

**PART I** *What is the material and what do I need to know in an emergency?***1. IDENTIFICATION OF THE SUBSTANCE/MIXTURE AND OF THE COMPANY UNDERTAKING****IDENTIFICATION of the SUBSTANCE or PREPARATION:**

**TRADE NAME:** METHOTREXATE INJECTION, USP  
**CHEMICAL NAME:** Active Ingredient: N-[4-[[[2,4-diamino-6-pteridiny] methyl]methylamino]benzoyl]-L-glutamic acid  
**CHEMICAL CLASS:** Active Ingredient: Folic Acid Analog  
**THERAPEUTIC CLASS:** Antimetabolite  
**HOW SUPPLIED:** 50 mg/2 mL, 100 mg/4 mL, 250 mg/10 mL and 1 gm/40 mL  
**RELEVANT USE of the SUBSTANCE:** Human Pharmaceutical  
**USES ADVISED AGAINST:** Other than Relevant Use

**COMPANY/UNDERTAKING IDENTIFICATION:**

**U.S. SUPPLIER/MANUFACTURER'S NAME:** TEVA  
**ADDRESS:** 1090 Horsham Road  
 North Wales, PA 19454  
 215-591-3000 [08:00 AM --> 05:00 PM]  
**BUSINESS PHONE:**  
**EUROPEAN SUPPLIER/MANUFACTURER'S NAME:** TEVA/TAPI  
**ADDRESS:** Sicor sri-Via Terrazzano  
 77-20017 Cho (MI), Italy  
 +39 02 93197 306 [08:00 AM --> 05:00 PM]  
**BUSINESS PHONE:**  
**EMERGENCY PHONE:** United States/Canada/Puerto Rico: 1-800/424-9300 (Chemtrec) [24-hrs]  
 International: 01-703-527-3887 (Chemtrec) [24-hours]  
**EMAIL:** [bernadette.pogozelski@tevapharm.com](mailto:bernadette.pogozelski@tevapharm.com)  
**DATE OF PREPARATION:** July 25, 2012  
**DATE OF REVISION:** New

ALL WHMIS required information is included in appropriate sections based on the ANSI Z400.1-2004 format. This product has been classified in accordance with the hazard criteria of the CPR and the SDS contains all the information required by the CPR. The product is also classified per all applicable EU Directives through EC 1907: 2006, the European Union CLP EC 1272/2008 and the Global Harmonization Standard.

**2. HAZARD IDENTIFICATION**

**GLOBAL HARMONIZATION AND EU CLP REGULATION (EC) 1272/2008 LABELING AND CLASSIFICATION:** According to Article 1, item 5 (a) of CLP Regulation (EC) 1272/2008, medicinal products in the finished state for human use, as defined in 2001/83/EC, are excepted from classification and other criteria of 1272/2008.

**EU LABELING/CLASSIFICATION:** According to Article 1 of European Union Council Directive 92/32/EEC, medical products in the finished state for human use (as defined by European Union Council Directives 67/548/EEC and 87/21/EEC) are not subject to the regulations and administrative provisions of European Union Council Directive 92/32/EEC.

See Section 16 for full EU classification information of this product.

**EMERGENCY OVERVIEW: Product Description:** This product is a clear, colorless, odorless, aqueous solution. **Health Hazards:** This product may be harmful if ingested or by inhalation. In therapeutic use, the most common adverse effects have been ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection. Serious allergic reactions have occurred when administered for therapeutic use. The active ingredient can cause harm to the fetus and may cause adverse effects on fertility. See Section 11 (Toxicological Information) for more information on possible therapeutic use effects. **Flammability Hazards:** This product is not flammable or combustible. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds (including nitrogen oxides). **Reactivity Hazards:** This product is not reactive. **Environmental Hazards:** This product may cause harm to animals and aquatic organisms if accidentally released to the environment. **Emergency Recommendations:** Emergency responders must wear personal protective equipment suitable for the situation to which they are responding.

**3. COMPOSITION and INFORMATION ON INGREDIENTS**

NOTE: In formulation, trace amounts of sodium hydroxide or hydrochloric acid may be used for pH adjustment. No residue of these materials is left in finished product and so hazards of these compounds are not addressed in this SDS.

CHEMICAL NAME	CAS #	EINECS #	% w/v	EU Classification (67/548/EEC) GHS and EU Classification (1272/2008 EC) Risk Phrases/Hazard Statements
ACTIVE INGREDIENT				
Methotrexate Sodium N-[4-[[[2,4-diamino-6-pteridiny] methyl]methylamino]benzoyl]-L-glutamic acid	15475-56-6	239-495-5	Proprietary	SELF CLASSIFICATION EU 67/548 Classification: Reproductive Toxicity Cat. 1 Risk Phrase Codes: R60/61 GHS and EU 1272/2008 Classification: Acute Oral Toxicity Cat. 5, Reproductive Toxicity Cat. 1A Hazard Codes: H303, H360Df Hazard Symbol/Pictogram: GHS08

See Section 16 for full classification information of this product.

### 3. COMPOSITION and INFORMATION ON INGREDIENTS

CHEMICAL NAME	CAS #	EINECS #	% w/v	EU Classification (67/548/EEC) GHS and EU Classification (1272/2008 EC) Risk Phrases/Hazard Statements
EXCIPIENTS				
Sodium Chloride	7647-14-5	231-598-3	Proprietary	EU 67/548 CLASSIFICATION: NOT APPLICABLE. GHS AND EU 1272/2008 CLASSIFICATION: NOT APPLICABLE.
Water	7732-18-5	231-791-2	Balance	EU 67/548 Hazard Classification: Not Applicable GHS and EU 1272/2008 HAZARD CLASSIFICATION: Not Applicable

See Section 16 for full classification information of this product

## PART II What should I do if a hazardous situation occurs?

### 4. FIRST-AID MEASURES

**DESCRIPTION OF FIRST AID MEASURES:** Contaminated individuals must be taken for medical attention if any adverse effects occur. Remove contaminated clothing and shoes. Wash clothing and thoroughly clean shoes before reuse. Take a copy of this SDS to health professional with victim.

**SKIN EXPOSURE:** If this product contaminates the skin, begin decontamination with running water. Minimum flushing is for 20 minutes. The contaminated individual must seek medical attention if any adverse effects occur after flushing.

**EYE EXPOSURE:** If this product enters the eyes, open contaminated individual's eyes while under gently running water. Use sufficient force to open eyelids. Have contaminated individual "roll" eyes. Minimum flushing is for 20 minutes. Contaminated individual must seek medical attention if adverse effect continues after flushing.

**INHALATION:** If this product is inhaled, remove victim to fresh air. The contaminated individual must seek medical attention if any adverse effects occur.

**INGESTION:** If this product is swallowed, CALL PHYSICIAN OR POISON CONTROL CENTER FOR MOST CURRENT INFORMATION. If professional advice is not available, seek medical attention. Do not induce vomiting. Never induce vomiting or give diluents (milk or water) to someone who is unconscious, having convulsions, or unable to swallow. If victim is convulsing, maintain an open airway and obtain immediate medical attention.

**MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE:** Pre-existing skin, renal, digestive system, pulmonary or blood disorders may be aggravated by exposures to this product. This product presents a reproductive hazard for both genders and may cause harm to a fetus; it should be handled as a no contact material in the workplace.

**INDICATION OF IMMEDIATE MEDICAL ATTENTION AND SPECIAL TREATMENT IF NEEDED:** Treat symptoms and eliminate exposure. The following information is available on possible treatment for adverse reactions to this product in therapeutic use.

Leucovorin is indicated to diminish the toxicity and counteract the effect of inadvertently administered overdose of Methotrexate. Leucovorin administration should begin as promptly as possible. As the time interval between Methotrexate administration and leucovorin initiation increases, the effectiveness of leucovorin in counteracting toxicity decreases. Monitoring of the serum Methotrexate concentration is essential in determining the optimal dose and duration of treatment with leucovorin. In cases of massive overdose, hydration and urinary alkalization may be necessary to prevent the precipitation of Methotrexate and/or its metabolites in the renal tubules. Generally speaking, neither hemodialysis nor peritoneal dialysis has been shown to improve Methotrexate elimination. However, effective clearance of Methotrexate has been reported with acute, intermittent hemodialysis using a high-flux dialyzer (Wall, SM et al: *Am J Kidney Dis* 28 (6): 846-854, 1996).

Symptoms of intrathecal overdose are generally central nervous system (CNS) symptoms, including headache, nausea and vomiting, seizure or convulsion, and acute toxic encephalopathy. In some cases, no symptoms were reported. There have been reports of death following intrathecal overdose. In these cases, cerebellar herniation associated with increased intracranial pressure, and acute toxic encephalopathy have also been reported. Accidental intrathecal overdose may require intensive systemic support, high dose systemic leucovorin, alkaline diuresis and rapid CSF drainage and ventriculolumbar perfusion. In post-marketing experience, overdose with Methotrexate has generally occurred with oral and intrathecal administration, although intravenous and intramuscular overdose have also been reported. There are published case reports of intravenous and intrathecal carboxypeptidase G2 treatment to hasten clearance of Methotrexate in cases of overdose.

### 5. FIRE-FIGHTING MEASURES

**FLASH POINT:** Not applicable.

**AUTOIGNITION TEMPERATURE:** Not applicable.

**FLAMMABLE LIMITS (in air by volume, %):** Not applicable.

**FIRE EXTINGUISHING MEDIA:** Unless incompatibilities exist for surrounding materials, carbon dioxide, water spray, 'ABC' type chemical extinguishers, foam, dry chemical and halon extinguishers can be used to fight fires involving this product.

**UNSUITABLE FIRE EXTINGUISHING MEDIA:** None known.

**SPECIAL HAZARDS ARISING FROM THE SUBSTANCE:** This solution is not flammable or combustible. When involved in a fire, this material may decompose and produce irritating vapors and toxic compounds (including nitrogen oxides).

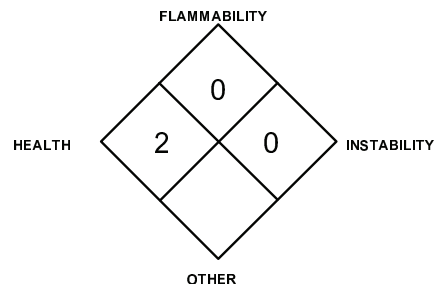
**Explosion Sensitivity to Mechanical Impact:** Not applicable.

**Explosion Sensitivity to Static Discharge:** Not applicable.

**SPECIAL PROTECTIVE ACTIONS FOR FIRE-FIGHTERS:** Structural firefighters

must wear Self-Contained Breathing Apparatus and full protective equipment. All personal protective gear and contaminated fire-response equipment should be decontaminated with soapy water before being returned to service. Move fire-exposed containers if it can be done without risk to firefighters. If possible, prevent runoff water from entering storm drains, bodies of water, or other environmentally sensitive areas.

#### NFPA RATING



Hazard Scale: 0 = Minimal 1 = Slight 2 = Moderate  
3 = Serious 4 = Severe

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## 6. ACCIDENTAL RELEASE MEASURES

**PERSONAL PRECAUTIONS, PROTECTIVE EQUIPMENT AND EMERGENCY PROCEDURES:** Spill kits, clearly labeled, should be kept in or near preparation and administrative areas. It is suggested that kits include an appropriate respirator, chemical splash goggles, two pairs of gloves, two sheets (12 x 12) of absorbent material, 250-mL and 1-liter spill control pillows and a small scoop to collect glass fragments (if applicable). Absorbents should be incinerable. Finally, the kit should contain two large waste-disposal bags. Avoid aerosols of this product during spill response procedures.

### **PROTECTIVE EQUIPMENT:**

**Small Spills/Spills in Hoods:** Personnel wearing gowns, double nitrile or latex gloves and eye protection should immediately clean spills of less than 5 mL outside a hood.

**Large Spills:** Use proper protective equipment, including double nitrile or latex gloves, full body gown, and full-face respirator equipped with an organic mist filter. Self-Contained Breathing Apparatus (SCBA) can be used instead of an air-purifying respirator.

### **METHODS FOR CLEAN-UP AND CONTAINMENT:**

**Cleanup of Small Spills:** Liquid spills should be gently covered with absorbent gauze pads. Remove the pads after absorption and dispose of properly. Clean the spill area (three times) using a bleach and detergent solution and then rinse with clean water.

**Spills in Hoods:** Decontamination of all interior hood surfaces may be required after the above procedures have been followed. If the HEPA filter of a hood is contaminated, label the unit "Do not use-contaminated" and have trained personnel wearing appropriate protective equipment change and dispose of the filter properly as soon as possible.

**Large Spills:** Review Sections 2, 8, 11 and 12 before proceeding with cleanup. For spills of amounts larger than 5 mL limit spread by gently covering with absorbent sheets or spill-control pads or pillows or, if a powder is involved, cover with damp cloths or towels. Be sure not to generate aerosols. Restrict access to the spill areas. The dispersion of mists or sprays into surrounding air and the possibility of inhalation is a serious matter and should be treated as such. Do not apply chemical in-activators as they may produce hazardous by-products. Thoroughly clean all contaminated surfaces three using a bleach and detergent solution and then rinse with clean water.

**All Spills:** Use procedures described above and then place all spill residues in an appropriate, labeled container and seal. Move to a secure area. Dispose of in accordance with Federal, State, and local hazardous waste disposal regulations (see Section 13, Disposal Considerations). For spills on water, contain, minimize dispersion and collect. Dispose of recovered product and report spill per regulatory requirements.

**ENVIRONMENTAL PRECAUTIONS:** Prevent material from entering sewer or confined spaces, waterways, soil or public waters. Do not flush to sewer. For spills on water, contain, minimize dispersion and collect.

**REFERENCE TO OTHER SECTIONS:** Review Sections 2, 8, 11, and 12 before proceeding with cleanup. See Section 13, Disposal Considerations for more information.

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## **PART III** *How can I prevent hazardous situations from occurring?*

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### **7. HANDLING and STORAGE**

**NOTE:** Consistent with the OSHA Bloodborne Pathogen regulation (29 CFR 1910.1030), observe Universal Precautions while using this product. Place used or product-contaminated hypodermic needles and syringes in a rigid "Sharps" container. Do not recap or clip used or product-contaminated hypodermic needles.

**PRECAUTIONS FOR SAFE HANDLING:** This product must be used by, or directly under the supervision of, a technically qualified individual. As with all chemicals, avoid getting this material ON YOU or IN YOU. Do not eat, drink, smoke, or apply cosmetics while handling this product. Wash hands thoroughly after handling this product or equipment and containers of this product. Follow SPECIFIC USE INSTRUCTIONS supplied with product. Particular care in working with this product must be practiced in pharmacies and other preparation areas, during manufacture of this product, and during patient administration. This product must be used by, or directly under the supervision of, a technically qualified individual. Open bulk containers slowly on a stable surface. Keep container tightly closed when not in use. Empty containers may contain residual amounts of this material; therefore, empty containers should be handled with care. Particular care in working with this product must be practiced in pharmacies and other preparation areas, during manufacture of this product, and during patient administration. Use of this product should be performed in a designated area for working with drugs. Contaminated waste must be properly handled. Work areas must be regularly decontaminated. Ensure vials are properly labeled.

**CONDITIONS FOR SAFE STORAGE:** Store containers in a cool, dry location, away from direct sunlight and sources of intense heat. Store away from incompatible materials (see Section 10, Stability and Reactivity). Product should be stored in secondary containers. Inspect all incoming containers before storage, to ensure containers are properly labeled and not damaged.

**SPECIFIC END USE(S):** This product is human pharmaceutical.

**PROTECTIVE PRACTICES DURING MAINTENANCE OF CONTAMINATED EQUIPMENT:** When cleaning non-disposable equipment, wear appropriate hand protection (double gloving is recommended), goggles, and lab coat. If applicable, wash equipment with bleach and detergent solution and rinse with clean water.

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### **8. EXPOSURE CONTROLS - PERSONAL PROTECTION**

#### **EXPOSURE LIMITS/CONTROL PARAMETERS:**

**VENTILATION AND ENGINEERING CONTROLS:** Use with adequate local ventilation or chemical fume hood to reduce exposure. Ensure eyewash/safety shower stations are available near areas where this product is used.

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## 8. EXPOSURE CONTROLS - PERSONAL PROTECTION (Continued)

### EXPOSURE LIMITS/CONTROL PARAMETERS (continued):

#### WORKPLACE EXPOSURE LIMITS/CONTROL PARAMETERS:

CHEMICAL NAME	CAS #	EXPOSURE LIMITS IN AIR							
		ACGIH-TLVs		OSHA-PELs		NIOSH-RELs		NIOSH	OTHER
		TWA ppm	STEL ppm	TWA ppm	STEL ppm	TWA ppm	STEL ppm	IDLH ppm	
Methotrexate Sodium	15475-56-6	NE	NE	NE	NE	NE	NE	NE	NE
Sodium Chloride	7647-14-5	NE	NE	NE	NE	NE	NE	NE	NE

NE = Not Established

See Section 16 for Definitions of Other Terms Used

**INTERNATIONAL OCCUPATIONAL EXPOSURE LIMITS:** Currently, the following exposure limits are in place for some components of this product. Limits change or are added and should be checked periodically.

**SODIUM CHLORIDE:**

Russia: STEL = 5 mg/m<sup>3</sup>, JUN 2003

**PROTECTIVE EQUIPMENT:** The following information on appropriate Personal Protective Equipment is provided to assist employers in complying with OSHA regulations found in 29 CFR Subpart I (beginning at 1910.132, including U.S. Federal OSHA Respiratory Protection (29 CFR 1910.134), OSHA Eye Protection 29 CFR 1910.133, OSHA Hand Protection 29 CFR 1910.138, OSHA Foot Protection 29 CFR 1910.136 and OSHA Body Protection 29 CFR 1910.132), equivalent standards of Canada (including CSA Respiratory Standard Z94.4-02, Z94.3-M1982, Industrial Eye and Face Protectors and CSA Standard Z195-02, Protective Footwear), or standards of EU member states (including EN 529:2005 for respiratory PPE, CEN/TR 15419:2006 for hand protection, and CR 13464:1999 for face/eye protection). Please reference applicable regulations and standards for relevant details.

**RESPIRATORY PROTECTION:** Maintain airborne contaminant concentrations below exposure limits listed above if applicable. If necessary, use only respiratory protection authorized under appropriate regulations. Oxygen levels below 19.5% are considered IDLH by U.S. OSHA. In such atmospheres, use of a full-facepiece pressure/demand SCBA or a full facepiece, supplied air respirator with auxiliary self-contained air supply is required under U.S. OSHA's Respiratory Protection Standard (1910.134-1998).

**EYE PROTECTION:** Wear splash goggles or safety glasses. Face shields are recommended if solutions are made. If necessary, refer to appropriate regulations.

**HAND PROTECTION:** Wash hands before putting on gloves and after removing gloves. During medical administration of this product, double glove with medical latex or nitrile gloves should be worn to avoid absorption of the product. During manufacture or other similar industrial operations, wear the appropriate hand protection for the process. Use double gloves for spill response, as stated in Section 6 (Accidental Release Measures) of this SDS. If necessary refer to appropriate regulations.

**SKIN PROTECTION:** Use appropriate protective clothing for the task (e.g., lab coat, etc.). If necessary, refer to the U.S. OSHA Technical Manual (Section VII: Personal Protective Equipment) or other appropriate regulations.

## 9. PHYSICAL and CHEMICAL PROPERTIES

The following information is for the drug product.

**PHYSICAL FORM:** Liquid.

**ODOR:** Practically odorless.

**MOLECULAR WEIGHT:** Mixture.

**pH:** 8.5

**HOW TO DETECT THIS SUBSTANCE (identification/warning properties):** There are no distinguishing characteristics of this product in event of accidental release.

**COLOR:** Clear.

**ODOR THRESHOLD:** Not applicable.

**MOLECULAR FORMULA:** Mixture.

The following information is for the Methotrexate Sodium active ingredient.

**FORM:** Powdered, crystalline solid.

**MOLECULAR WEIGHT:** 454.45

**ODOR:** Odorless.

**VAPOR DENSITY:** Not applicable.

**BOILING POINT @ 760 mmHg:** Not available.

**MELTING POINT:** Not available.

**pH:** Not applicable for solid.

**SOLUBILITY IN WATER:** Soluble.

**OTHER SOLUBILITIES:** Not available.

**COEFFICIENT OF WATER/OIL DISTRIBUTION:** Log P: -0.241 (predicted)

**COLOR:** White to off-white.

**MOLECULAR FORMULA:** C<sub>20</sub>H<sub>22</sub>N<sub>8</sub>O<sub>5</sub>

**ODOR THRESHOLD:** Not applicable.

**VAPOR PRESSURE (air = 1) @ 25°C:** Not available.

**EVAPORATION RATE (nBuAc = 1):** Not applicable.

**% VOLATILITY:** No data available.

**DENSITY:** Not available.

**FLASH POINT:** Not available.

## 10. STABILITY and REACTIVITY

**CHEMICAL STABILITY:** Normally stable.

**DECOMPOSITION PRODUCTS:** *Combustion:* Products of thermal decomposition may include nitrogen oxides and oxygen.

*Hydrolysis:* None known.

**MATERIALS WITH WHICH SUBSTANCE IS INCOMPATIBLE:** Strong acids and other material incompatible with typical medical preparations and materials that are incompatible with water.

**POSSIBILITY OF HAZARDOUS REACTION/POLYMERIZATION:** None known.

**CONDITIONS TO AVOID:** Exposure to or contact with extreme temperatures, incompatible chemicals.

## PART IV *Is there any other useful information about this material?*

### 11. TOXICOLOGICAL INFORMATION

**SYMPTOMS OF EXPOSURE BY ROUTE OF EXPOSURE:** The main route of occupational exposure to this product is via inhalation of mists or sprays and skin or eye contact. The anticipated symptoms of exposure, by route of exposure are described further in this section.

## 11. TOXICOLOGICAL INFORMATION (Continued)

**INHALATION:** Inhalation of mists or sprays of this material may irritate the mucous membranes and upper respiratory tract. Symptoms of such exposure may include coughing, sneezing, and congestion.

**CONTACT WITH SKIN OR EYES:** Eye contact with this material may be moderately irritating. Symptoms of eye contact may include redness and watering. Skin contact with this material may be irritating. Symptoms of skin contact may include redness and itching.

**SKIN ABSORPTION:** No data is available on potential absorption of this product through intact skin.

**INGESTION:** Ingestion of this product is not anticipated to be a significant route of occupational exposure. Ingestion may be harmful and cause adverse effects as described under 'Other Potential Health Effects'.

**INJECTION:** Accidental injection of this product, via laceration or puncture by a contaminated object may cause pain and irritation in addition to the wound. Other effects described under 'Other Potential Health Effects'.

**OTHER POTENTIAL HEALTH EFFECTS-Therapeutic Doses:** When used in therapeutic injectable preparations, the most common adverse effects have been ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects are malaise, undue fatigue, chills and fever, dizziness and decreased resistance to infection. Other adverse effects described by body system have included:

- **Alimentary System:** Gingivitis, pharyngitis, stomatitis, anorexia, nausea, vomiting, diarrhea, hematemesis, melena, gastrointestinal ulceration and bleeding, enteritis, pancreatitis.
- **Blood and Lymphatic System Disorders:** Suppressed hematopoiesis, anemia, aplastic anemia, pancytopenia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, eosinophilia, lymphadenopathy and lymphoproliferative disorders (including reversible). Hypogammaglobulinemia has been reported rarely.
- **Cardiovascular:** Pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).
- **Central Nervous System:** Headaches, drowsiness, blurred vision, transient blindness, speech impairment including dysarthria and aphasia, hemiparesis, paresis and convulsions have also occurred following administration of Methotrexate. Following low doses, there have been occasional reports of transient subtle cognitive dysfunction, mood alteration or unusual cranial sensations, leukoencephalopathy, or encephalopathy.
- **Hepatobiliary Disorders:** Hepatotoxicity, acute hepatitis, chronic fibrosis and cirrhosis, hepatic failure, decrease in serum albumin, liver enzyme elevations.
- **Musculoskeletal System:** Stress fracture.
- **Ophthalmic:** Conjunctivitis, serious visual changes of unknown etiology.
- **Pulmonary System:** Respiratory fibrosis, respiratory failure, alveolitis, interstitial pneumonitis deaths have been reported, and chronic interstitial obstructive pulmonary disease has occasionally occurred.
- **Skin:** Erythematous rashes, pruritus, urticaria, photosensitivity, pigmentary changes, alopecia, ecchymosis, telangiectasia, acne, furunculosis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, skin necrosis, skin ulceration, and exfoliative dermatitis.
- **Urogenital System:** Severe nephropathy or renal failure, azotemia, cystitis, hematuria, proteinuria; defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, and gynecomastia; infertility, abortion, fetal death, fetal defects.
- **Other:** There have been case reports of sometimes fatal opportunistic infections in patients receiving Methotrexate therapy for neoplastic and non-neoplastic diseases. *Pneumocystis carinii* pneumonia was the most common opportunistic infection. There have also been reports of infections, pneumonia, cytomegalovirus infection, including cytomegaloviral pneumonia, sepsis, fatal sepsis, nocardiosis; histoplasmosis, cryptococcosis, *Herpes zoster*, *H. simplex* hepatitis, and disseminated *H. simplex*. Other rarer reactions related to or attributed to the use of Methotrexate such as nodulosis, vasculitis, arthralgia/myalgia, loss of libido/impotence, diabetes, osteoporosis, sudden death, lymphoma, including reversible lymphomas, tumor lysis syndrome, soft tissue necrosis and osteonecrosis. Anaphylactoid reactions have been reported.

### HEALTH EFFECTS OR RISKS FROM EXPOSURE:

**Acute:** This product may cause irritation by all routes. Accidental ingestion may be harmful.

**Chronic:** Chronic exposure to this product may cause adverse effects as described under 'Other Potential Health Effects'. May cause harm to fetus or adverse effects on fertility for both genders.

**TARGET ORGANS:** **Acute:** Occupational Exposure and Therapeutic Use: Skin. **Chronic:** Occupational Exposure: Skin. Therapeutic Use: See 'Other Potential Health Effects'.

**TOXICITY DATA:** The following toxicity data are currently available for active ingredient of this product. Data are available for the excipient ingredient, but are not presented in this SDS. Contact Teva for more information.

#### METHOTREXATE SODIUM:

LD<sub>50</sub> (Intraperitoneal-Mouse) 27 mg/kg  
LD<sub>50</sub> (Unreported-Mouse) 380 mg/kg

#### METHOTREXATE SODIUM (continued):

TDLo (Intraperitoneal-Rat) 200 µg/kg: female 9 day(s) after conception: Reproductive: Fertility: post-implantation mortality (e.g. dead and/or resorbed implants per total number of implants); Effects on Embryo or Fetus: fetotoxicity (except death, e.g., stunted fetus)

#### METHOTREXATE SODIUM (continued):

TDLo (Intravenous-Rabbit) 19,200 µg/kg: female 12 day(s) after conception: Reproductive: Fertility: litter size (e.g. # fetuses per litter, measured before birth); Effects on Embryo or Fetus: fetotoxicity (except death, e.g., stunted fetus), cytological changes (including somatic cell genetic material)

HAZARDOUS MATERIAL IDENTIFICATION SYSTEM			
HEALTH HAZARD		(BLUE)	2*
FLAMMABILITY HAZARD		(RED)	0
PHYSICAL HAZARD		(YELLOW)	0
PROTECTIVE EQUIPMENT			
EYES	RESPIRATORY	HANDS	BODY
	See Section 8		See Section 8
For Routine Industrial Use and Handling Applications			

Hazard Scale: 0 = Minimal 1 = Slight 2 = Moderate  
3 = Serious 4 = Severe \* = Chronic hazard

## 11. TOXICOLOGICAL INFORMATION (Continued)

### TOXICITY DATA (continued):

#### METHOTREXATE SODIUM (continued):

TDLo (Intravenous-Rabbit) 19,200 µg/kg; female 12 day(s) after conception: Reproductive: Specific Developmental Abnormalities: Central Nervous System, craniofacial (including nose and tongue), musculoskeletal system

#### METHOTREXATE SODIUM (continued):

TDLo (Intravenous-Rabbit) 19,200 µg/kg; female 12 day(s) after conception: Reproductive: Effects on Embryo or Fetus: fetotoxicity (except death, e.g., stunted fetus)  
TDLo (Unreported-Mouse) 90 mg/kg/10 days-intermittent: Related to Chronic Data: death

#### METHOTREXATE SODIUM (continued):

DNA Inhibition (Human Cells-Not Otherwise Specified) 10 nmol/L  
Cytogenetic Analysis (Human Lymphocyte) 100 nmol/L  
DNA Inhibition (Mouse Lymphocyte) 1 µmol/L  
Mutation Test Systems-Not Otherwise Specified (Mouse Lymphocyte) 1 µmol/L  
Cytogenetic Analysis (Intraperitoneal-Mouse) 2 mg/kg  
Micronucleus Test (Intraperitoneal-Mouse) 2 mg/kg

**CARCINOGENIC POTENTIAL OF COMPONENTS:** No controlled human data exist regarding the risk of neoplasia with Methotrexate. Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Non-Hodgkin's lymphoma and other tumors have been reported in patients receiving low-dose oral Methotrexate. However, there have been instances of malignant lymphoma arising during treatment with low-dose oral Methotrexate, which have regressed completely following withdrawal of Methotrexate, without requiring active anti-lymphoma treatment. The remaining components of this product are not found on the following lists: U.S. EPA, U.S. NTP, U.S. OSHA, U.S. NIOSH, GERMAN MAK, IARC, or ACGIH and therefore is neither considered to be nor suspected to be a cancer-causing agent by these agencies.

**IRRITANCY OF PRODUCT:** This product may irritate the respiratory system, mucous membranes, and eyes.

**SENSITIZATION TO THE PRODUCT:** Severe, occasionally fatal, dermatologic reactions, including toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, have been reported in children and adults, within days of oral, intramuscular, intravenous, or intrathecal Methotrexate administration. Reactions were noted after single or multiple low, intermediate, or high doses of Methotrexate in patients with neoplastic and non-neoplastic diseases.

**REPRODUCTIVE TOXICITY INFORMATION:** This product is rated Pregnancy Category X (Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits). There are no adequate and well-controlled studies in pregnant women. No information on animal reproduction studies is available.

**Mutagenicity:** Although there is evidence that Methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain.

**Embryotoxicity/Teratogenicity:** Methotrexate causes embryotoxicity, abortion, and fetal defects in humans.

**Reproductive Toxicity:** Methotrexate has also been reported to cause impairment of fertility, oligospermia and menstrual dysfunction in humans, during and for a short period after cessation of therapy.

**BIOLOGICAL EXPOSURE INDICES:** Currently, there are no Biological Exposure Indices (BEIs) determined for the components of this product.

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## 12. ECOLOGICAL INFORMATION

ALL WORK PRACTICES MUST BE AIMED AT ELIMINATING ENVIRONMENTAL CONTAMINATION.

**MOBILITY:** No information is available on mobility of this product.

**PERSISTENCE AND BIODEGRADABILITY:** No information on persistence or biodegradability is available for this product.

**BIO-ACCUMULATION POTENTIAL:** No information available.

**ECOTOXICITY:** This product may be harmful to contaminated plant and animal life, especially in large quantities. All releases to terrestrial, atmospheric and aquatic environments should be avoided. No data are currently available for this product.

**RESULTS OF PBT AND vPvB ASSESSMENT:** No Data Available. PBT and vPvB assessments are part of the chemical safety report required for some substances in European Union Regulation (EC) 1907/2006, Article 14.

**OTHER ADVERSE EFFECTS:** The components of this product are not listed as having ozone depletion potential.

**ENVIRONMENTAL EXPOSURE CONTROLS:** Controls should be engineered to prevent release to the environment, including procedures to prevent spills, atmospheric release and release to waterways.

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## 13. DISPOSAL CONSIDERATIONS

**WASTE TREATMENT/DISPOSAL METHODS:** Waste disposal must be in accordance with appropriate Federal, State, and local regulations. This product, if unaltered by use, may be disposed of by treatment at a permitted facility or as advised by your local hazardous waste regulatory authority. All gowns, gloves, and disposable materials used in the preparation or handling of this drug should be disposed of in accordance with established hazardous waste disposal procedures. Incineration is recommended. Reusable equipment should be cleaned with soap and water. It is the responsibility of the generator to determine at the time of disposal whether the product meets the criteria of a hazardous waste per regulations of the area in which the waste is generated and/or disposed of. Incineration is recommended for the product and disposable equipment. Shipment of wastes must be done with appropriately permitted and registered transporters.

**DISPOSAL CONTAINERS:** Waste materials must be placed in and shipped in appropriate 5-gallon or 55-gallon poly or metal waste pails or drums. Permeable cardboard containers are not appropriate and should not be used. Ensure that any required marking or labeling of the containers be done to all applicable regulations.

**PRECAUTIONS TO BE FOLLOWED DURING WASTE HANDLING:** Wear proper protective equipment when handling waste materials.

**U.S. EPA WASTE NUMBER:** Not applicable.

### 13. DISPOSAL CONSIDERATIONS (Continued)

EWC WASTE CODE: Wastes from Human or Animal Health Care or Related Research: 18 01 08: Medicines Other Than Those Mentioned in 18 01 07.

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### 14. TRANSPORTATION INFORMATION

U.S. DEPARTMENT OF TRANSPORTATION: This product is NOT classified as dangerous goods, per U.S. DOT regulations, under 49 CFR 172.101.

TRANSPORT CANADA TRANSPORTATION OF DANGEROUS GOODS REGULATIONS: This material does not meet the criteria of classification of Dangerous Goods, per regulations of Transport Canada.

INTERNATIONAL AIR TRANSPORT ASSOCIATION (IATA): This product does not meet the criteria as Dangerous Goods, per rules of IATA.

INTERNATIONAL MARITIME ORGANIZATION (IMO) DESIGNATION: This product is NOT classified as Dangerous Goods by the International Maritime Organization.

EUROPEAN AGREEMENT CONCERNING THE INTERNATIONAL CARRIAGE OF DANGEROUS GOODS BY ROAD (ADR): This product does not meet the criteria as Dangerous Goods of the United Nations Economic Commission for Europe.

TRANSPORT IN BULK ACCORDING TO THE IBC CODE: Not applicable.

ENVIRONMENTAL HAZARDS: This product does not meet the criteria of environmentally hazardous according to the criteria of the UN Model Regulations (as reflected in the IMDG Code, ADR, RID, and ADN) and is not specifically listed in Annex III under MARPOL 73/78.

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### 15. REGULATORY INFORMATION

#### **ADDITIONAL U.S. REGULATIONS:**

U.S. SARA REPORTING REQUIREMENTS: This product is not subject to the reporting requirements of Sections 302, 304, and 313 of Title III of the Superfund Amendments and Reauthorization Act.

U.S. SARA THRESHOLD PLANNING QUANTITY: There are no specific Threshold Planning Quantities for this material. The default Federal SDS submission and inventory requirement filing threshold of 10,000 lb (4,540 kg) may apply, per 40 CFR 370.20.

U.S. SARA HAZARD CATEGORIES (SECTION 311/312, 40 CFR 370-21): ACUTE: Yes; CHRONIC: Yes; FIRE: No; REACTIVE: No; SUDDEN RELEASE: No

U.S. CERCLA REPORTABLE QUANTITY (RQ): Not applicable.

U.S. TSCA INVENTORY STATUS: This product is regulated under Food and Drug Administration (FDA) standards; this product is not subject to requirements under TSCA.

OTHER U.S. FEDERAL REGULATIONS: This product is regulated under FDA regulations.

CALIFORNIA SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT (PROPOSITION 65): The Methotrexate Sodium component of this product is listed on the California Proposition 65 Lists. **WARNING!** This product contains a compound known to the State of California to cause developmental harm.

#### **ADDITIONAL CANADIAN REGULATIONS:**

CANADIAN DSL/NDSL STATUS: This product is regulated by the Therapeutic Products Programme (TPP) of Health Canada; it is exempt from the requirements of CEPA.

CANADIAN ENVIRONMENTAL PROTECTION ACT (CEPA) PRIORITY SUBSTANCES LISTS: Components are not on the CEPA substances lists.

OTHER CANADIAN REGULATIONS: Requirements under the Canadian Health Canada, Laboratory Biosafety Guidelines may be applicable.

CANADIAN WHMIS CLASSIFICATION and SYMBOLS: The WHMIS Requirements of the Hazardous Products Act does not apply in respect of the advertising, sale or importation of any cosmetic, device, drug or food within the meaning of the Food and Drugs Act.

#### **ADDITIONAL EUROPEAN REGULATIONS:**

SAFETY, HEALTH, AND ENVIRONMENTAL REGULATIONS/LEGISLATION SPECIFIC FOR THE PRODUCT: Formulated, finished medicinal products for human use, are subject to Directive 2001/83/EC and subsequent amendments to the directive.

CHEMICAL SAFETY ASSESSMENT: No Data Available. The chemical safety assessment is required for some substances according to European Union Regulation (EC) 1907/2006, Article 14.

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### 16. OTHER INFORMATION

ANSI LABELING (Z129.1, Provided to Summarize Occupational Hazard Information): **WARNING!** MAY CAUSE RESPIRATORY SYSTEM, EYE, AND SKIN IRRITATION. MAY BE HARMFUL IF LARGE AMOUNT IS INGESTED. CAN CAUSE HARM TO DEVELOPING FETUS OR DAMAGE FERTILITY. Do not taste or swallow. Avoid contact with skin, eyes, and clothing. Keep container closed. Wear gloves, goggles, and suitable body protection. **FIRST-AID**: If swallowed, do not induce vomiting. Never give anything by mouth to an unconscious person. In case of contact, immediately flush skin with copious amounts of warm water for 20 minutes. Remove contaminated clothing and shoes. If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Seek medical attention. **IN CASE OF FIRE**: Use water fog, dry chemical or CO<sub>2</sub>, or alcohol foam. **IN CASE OF SPILL**: Sweep up or vacuum spilled product or absorb spilled liquid on appropriate sorbent materials. Decontaminate area with soapy water and triple rinse area. Place in a suitable container. Refer to SDS for additional information.

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## 16. OTHER INFORMATION (Continued)

**GLOBAL HARMONIZATION AND EU CLP REGULATION (EC) 1272/2008 LABELING AND CLASSIFICATION:** According to Article 1, item 5 (a) of CLP Regulation (EC) 1272/2008, medicinal products in the finished state for human use, as defined in 2001/83/EC, are excepted from classification and other criteria of 1272/2008.

**67/548/EEC EU LABELING/CLASSIFICATION:** According to Article 1 of European Union Council Directive 92/32/EEC, medical products in the finished state for human use (as defined by European Union Council Directives 67/548/EEC and 87/21/EEC) are not subject to the regulations and administrative provisions of European Union Council Directive 92/32/EEC.

### CLASSIFICATION FOR COMPONENTS:

**FULL TEXT GLOBAL HARMONIZATION AND EU CLP REGULATION (EC) 1272/2008:**

#### METHOTREXATE SODIUM:

**Classification:** Acute Oral Toxicity Category 5, Reproductive Toxicity Category 1A

**Hazard Statements:** H303: May be harmful if swallowed. H360Df: May damage the unborn child. Suspected of damaging fertility.

#### ALL OTHER COMPONENTS:

An official classification for these substances has not been published in the CLP 1272: 2008 and is not applicable for self-classification.

**FULL TEXT EU 67/548/EEC:**

#### METHOTREXATE SODIUM:

**Classification:** Reproductive Toxicity Category 1

**Risk Phrases:** R60: May impair fertility. R61: May cause harm to the unborn child.

#### ALL OTHER COMPONENTS:

An official classification for these substances has not been published in Commission Directives 93/72/EEC, 94/69 EC, 96/54/EC or subsequent directives and is not applicable for self-classification.

**REVISION DETAILS:** New

**REFERENCES AND DATA SOURCES:** Contact the supplier for information.

**METHODS OF EVALUATING INFORMATION FOR THE PURPOSE OF CLASSIFICATION:** Bridging principles were used to classify this product.

**PREPARED BY:** CHEMICAL SAFETY ASSOCIATES, Inc. • PO Box 1961, Hilo, HI 96721-1961 • (800) 441-3365

**DATE OF PRINTING:** July 30, 2012

**REVISION HISTORY:** New

*The Vendee (or any other third party) assumes full risk and responsibility for any injury or damage that may occur from the manufacture, use or other exposure to the material. No warranty is expressed or implied regarding the accuracy of the data set forth herein or the results that may be obtained from the use or reliance thereof. Teva, Inc. assumes no responsibility for any injury that may arise from the manufacture, use or other exposure to the material if reasonable safety procedures are not adhered to as stipulated in the data sheet attached hereto. Additionally, Teva, Inc. assumes no responsibility for injury to any person proximately caused by the inappropriate or unintended use of the material even if such reasonable safety procedures are followed.*

## DEFINITIONS OF TERMS

For information on medical terms used in this SDS consult an on-line database such as Medline Plus: <http://www.nlm.nih.gov/medlineplus/druginformation.html>. A large number of abbreviations and acronyms appear on a SDS. Some of these, which are commonly used, include the following:

**CAS #:** This is the Chemical Abstract Service Number that uniquely identifies each constituent.

### EXPOSURE LIMITS IN AIR:

**CEILING LEVEL:** The concentration that shall not be exceeded during any part of the working exposure.

**ACGIH** - American Conference of Governmental Industrial Hygienists, a professional association which establishes exposure limits.

**Ceiling Level (C).** Skin absorption effects must also be considered.

**DFG MAK Germ Cell Mutagen Categories:** 1: Germ cell mutagens which have been shown to increase the mutant frequency in the progeny of exposed humans. 2: Germ cell mutagens which have been shown to increase the mutant frequency in the progeny of exposed mammals.

**3A:** Substances which have been shown to induce genetic damage in germ cells of human of animals, or which produce mutagenic effects in somatic cells of mammals *in vivo* and have been shown to reach the germ cells in an active form. **3B:** Substances which are suspected of being germ cell mutagens because of their genotoxic effects in mammalian somatic cell *in vivo*; in exceptional cases, substances for which there are no *in vivo* data, but which are clearly mutagenic *in vitro* and structurally related to known *in vivo* mutagens. 4: Not applicable (Category 4 carcinogenic substances are those with non-genotoxic mechanisms of action. By definition, germ cell mutagens are genotoxic. Therefore, a Category 4 for germ cell mutagens cannot apply. At some time in the future, it is conceivable that a Category 4 could be established for genotoxic substances with primary targets other than DNA [e.g. purely aneugenic substances] if research results make this seem sensible.) 5: Germ cell mutagens, the potency of which is considered to be so low that, provided the MAK value is observed, their contribution to genetic risk for humans is expected not to be significant.

**DFG MAK Pregnancy Risk Group Classification:** **Group A:** A risk of damage to the developing embryo or fetus has been unequivocally demonstrated. Exposure of pregnant women can lead to damage of the developing organism, even when MAK and BAT (Biological Tolerance Value for Working Materials) values are observed. **Group B:** Currently available information indicates a risk of damage to the developing embryo or fetus must be considered to be probable. Damage to the developing organism cannot be excluded when pregnant women are exposed, even when MAK and BAT values are observed. **Group C:** There is no reason to fear a risk of damage to the developing embryo or fetus when MAK and BAT values are observed. **Group D:** Classification in one of the groups A-C is not yet possible because, although the data available may indicate a trend, they are not sufficient for final evaluation.

**IDLH-Immediately Dangerous to Life and Health:** This level represents a concentration from which one can escape within 30-minutes without suffering escape-preventing or permanent injury.

**LOQ:** Limit of Quantitation.

**MAK:** Federal Republic of Germany Maximum Concentration Values in the workplace.

**NE:** Not Established. When no exposure guidelines are established, an entry of NE is made for reference.

**NIC:** Notice of Intended Change.

**NIOSH CEILING:** The exposure that shall not be exceeded during any part of the workday. If instantaneous monitoring is not feasible, the ceiling shall be assumed as a 15-minute TWA exposure (unless otherwise specified) that shall not be exceeded at any time during a workday.

**NIOSH RELs:** NIOSH's Recommended Exposure Limits.

### EXPOSURE LIMITS IN AIR (continued):

**PEL-Permissible Exposure Limit:** OSHA's Permissible Exposure Limits. This exposure value means exactly the same as a TLV, except that it is enforceable by OSHA. The OSHA Permissible Exposure Limits are based in the 1989 PELs and the June, 1993 Air Contaminants Rule (Federal Register: 58: 35338-35351 and 58: 40191). Both the current PELs and the vacated PELs are indicated. The phrase, "Vacated 1989 PEL," is placed next to the PEL that was vacated by Court Order.

**SKIN:** Used when there is a danger of cutaneous absorption.

**STEL-Short Term Exposure Limit:** Short Term Exposure Limit, usually a 15-minute time-weighted average (TWA) exposure that should not be exceeded at any time during a workday, even if the 8-hr TWA is within the TLV-TWA, PEL-TWA or REL-TWA.

**TLV-Threshold Limit Value:** An airborne concentration of a substance that represents conditions under which it is generally believed that nearly all workers may be repeatedly exposed without adverse effect. The duration must be considered, including the 8-hour.

**TWA-Time Weighted Average:** Time Weighted Average exposure concentration for a conventional 8-hr (TLV, PEL) or up to a 10-hr (REL) workday and a 40-hr workweek.

### HAZARDOUS MATERIALS IDENTIFICATION SYSTEM HAZARD

**RATINGS:** This rating system was developed by the National Paint and Coating Association and has been adopted by industry to identify the degree of chemical hazards.

**HEALTH HAZARD: 0 (Minimal Hazard):** No significant health risk, irritation of skin or eyes not anticipated. *Skin Irritation:* Essentially non-irritating. PII or Draize = "0". *Eye Irritation:* Essentially non-irritating, or minimal effects which clear in < 24 hours [e.g. mechanical irritation].

*Draize = "0". Oral Toxicity LD<sub>50</sub> Rat: < 5000 mg/kg. Dermal Toxicity LD<sub>50</sub>Rat or Rabbit: < 2000 mg/kg. Inhalation Toxicity 4-hrs LC<sub>50</sub> Rat: < 20 mg/L;*

*1 (Slight Hazard: Minor reversible Injury may occur; slightly or mildly irritating. Skin Irritation: Slightly or mildly irritating. Eye Irritation: Slightly or mildly irritating. Oral Toxicity LD<sub>50</sub> Rat: > 500-5000 mg/kg. Dermal Toxicity LD<sub>50</sub>Rat or Rabbit: > 1000-2000 mg/kg. Inhalation Toxicity LC<sub>50</sub> 4-hrs Rat: > 2-20 mg/L;*

*2 (Moderate Hazard: Temporary or transitory injury may occur. Skin Irritation: Moderately irritating; primary irritant; sensitizer. PII or Draize > 0, < 5. Eye Irritation: Moderately to severely irritating and/or corrosive; reversible corneal opacity; corneal involvement or irritation clearing in 8-21 days. Draize > 0, ≤ 25. Oral Toxicity LD<sub>50</sub> Rat: > 50-500 mg/kg. Dermal Toxicity LD<sub>50</sub>Rat or Rabbit: > 200-1000 mg/kg. Inhalation Toxicity LC<sub>50</sub> 4-hrs Rat: > 0.5-2 mg/L;*

*3 (Serious Hazard: Major injury likely unless prompt action is taken and medical treatment is given; high level of toxicity, corrosive. Skin Irritation: Severely irritating and/or corrosive; may destroy dermal tissue, cause skin burns, dermal necrosis. PII or Draize > 5-8 with destruction of tissue. Eye Irritation: Corrosive, irreversible destruction of ocular tissue; corneal involvement or irritation persisting for more than 21 days. Draize > 80 with effects irreversible in 21 days. Oral Toxicity LD<sub>50</sub> Rat: > 1-50 mg/kg. Dermal Toxicity LD<sub>50</sub>Rat or Rabbit: > 20-200 mg/kg. Inhalation Toxicity LC<sub>50</sub> 4-hrs Rat: > 0.05-0.5 mg/L;*

*4 (Severe Hazard: Life-threatening; major or permanent damage may result from single or repeated exposure. Skin Irritation: Not appropriate. Do not rate as a "4", based on skin irritation alone. Eye Irritation: Not appropriate. Do not rate as a "4", based on eye irritation alone. Oral Toxicity LD<sub>50</sub> Rat: ≤ 1 mg/kg. Dermal Toxicity LD<sub>50</sub>Rat or Rabbit: ≤ 20 mg/kg. Inhalation Toxicity LC<sub>50</sub> 4-hrs Rat: ≤ 0.05 mg/L.)*

**FLAMMABILITY HAZARD: 0 (Minimal Hazard):** Materials that will not burn in air when exposure to a temperature of 815.5°C [1500°F] for a period of 5 minutes; 1 (Slight Hazard-Materials that must be pre-heated before ignition can occur. Material require considerable pre-heating, under all ambient temperature conditions before ignition and combustion can occur,



## DEFINITIONS OF TERMS (Continued)

### HAZARDOUS MATERIALS IDENTIFICATION SYSTEM HAZARD RATINGS (continued):

**FLAMMABILITY HAZARD (continued): 1 (continued):** Including: Materials that will burn in air when exposed to a temperature of 815.5°C (1500°F) for a period of 5 minutes or less; Liquids, solids and semisolids having a flash point at or above 93.3°C [200°F] (e.g. OSHA Class III B, or; Most ordinary combustible materials [e.g. wood, paper, etc.]); **2 (Moderate Hazard-Materials** that must be moderately heated or exposed to relatively high ambient temperatures before ignition can occur. Materials in this degree would not, under normal conditions, form hazardous atmospheres in air, but under high ambient temperatures or moderate heating may release vapor in sufficient quantities to produce hazardous atmospheres in air, including: Liquids having a flash-point at or above 37.8°C [100°F]; Solid materials in the form of course dusts that may burn rapidly but that generally do not form explosive atmospheres; Solid materials in a fibrous or shredded form that may burn rapidly and create flash fire hazards (e.g. cotton, sisal, hemp; Solids and semisolids that readily give off flammable vapors.); **3 (Serious Hazard-Liquids and solids** that can be ignited under almost all ambient temperature conditions. Materials in this degree produce hazardous atmospheres with air under almost all ambient temperatures, or unaffected by ambient temperature, are readily ignited under almost all conditions, including: Liquids having a flash point below 22.8°C [73°F] and having a boiling point at or above 38°C [100°F] and below 37.8°C [100°F] [e.g. OSHA Class IB and IC]; Materials that on account of their physical form or environmental conditions can form explosive mixtures with air and are readily dispersed in air [e.g., dusts of combustible solids, mists or droplets of flammable liquids]; Materials that burn extremely rapidly, usually by reason of self-contained oxygen [e.g. dry nitrocellulose and many organic peroxides]; **4 (Severe Hazard-Materials** that will rapidly or completely vaporize at atmospheric pressure and normal ambient temperature or that are readily dispersed in air, and which will burn readily, including: Flammable gases; Flammable cryogenic materials; Any liquid or gaseous material that is liquid while under pressure and has a flash point below 22.8°C [73°F] and a boiling point below 37.8°C [100°F] [e.g. OSHA Class IA; Material that ignite spontaneously when exposed to air at a temperature of 54.4°C [130°F] or below [e.g. pyrophoric].

**PHYSICAL HAZARD: 0 (Water Reactivity):** Materials that do not react with water. *Organic Peroxides:* Materials that are normally stable, even under fire conditions and will not react with water. *Explosives:* Substances that are Non-Explosive. *Unstable Compressed Gases:* No Rating. *Pyrophorics:* No Rating. *Oxidizers:* No "0" rating allowed. *Unstable Reactives:* Substances that will not polymerize, decompose, condense or self-react; **1 (Water Reactivity):** Materials that change or decompose upon exposure to moisture. *Organic Peroxides:* Materials that are normally stable, but can become unstable at high temperatures and pressures. These materials may react with water, but will not release energy. *Explosives:* Division 1.5 and 1.6 substances that are very insensitive explosives or that do not have a mass explosion hazard. *Compressed Gases:* Pressure below OSHA definition. *Pyrophorics:* No Rating. *Oxidizers:* Packing Group III; *Solids:* any material that in either concentration tested, exhibits a mean burning time less than or equal to the mean burning time of a 3:7 potassium bromate/cellulose mixture and the criteria for Packing Group I and II are not met. *Liquids:* any material that exhibits a mean pressure rise time less than or equal to the pressure rise time of a 1:1 nitric acid (65%)/cellulose mixture and the criteria for Packing Group I and II are not met. *Unstable Reactives:* Substances that may decompose, condense or self-react, but only under conditions of high temperature and/or pressure and have little or no potential to cause significant heat generation or explosive hazard. Substances that readily undergo hazardous polymerization in the absence of inhibitors; **2 (Water Reactivity):** Materials that may react violently with water. *Organic Peroxides:* Materials that, in themselves, are normally unstable and will readily undergo violent chemical change, but will not detonate. These materials may also react violently with water. *Explosives:* Division 1.4 – Explosive substances where the explosive effect are largely confined to the package and no projection of fragments of appreciable size or range are expected. An external fire must not cause virtually instantaneous explosion of almost the entire contents of the package. *Compressed Gases:* Pressurized and meet OSHA definition but < 514.7 psi absolute at 21.1°C (70°F) [500 psig]. *Pyrophorics:* No Rating. *Oxidizers:* Packing Group II; *Solids:* any material that, either in concentration tested, exhibits a mean burning time of less than or equal to the mean burning time of a 2:3 potassium bromate/cellulose mixture and the criteria for Packing Group I are not met. *Liquids:* any material that exhibits a mean pressure rise time less than or equal to the pressure rise of a 1:1 aqueous sodium chlorate solution (40%)/cellulose mixture and the criteria for Packing Group I are not met. *Unstable Reactives:* Substances that may polymerize, decompose, condense, or self-react at ambient temperature and/or pressure, but have a low potential for significant heat generation or explosion. Substances that readily form peroxides upon exposure to air or oxygen at room temperature; **3 (Water Reactivity):** Materials that may form explosive reactions with water. *Organic Peroxides:* Materials that are capable of detonation or explosive reaction, but require a strong initiating source, or must be heated under confinement before initiation; or materials that react explosively with water. *Explosives:* Division 1.2 – Explosive substances that have a fire hazard and either a minor blast hazard or a minor projection hazard or both, but do not have a mass explosion hazard. *Compressed Gases:* Pressure ≥ 514.7 psi absolute at 21.1°C (70°F) [500 psig]. *Pyrophorics:* No Rating. *Oxidizers:* Packing Group I; *Solids:* any material that, in either concentration tested, exhibits a mean burning time less than the mean burning time of a 3:2 potassium bromate/cellulose mixture. *Liquids:* Any material that spontaneously ignites when mixed with cellulose in a 1:1 ratio, or which exhibits a mean pressure rise time less than the pressure rise time of a 1:1 perchloric acid (50%)/cellulose mixture. *Unstable Reactives:* Substances that may polymerize, decompose, condense or self-react at ambient temperature and/or pressure and have a moderate potential to cause significant heat generation or explosion.; **4 (Water Reactivity):** Materials that react explosively with water without requiring heat or confinement. *Organic Peroxides:* Materials that are readily capable of detonation or explosive decomposition at normal temperature and pressures. *Explosives:* Division 1.1 and 1.2-explosive substances that have a mass explosion hazard or have a projection hazard. A mass explosion is one that affects almost the entire load instantaneously. *Compressed Gases:* No Rating. *Pyrophorics:* Add to the definition of Flammability "4". *Oxidizers:* No "4" rating. *Unstable Reactives:* Substances that may polymerize, decompose, condense or self-react at ambient temperature and/or pressure and have a high potential to cause significant heat generation or explosion).

### NATIONAL FIRE PROTECTION ASSOCIATION HAZARD RATINGS:

**HEALTH HAZARD: 0** Materials that, under emergency conditions, would offer no hazard beyond that of ordinary combustible materials. Gases and vapors with an LC<sub>50</sub> for acute inhalation toxicity greater than 10,000 ppm. Dusts and mists with an LC<sub>50</sub> for acute inhalation toxicity greater than 200 mg/L. Materials with an LD<sub>50</sub> for acute dermal toxicity greater than 2000 mg/kg. Materials with an LD<sub>50</sub> for acute oral toxicity greater than 2000 mg/kg. Materials essentially non-irritating to the respiratory tract, eyes, and skin.

### NATIONAL FIRE PROTECTION ASSOCIATION HAZARD RATINGS (continued):

**HEALTH HAZARD (continued): 1** Materials that, under emergency conditions, can cause significant irritation. Gases and vapors with an LC<sub>50</sub> for acute inhalation toxicity greater than 5,000 ppm but less than or equal to 10,000 ppm. Dusts and mists with an LC<sub>50</sub> for acute inhalation toxicity greater than 10 mg/L but less than or equal to 200 mg/L. Materials with an LD<sub>50</sub> for acute dermal toxicity greater than 1000 mg/kg but less than or equal to 2000 mg/kg. Materials that slightly to moderately irritate the respiratory tract, eyes and skin. Materials with an LD<sub>50</sub> for acute oral toxicity greater than 500 mg/kg but less than or equal to 2000 mg/kg. **2** Materials that, under emergency conditions, can cause temporary incapacitation or residual injury. Gases with an LC<sub>50</sub> for acute inhalation toxicity greater than 3,000 ppm but less than or equal to 5,000 ppm. Any liquid whose saturated vapor concentration at 20°C (68°F) is equal to or greater than one-fifth its LC<sub>50</sub> for acute inhalation toxicity, if its LC<sub>50</sub> is less than or equal to 5000 ppm and that does not meet the criteria for either degree of hazard 3 or degree of hazard 4. Dusts and mists with an LC<sub>50</sub> for acute inhalation toxicity greater than 2 mg/L but less than or equal to 10 mg/L. Materials with an LD<sub>50</sub> for acute dermal toxicity greater than 200 mg/kg but less than or equal to 1000 mg/kg. Compressed liquefied gases with boiling points between -30°C (-22°F) and -55°C (-66.5°F) that cause severe tissue damage, depending on duration of exposure. Materials that are respiratory irritants. Materials that cause severe, but reversible irritation to the eyes or are lachrymators. Materials that are primary skin irritants or sensitizers. Materials whose LD<sub>50</sub> for acute oral toxicity is greater than 50 mg/kg but less than or equal to 500 mg/kg. Dusts and mists with an LC<sub>50</sub> for acute inhalation toxicity greater than 10 mg/L but less than or equal to 200 mg/L. Materials with an LD<sub>50</sub> for acute dermal toxicity greater than 1000 mg/kg but less than or equal to 2000 mg/kg. Materials that slightly to moderately irritate the respiratory tract, eyes and skin. Materials with an LD<sub>50</sub> for acute oral toxicity greater than 500 mg/kg but less than or equal to 2000 mg/kg. **3** (materials that, under emergency conditions, can cause serious or permanent injury): Gases and vapors whose LC<sub>50</sub> for acute inhalation toxicity is greater than 1,000 ppm but less than or equal to 3,000 ppm. Dusts and mists whose LC<sub>50</sub> for acute inhalation toxicity is greater than 0.5 mg/L but less than or equal to 2 mg/L. Materials whose LD<sub>50</sub> for acute dermal toxicity is greater than 40 mg/kg but less than or equal to 200 mg/kg. Materials whose LD<sub>50</sub> for acute oral toxicity is greater than 5 mg/kg but less than or equal to 50 mg/kg. Any liquid whose saturated vapor concentration at 20°C (68°F) is equal to or greater than one-fifth its LC<sub>50</sub> for acute inhalation toxicity, if its LC<sub>50</sub> is less than or equal to 3000 ppm and that does not meet the criteria for degree of hazard 4. Compressed liquefied gases with boiling points between -30°C (-22°F) and -55°C (-66.5°F) that cause frostbite and irreversible tissue damage. Materials that are respiratory irritants. Cryogenic gases that cause frostbite and irreversible tissue damage. Materials that are corrosive to the respiratory tract. Materials that are corrosive to the eyes or cause irreversible corneal opacity. Materials that are corrosive to the skin. **4** (materials that, under emergency conditions, can be lethal): Gases and vapors whose LC<sub>50</sub> for acute inhalation toxicity less than or equal to 1,000 ppm. Dusts and mists whose LC<sub>50</sub> for acute inhalation toxicity is less than or equal to 0.5 mg/L. Materials whose LD<sub>50</sub> for acute dermal toxicity is less than or equal to 40 mg/kg. Materials whose LD<sub>50</sub> for acute oral toxicity is less than or equal to 5 mg/kg. Any liquid whose saturated vapor concentration at 20°C (68°F) is equal to or greater than one-fifth its LC<sub>50</sub> for acute inhalation toxicity, if its LC<sub>50</sub> is less than or equal to 1000 ppm.

**FLAMMABILITY HAZARD: 0** Materials that will not burn under typical fire conditions, including intrinsically noncombustible materials such as concrete, stone, and sand; Materials that will not burn in air when exposed to a temperature of 816°C (1500°F) for a period of 5 minutes in accordance with Annex D. **1** Materials that must be preheated before ignition can occur. Materials in this degree require considerable preheating, under all ambient temperature conditions, before ignition and combustion can occur. Materials that will burn in air when exposed to a temperature of 816°C (1500°F) for a period of 5 minutes in accordance with Annex D. Liquids, solids and semisolids having a flash point at or above 93.4°C (200°F) (i.e. Class III B liquids). Liquids with a flash point greater than 35°C (95°F) that do not sustain combustion when tested using the *Method of Testing for Sustained Combustibility*, per 49 CFR 173, Appendix H or the UN *Recommendation on the Transport of Dangerous Goods, Model Regulations* (current edition) and the related *Manual of Tests and Criteria* (current edition). Liquids with a flash point greater than 35°C (95°F) in a water-miscible solution or dispersion with a water non-combustible liquid/solid content of more than 85 percent by weight. Liquids that have no fire point when tested by ASTM D 92 Standard Test Method for Flash and Fire Points by Cleveland Open Cup, up to a boiling point of the liquid or up to a temperature at which the sample being tested shows an obvious physical change. Combustible pellets with a representative diameter of greater than 2 mm (10 mesh). Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed up flash point of the solvent. Most ordinary combustible materials. **2** Materials that must be moderately heated or exposed to relatively high ambient temperatures before ignition can occur. Materials in this degree would not under normal conditions form hazardous atmospheres with air, but under high ambient temperatures or under moderate heating could release vapor in sufficient quantities to produce hazardous atmospheres with air: Liquids having a flash point at or above 37.8°C (100°F) and below 93.4°C (200°F) (i.e. Class II and Class III A liquids.) Solid materials in the form of powders or coarse dusts of representative diameter between 420 microns (40 mesh) and 2 mm (10 mesh) that burn rapidly but that generally do not form explosive mixtures in air. Solid materials in fibrous or shredded form that burn rapidly and create flash fire hazards, such as cotton, sisal and hemp. Solids and semisolids that readily give off flammable vapors. Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed cup flash point of the solvent. **3** Liquids and solids that can be ignited under almost all ambient temperature conditions. Materials in this degree produce hazardous atmospheres with air under almost all ambient temperatures or, though unaffected by ambient temperatures, are readily ignited under almost all conditions: Liquids having a flash point below 22.8°C (73°F) and having a boiling point at or above 37.8°C (100°F) and those liquids having a flash point at or above 22.8°C (73°F) and below 37.8°C (73°F) and below 37.8°C (100°F) (i.e. Class IB and IC liquids). Materials that, on account of their physical form or environmental conditions, can form explosive mixtures with air and are readily dispersed in air. Flammable or combustible dusts with a representative diameter less than 420 microns (40 mesh). Materials that burn with extreme rapidity, usually by reason of self-contained oxygen (e.g. dry nitrocellulose and many organic peroxides). Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed cup flash point of the solvent.

## DEFINITIONS OF TERMS (Continued)

### NATIONAL FIRE PROTECTION ASSOCIATION HAZARD RATINGS (continued):

**FLAMMABILITY HAZARD (continued):** **4** Materials that will rapidly or completely vaporize at atmospheric pressure and normal ambient temperature or that are readily dispersed in air and will burn readily: Flammable gases. Flammable cryogenic materials. Any liquid or gaseous materials that is liquid while under pressure and has a flash point below 22.8°C (73°F) and a boiling point below 37.8°C (100°F) (i.e. Class IA liquids). Materials that ignite when exposed to air. Solids containing greater than 0.5 percent by weight of a flammable or combustible solvent are rated by the closed cup flash point of the solvent.

**INSTABILITY HAZARD: 0** Materials that in themselves are normally stable, even under fire conditions. Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) below 0.01 W/mL. Materials that do not exhibit an exotherm at temperatures less than or equal to 500°C (932°F) when tested by differential scanning calorimetry. **1** Materials that in themselves are normally stable, but that can become unstable at elevated temperatures and pressures. Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) at or above 0.01 W/mL and below 10 W/mL. **2** Materials that readily undergo violent chemical change at elevated temperatures and pressures: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) at or above 10 W/mL and below 100W/mL. **3** Materials that in themselves are capable of detonation or explosive decomposition or explosive reaction, but that require a strong initiating source or that must be heated under confinement before initiation: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) at or above 100 W/mL and below 1000 W/mL. Materials that are sensitive to thermal or mechanical shock at elevated temperatures and pressures. **4** Materials that in themselves are readily capable of detonation or explosive decomposition or explosive reaction at normal temperatures and pressures: Materials that have an estimated instantaneous power density (product of heat of reaction and reaction rate) at 250°C (482°F) of 1000 W/mL or greater. Materials that are sensitive to localized thermal or mechanical shock at normal temperatures and pressures.

### FLAMMABILITY LIMITS IN AIR:

Much of the information related to fire and explosion is derived from the National Fire Protection Association (NFPA). **Flash Point** - Minimum temperature at which a liquid gives off sufficient vapors to form an ignitable mixture with air. **Autoignition Temperature**: The minimum temperature required to initiate combustion in air with no other source of ignition. **LEL** - the lowest percent of vapor in air, by volume, that will explode or ignite in the presence of an ignition source. **UEL** - the highest percent of vapor in air, by volume, that will explode or ignite in the presence of an ignition source.

### TOXICOLOGICAL INFORMATION:

**Human and Animal Toxicology:** Possible health hazards as derived from human data, animal studies, or from the results of studies with similar compounds are presented. Definitions of some terms used in this section are: **LD<sub>50</sub>** - Lethal Dose (solids and liquids) which kills 50% of the exposed animals; **LC<sub>50</sub>** - Lethal Concentration (gases) which kills 50% of the exposed animals; **ppm** concentration expressed in parts of material per million parts of air or water; **mg/m<sup>3</sup>** concentration expressed in weight of substance per volume of air; **mg/kg** quantity of material, by weight, administered to a test subject, based on their body weight in kg. Other measures of toxicity include **TDLo**, the lowest dose to cause a symptom and **TCLo** the lowest concentration to cause a symptom; **TDo**, **LDLo**, and **LDo**, or **TC**, **TCo**, **LCLo**, and **LCo**, the lowest dose (or concentration) to cause lethal or toxic effects. **Cancer Information:** The sources are: **IARC** - the International Agency for Research on Cancer; **NTP** - the National Toxicology Program, **RTECS** - the Registry of Toxic Effects of Chemical Substances, **OSHA** and **CAL/OSHA**. IARC and NTP rate chemicals on a scale of decreasing potential to cause human cancer with rankings from 1 to 4. Subrankings (2A, 2B, etc.) are also used. **Other Information:** **BEI** - ACGIH Biological Exposure Indices, represent the levels of determinants which are most likely to be observed in specimens collected from a healthy worker who has been exposed to chemicals to the same extent as a worker with inhalation exposure to the TLV.

### REPRODUCTIVE TOXICITY INFORMATION:

A **mutagen** is a chemical which causes permanent changes to genetic material (DNA) such that the changes will propagate through generational lines. An **embryotoxin** is a chemical which causes damage to a developing embryo (i.e. within the first eight weeks of pregnancy in humans), but the damage does not propagate across generational lines. A **teratogen** is a chemical which causes damage to a developing fetus, but the damage does not propagate across generational lines. A **reproductive toxin** is any substance which interferes in any way with the reproductive process.

### ECOLOGICAL INFORMATION:

EC is the effect concentration in water. **BCF** = Bioconcentration Factor, which is used to determine if a substance will concentrate in lifeforms which consume contaminated plant or animal matter. **TL<sub>m</sub>** = median threshold limit; Coefficient of Oil/Water Distribution is represented by **log K<sub>ow</sub>** or **log K<sub>oc</sub>** and is used to assess a substance's behavior in the environment.

### REGULATORY INFORMATION:

#### U.S. and CANADA:

**ACGIH:** American Conference of Governmental Industrial Hygienists, a professional association which establishes exposure limits.

This section explains the impact of various laws and regulations on the material. **EPA** is the U.S. Environmental Protection Agency. **NIOSH** is the National Institute of Occupational Safety and Health, which is the research arm of the U.S. Occupational Safety and Health Administration (**OSHA**). **WHMIS** is the Canadian Workplace Hazardous Materials Information System. **DOT** and **TC** are the U.S. Department of Transportation and the Transport Canada, respectively. Superfund Amendments and Reauthorization Act (**SARA**); the Canadian Domestic/Non-Domestic Substances List (**DSL/NDL**); the U.S. Toxic Substance Control Act (**TSCA**); Marine Pollutant status according to the **DOT**; the Comprehensive Environmental Response, Compensation, and Liability Act (**CERCLA** or **Superfund**); and various state regulations. This section also includes information on the precautionary warnings which appear on the material's package label. **OSHA** - U.S. Occupational Safety and Health Administration.

#### EUROPEAN and INTERNATIONAL:

The **DFG**: This is the Federal Republic of Germany's Occupation Health Agency, similar to the U.S. OSHA. **EU** is the European Community (formerly known as the **EEC**, European Economic Community). **EINECS**: This is the European Inventory of Now-Existing Chemical Substances. The **ARD** is the European Agreement Concerning the International Carriage of Dangerous Goods by Road and the **RID** are the International Regulations Concerning the Carriage of Dangerous Goods by Rail. **AICS** is the Australian Inventory of Chemical Substances.