|------------------------------|-----|----|
| | YES | NO |
| - Exposure scenario attached | | X |

| | | |
|---|--|---|
| - Chemical Safety Assessment (CSA) attached | | X |
| - Industry or sector specific guidance available and attached | | X |

SECTION 8 EXPOSURE CONTROLS/PERSONAL PROTECTION

8.1. Control parameters

| | |
|--|---|
| - National/European Occupational Exposure Limits | unknown |
| - Other National/European Occupational Exposure Limits | unknown |
| - Recommended monitoring procedures | The measurement of substances in the workplace must be carried out with standardized methods (eg EN 689:1997: Workplace atmospheres - Guide for assessment of exposure by inhalation to chemical agents for comparison with limit values and measurement strategy; UNI EN 482:2006: atmospheres in the workplace - General requirements for the provision of procedures for the measurement of chemical agents) or, failing that, with appropriate methods. |
| - DNEL values (components) | unknown |
| - PNEC values (components) | unknown |

8.2. Exposure controls

| | YES | NO |
|---|-----|----|
| - Exposure scenario attached | | X |
| - Chemical Safety Assessment (CSA) attached | | X |

8.2.1. Appropriate engineering controls

The adoption of the most appropriate technical controls is also based on the local Risk Assessment done by the employer in its workplace conditions (use of the substance) when a unique and standardized exposure scenario described in a dossier registered REACH is not available.

8.2.2. Individual protection measures, such as Personal Protective Equipment (PPE)

| | |
|---------------------------------|--|
| a) Eye and Face protection | Safety goggles as for EN 166; facial shield |
| b) Skin protection | |
| - <i>hands protection</i> | Wear protective gloves. Gloves resistant to chemical agents as for the EN 374, parts 1, 2 e 3 and the European Directive 89/89/CEE. The glove material has to be made of rubber or polyethylene impermeable and resistant to the substance. Make the choice of the glove material on consideration of the penetration times, rates of diffusion and degradation. The selection of suitable gloves not only depends on the material, but also on further marks of quality and varies from manufacturer to manufacturer. |
| - <i>other, body protection</i> | Select the suitable protective equipment based on the activity of use and possible exposure. Wear gauntlets, boots, bodysuit and other devices in accordance with EN 13982. |
| c) Respiratory protection | Dust mask with approved dust filter. |

Use only devices approved by the Competent Authorities such as NIOSH (USA) and CEN (EU)

In the case of brief exposure or minimal exposure use respiratory filter; in case of intensive and sustained exposition wear self-contained breathing.

Where risk assessment shows air-purifying respirators are appropriate use a dust mask type P3 (EN 143) respirator

d) Thermal hazards

Not foreseen in the standard use. Assess possible Personal Protection Equipment on the basis of specific uses of the substance.

8.2.3 Environmental exposure controls

| | YES | NO |
|---|-----|----|
| - Exposure scenario attached | | X |
| - Chemical Safety Assessment (CSA) attached | | X |

SECTION 9 PHYSICAL AND CHEMICAL PROPERTIES

9.1. Information on basic physical and chemical properties

| | |
|--|--|
| Appearance: | White or whitish solid (Crystalline powder) |
| Odor: | - |
| Odour threshold: | - |
| pH: | Data not available in the literature search carried out |
| Melting point/freezing point: | 260-270 °C |
| Boiling point: | 497.8 °C (predicted) ⁽¹⁾ |
| Flash point: | 254.8 °C (predicted) ⁽¹⁾ |
| Auto-ignition temperature: | Data not available in the literature search carried out |
| Surface tension: | 58.1 dyne/cm (predicted) ⁽¹⁾ |
| Vapour pressure: | 5.39 x 10 ⁻¹² mmHg at 25°C (predicted) ⁽¹⁾ |
| Density: | 1.28 g/cm ³ (predicted) ⁽¹⁾ |
| Water solubility: | 84.27 mg/l (predicted) ⁽¹⁾ |
| Organic solvent solubility: | Data not available in the literature search carried out |
| Partition coefficient Octanol/water (Log Kow): | 2.02(predicted) ⁽¹⁾ |
| Explosive properties: | Data not available in the literature search carried out |
| Oxidising properties: | Data not available in the literature search carried out |

9.2. Other information

| | |
|---------------------|--|
| Henry Law constant: | 1.17 x 10 ⁻¹¹ atm-m ³ /mole (predicted) ⁽¹⁾ |
|---------------------|--|

SECTION 10 STABILITY AND REACTIVITY

10.1. Reactivity

Stable in normal conditions of storage.

10.2. Chemical stability

The substance is stable at the normal condition of temperature and pressure and if stored in closed containers in well ventilated and cool place.

- Stabilisers:

- Change in physical appearance

| NO | YES | Used stabiliser |
|----|-----|-----------------|
| X | - | |
| X | - | |

10.3. Possibility of hazardous reactions

- Possibility of an exothermic reaction:

- Possibility of a reaction releasing excessive pressure

- Possible degradation with instable product formation

| NO | YES |
|----|-----|
| X | - |
| X | - |
| X | - |

10.4. Condition to avoid

Keep protected from light, humidity and high temperatures.

10.5. Incompatible materials

Strong oxidizing agents

10.6. hazardous decomposition products

If heated at high temperatures, decomposes releasing fumes and toxic gases of COx, NOx.

SECTION 11 INFORMATION ON TOXICOLOGICAL EFFECTS

- **Exposure routes:**

- *Inhalation:*

- *Ingestion:*

- *Skin contact:*

- *Eye contact:*

| YES | NO |
|-----|----|
| X | |
| X | |
| X | |
| X | |

- **Effects (acute, delayed, chronic) following the exposure (short and/or prolonged):**

- *Inhalation:*

Suspected of damaging fertility.

May be harmful or sensitizing by inhalation

- *Ingestion:*

May be harmful if swallowed

- *Skin contact:*

May be irritant or sensitizing.

- *Eye contact:*

May be irritant

- **Toxico-kinetics information (ADME=Adsorption, Distribution, Metabolism, Excretion):** ⁽³⁾

In healthy dogs, maximal plasma levels of trilostane occur within 1.5 hours, returning to baseline levels within twelve hours, although large inter-dog variation occurs. There is no accumulation of trilostane or its metabolites over time.

- Acute toxicity effects:

- Oral: ⁽²⁾⁽⁴⁾ LD₅₀ rat > 15 g/kg
LD₅₀ mouse > 15 g/kg
- Dermal: Data not available in the literature search carried out
- Inhalation: Data not available in the literature search carried out
- Other effects: ⁽²⁾⁽⁴⁾ LD₅₀ Intraperitoneal – rat = 1055 mg/kg
LD₅₀ Intraperitoneal – mouse = 1205 mg/kg
LD₅₀ subcutaneous – rat = 7050 gm/kg
LD₅₀ subcutaneous – mouse > 15 gm/kg
LD₅₀ intravenous – rat = 102 gm/kg
LD₅₀ intravenous – mouse = 109 gm/kg

RTECS Number: **BV8044200**

- Corrosion/Irritation effects: Data not available in the literature search carried out

- Severe ocular lesion : Data not available in the literature search carried out

- Sensitisation: Data not available in the literature search carried out

- Repeated dose toxicity (experimental.): ⁽³⁾

The most common adverse reactions reported in studies performed in dogs are poor/reduced appetite, vomiting, lethargy/dullness, diarrhea and weakness. Occasionally, more serious reactions, including severe depression, hemorrhagic diarrhea, collapse, hypoadrenocortical crisis or adrenal necrosis/rupture may occur, and may result in death.

In a long term follow-up study of dogs in the US effectiveness study, the adverse reactions were similar to the short-term study. Vomiting, diarrhea and general gastrointestinal signs were most commonly observed. Lethargy, inappetence/anorexia, heart murmur or cardiopulmonary signs, inappropriate urination/incontinence, urinary tract infections or genitourinary disease, and neurological signs were reported.

- CMR effects:

- Germinal cell mutagenicity : Data not available in the literature search carried out

- Carcinogenicity : Data not available in the literature search carried out

- Reproductive toxicity: ^{(3) (4)}

Trilostane is associated with teratogenic effects and early pregnancy loss in laboratory animals.

Type of test: TDL0 oral - human

Dose : 48 mg/kg

Sex/Duration : male 14 day(s) pre-mating

Toxic effects : Reproductive - Paternal Effects - other effects on male

Type of test: TDL0 oral - rat

Dose : 1050 mg/kg

Sex/Duration : male 7 day(s) pre-mating

Toxic effects : Reproductive - Paternal Effects - other effects on male

Type of test: TDL0 oral - monkey

Dose : 5 mg/kg

Sex/Duration : female 25-29 day(s) after conception

Toxic effects : Reproductive - Fertility - abortion

- Specific Target Organ Toxicity (STOT)-single exposure: Data not available in the literature search carried out

- **Specific Target Organ Toxicity (STOT)- repeated exposure** : Data not available in the literature search carried out
- **Aspiration hazards**: Data not available in the literature search carried out
- **Epidemiological information**: Data not available in the literature search carried out

SECTION 12 ECOLOGICAL INFORMATION

12.1. Toxicity

Data not available in the literature search carried out

12.2. Persistence and degradability

Data not available in the literature search carried out

12.3. Bioaccumulative potential

BCF = 325.44 (predicted) ⁽¹⁾

Log Pow = 2.02 (predicted by EpiSuite) ⁽¹⁾

12.4. Mobility in soil

Data not available in the literature search carried out

12.5. Results of PBT e vPvB assessment

Assessment is not available - in relation to the value of logPow and BCF a bioaccumulation potential is not expected.

12.6. Other adverse effects

Not known

SECTION 13 DISPOSAL CONSIDERATION

13.1. Waste treatment methods

- Mixture wastes:
- Contaminated packaging:

| Incineration | Recycling | Landfilling |
|--------------|-----------|-------------|
| X | | |
| | X | |

Should never be disposed through wastewater.

Refers to Community/National/Local requirements concerning the waste disposal.

SECTION 14 TRANSPORT INFORMATION

The substance is not classified for transport.

SECTION 15 REGULATORY INFORMATION

15.1 Safety, Health and Environmental regulation/legislation specific for the mixture or its ingredients

Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work and following amendment and National reinforcements..

Council Directive 89/686/EEC of 21 December 1989 on the approximation of the laws of the Member States relating to the personal protective equipment

Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) Official Journal L 131 , 05/05/1998 P. 0011 - 0023

Regulation (EC) no 689/2008 of the european parliament and of the council of 17 June 2008 concerning the export and import of dangerous chemicals.

15.2. Chemical Safety Assessment

- Exposure scenario attached
- Chemical Safety Assessment (CSA) attached

| YES | NO |
|-----|----|
| | X |
| | X |

SECTION 16 OTHER INFORMATION

Revisions:

- **Revision n. 03 dated** February 2011 (regarding all sections in according to Regulation no. 453/2010).

Bibliographic sources:

- (1) Chemspider Database, search for CAS 13647-35-3
- (2) ChemIDplus Lite Database, search for CAS 13647-35-3
- (3) Daily Med, Current Medication Information, VETORYL (trilostane) capsule
- (4) RTECS Database for CAS 13647-35-3.

Acronyms

- ACGIH: American Conference of Governmental Industrial Hygienists

- ADR: Agreement concerning the carriage of dangerous goods by Road
- BCF: Bioaccumulative factor
- BEI : Biological Exposure Indices (Indici di esposizione biologica)
- CAS: Chemical Abstract Service (division of the American Chemical Society)
- CLP: Classification, Labelling and Packaging
- CMR: Carcinogens, Mutagens, Toxic for reproduction substances
- EINECS: European Inventory of existing Commercial Substances
- EPA: US Environmental Protection Agency
- GHS: Globally Harmonised System
- IARC: International Agency for Research on Cancer
- IATA: International Air Transport Association Code
- IMDG: International Maritime Dangerous Goods Code
- IUPAC: International Union of Pure and Applied Chemistry
- LOEL: Lowest Observed Effect Level
- NOAEL: No Observed Adverse Effect Level)
- NTP: National Toxicology Program
- OEL: Occupational Exposure Limit
- OSHA: Occupational Safety and Health Administration
- PPE : Personal protective Equipment
- PBT: Persistent, Bioaccumulative and Toxic substances
- RID: Regulation concerning the International carriage of Dangerous goods by rail
- TLV/TWA: Threshold Limit Value/Threshold Weighted Average
- vPvB: very Persistent, very Bioaccumulative

Information related to the regulation CE/1272/2008

List of hazards statements

H361f: Suspected of damaging fertility.

List of P statements

Prevention

P201 Obtain special instructions before use.
P202 Do not handle until all safety precautions have been read and understood.
P281 Use personal protective equipment as required.

Reaction

P308+P313: IF exposed or concerned: Get medical advice/attention.

Storage

P405 Store locked up.

Disposal

P501: Dispose of contents/container in accordance with local/regional/ national/international regulation.

Information related to the Directive 67/ 548/ CEE, Directive 1999/45/CE and Regulation (CE) n. 1907/2006

R phrases

R62: Possible risk of impaired fertility.

Information on workers training

Follow criteria of Directive 98/24/CE, its amendments and National reinforcements

Restriction of use : None

Substance under authorisation : no

DISCLAIMER

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